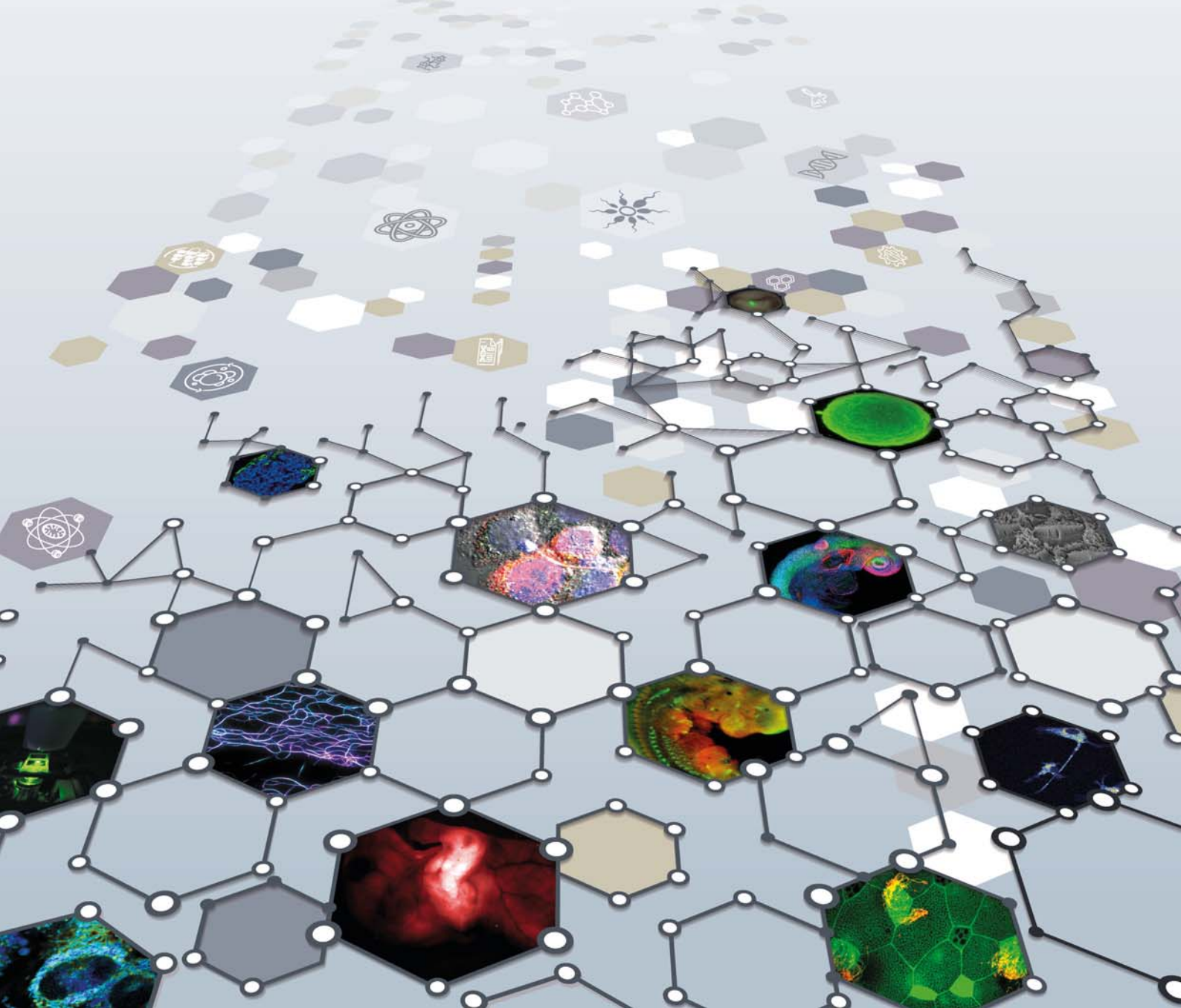
Institute of Biotechnology

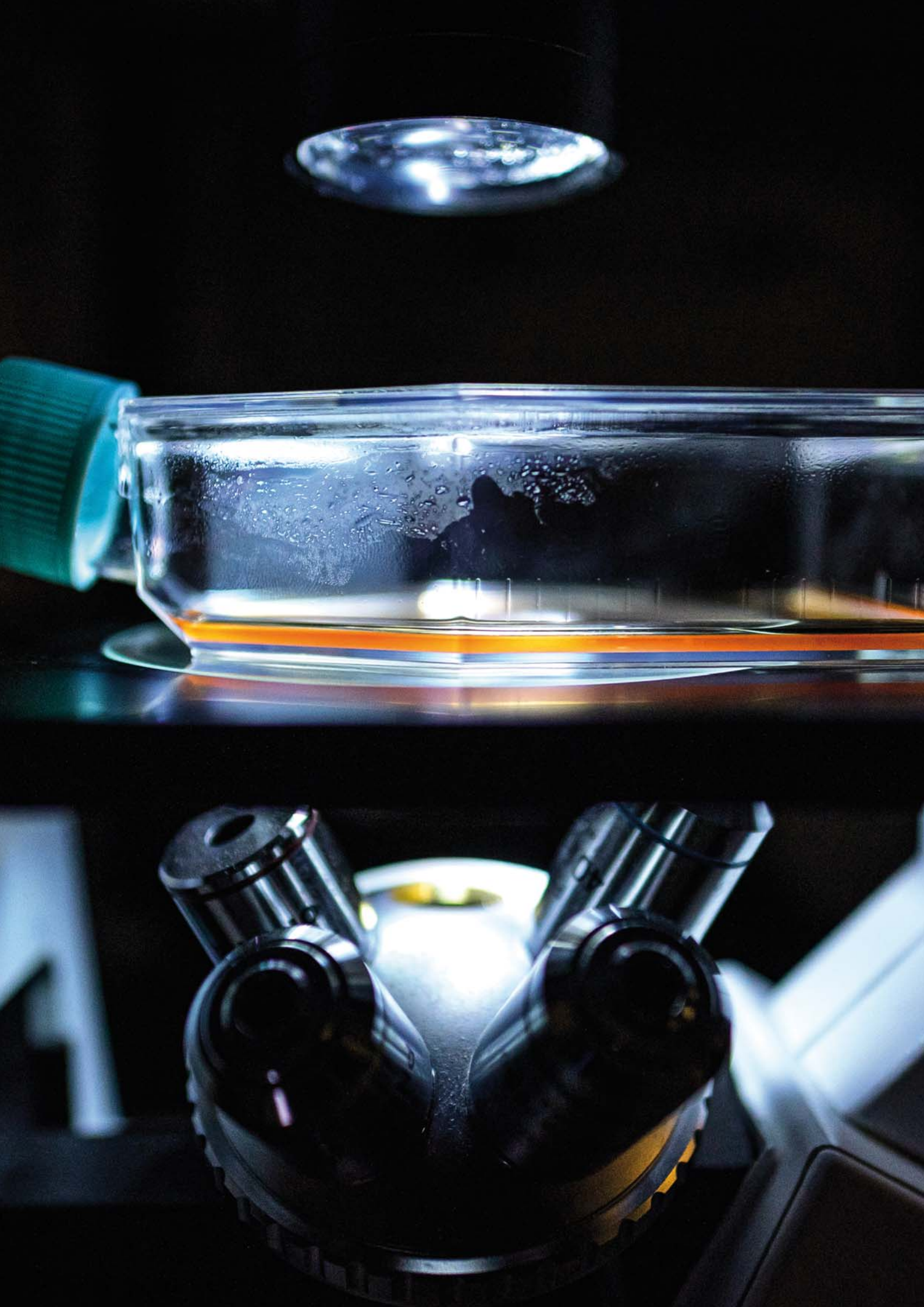
CZECH ACADEMY OF SCIENCES

2015–2019



IBT

Content



Dear Reader

Jana Peknicova, Director of IBT

You are opening the five-year Scientific Report of the Institute of Biotechnology of the Czech Academy of Sciences, v. v. i. (IBT), which summarizes its activities during the period between the years 2015 and 2019. It focuses on basic research in molecular biology at its highest level, with prospective transfer of biotechnological methods and molecular tools to diagnose and treat pathological conditions of cells into human and veterinary medicine or into other key areas of human activity.

Professors V. Hořejší, V. Viklický and P. Šebo stood by the cradle of the Institute, which was founded in 2008.

Last year, this young institute thus celebrated its 10th anniversary. Its beginnings were not easy; most groups were newly formed, and the Institute had limited financial possibilities to assist their establishment and development. Another limitation was the allotted space in the Prague area of Krč. Despite these problems, by honest and intensive scientific work, our researchers have shown that they are able to produce a number of good publications in international journals with a solid impact factor every year.

At present, there are two main areas of basic research covering the Development of Therapeutic and Diagnostic Procedures, and Structural Biology and Protein Engineering. Laboratories of both directions of research work together, have a number of joint publications and outputs into practice, creating one whole. The Institute also operates three high-quality core facilities.

The period covered by this report has also been a period of changes in the Institute structure – new laboratories have been established. Many new researchers and students, both from our country and from abroad, completed the numbers of laboratory members at positions of postdocs, students and senior scientists. The scientists from our Institute have also been able to obtain funds from national and international private sources in appreciable amounts, which now represents more than half of the Institute budget.

„At present, IBT is a consolidated Institute that not only demonstrates viability, but continuous growth.“

A key place in the development of the Institute is held by its involvement in project BIOCEV, a joint project of six institutes of the Czech Academy of Sciences (Institute of Molecular Genetics, Institute of Biotechnology, Institute of Microbiology, Institute of Physiology, Institute of Experimental Medicine and Institute of Macromolecular Chemistry) and two faculties of Charles University (Faculty of Science and First Faculty of Medicine), whose objective is to establish and operate scientific centres of excellence in biotechnology and biomedicine.

The Institute moved to a new building in the BIOCEV Centre in Vestec in January 2016 and is involved in two of five research programs of the Centre. IBT wants to take full advantage of this opportunity and produce top-grade scientific results, which will be transferred into clinical practice. The Institute is also involved in two programmes of the „Strategy AV21".

Our Institute maintains collaboration with other Institutes of the Academy and Universities, both in grant applications and publication activity. Our study programmes (Bachelor, Master, PhD) are performed in cooperation with the Universities. Some of our scientists lecture at Universities and work in expert committees and scientific councils of faculties.

International cooperation is one of the key factors for work of all our groups and is promoted at all levels at the Institute. Our groups participate in joint projects, bilateral agreements, or simply in solving a particular scientific problem. We have received eminent scientists from abroad and enjoyed their interesting lectures. As well, our institute is open to foreign PhD students.

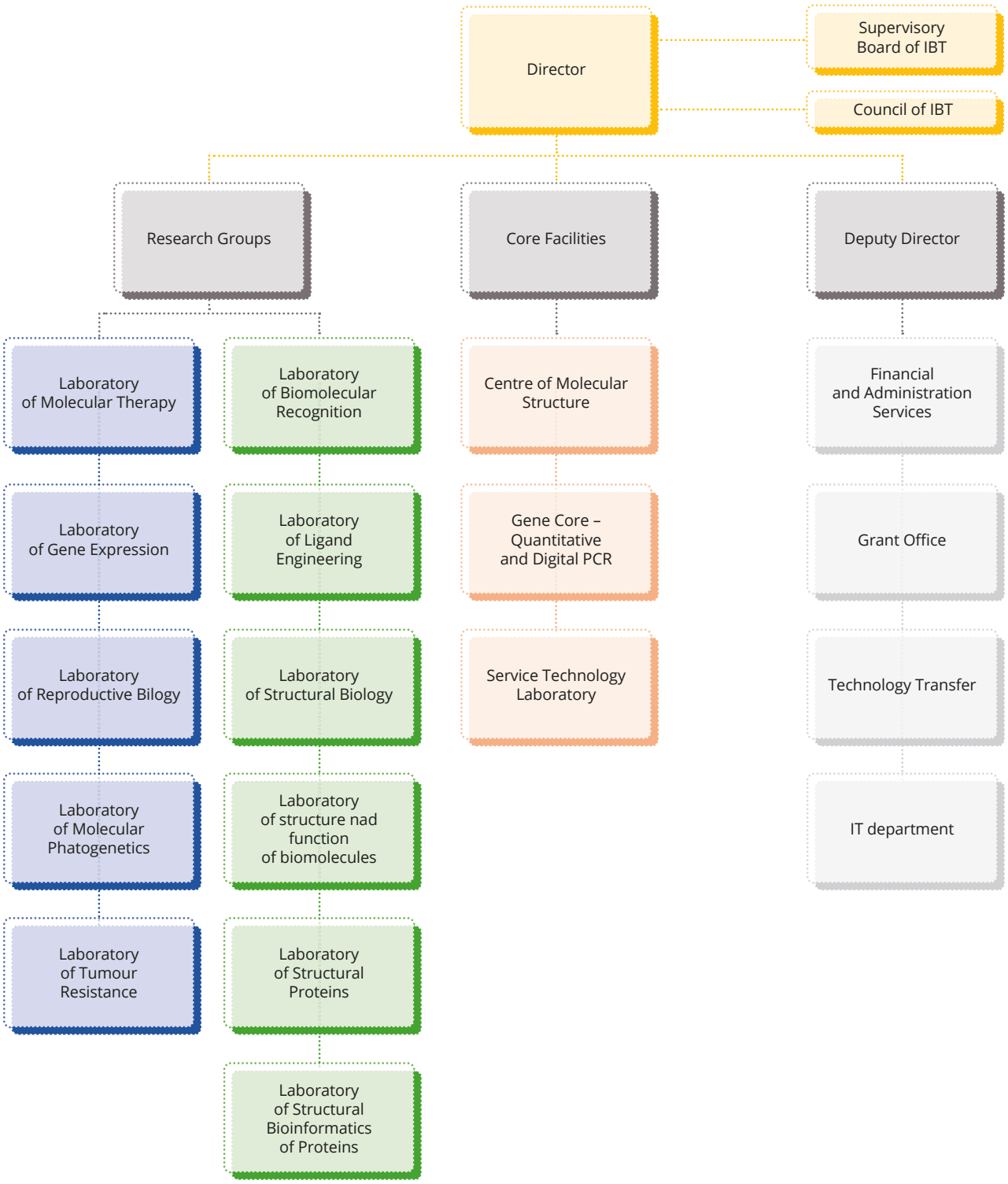
Scientists from our Institute are also active in popularizing scientific results, by giving lectures and participating in the „Week of Science" and „Open-Door Days" organized by the Academy, as well as by appearances in various media (TV, print).

At present, IBT is a consolidated Institute that not only demonstrates viability, but continuous growth, which is documented in this Scientific Report. I am convinced that the Institute of Biotechnology has all the necessary prerequisites for further development, fostering acquisition of ground-breaking knowledge and results, and consequently publications in top scientific journals. As such, the Institute represents an invaluable platform for transfer of highly innovative scientific findings to their practical application.

Vestec, July, 2019

IBT

Organization scheme



IBT

Councils and Boards

Supervisory Board (From 15th of February 2018)

RNDr. Martin Bilej, DrSc.
RNDr. Petr Malý, CSc.
Ing. Miroslava Anděrová, CSc.
Ing. Petr Bobák, CSc
Ing. Pavel Trefil, Ph.D., DrSc.

Supervisory Board (Until 14th of February 2018)

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prof. RNDr. Zdena Palková, CSc.
Ing. Jiří Špička
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Council of IBT (From 26th of March 2019)

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prof. Ing. Bohdan Schneider, CSc., DSc.
RNDr. Cyril Bařinka, Ph.D.
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Ing. Jan Dohnálek, Ph.D.
RNDr. Zdeněk Lánský, Ph.D.
RNDr. Gabriela Pavlínková, Ph.D.
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Council of IBT (Until 26th of April 2018)

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prof. Ing. Jiří Neužil, CSc.
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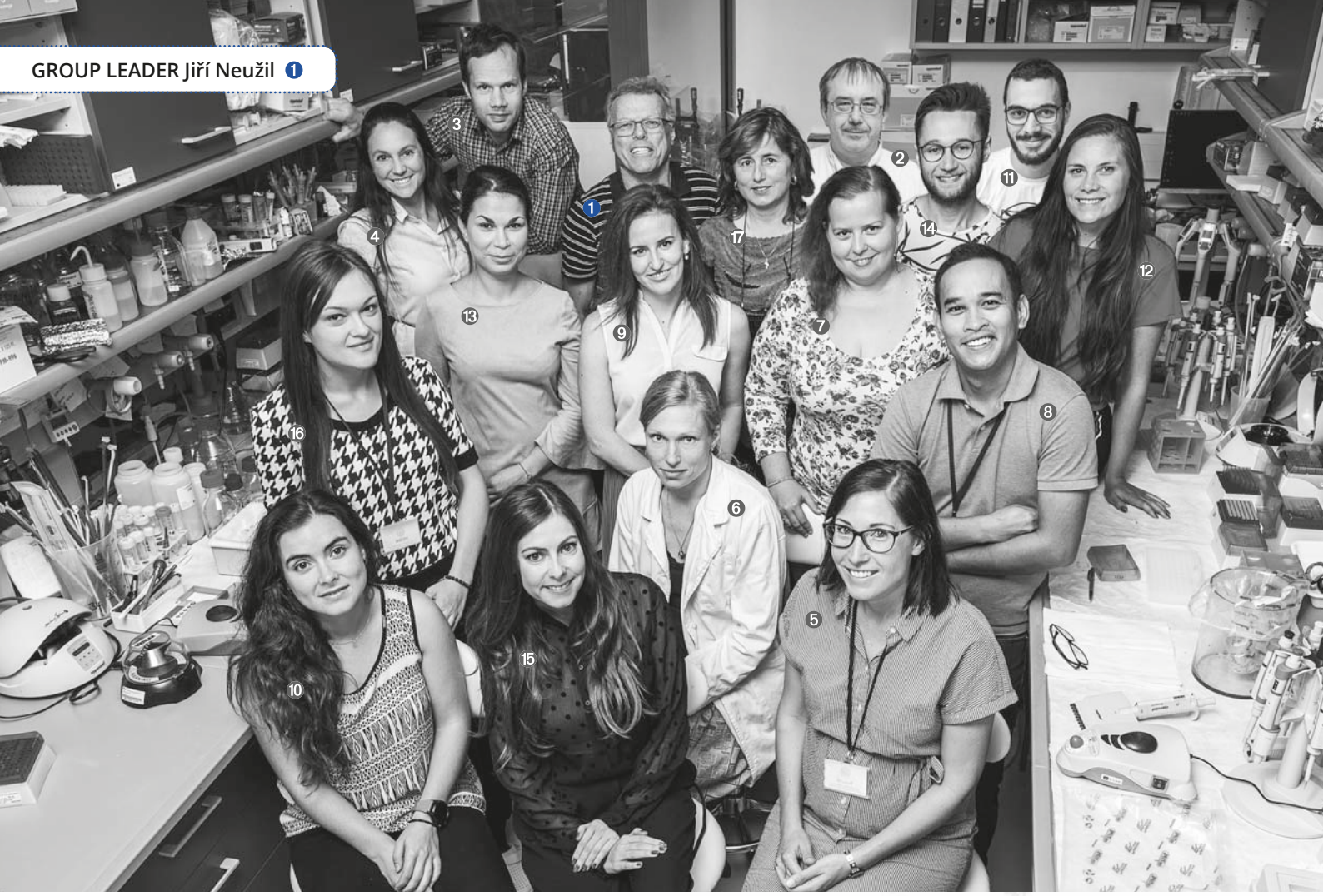
RNDr. Jiří Moos, CSc.



LABORATORY OF

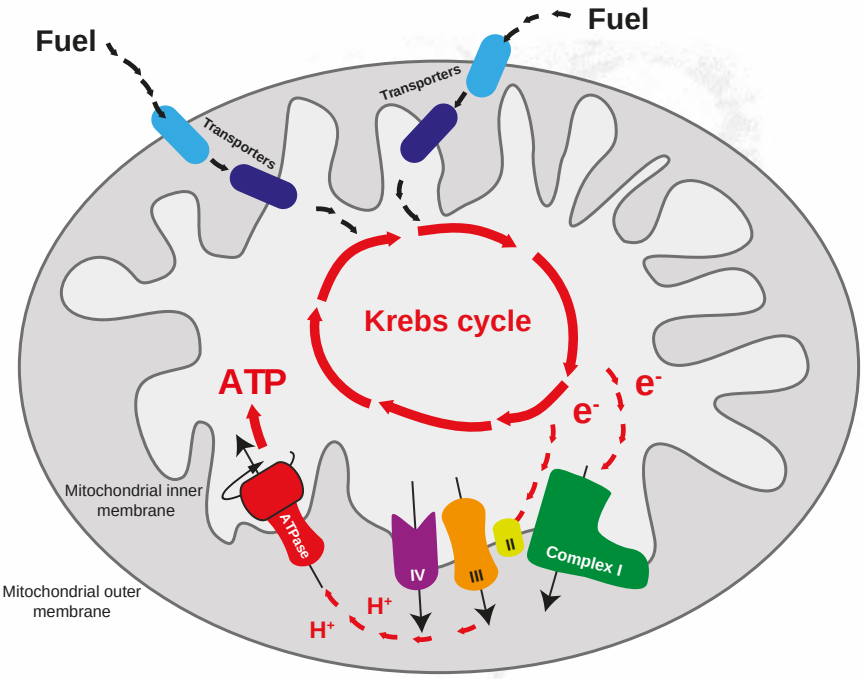
Molecular Therapy

HEAD: Jiří Neužil ❶ **RESEARCHERS:** Ladislav Anděra ❷ Jakub Rohlena ❸ Soňa Hubáčková ❹ **POSTDOC:** Štěpána Boukalová ❺ Renata Zobalová ❻ Zuzana Nahácka ❼ Berwini Endaya ❽ **PhD STUDENTS:** Zuzana Ezrová ❾ Silvia Novais ❿ Mirko Miloševič ⓫ Eliška Davidová ⓬ Maria Dubišová ⓭ Michal Kraus ⓮ Dana Sovilj ⓰ **TECHNICIAN:** Kateřina Jarošová ⓯ Simona Benešová ⓱

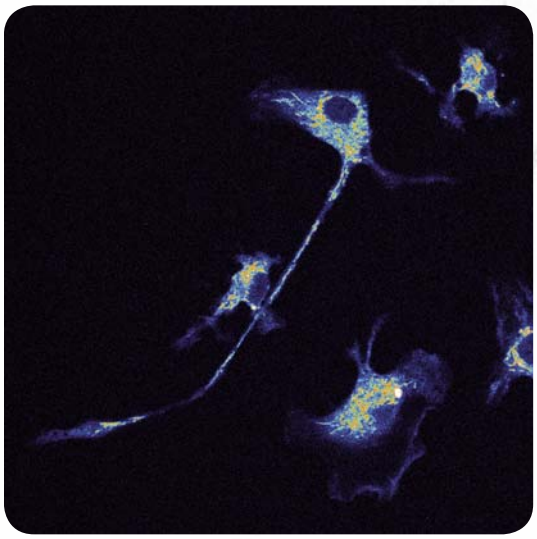
We focus on the **role of mitochondria in cancer** and on **targeting mitochondria for cancer therapy**. We study the role of respiration in cancer development. We showed that cancer cells with a respiration defect lose their tumorigenic potential, and need to acquire whole mitochondria from the tumor stroma by horizontal transfer and re-establish respiration in order to form tumors. We demonstrated that cancer cells do not need respiration to produce ATP. Instead, they need it to propel biosynthesis of pyrimidines, basic building blocks of nucleic acids that are required for proliferation and tumor growth. We also study **respiratory complex II** in the context of cancer. We are interested in its basic biology, its impact on cellular metabolism, and its role in cell death induction in cancer cells. Finally, we invested considerable effort in developing **mitochondria-targeted anticancer agents** that inhibit mitochondrial respiration. One of these agents, mitochondrially targeted tamoxifen (MitoTam), is in phase Ib clinical trial in cancer patients, showing very promising results.


Figure 1. Mitochondrion – our favorite organelle. ***(A)*** *A simplified scheme of energy production in mitochondria.* ***(B, C)*** *Metabolic imaging of mitochondria in cells using two-photon microscopy* ***(D)*** *Mitochondrion of a cancer cell as visualised by electron microscopy.*

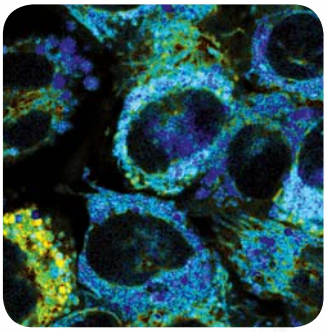
(A)



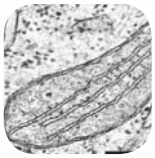
(B)



(C)



(D)



- We showed that mitochondrial respiration is essential for tumorigenesis, and respiration-deficient cancer cells recover respiration by horizontal transfer of whole mitochondria from the stroma.
- We demonstrated that respiration is needed in tumor cells to drive *de novo* synthesis of pyrimidines, not to produce ATP.
- We developed MitoTam, a mitochondria-targeted anticancer agent directed at the respiratory chain. MitoTam is now in phase Ib clinical trial in cancer patients.
- We discovered that respiratory complex II is a promising target for anticancer drugs.
- We showed that complex II changes its conformation to regulate cellular metabolism in response to respiratory dysfunction.

LABORATORY OF

Gene Expression

HEAD: Mikael Kubista ❶ **RESEARCHERS:** Radek Šindelka ❷ Lukáš Valihrach ❸ David Švec ❹
POSTDOC: Viktoriia Iegorova ❺ **PhD STUDENTS:** Peter Androvič ❻ Pavel Abaffy ❼ Ravindra Naraine ❽ Daniel Kraus ❾ Mansi Harvadan Maheta ❿ Šárka Benešová ⓫ **STUDENT:** Daniel Žucha ⓬ **TECHNICIAN:** Veronika Kašparová ⓭

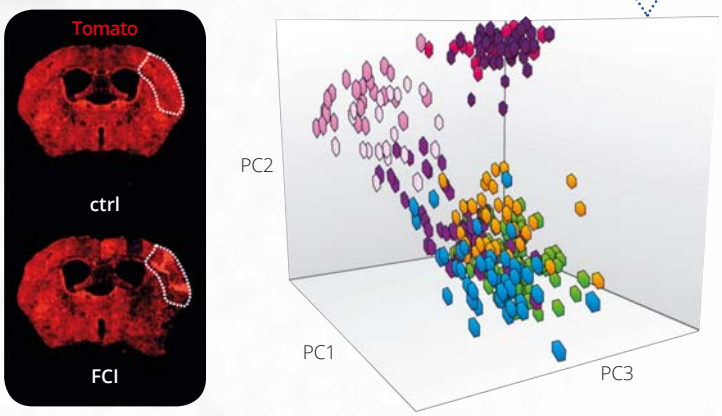
The Laboratory of Gene Expression is the Czech's leading academic laboratory specialized in high-throughput **gene expression profiling** and **single-cell analysis.** At our laboratory, we apply some of the most modern techniques such as quantitative PCR, digital PCR and RNA-sequencing to study several interesting and pertinent biological questions. These currently include focused research projects in the fields of developmental biology, stem cells and applied projects in cancer and neurological research. Additionally, we are active in the development of novel methods for the detection of nucleic acids. We also contribute to the scientific body on the standardization of workflow involving nucleic acid research.



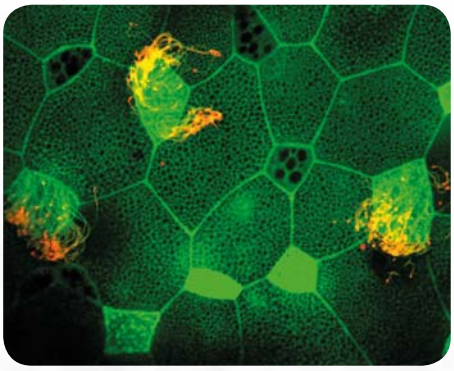
Developmental studies *are mainly based on the model organism Xenopus laevis, where we study:*
- *role of nitric oxide signaling during early development, regeneration and wound healing*
- *comparison of gene expression and signaling pathways during regeneration, wound healing and tumor progression*
- *localization of maternal RNAs in oocytes and their distribution among blastomeres during early development of fishes and amphibians.*

Glial cell biology *and new method development/implementation include:*
- *Characterization of glial cells after brain injuries and during the progression of neurodegenerative diseases, especially Alzheimer's disease and Amyotrophic lateral sclerosis*
- *Gene expression profiling of glial cells during aging and its impact on the mechanisms of ischemia*
- *The role of microRNA in central nervous injury, particularly in spinal cord injury*
- *Development and implementation of single cell RT-qPCR, ddPCR, miRNA profiling and single cell RNA-Seq analyses*

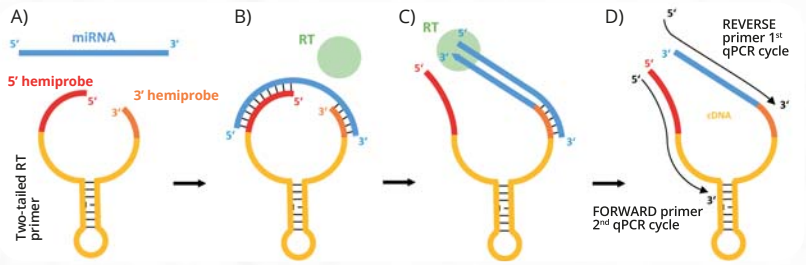
In the field of ***Cancer research,*** *we use:*
- *A unique robotic microscope (CellCelector) for morphological and immune-histochemical characterization of circulating tumor cells, followed by molecular profiling (BioMark) through the assessment of a panel of mRNA markers*
- *We characterize the mechanisms of horizontal transfer of mitochondrial DNA between cells.*



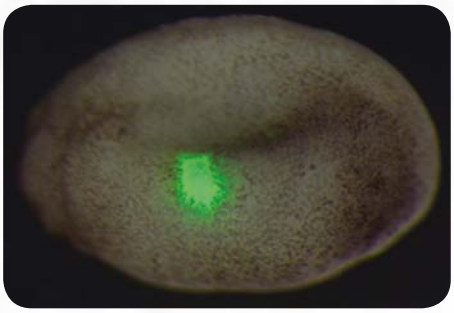
Heterogeneity of oligodendroglial lineage after focal cerebral ischemia in mice.



Nitric oxide produced in embryonic epidermis.



Two-tailed RT-qPCR for miRNA quantification.



Embryonic wound healing and nitric oxide production.

- Since its establishment, our laboratory has made several interesting discoveries. In the field of development biology, we have contributed to resolving the spatial transcriptome and proteome within the Xenopus egg and discovered a new group of **asymmetrically localized** RNAs called extremely animal. In addition, we have identified several novel putative localization motifs that may contribute to the vegetal RNA localization (Sindelka et al. 2018, Sindelka et al. 2017). Our research on healing has revealed that **nitric oxide** is a crucial factor regulating the development of the epidermis and also embryonic wound healing (Tomankova et al. 2017, Abaffy et al. 2019).

- In the field of neurobiology, we have described the **differentiation of oligodendroglial lineage** cells during post-ischemic regeneration and the **role of Shh-signaling pathways** in the process (Honsa et al. 2016, Valny et al. 2018). We have also developed a new method for highly accurate miRNA quantification, along with an associated **quality control panel** for circulating microRNA studies and applied it in several research projects (Androvic et al. 2017, Androvic et al. 2019, Smieszek et al. 2019).

- The Laboratory of Gene Expression maintains a healthy collaborative relationship with many local and international partners, such as the University of Notre Dame, USA; Czech Academy of Sciences (Institute of Animal Physiology and Genetics, Institute of Experimental Medicine, Institute of Molecular Genetics); University of South Bohemia; Charles University.

- Educating the younger generation of scientist is also of great importance to our laboratory. Therefore we are regularly **teach** the genomics methods and single cell analysis at the Faculty of Sciences of the Charles University and also co-organize several specialized courses with TATAA Biocenter. Our laboratory remains focused on its continued contribution to both education and to basic and applied research, and we anticipate even more interesting discoveries as we grow.

LABORATORY OF

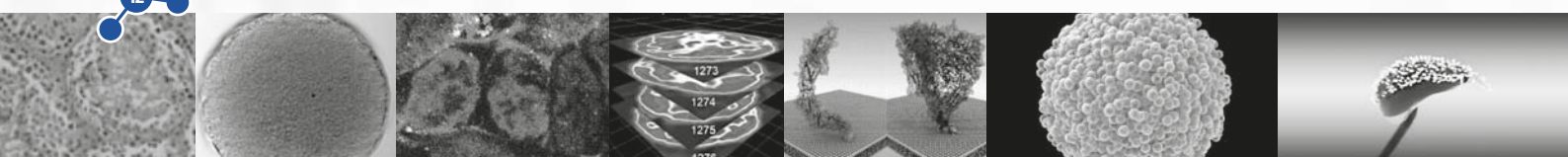
Reproductive Biology

HEAD: Kateřina Komrsková ❶ **RESEARCHERS:** Jana Pěknicová ❷ Věra Jonáková ❸ Pavla Postlerová ❹ Michaela Frolíková ❺ Nataša Šebková, Lukáš Děd ❻ Jana Svobodová ❼ **PHD STUDENTS:** Veronika Páleníková ❽ Tereza Bosáková ❾ **STUDENT:** Kryštof Bašus ❿ **TECHNITIAN:** Eliška Valášková ⓫

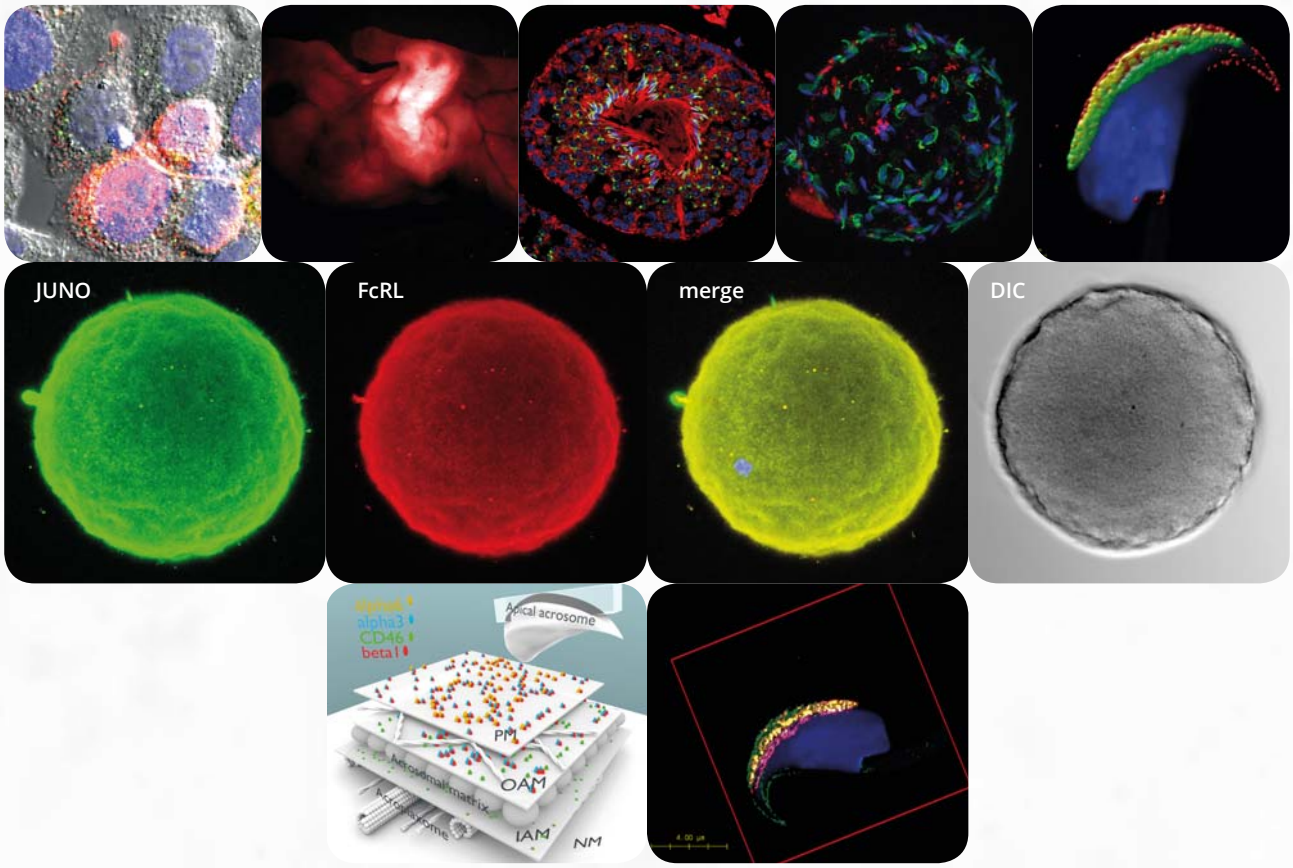
The group of Reproductive Biology **studies fertilization processes focusing on both sperm and eggs.** The results are translated to new diagnostic tools for quality assessment and gamete selection to be utilized in Centers of Assisted Reproduction. The group targets sperm maturation and sperm-egg interaction with overlap to clinical practice. The area of interest covers sperm antibodies characterization in infertile couples, monitoring of sperm quality in patients with testicular cancer and diabetes mellitus and selecting epigenetic markers associated with human infertility.

TOP ACHIEVEMENTS

- Human specific **FcRL3** was selected as a **novel egg plasma membrane receptor** interacting via Fc-homologous extracellular domain with Ig domain of **IZUMO1** in sperm membrane during human fertilization.
- Sperm-specific localization for **integrin subunit heterodimers and CD46** was determined, and our data showed a complexity of membranes overlaying specialized microdomain structures in the sperm head (Frolikova et al., 2016, 2019).
- Putative mechanism of **CD9** and **CD81** in tetraspanin web formation and sperm and egg localization during fertilization was determined in mammals including human (Frolikova et al., 2018; Jankovicova et al., 2019).



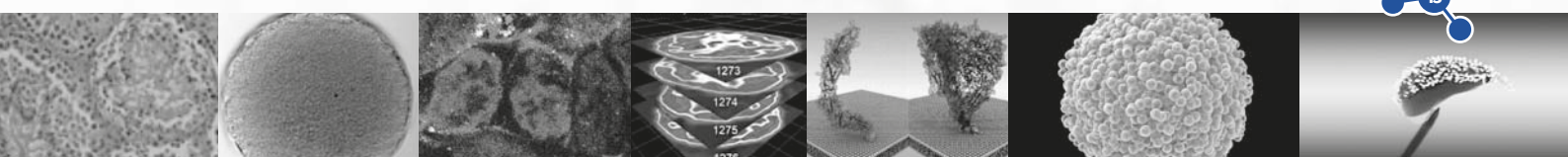
- Our **transgenic models** are utilised in cancer research and bioprinting collaboration with the Group of Molecular Therapy, IBT (Dong et al., 2017; Bajzikova et al., 2017) and Laboratory for Reproduction, Vrije Universiteit Brussel (Baert et al., 2019).
- Specific antibodies against **sperm surface receptors** and **intra-acrosomal proteins** developed in our laboratory are part of the diagnostic kits designed for sperm quality assessment in **Centres of Assisted Reproduction** and study of sperm maturation (Zigo et al., 2015, 2018, 2019; Capkova et al., 2016; Kerns et al., 2018).
- The priority study showed **transgenerational inheritance** of the epigenetic profiles changes induced by exposure to **endocrine disruptor** (Brieño-Enríquez et al., 2015; Vieweg and Dvorakova-Hortova et al., 2015).



First line, from left to right:
- *CHO cells mimic the human egg model co-transfected with both JUNO (red) and fusion protein FcRL (green) with attached human sperm, nuclei (blue).*
- *C57BL/6N$^{Su9\text{-}DsRed2}$ embryo: Red fluorescent protein expressed in mitochondria is visible under fluorescent light and confirmed by geno-typing.*
- *Testis: cross section using transgenic mouse C57BL/6N $^{acr3\text{-}EGFP/Su9\text{-}DsRed2}$, acrosome in developing spermatids and sperm (green), mitochondria (red), nuclei (blue).*
- *Super-resolution microscopy (STED) of mouse oocyte shows the localization of proteins Izumo1 (green), Fcrl (red) and nucleus (blue).*
- *Super-resolution microscopy (SIM) shows the localization of CD46 (green) on the inner and outer acrosomal membrane and β1-integrin (red) on the plasma and outer acrosomal membrane.*

Second line:
- *Co-localization analysis provided positive results on joint localization of JUNO –FcRL proteins on human egg.*

Third line from left to right:
- *3D cartoon summarizes the localization of CD46 and α3, α6 and β1-integrins among different membrane structures of the intact mouse sperm head in apical acrosomal area.*
- *SIM visualization of mutual position of CD46 (magenta) and β1-integrin (green) analysed by Huygens software, colocalization area of selected proteins in the outer acrosomal membrane (yellow) is based on Pearson's correlation coefficient; nucleus (blue).*

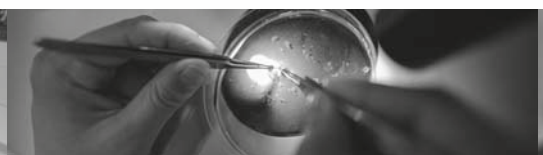


LABORATORY OF

Molecular Pathogenetics

HEAD: Gabriela Pavlínková ❶ **RESEARCHERS:** Romana Bohuslavová ❷ **PhD STUDENTS:** Ondřej Smolík ❸
STUDENTS: Simona Vochyánová ❹ Jessica Malfatti ❺ Natália Wirthová ❻ Kateřina Matějková ❼ Adam Pavlínek ❽
TECHNICIANS: Michaela Lišáková ❾ Iva Filová ❿ Žaneta Kárníková ⓫

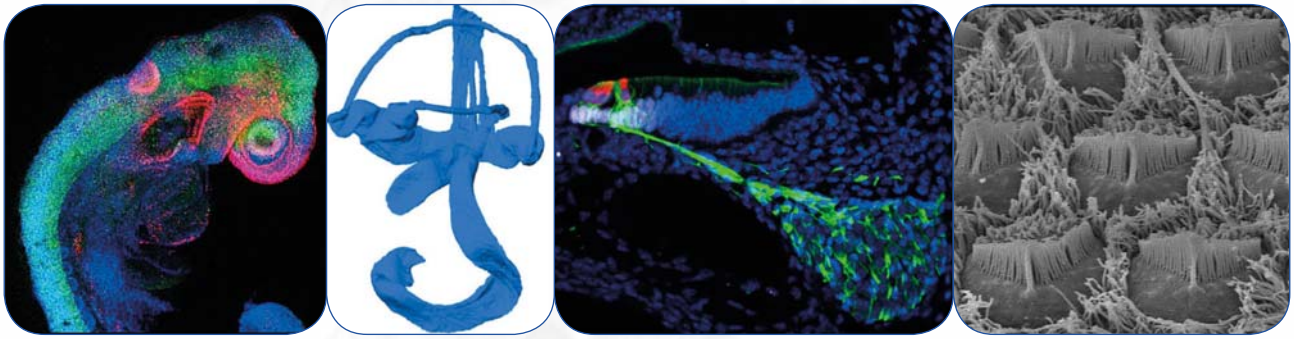
Our research program is focused on transcriptional regulation during embryonic development, the molecular mechanisms of developmental programming, and identification of the molecular causes of abnormal embryonic development and disease predispositions. We are particularly interested in HIF-1, ISL1, SOX2, and NEUROD1 transcription factor networks and in how their dysfunction affects embryonic development and can increase the predispositions of an individual to diseases such as diabetes, heart disease, or hearing loss. Our current research projects aim to characterize how these transcriptional networks affect neuronal, neurosensory, heart, and pancreas development. We also analyze the combinatorial effects of the environment (e.g. maternal diabetes) and genetic mutations. We use molecular genetic approaches in the mouse models to investigate both the cellular mechanisms (i.e. morphologic and anatomical analyses) and the molecular mechanisms (i.e. using single cell and bulk transcriptome analyses, and biochemistry) to identify molecular targets for the development of preventive and diagnostic strategies.

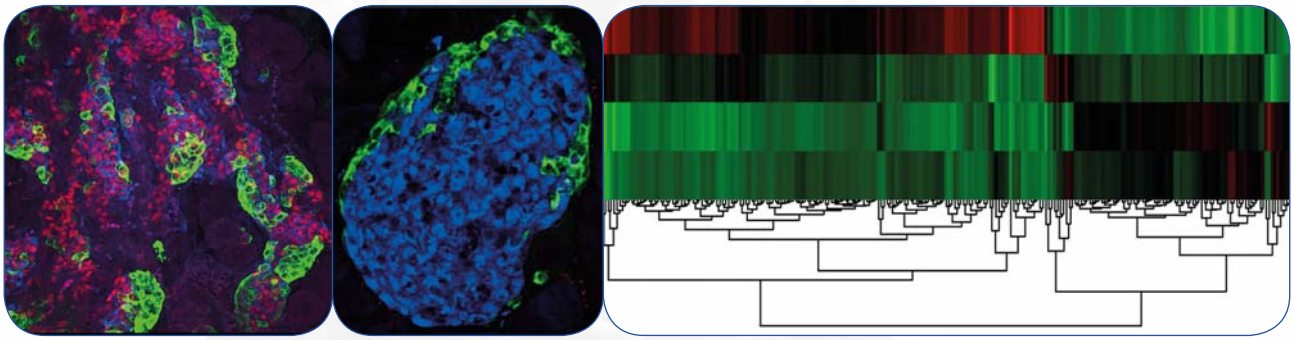

*In **the inner ear,** we study how elimination of selected transcription factors affects the development of the sensory epithelium, neurons, and innervation, and how these changes affect the hearing function. We use computer-assisted 3D-reconstruction, confocal microscopy and electron microscopy. In **the pancreas,** we are focused on the development of endocrine cells, particularly specification and differentiation of beta- and alpha cells, and how genetic mutations of transcription factors influence these processes. We are also interested in the interactions of the environment and genetic mutations and in how these changes affect the heart development, cardiac function, congenital heart defect development, and predisposition **to heart** disease.*

FIGURES

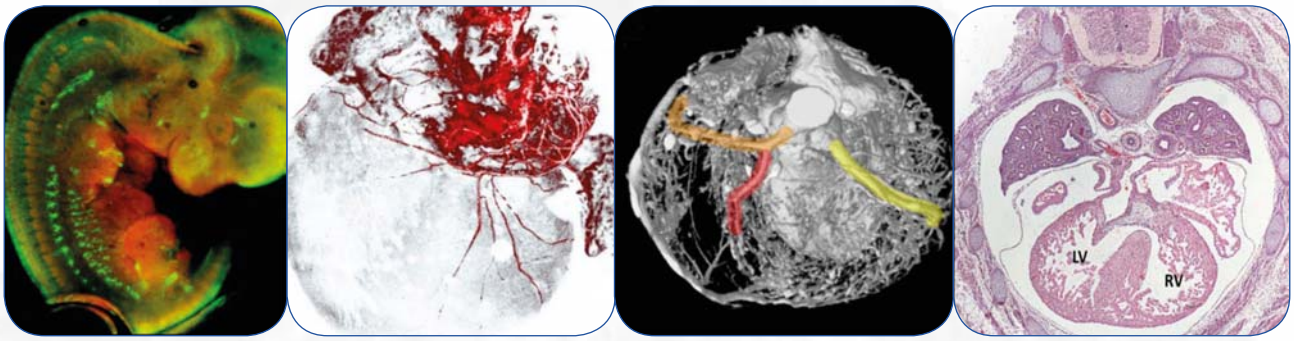
Inner ear



Pancreas



Heart



TOP ACHIEVEMENTS

- We found that genetic deletion of HIF-1α results in increased cell death and decreased proliferation of neuronal progenitors of the sympathetic system and formation of cardiac sympathetic innervation (Bohuslavova et al. 2019), suggesting that dysregulated HIF-1α may contribute to cardiac dysfunction and disease associated with defects in the cardiac sympathetic system. In addition, a global reduction in the Hif1a gene dosage increases predisposition of the offspring exposed to maternal diabetes to cardiac dysfunction. This also underscores HIF-1 as a critical factor in the fetal programming of adult cardiovascular disease (Cerychova et al. 2018).

- Using a novel conditional NEUROD1 deletion model, we demonstrated that absence of the primary afferent topology leads to a dysfunctional tonotopy of the auditory system. Such effects have never been investigated in other sensory systems because of the lack of comparable single gene mutation models (Macova et al. 2019).

- We generated transgenic mice expressing Isl1 under Pax2 regulatory sequences, which exhibit hyperactivity, progressive age-related decline in hearing, and the deterioration of the medial olivocochlear efferent system (Chumak et al. 2016). Additionally, these mice have aberrant development of the vestibular system and the central nervous system, in particular the cerebellum. We showed that the Isl1 transgene significantly affects the functions of GABAergic neurons, which may relate to attention deficit hyperactivity disorder in people (Bohuslavova et al. 2017).

LABORATORY OF

Tumour resistance

HEAD: Jaroslav Truksa ❶ **POSTDOCS:** Cristian Sandoval-Acuña ❷ Natalia Torrealba ❸
PhD. STUDENTS: Veronika Tomková ❹ Sukanya Jadhav ❺ **RESEARCH ASSISTANTS:** Ekaterina Simonova ❻
Lea Marie Beranová ❼ **STUDENT**: Michaela Vondráčková ❽ **TECHNICIAN:** Šárka Smržová ❾

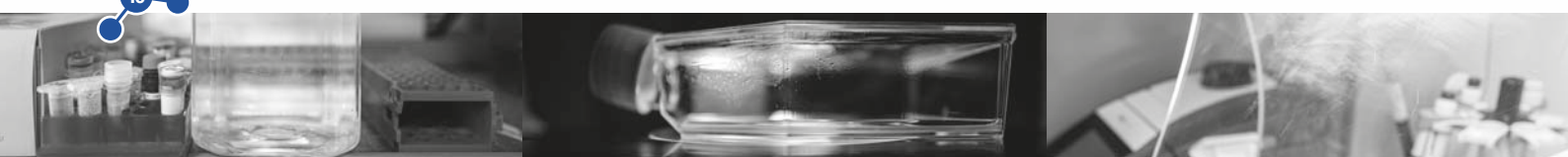
The major research topics investigated in the lab are (1) Understanding the molecular mechanisms underlying cancer resistance, proliferation and recurrence, (2) Describing the biology of cancer stem-like cells with particular interest in their iron metabolism, (3) Developing novel approaches that target cancer cells based on mitochondrial targeting and interference with iron metabolism, (4) Deciphering the molecular mechanisms that govern systemic iron metabolism.

We cultivate cancer stem-like cells (CSCs) that grow as three dimensional „spheres" and resemble more closely real tumours. CSCs show upregulation of the ABC transporters that confer resistance to commonly used anti-cancer drugs and exhibit marked changes in their iron metabolism, resulting in high iron dependence and higher susceptibility to iron withdrawal.

Based on the high iron requirements of cancer cells in general, we are developing novel promising iron chelators that are targeted to mitochondria as a crucial organelles responsible for the synthesis of both biologically utilized forms of iron, the FeS clusters and heme. The novel compounds show markedly profound cytostatic and cytotoxic effects on cancer cells while sparing non-malignant cells.

We also aim to elucidate the molecular mechanisms that underlie tamoxifen-resistance in breast cancer cells. We have found increased level of mitochondrial reactive oxygen species and altered mitochondrial structure and function in cells resistant to tamoxifen. Importantly, we have also shown that high expression of miR-301a-3P in estrogen positive breast cancer cells results in inhibition of estrogen signalling, thus participating in the transition to tamoxifen resistance.

We further focus on the normal systemic iron homeostasis with particular interest in hepcidin, erythroferrone and matriptase-2 as critical molecular components that govern the organismal response to iron deficiency, iron overload, hypoxia or enhanced erythropoiesis.



FIGURES

Figure 1: *(A) Cells grown in the three dimensional culture form „spheres". Importantly, when cultivated with a mitochondrially targeted chelator they form less „spheres" that are smaller. (B) MCF7 cells bearing GFP labelled mitochondria treated with mitochondrially targeted chelator exhibit mitochondrial fragmentation. (C) Addition of mitochondrially targeted chelator results in induction of mitophagy which is visualized by specific mitophagy dye (green) while lysosomes are visulalized in red.*

Figure 2: *Mouse model of the Iron Deficient Iron Refractory Anemia (IRIDA) showing alopecia and hypochromic microcytic anemia is known as the mask mouse and is caused by a mutation in the Tmprss6 gene encoding matriptase-2.*

Figure 1: The effect of mitochondrial iron chelator on cancer cells.

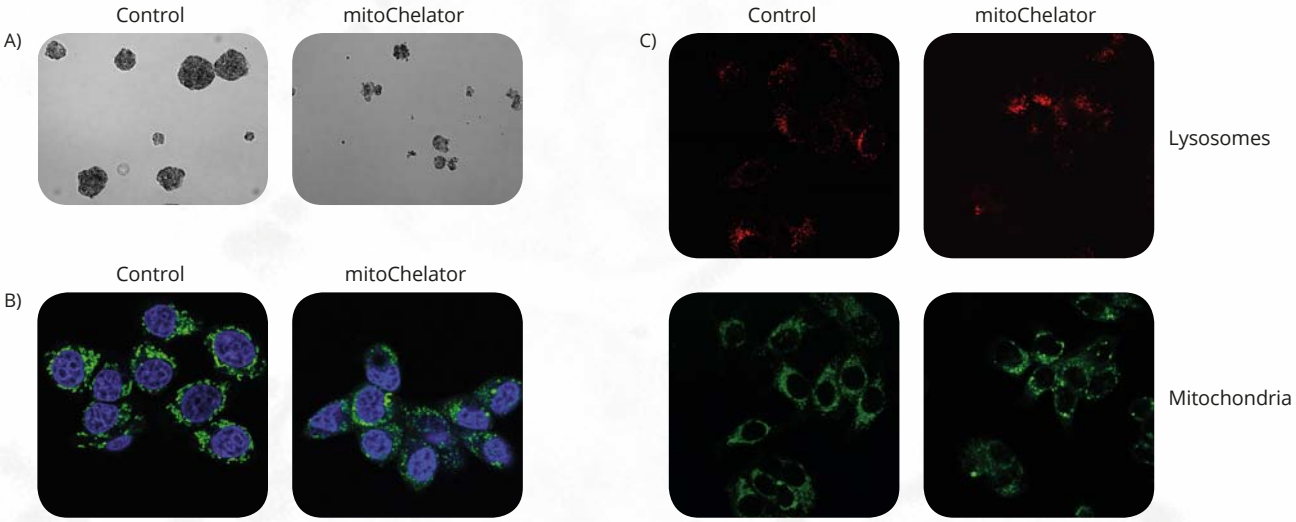


Figure 2: The mask mouse: model of Iron deficiency Iron Refractory Anemia.

TOP ACHIEVEMENTS

- We have analyzed iron metabolism in cancer stem-like cells and identified an iron metabolism-related gene signature that suggest that these cells are „iron addicted" and more prone to iron chelation (Rychtarčíková *et al., Oncotarget* 2017).
- We have described the role of miR-301a-3P as an oncomir that directly inhibits estrogene signalling in estrogen positive breast cancer cells rendering them hormone-insensitive and not responsive to therapy (Lettlová et al., *Cellular Physiology and Biochemistry* 2018).
- In cooperation with the Molecular Therapy Group we have participated in the studies describing mitochondrial transfer between rho zero cancer cells and the host with dihydroorotate dehydrogenase as a key enzyme that is required for the process (Tan et al., *Cell metabolism* 2015; Dong *et al., eLife* 2018, Bajzíková et al., *Cell metabolism* 2019).
- We have described novel aspects of erythroferrone, transferrin receptor2 and matriptase-2 regulation in normal mice and the *mask* mice, representing the model of Iron Refractory Iron Deficiency Anemia (IRIDA) in cooperation with J. Krijt, from the 1st Medical Faculty, Charles University (Frýdlová *et al., PloS one* 2016; Gurieva *et al. Blood Cells Molecules and Diseases* 2017; Frýdlová *et al., PloS one* 2019).
- We have filled two European patents describing novel mitochondrially targeted iron chelators in cooperation with the Service Technology Laboratory and Smart Brain s.r.o.
- We have received the prestigious grant support from the Kellner Family Foundation for the project entitled „Expression and regulation of multidrug resistance proteins in tumour-inititating cells (TICs)" (2013 – 2017).

LABORATORY OF

Biomolecular Recognition

HEAD: Bohdan Schneider ❶ **RESEARCHERS:** Lada Biedermannová ❷ Gustavo Fuertes Vives ❸ Yingliang Liu ❹ Pavel Mikulecký ❺ Prokopis Andrikopoulos ❻ **STUDENTS:** Jakub Svoboda ❼ Tereza Nepokojová ❽ Lucie Kolářová ❾ Iva Nečasová ❿ Aditya Suresh Chaudhari ⓫ Štěpán Herynek ⓬ Maroš Huličiak ⓭ Phuong Ngoc Pham ⓮
TECHNICIAN: Markéta Janovská ⓯ Lubica Škultétyová ⓰ Michaela Nekardová ⓱ Natalie Huhn ⓲

The focus of our laboratory is to elucidate the driving forces responsible for specific recognition between biomolecules – proteins and nucleic acids. The three main approaches we use are protein engineering, structural bioinformatics and biophysical studies.

• **Cytokines.** We are interested in the specificity of interactions between medically important human cytokines, mostly related to the family of Interleukin 10. They are important in the immunity response to viral and bacterial infection, and errors in their regulation cause serious autoimmune and/or allergic health disorders and may promote malignancy. We study the possibilities to generate more stable variants of these proteins and to modulate the specificity and affinity of the complex formation. An important direction is de novo development of proteins specifically binding the cytokines and/or their receptors by techniques of directed evolution, ribosome display and yeast display.

• Another area of our study is **the structure of nucleic acids** – DNA and RNA. Nucleic acids are structurally plastic molecules, and their biological roles are enabled by adaptation to their binding partners. We study structural aspects of both double and single-stranded DNA and their recognition by other molecules. To enable detailed study of nucleic acid structure, we develop unique analytical tools which we share with the scientific community. We also study how biomolecules interact with their aqueous environment by analyzing the structure of the solvation shell around biomolecules. We analyze large sets of crystal structures to determine structural patterns in the first hydration shell of amino acids residues in proteins and of dinucleotide steps in DNA.

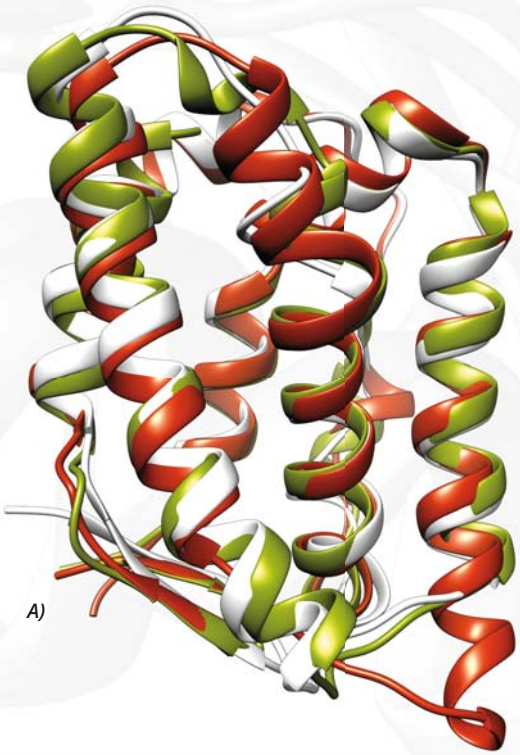
• **Dynamics of Biomolecules.** In collaboration with the ELI-Beamlines laser facility, we explore new frontiers of biomolecular research by analyzing photon-material interactions using electromagnetic radiation of wavelengths from X-rays to infrareds. This is helping us to elucidate the mechanisms of biomolecular processes across multiple time scales.



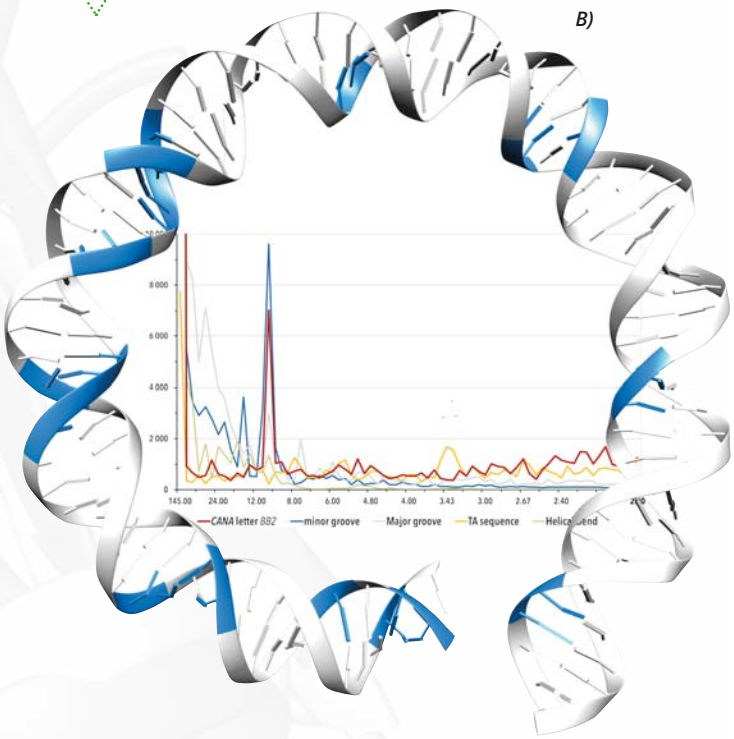
FIGURES

Figure A): *Localized and relatively small structural differences can radically change the stability and function of signaling proteins. Superimposition of IL-20 (white), IL-24 wild type (green), and our stable but inactive IL-24 variant (PDB 6gg1, red), which did not signal. Reverse engineering identified the residue that restored most of the signaling ability without marked loss of stability (Zahradnik et al. FEBS J. (2019)).*

Figure B): *Our analysis of DNA dinucleotide conformations allowed to understand how DNA bends in the nucleosome core particle (NCP). One of the conformations, so called BII form, is highlighted in blue in the ribbon representation of one of the NCP crystal structures. The inset shows the periodicity of the BII conformers in all non-redundant NCP structures. The periodicity, which was analyzed by the Fourier transform, revealed that the BII conformation repeats each tenth step in these structures that corresponds to one double helical turn (Schneider et al. Genes (2017)).*



A)

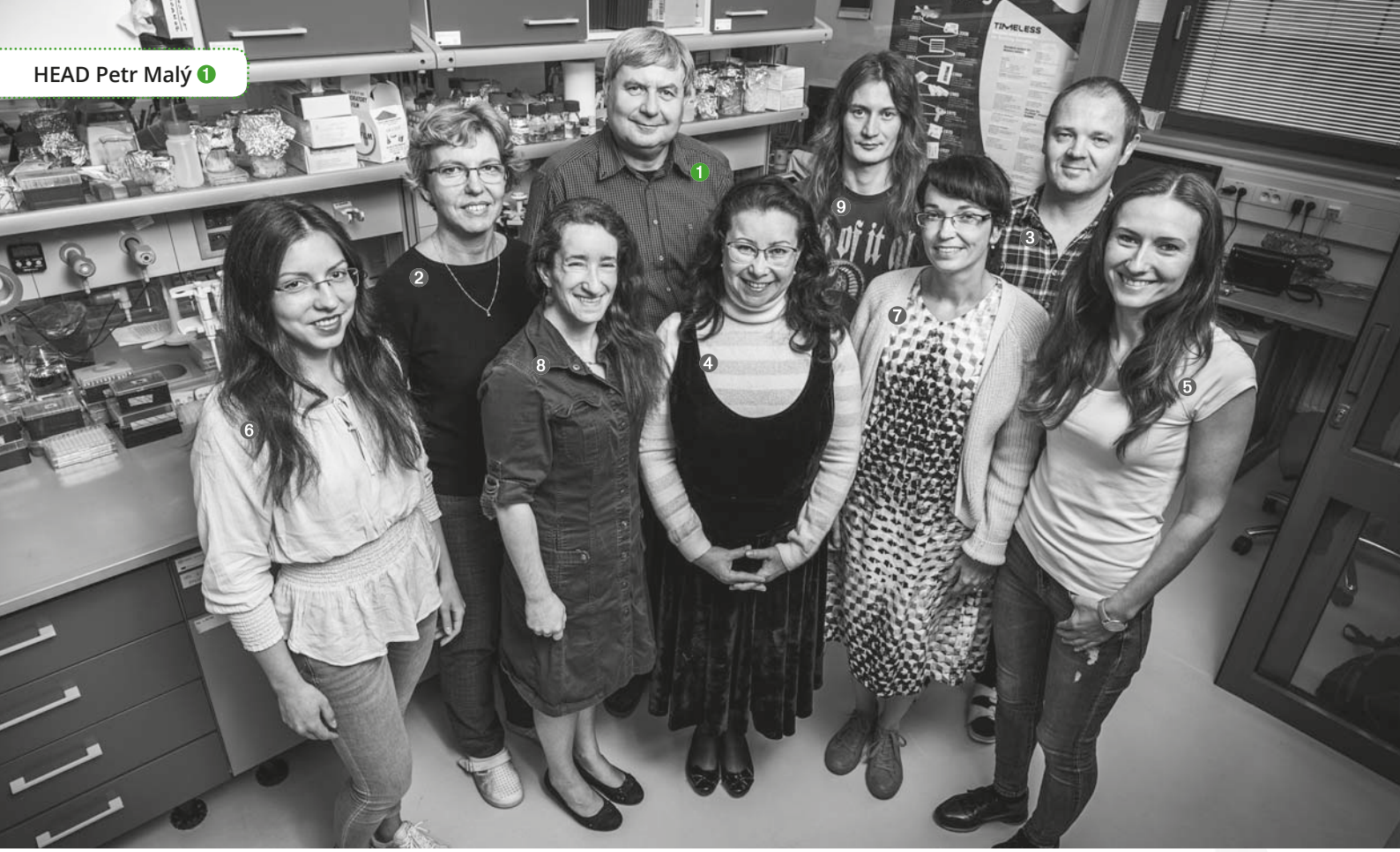


B)

TOP ACHIEVEMENTS

- We have developed a small protein scaffold that has been trained to bind to Interleukin 10 (Pham et al., in preparation, 2019).
- We designed and produced a stabilized variant of Interleukin 24, which retained most of the wild type signaling activity (FEBS Journal 286 (2019), doi: 10.1016/j.fsi.2018.05.008).
- We elucidated the structural basis for receptor specificity by solving the crystal structure of human interferon-gamma receptor 2 (Acta Crystallofraphica D72 (2016), doi: 10.1016/j.fsi.2018.05.008).
- We have developed unique analytical tools for the bioinformatic study of nucleic acids (Acta Crystallographica D74 (2018), doi: 10.1107/S2059798318000050). The tools are available at the website www.dnatco.org and are used by the community of structural biologists (Nucleic Acids Research 44 (2016), doi: 10.1093/nar/gkw381).
- Our analysis of protein hydration (Acta Crystallographica D71 (2015), doi: 10.1107/S1399004715015679) is available as the web-based atlas at www.dnatco.org/watAA (Physical Chemistry & Chemical Physics 19 (2017), doi: 10.1039/c7cp00187h.).
- We have unveiled the ultrafast photodynamics of flavin cofactors by a combination of femtosecond-stimulated Raman spectroscopy and quantum chemistry calculations (Andrikopoulos et al., manuscript under revision).
- Our laboratory actively participates at ELIXIR and Instruct-ERIC infrastructural projects.
- We have established close collaboration with laboratories at the Weizmann Institute of Science in Israel, with RCSB PDB at Rutgers University in the USA, and have a collaborative project with ELI-Beamlines in Czech Republic.
- We are teaching semestral courses at Charles University in Prague and South Bohemian University in Ceske Budejovice.





LABORATORY OF

Ligand Engineering

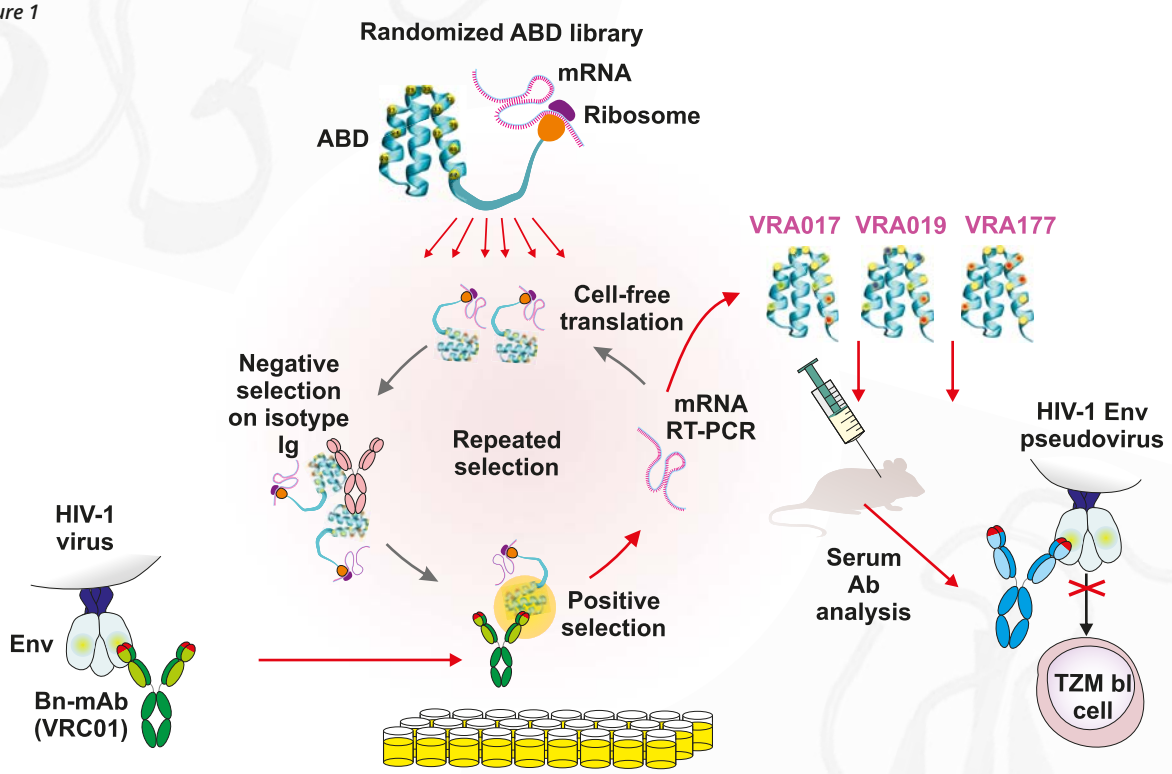
HEAD: Petr Malý ❶ **RESEARCHERS:** Hana Petroková ❷ Milan Kuchař ❸ Natalya Panova ❹ **POSTDOC:** Veronika Lišková ❺ **PhD STUDENTS:** Yaroslava Groza ❻ Lucie Vaňková, Marie Hlavničková **TECHNICIANS:** Linda Malá ❼ Petra Kadlčáková ❽ Michal Malý ❾

Proteins are molecules of extraordinary structural diversity, which ensures their specialized functions in living organisms. The mission of our research group is to develop novel classes of **binding proteins with the required specificity and biological function.** To reach this goal, we use methods of protein engineering, including directed evolution of proteins and semi-rational design for the selection of binding proteins from highly complex combinatorial libraries derived from small protein domains. The developed binding proteins can substitute for monoclonal antibodies in a wide range of biomedical applications and can serve as a useful alternative for *in vitro* and *in vivo* diagnostics, development of more efficient vaccines, and as non-immunoglobulin biologics in the drug development. To generate **"tailor-made proteins",** we use two types of small **protein domain scaffolds.** We established the three-helix bundle albumin-binding domain **(ABD)** of streptococcal protein G as a master scaffold with 11 designed amino acid positions selected for the randomization, thus providing a theoretical complexity up to 10^{14} protein variants. This protein domain concept has already been used for the generation of **a portfolio of novel binding proteins targeted to human cytokines or their receptors, prostate cancer oncomarkers or Shiga toxins.** Currently, we have been working on the loop and beta sheet concepts of highly complex combinatorial libraries with 12 randomized amino acid residues based on the structure of human muscle protein domain called **"Myomesin".**

FIGURES

Figure 1. Principle of elicitation of Env-specific neutralizing serum antibodies using protein binders selected from the ABD library. *Broadly neutralizing monoclonal antibody VRC01 was used as a target for the selection of binders from a combinatorial ABD library with a theoretical complexity of 10^{14} variants. The negative selection was used to minimize binders not involved in the epitope recognition. Positive selection was performed in 96-well plates with immobilized VRC01 bn-mAb, followed by mRNA isolation, reverse transcription to DNA, and ribosome display selection. After several selection rounds, a library of cDNA variants called VRA binders was introduced into a plasmid vector. Three VRA variants, VRA017, VRA019 and VRA177, were identified as the most promising candidates and in the form of fusion proteins, including a truncated VRA017S version, were used for immunization of experimental mice followed by the analysis of their ability to elicit HIV-1 Env-specific and HIV-1 pseudovirus-neutralizing serum antibodies.*

Figure 1



TOP ACHIEVEMENTS

- We have developed three collections of **immunosuppressive ABD-derived binding proteins** targeting the IL-23/Th-17 pro-inflammatory axis that function as blockers of human IL-23 cytokine **(ILP proteins),** IL-23 receptor **(REX proteins)** and IL-17 receptor A **(ARS proteins).** [IJMS, 2018; 19(10): 3089] – [Autoimmunity, 2017; 50: 102-113] – [Proteins, 2014; 82: 975-989].

- In collaboration, we have engineered unique strains of probiotic bacterium ***Lactococcus lactis*** **secreting ILP and REX proteins** as models for experimental treatment of **inflammatory bowel disease** (IBD) in the mouse. [Microorganisms, 2019; 7(5): 152] – [IJMS, 2018; 19(7): 1933].

- We have developed **VRA protein binders mimicking HIV-1 gp120/Env epitopes** recognized by broadly neutralizing antibody VRC01. These proteins as immunogens elicit the antibody response against HIV-1 gp120 and the **sera of the immunized mice neutralize HIV-1 pseudoviruses.** VRA proteins thus represent innovative tools for the development of a **vaccine preventing from HIV-1 infection and development of AIDS.** [EBioMedicine, 2019; 47:247-256].

- We have generated a collection of **D7 protein variants** recognizing insoluble human fibrin and these proteins **deliver liposomes to human thrombi** in 3D model of middle cerebral artery. D7 proteins as „surface navigators" of labelled liposomes are models for ***in vivo*** **imaging of stroke** by MRI. [Pharmaceutics, 11(12): 642, 2019]

- We have selected and characterized **binding proteins** specific for **prostate cancer oncomarkers** PSP94 and human kallikrein-2 and -11 that can be used as **capture proteins for a microfluidic chip** or other in vitro diagnostic tools [Protein & Cell; 2015; 6(10): 774-779].

- The REX and ILP proteins have been covered by **two Czech patents** (reg. Nos. 304514, 2014; 307849, 2019) and **European patent:** WO 2014/079399, reg. No. 2922560, 2016, published 2017/01.



LABORATORY OF

Structural Biology

HEAD: Cyril Bařinka ❶ **RESEARCHER:** Zora Nováková ❷ **POSTDOC:** Jan Komárek ❸ Zsofia Kutil ❹ Jakub Ptáček ❺
PhD STUDENTS: Gargi Das ❻ Kseniya Ustinova ❼ Jana Nedvědová ❽ Shivam Shukla ❾
STUDENTS: Veronika Kropáčková ❿ Dariia Pavlenko ⓫ Daria Khuntsariya ⓬ **TECHNICIANS:** Barbora Havlínová ⓭ Iva Jelínková ⓮ Petra Baranová ⓯ Lucia Motlová ⓰ Michal Svoboda ⓱

Our laboratory strives to **elucidate the molecular details of the structure and function** of several pharmaceutically important zinc-dependent hydrolases, the most notably the members of **histone deacetylase (HDAC)** and **glutamate carboxypeptidase II (GCPII)** families. Furthermore, we exploit **protein engineering and structure-assisted drug discovery to develop macromolecules and small molecule ligands,** respectively, that can be used as research tools and/or advanced into clinical studies.

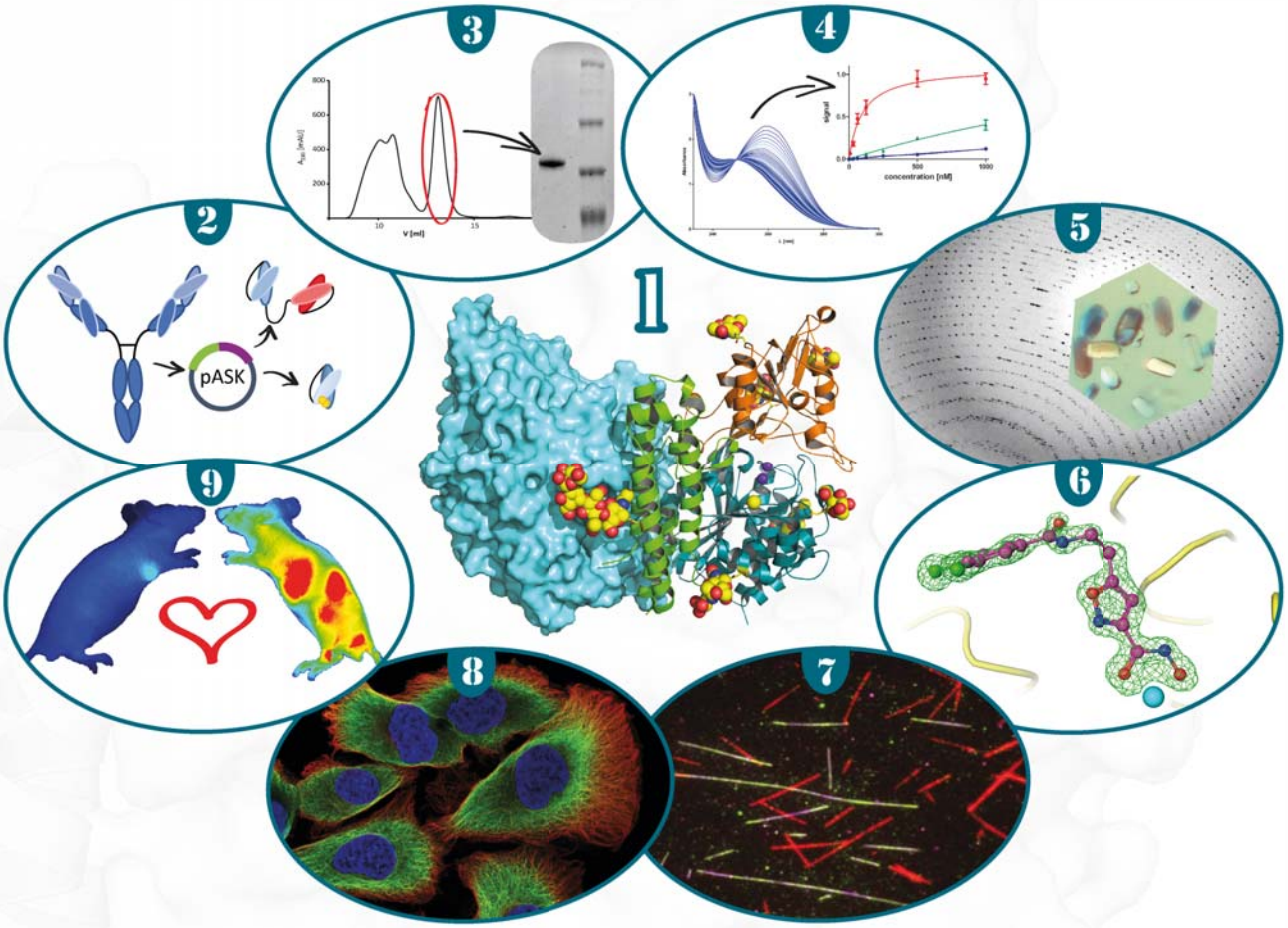
GCPII, also known as prostate specific membrane antigen (PSMA), is implicated in several (patho)physiological processes. **In the nervous system,** GCPII exerts its peptidase activity by hydrolyzing a peptidic neurotransmitter. Accordingly, GCPII-specific **inhibitors** have been reported to be **neuroprotective in** multiple preclinical models of **neurodegeneration.** Furthermore, over-expression of GCPII **in prostate carcinoma** makes the enzyme a prime marker for prostate cancer **imaging in clinics** and a promising **target of future therapeutic interventions.**

Lysine acetylation is a major post-translational modification **found on most proteins of the human proteome** and as such it impacts a broad spectrum of cellular functions, including gene expression, immune surveillance and energy metabolism. At the molecular level, the protein acetylation status is **defined by** opposing **activities of** histone acetyltransferases (writers) and **histone deacetylases** (HDACs; erasers). Eighteen HDACs have been identified in humans and our **laboratory is interested in (i) deciphering the structure-function relationship, (ii) defining the physiological functions, and (iii) designing specific inhibitors of HDAC6 and HDAC11 isoforms.**



FIGURES

Our research revolves around proteins (1). *We first clone and* ***engineer a protein of interest*** *by molecular biology approaches* ***(2)*** *and then we heterologously* ***express and purify*** *it to homogeneity* ***(3)****. To unravel the structure and function of the studied targets we use a variety of* ***biochemical and biophysical techniques*** *(4), including* ***X-ray crystallography (5)*** *and cryoEM.* ***Detailed structural characterization (6)*** *facilitates* ***development of specific inhibitors*** *and provides* ***mechanistic understanding of the protein function*** *in vitro* ***(7).*** *Finally, we further corroborate and* ***translate our findings into*** *more complex environments including* ***living cells (8)*** *and* ***whole organisms (9).***



Our research revolves around proteins (1).

TOP ACHIEVEMENTS

- We **discovered that HDAC11 serves as a proficient fatty-acid deacylase.** These findings will facilitate both uncovering additional biological functions of the enzyme and design of isoform specific HDAC11 inhibitors.
- We developed, engineered and structurally/functionally characterized **antibodies and Anticalin scaffolds** specifically **targeting human GCPII.** These biologics **have been patented** and further efforts are aimed at their **translation** as diagnostics and therapeutics **into human medicine.**
- In a series of studies, we provided **mechanistic underpinnings for the enzymatic specificity of HDAC6** on short peptides and the most importantly on tubulin, the major physiological substrate of HDAC6.
- Our **drug-discovery efforts** were published in **15 manuscripts** (from 2015) providing a wealth of structural and biological data **facilitating development of** small molecule **inhibitors targeting PSMA and HDAC6.**
- We implemented a versatile and robust **platform for heterologous expression and purification of recombinant proteins.** This methodology is extensively **used** in our lab projects as well as **by a wide network of our collaborators and** in our **commercially** oriented on-demand protein production.



LABORATORY OF

Structure and Function of Biomolecules

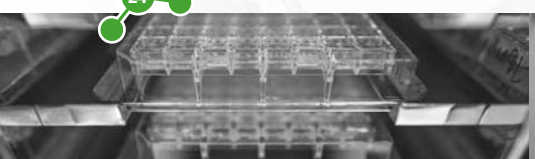
HEAD: Jan Dohnálek ❶ **RESEARCHERS:** Jindřich Hašek ❷ Tereza Skálová ❸ Mária Trundová ❹ Tomáš Kovaľ ❺ Jarmila Dušková ❻ Petr Kolenko ❼ **POSTDOC:** Jan Stránský ❽ **STUDENTS:** Leona Švecová ❾ Kristýna Adámková ❿ Martin Malý ⓫ Terezia Kovaľová ⓬ Aleš Kravic ⓭ Blanka Husťáková ⓮ **IT TECHNICIAN:** Michal Strnad ⓯

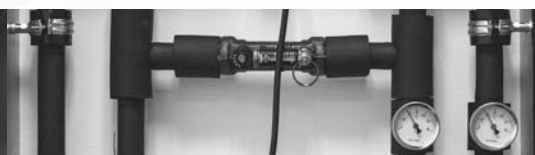
We focus on the relationship between structure and function of proteins, which contributes towards a better understanding and treatment of diseases and, in some cases, aims at biotechnologies. We have explained structural characteristics of mammalian natural killer cell receptors and their ligands, which regulate response of innate immune system to cancer cells, enabling their destruction. Our results suggest a zipper-like model of the synapse between the killer and target cells with fine details of the interaction. This knowledge can be utilized for development of cancer treatment strategies.

In gram-positive bacteria we identified and showed structural properties of protein HelD, a partner of RNA polymerase. HelD is involved in transcription regulation and we aim at answering all its structure-function questions. Better insights into the key cellular processes enable development of new antibacterial strategies.

S1-P1 nucleases are present in pathogenic bacteria, protozoan parasites, plants, and fungi. We have shown the key features of the plant nuclease TBN1 with proven anticancer properties. For nuclease S1 from *Aspergillus oryzae,* we explained its structure with the first detailed study of ligand binding, important for development of non-natural binders. We have also characterized a bacterial representative from *Legionella pneumophila* causing the Legionnaires' disease. These studies lead to better understanding of the function of non-specific nucleases and new potential for cancer treatment, fight against opportunistic pathogens and development of biotechnologies for treatment of DNA/RNA-containing materials.

In protein crystallography, one of our main structural tools, we develop new methods and computational approaches, with focus on crystallization, data processing, and structure refinement.





FIGURES

Figure 1: *Our primary structural method is X-ray crystallography which enables high resolution structure determination with atomic details. A crystal is mounted at the end of the pin on a goniometer and exposed to an intensive X-ray beam. The produced X-ray pattern on the detector contains information about three-dimensional arrangement of the protein molecules and atoms.*

Figure 2: *Using X-ray diffraction, we have determined the structure of the extracellular part of an immune receptor NKR-P1 (two domains – magenta and pink) in complex with its ligand LLT1 from partner cell (two domains – light and dark green). NKR-P1 was found in two binding modes in this crystal structure – primary and secondary mode. The discovery of two binding modes brings up questions of possible clusters or chains formation of these proteins between cell surfaces, to increase the stability of the cell-cell contact.*

Figure 3: *Molecular envelopes of protein HelD – a partner protein of Bacillus subtilis RNA polymerase in presence (pink) and absence (cyan) of ligand, determined with small angle X-ray scattering. The protein changes its overall shape upon binding of AMP-PNP, an analogue of ATP. This shows the importance of structural changes for its function – ATP-dependent enhancement of transcription.*

Figure 4: *Atomic details of the X-ray structure of ligands mimicking reaction products binding in the active site of S1 nuclease from Aspergillus oryzae. Notice the phosphate ion still in contact but leaving the zinc cluster. The oxygen atom of the ribose moiety of the cleaved nucleotide, which was previously involved in the sugar-phosphate bond, is now stabilized in its current position by the side chain of the lysine residue (the hydrogen bond is represented by dashed line). The observed electron density for the ligands (black mesh) enables very precise localization of the individual atoms important for our understanding of the exact details of the catalytic cycle.*

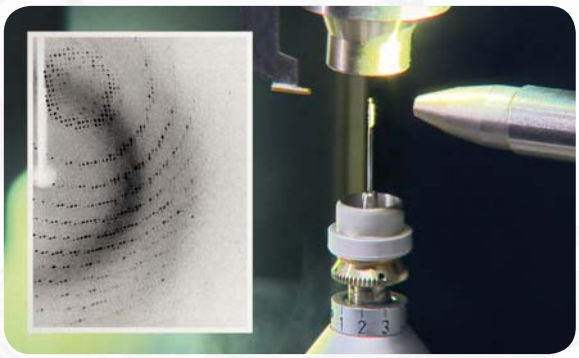
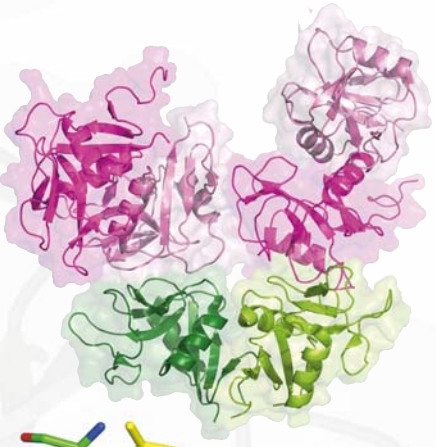


Figure 1.

Figure 2.



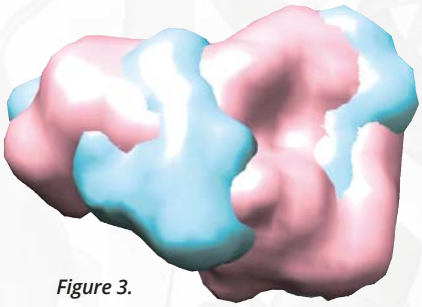


Figure 3.

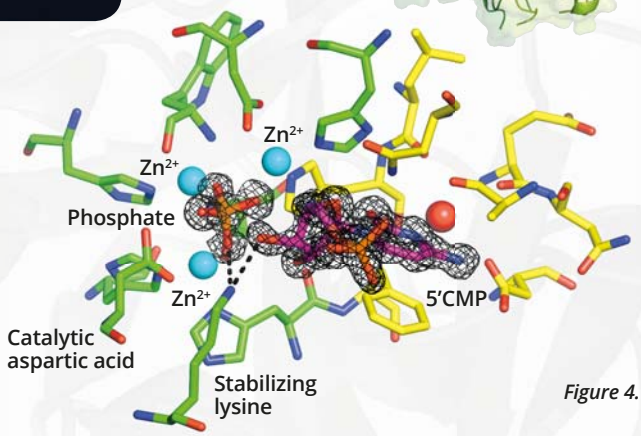
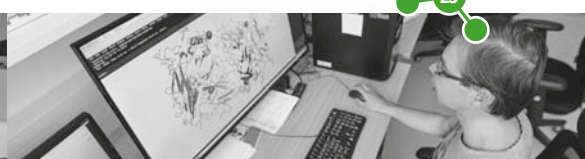


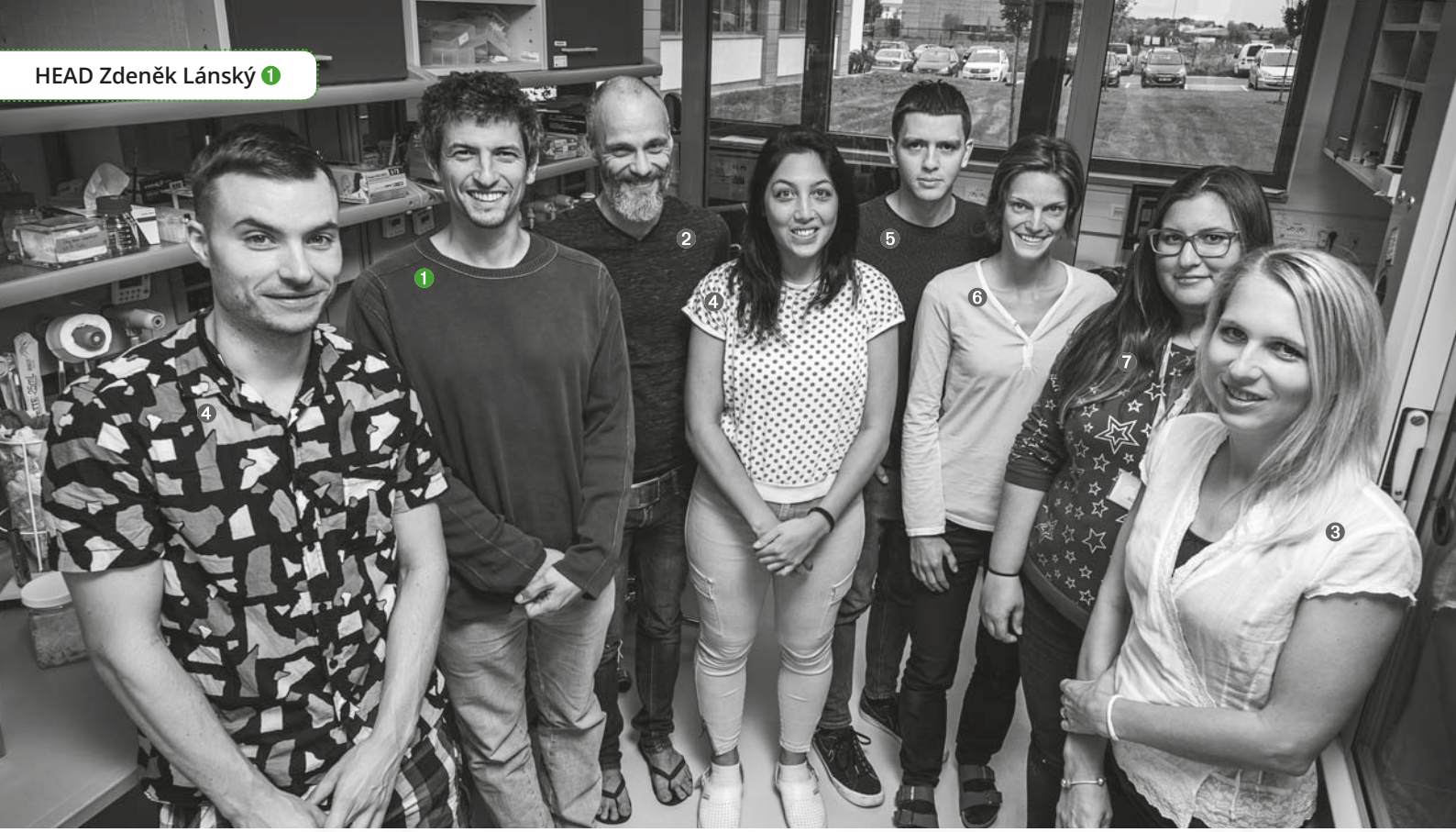
Figure 4.

TOP ACHIEVEMENTS

- Design and realization of the crystallographic facility of the Centre of molecular structure in Biocev.
- Experimental explanation of behavior and complex formation between natural killer cell receptors and their protein ligands.
- The first detailed structural study of nucleotide/inhibitor interactions with S1-P1 type of nuclease with consequences for applications.
- Characterization of *Legionella pneumophila* nuclease showing its extreme properties.
- Structural characterization of the RNA polymerase-interacting partner protein HelD necessary for full understanding of transcription in gram positive bacteria.
- Discovery of active site complementation in α-L-fucosidases and of a new hexameric arrangement of isoenzyme 1 from *Paenibacillus thiaminolyticus.*
- Discovery of a new type of covalent link in protein bilirubin oxidase and structural explanation of its meaning for the active site formation.







LABORATORY OF

Structural Proteins

HEAD: Zdeněk Lánský ❶ **RESEARCHERS:** Marcus Braun ❷ **POSTDOC:** Lenka Gryčová ❸
PHD STUDENTS: Jochen Krattenmacher ❹ Valerie Siahaan ❹ Ilia Zhernov ❺ Verena Henrichs ❻
TECHNICIAN: Yulia Bobrova ❼

Cytoskeletal networks form the internal dynamic scaffold of living cells essential for key cellular processes, such as cell division, cell motility or morphogenesis. Ensembles of cytoskeletal proteins self-assemble to drive these processes. **Our aim is to understand the principles that underpin** their collective action resulting in the generation of a **coherent behaviour of the cytoskeletal networks.**

We study i) **neuronal pathfinding,** a foundational process in ontogenetic development, ii) **contractility of actin networks** and their anchoring to the plasma membrane, key mechanisms in cytokinesis, the final stage of cell division, iii) **regulatory roles of intrinsically disordered, microtubule-associated proteins,** essential axonal factors known for their roles in a number of neurodegenerative diseases, iv) **long-range intracellular transport** and trafficking of organelles, key for example for the maintenance of neuronal function and v) **formation of ciliary structures,** essential for sensing the environmental cues such as signaling molecules, light, and mechanical stimuli.

We use two main strategies: a bottom-up approach – reconstituting elements of the cytoskeletal networks from individual components in vitro, and a top-down approach – deconstructing the networks in vivo. We use genetic manipulations, biochemical and biophysical methods and mathematical modeling. Central to our approach are imaging and force measurement techniques with single molecule resolution. **Employing methods of physics, we quantitatively describe the studied biological systems and predict their behaviour**.

FIGURES

Fig. 1.: Multicolour micrograph showing an in vitro reconstituted contractile network composed of phalloidin-stabilized, rhodamine-labeled actin filaments (cyan) and GFP-labelled actin crosslinker anillin (magenta). Anillin molecules diffusing in the overlaps between actin filaments harvest the thermal energy of the environment to generate entropic force, which drives the contraction of the network. No molecular motors or nucleotide hydrolysis are required for this process.

Fig. 2.: Multicolor three-dimensional confocal reconstruction of Cy5-labeled giant unilamellar vesicle (red) entangled in a reconstituted network of phalloidin-stabilized, rhodamine-labeled actin filaments (cyan). The interaction between the lipid vesicle and the actin filaments is mediated by the actin crosslinker anillin.

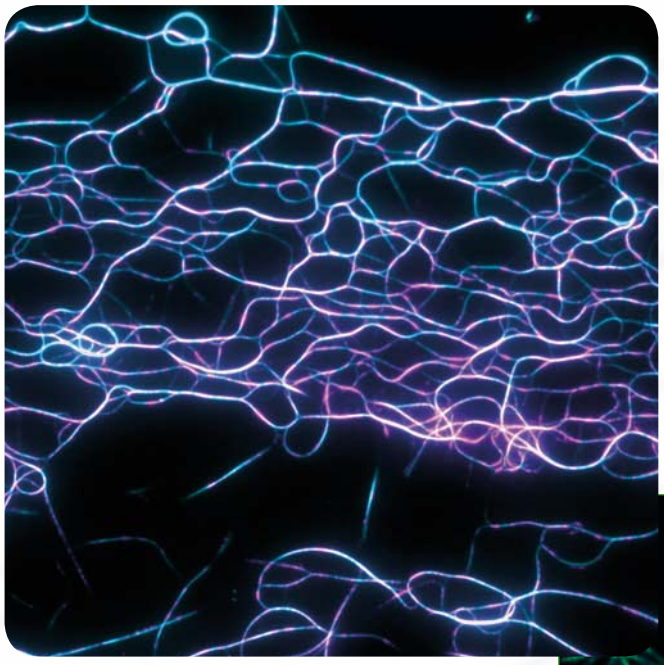


Figure 1: Actin – anillin contractile network.

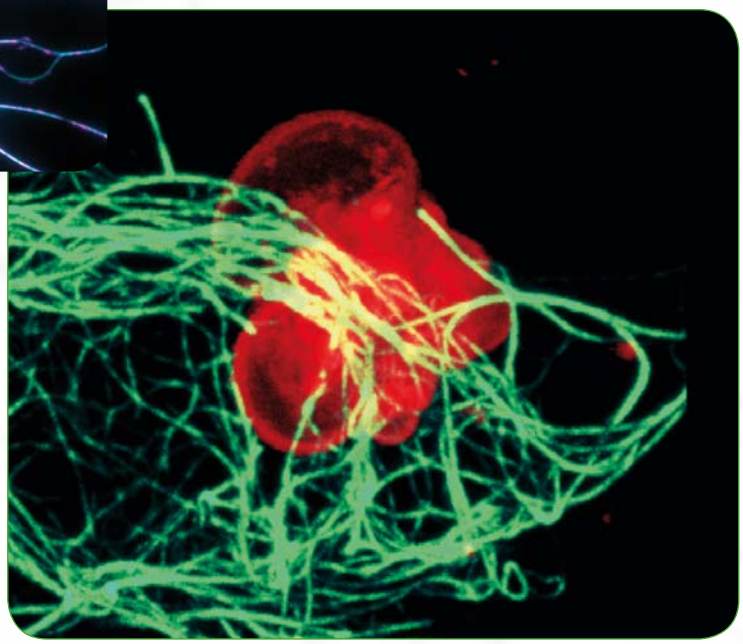


Figure 2: Actin on giant unilamellar vesicle.

TOP ACHIEVEMENTS

- We have disclosed the regulatory roles of tubulin C-termini in the assembly of flagellar microtubule doublets (Science, 2019, 363(6424):285-288).
- We found kinetically distinct phases of intrinsically disordered protein tau on microtubules and uncovered the regulatory roles of these phases (Nature Cell Biology, 2019, 21(9):1086-1092).
- We have shown that diff usive tail anchorage determines the velocity and force produced by kinesin-14 between crosslinked microtubules (Nature Communications, 2018, 9(1):2214).
- We found that, through a self-inhibitory feedback loop, changes in the microtubule overlap length regulate kinesin-14-driven microtubule sliding (Nature Chemical Biology, 2017,13: 1245-1252).



LABORATORY OF

Structural Bioinformatics of Proteins

HEAD: Jiří Černý ❶ **POSTDOCS:** Zahra Aliakbartehrani ❷ Michal Tykač ❸ **STUDENT:** Paulína Božíková ❹

Biomolecules – proteins and nucleic acids – are the basis of all living organisms. Their interactions, as well as the interactions with small molecules such as drugs, are the driving force determining every moment of a life of an organism. Moreover, these interactions form the basis for understanding the principles and designing the treatments for various diseases.

The international team working at the Laboratory of Structural Bioinformatics of Proteins uses computational modelling in order to improve the understanding of both, the structure and the interactions of biomolecules.

One should keep in mind that biomolecules are not static objects. To the contrary, they are in endless motion which is frequently the basis of their function.

A huge amount of information can be extracted from the structural databases and simulations; this includes the atomic positions in space and eventually how these change in time as well as the relative stability of any particular form of a biomolecule.

Still, these data need to be processed for the key descriptors of functions of particular biomolecules. A plethora of existing methods is used in achieving this goal, but often new approaches are required as well. In such cases, we develop and implement these new methods into new computational tools.

In close co-operation with experimentally-focused research-groups, we explore the phenomena responsible for both healthy and disease-stricken biological processes.

Figures 1: *Analysis of RNA structure containing tetraloop motif (left). The detailed annotation and validation of the structure using intuitive graphical representation based on assignment of dinucleotide conformations is available at our web service dnatco.org (right).*

Figures 2: *Structural transition of the N-methyl-D-aspartate receptor (NMDAR) between the closed state, the agonist activated state (RAA), and the open state of the receptor. Different tilt of the outer TMD helices resulting from the iris like movement can be seen. The MD simulation revealed large rearrangement at the level of the ATD and LBD domains during the structural transition between closed and open states. The transition can be described as a rotation of intact ATD and LBD domains from different subunits shown in blue/orange for GluN1/Glun2B subunits.*

Figure 1

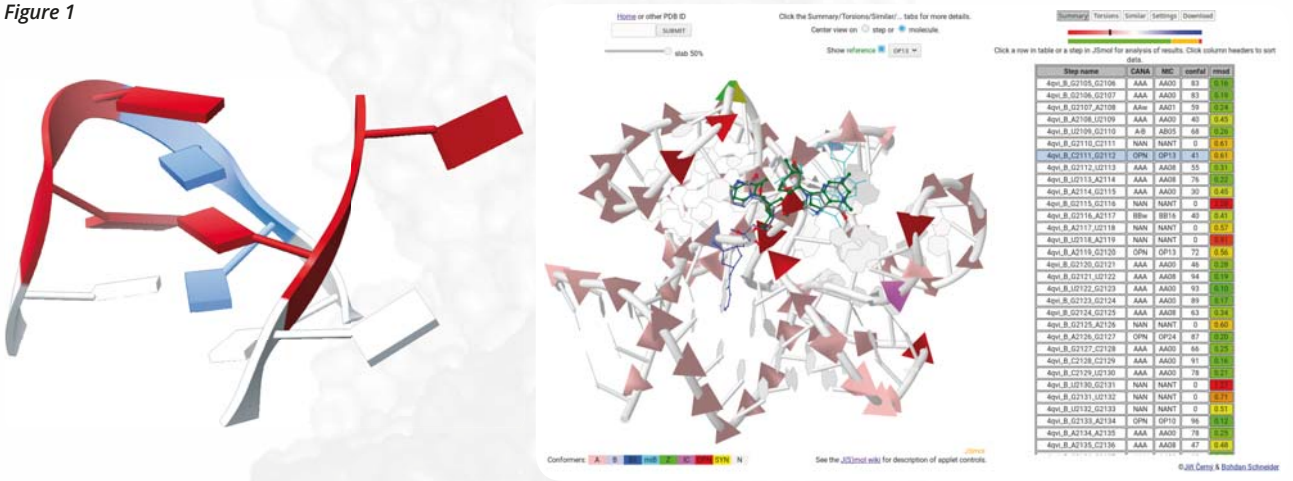
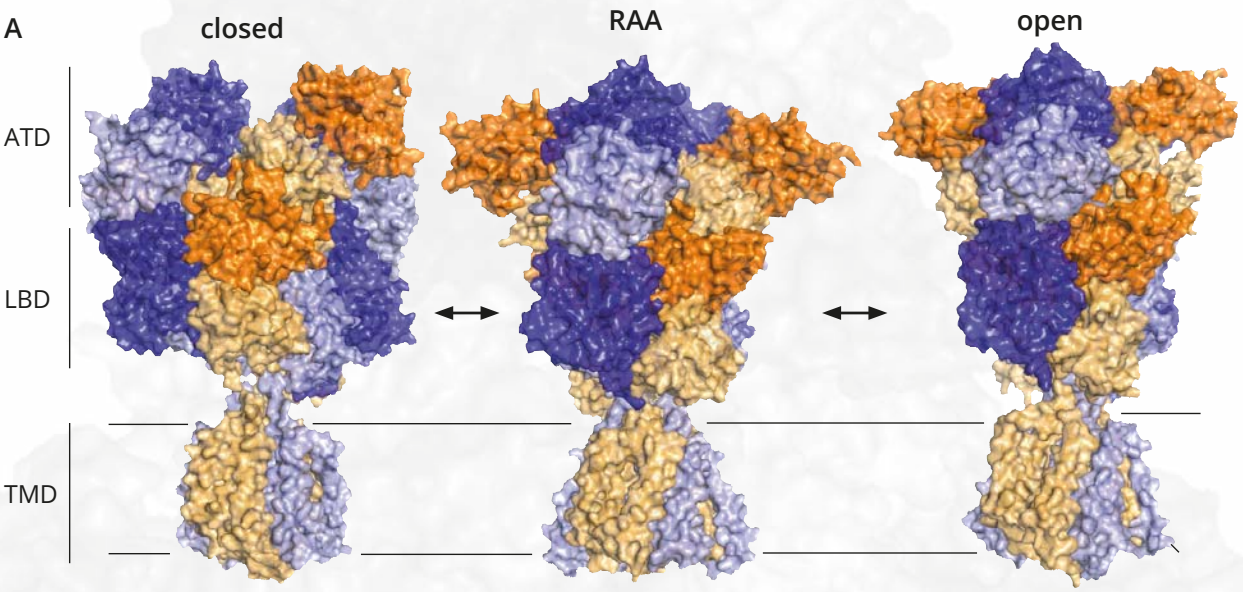
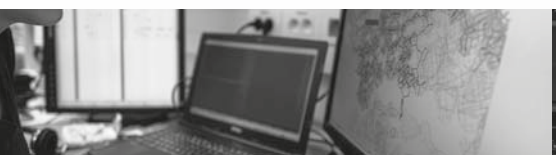


Figure 2



- We have developed a new algorithm for Enriched Conformational Sampling of DNA and Proteins with a Hybrid Hamiltonian Derived from the Protein Data Bank. (International Journal of Molecular Sciences, 2018, 19(11):3405, 10.3390/ijms19113405).
- We have revealed a new role of the LILI motif of M3-S2 linkers in the NMDA receptor channel gating. (Frontiers in Molecular Neuroscience, 2018, 10.3389/fnmol.2018.00113) and descibed NMDA Receptor Opening and Closing by Molecular Dynamics simulations (Biomolecules, 2019, 10.3390/biom9100546).
- A DNA structural alphabet provides new insight into DNA flexibility (Acta Cryst. D, 2018, 74(1):52-64, 10.1107/S2059798318000050) and Distinguishes Structural Features of DNA Bound to Regulatory Proteins and in the Nucleosome Core Particle (Genes, 2017, 8(10):278, 10.3390/genes8100278).
- Our methods and data are also available as web services, DNATCO: assignment of DNA conformers at dnatco.org (Nucleic Acids Research, 2016, 10.1093/nar/gkw381) and WatAA: Atlas of Protein Hydration. Exploring synergies between data mining and ab initio calculations (Physical Chemistry Chemical Physics, 2017, 19(26), 10.1039/c7cp00187h).



HEAD Jan Dohnálek ❶

CORE FACILITY

Centre of Molecular Structure

HEAD: Jan Dohnálek ❶ **RESEARCHERS:** Jiří Pavlíček ❷ Jan Stránský ❸ Tatsiana Charnavets ❹ Petr Pompach ❺
TECHNICIANS: Lubica Škultétyová ❻ Pavla Vaňková ❼ **IT TECHNICIAN:** Michal Strnad ❽
ADMIN: Magdalena Schneiderová ❾

The Centre of Molecular Structure (CMS) provides state-of-the-art equipment, expertise and services for characterization of biological molecules and for structural analysis. CMS provides services in an Open Access regime, to internal IBT users and also to any academics or industrial customers. The facilities are operated under the Czech Infrastructure for Integrative Structural Biology and belong to the Czech centre of the European structural biology infrastructure Instruct-ERIC. The facility educates Czech and foreign students and young scientists in a number of workshops throughout the year.

Biophysical techniques enable assessment of the quality, stability and interaction properties of hundreds of bio-molecular samples of (not only) demanding structural biology projects, be it regular checks, thorough analysis of properties or optimization of molecular constructs or handling protocols.

The core facility Crystallisation of proteins and nucleic acids enables thousands of crystallization experiments using robotic or manual setup, automated monitoring of crystal growth, experiments at selected temperatures or under defined conditions to prepare samples for further crystallographic studies.

The Diffraction facility offers crystal quality screening, *in situ* crystal testing, single crystal data collection and processing, small angle X-ray scattering (SAXS) experiments with robotic sample loading and online UV-VIS spectrometry, and SAXS data processing. Hundreds of samples are processed per year in the self-assisted mode or with full staff support.

The core facility Structural mass spectrometry provides analyses of hundreds of samples and supports many internal and external structural biology projects. The main focus of the services lies in monitoring of proteins structural changes and protein-protein interaction by chemical cross-linking and hydrogen-deuterium exchange. The facility attracts academics and industrial users from abroad.

www.ciisb.org, www.instruct-eric.eu/centre/biocev/, www.ibt.cas.cz/core-facility/CMS/



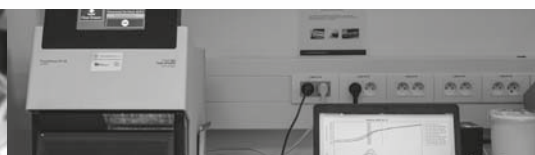


Figure 1: *Intermolecular cross–links connecting the NLS region of proC2 to helices H1 and H3 of 14–3–3; and the proC2 domain p12 to the 14–3–3ζ helix H3.*

Results suggest that 14–3–3 protein binding to caspase–2 may play a key role in regulating caspase–2 activation. [Smidova, A. et al. (2018). 14–3–3 protein masks the nuclear localization sequence of caspase-2. FEBS J., 285(22), 4196-4213.].

Figure 2*: Initial factor eIF3 bound to the 40S ribosomal subunit modeled based on the obtained cross-links.*

Chemical cross-linking in combination with high resolution mass spectrometry were successfully used for monitoring of relative positions of eIF3 subunits and compared them when bound to other eIFs molecules or 40S ribosomal subunit. [Zeman, J. et al. (2019). Binding of eIF3 in complex with eIF5 and eIF1 to the 40S ribosomal subunit is accompanied by dramatic structural changes. Nucleic Acids Research, 1, 1-19.]

Figure 1

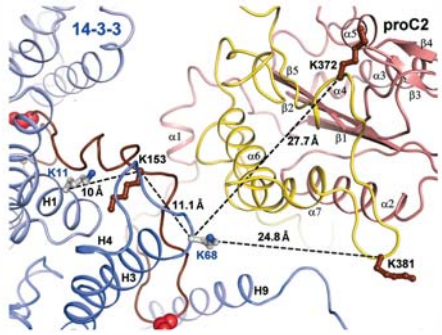
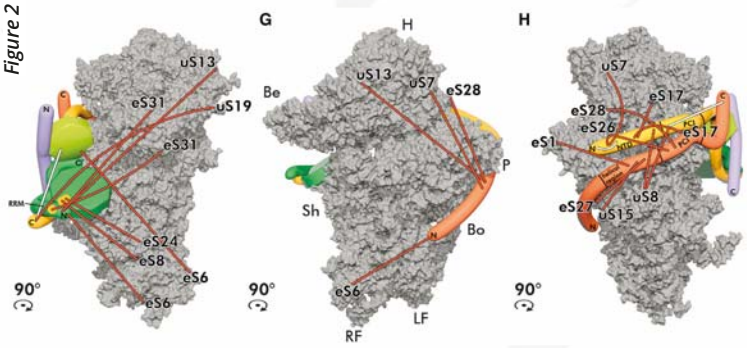
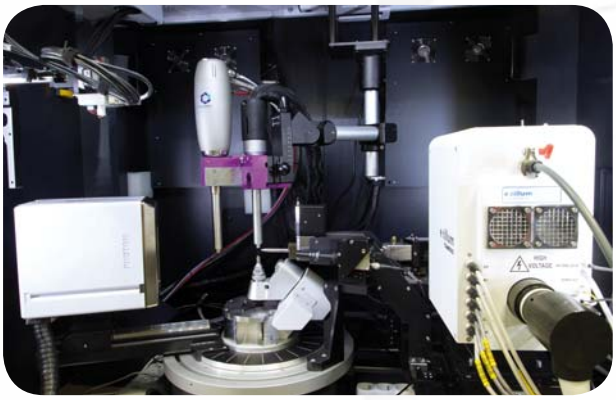


Figure 2



Mass spectrometer 15T solariX XR



Diffractometer D8 Venture with cryo and HC–Lab nozzles

- Ultra high resolution mass spectrometer 15T solariX XR (Bruker Daltonics)
- MALDI-TOF mass spectrometer Autoflex Speed (Bruker Daltonics)
- Excimer laser COMPex (Coherent)
- Single crystal diffractometer D8 Venture (Bruker) with MetalJet D2 X-ray source, area detector Photon II, automated *in situ* ISX stage and crystal humidifiier HC–Lab
- SAXSpoint 2.0 (Anton Paar) with MetalJet C2+ X-ray source, area detector Eiger 1 M, automated sample loader and *in situ* UV-VIS spectrophotometry
- Robotics for crystallization and crystal growth monitoring – Gryphon (ARI), NT8 (Formulatrix), crystallization hotel RI1000 (Formulatrix)
- Circular Dichroism (CD) spectropolarimeter Chirascan Plus (Applied Photophysics).
- Vertex 70v Fourier-transform Infrared (FTIR) Spectrometer
- Monolith NT.150 microscale thermophoresis
- Malvern Microcal iTC200 isothermal titration calorimeter



HEAD: Lucie Langerová ❶

GENECORE

Quantitative and Digital PCR

HEAD: Lucie Langerová ❶ **POSTDOC:** David Švec ❷ **TECHNICIAN:** Filip Franko ❸ Eva Rohlová ❹

The GeneCore – Quantitative and digital PCR Core Facility is one of Europe's leading academic service providers specialized particularly in high-throughput gene expression analysis using quantitative polymerase chain reaction (qPCR). Our ten years of experience has enabled us to participate in many various research projects, including those involving the fast-advancing field of single-cell analysis. We maintain a close cooperation with the Laboratory of Gene Expression, IBT CAS v.v.i. and aim to provide a flawless experimental design, while providing the highest quality of working material.

At GeneCore, we assist researchers with their project design, biological material sampling and analysis of their results, including any necessary consultations for troubleshooting. During the experiments, we run a set of verified molecular tools, which ensure high fidelity and enable the detection of any possible reaction inhibition, contamination or sample degradation.

The fast pace of advancements within the field of Molecular Biology is appreciated at GeneCore. As a result, we offer some of the most up-to-date methodologies to aid researchers in answering their biological questions while continually adding new methods to our ever-growing portfolio. This is clearly demonstrable in the rapidly progressing field of



RNA-Seq, where we offer advanced assistance with **library preparations,** quality control and design of RNA-Seq experiments, which are essential for a successful project.

Another cutting-edge field of science that has resulted in several renowned publications, involves the assessment of the importance of small regulatory RNAs, such as miRNAs. To follow up these and similar discoveries, we offer a novel method developed by the Laboratory of Gene Expression named Two-tailed RT-qPCR. **Two-tailed RT-qPCR** allows for the quantification of miRNA with substantial sensitivity, while allowing discrimination between even highly similar miRNA sequences. Despite the method's complexity, the technique is cost effective. GeneCore is currently the only core facility worldwide that offers the experimental design and validation of the Two-tailed RT-qPCR method.

The number of research teams seeking our services and advice is steadily growing and we are delighted to be a part of many outstanding research projects, especially as they have led to many impactful publications.

We help you to tell your story.

Potential for cooperation: *GeneCore offers collaboration both to intra-institutional and external researchers from the Czech Republic and we are always open to widen our international cooperation. Our aim is to make state-of-the-art qPCR and dPCR technologies, as well as offer expertise related to nucleic acids analysis. We can contribute to clients' workflow from the extraction of samples, nucleic acid quality control, PCR-based methods and preparation of samples for RNA-Seq. Academic researchers are also welcome to perform their experiments at our facility under our supervision.*

- Sample extraction and nucleic acid quality control
- Assay design (qPCR and dPCR)
- qPCR and high-throughput qPCR (gene expression, genotyping)
- digital PCR (copy number variation, SNP or absolute quantification)
- Single cell expression profiling
- Library preparation, quality control and experimental design of RNA-Seq
- miRNA analysis (Two-Tailed RT-qPCR – design and validation)
- Elementary data analysis



CORE FACILITY

Service Technology Laboratory

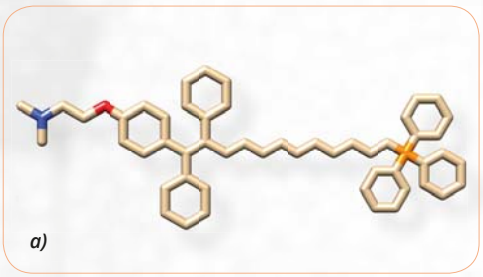
HEAD: Lukáš Werner ❶ Kristýna Blažková ❷ Jan Štursa ❸

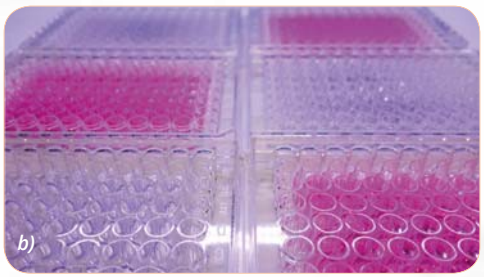
The Service Technology Laboratory (STL) is a core facility focused mainly on medicinal chemistry, preclinical development and advanced technology transfer. STL is a member of the AV21-CAS Strategy for preclinical evaluation of potential new drugs that identifies molecules suitable for further development in medicinal applications. Our job is to design and synthesize new potentially biologically active substances, which are used by our collaborators for basic or applied research. Our experience includes *in vitro* screening of newly prepared substances and evaluation of Structure Activity Relationship (SAR); basic toxicological assessments such as Maximum Tolerated Dose studies (MTD) or pharmacokinetic studies (FK). Pilot pharmacodynamics studies for oncological indications is another segment of our activities. Our laboratory also provides services beyond common academic research mainly relevant to advanced drug development and clinical trials. We synthesize substances, impurities and metabolites in certified quality suitable for advanced preclinical evaluation under the GLP system. STL has experience with a process scale-up as well as with a process transfer for GMP manufacturing. Our most advanced product – MitoTam is currently in phase 1b clinical trial where STL provides administrative and technical support. The vast body of documentation prepared in our laboratory has been successfully audited and approved by the State Institute for Drug Control. STL also offers custom synthesis in the field of organic chemistry either on a contract basis or as a part of academic collaboration.



FIGURES

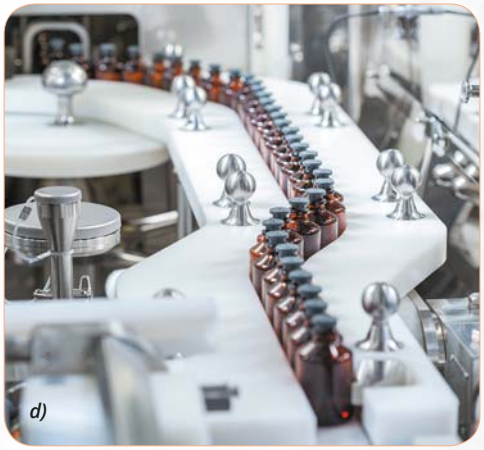
When newly synthesized molecule shows an interesting biological effect, an extensive preclinical, toxicological and pharmacokinetic testing must occur (a-c). The substance to be developed must be synthesized in a certified quality (d) and subsequently tested usually in mice, rats and dogs (c). After a successful preclinical phase and State Institute for Drug Control approval, the drug can progress to a phase 1 clinical trial. STL was responsible for the development of an original anticancer compound – MitoTam (a) – which has passed through this process. For the patients, MitoTam must have been manufactured in certified medicinal quality (d-e) which was achieved by the external cooperation. MitoTam (a) is currently administered to patients by intravenous infusion and some patients in the study have fortunately experienced a significant clinical benefit of the treatment (f).

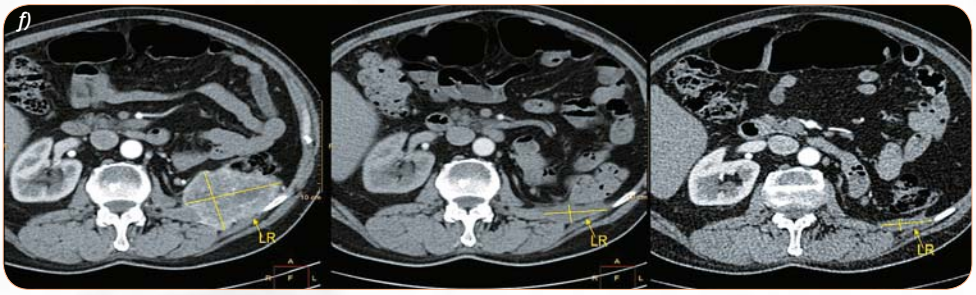

a)


b)


c)


d)


d)



TOP ACHIEVEMENTS

- **2019** – negotiation of patent licensing with the global leader in the field of longevity research: PCT/EP2017/079362 – *Compounds for treatment of senescence-related disorders.*
- **2018** – approval of clinical phase 1 trial: *A First in Human, Open-Label Phase I/Ib study to evaluate the Safety, Tolerability, Pharmacokinetics and Clinical Activity of MitoTam in patients with advanced solid tumors.*
- **Liocore** – a new lipid-based chemo-preventive food supplement was developed in collaboration with Institute of Molecular Genetics of the ASCR.
- **Contract collaborations** for prospective clinical trials: Charles University – 1st Faculty of Medicine (Department of Pathological Physiology); 2nd Faculty of Medicine (Childhood Leukaemia Investigation Center); Faculty of Science (Department of parasitology); University Hospital Královské Vinohrady (Department of Laboratory Diagnostics, Laboratory Genetics); IBT-CAS (Laboratory of Tumor Therapy, Laboratory of Tumor Resistance).
- **Co-Investigator** in the program: Preclinical evaluation of potential drug candidates – Research Topic no. 18 within Strategy AV21 – Czech Academy of Sciences.



IBT

Units

DIRECTOR: Jana Pěknicová ❸

HEAD OF FINANTIAL AND ADMINISTRATION SERVICES: Jan Škoda ❻

SECRETARIAT: Leona Petržílková ❷ Monika Kopřivová ❹

ACCOUNTING DEPARTMENT: Ivana Brabencová ❾ Hana Pěknicová ❽ Klára Knížková ⓭

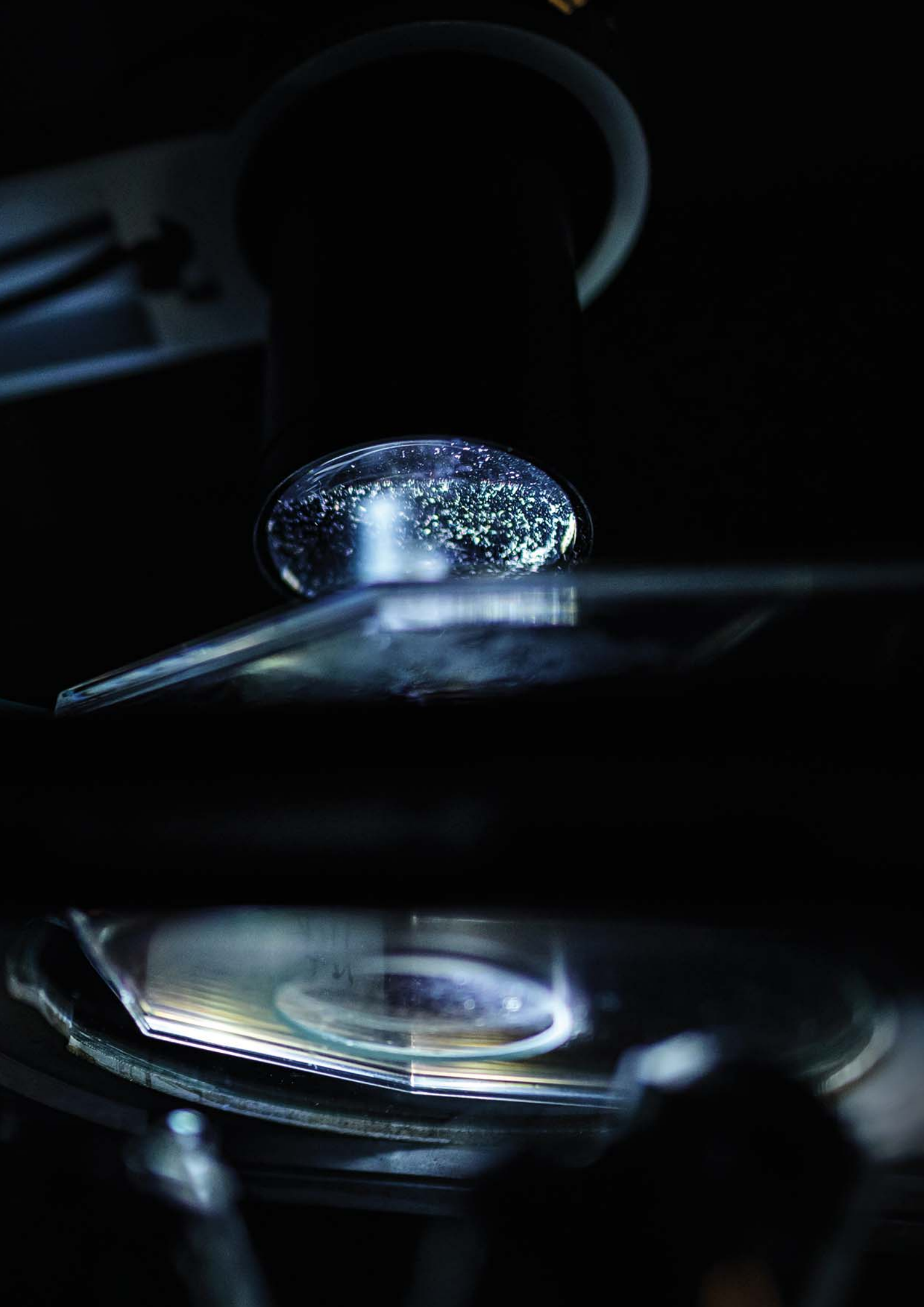
HR DEPARTMENT: Kateřina Drastilová ❺ Veronika Popová ⓬

GRANT OFFICE: Magdalena Schneiderová ❿ Kateřina Sedláčková ❶ Hana Zambarda

TECHNOLOGY TRANSFER: Stanislav Sámek ⓮

IT DEPARTMENT: Jiří Bárta ⓯ Jakub Strouhal ⓫

MAINTENANCE: Rudolf Fryml ❼



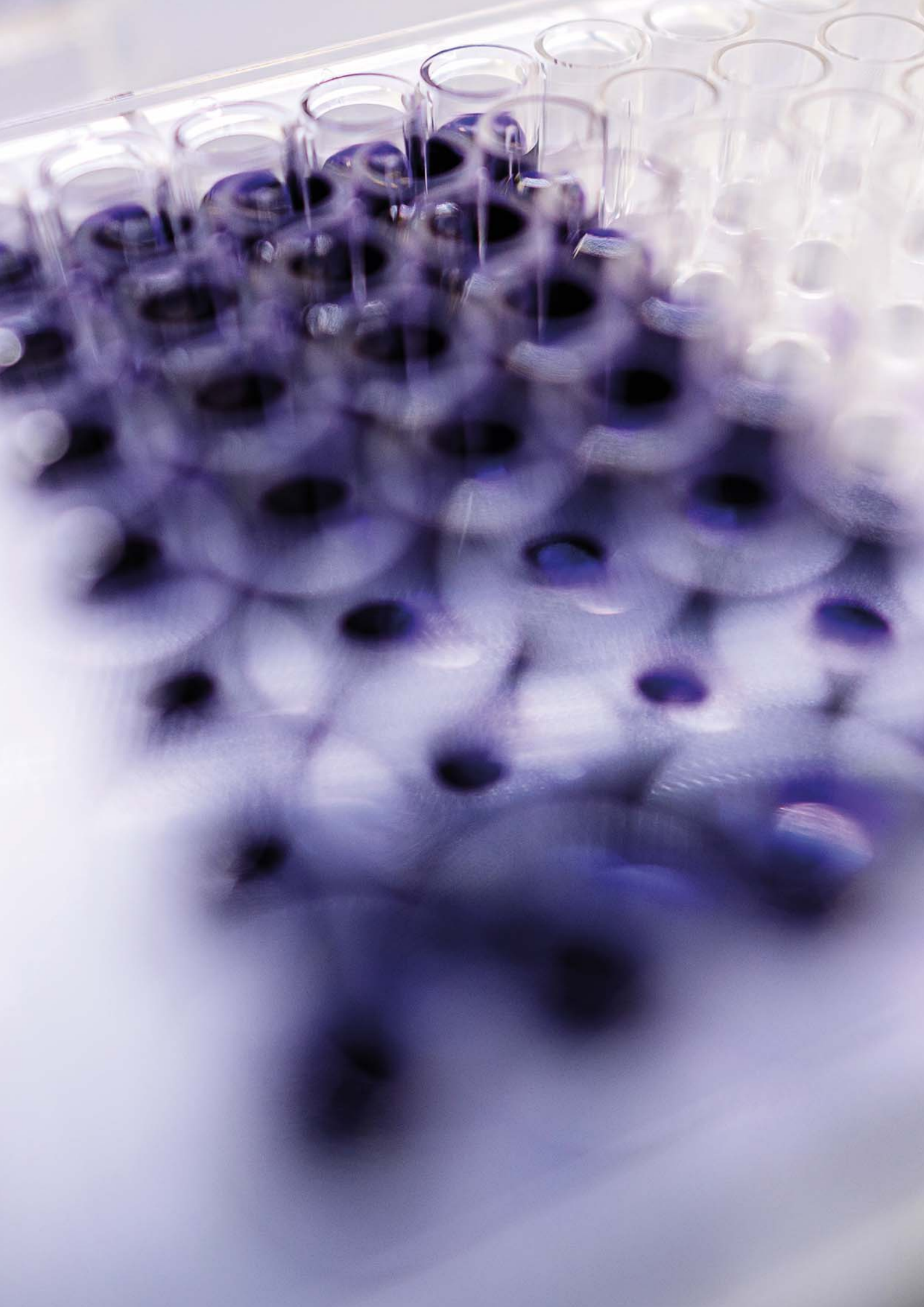
IBT

Projects

GAP301/12/1513	GA ČR	Novel biologics for cancer imaging	2012	2016
13-02154S	GA ČR	Gene expression profiling and functional characterization of glial cell subpopulations following ischemic brain injury	2013	2016
13-07996S	GA ČR	Molecular mechanisms in specification and differentiation of neurosensory cells in the inner ear development	2013	2016
13-28830S	GA ČR	Iron metabolism of the tumour-initiating cells	2013	2017
14-05547S	GA ČR	Molecular mechanisms involved in mammalian sperm capacitation and acrosome reaction	2014	2016
LG14009	MŠMT	Structure and function of proteins for biotechnologies and drug design	2014	2016
15-02203S	GA ČR	Acquisition of the mitochondrial genome by cells with damaged mitochondrial DNA restores the mitochondrial function and tumorigenic capacity	2015	2017
15-05228S	GA ČR	Deciphering the cellular role of HelD, a helicase-like protein associated with bacterial RNA polymerase	2015	2017
15-08239S	GA ČR	The diagnostic and prognostic role of microRNA signature in rectal cancer	2015	2017
15-15181S	GA ČR	Harnessing soluble forms of NK cell receptors and their ligands for the generation of novel anticancer immunotherapeutics	2015	2017
15-17488S	GA ČR	Force coupling between microtubules and actin filaments by unconventional myosins	2015	2017
15-19640S	GA ČR	Molecular basis of substrate recognition by histone deacetylase 6	2015	2017
15-30880	AZV	Proteomic and genetic assessment of sperm quality for the enhancement of assisted reproduction in infertile patients with diabetes mellitus	2015	2018
15-32198	AZV	Construction of recombinant mimotopes for induction of neutralizing antibodies against HIV-1 gp120 glycoprotein using high-affinity binders approach	2015	2018
LH15074	MŠMT	Elucidating the mechanism of asymmetric cell division using Xenopus oocytes as model system	2015	2017
TH01010837	TA ČR	Development of unique vaccines against serious diseases of animals	2015	2016
16-06825S	GA ČR	Programming of the developing heart by maternal diabetes	2016	2018
16-07500S	GA ČR	Distribution of biomolecules studied on single cell and subcellular levels in Xenopus early stages to reveal mechanisms of asymmetric cell division	2016	2018
16-10214S	GA ČR	Age-related changes in brain diffusivity, extracellular matrix composition and glial physiology – impact on pathogenesis of ischemia	2016	2018
16-12719S	GA ČR	Role of receptor tyrosine kinase Her2 in mitochondria	2016	2018
16-12816S	GA ČR	Addiction to oxidative phosphorylation in cancer and its relation to tumour initiation and therapy	2016	2018
16-20507S	GA ČR	Interleukins of the IL-10 family: specificity and targeted modulation of interactions with receptors	2016	2018
16-22823S	GA ČR	The role of mitochondrial bioenergetics in the resistance of quiescent cells to oxidative stress	2016	2018
16-27676A	AZV	Immunomodulatory ligands targeted to IL-23/Th17 pro-inflammatory axis as novel tools for development of topical drugs for treatment of psoriasis	2016	2019

16-29738A	AZV	Detection and evaluation of circulating tumor cells (CTCs) in patients with lung adenocarcinoma by microfluid chip technology	2016	2019
16-30299A	AZV	Nanoliposomal systems for rapid diagnosis of thrombi by MRI	2016	2019
16-31604A	AZV	Mitochondrial targeting as efficient treatment of pancreatic cancer and type 2 diabetes mellitus	2016	2019
CZ.02.1.01/0.0/0.0/ 15_003/0000447	MŠMT	Structural dynamics of biomolucalar systems	2016	2022
LM2015043	MŠMT	INSTRUCT: Czech infrastructure for integrative structural biology	2016	2017
LM2015047	MŠMT	ELIXIR CZ: Czech National Infrastructure for Biological Data	2016	2017
LQ1604	MŠMT	BIOCEV – from fundamental to applied research	2016	2020
17-32727A	GA ČR	Innovative strategies for personalized medicine: molecular approaches targeting the impact of inherited metabolic diseases caused by PPO mutations	2017	2020
17-01192J	GA ČR	The role of mitochondrial respiration in tumour initiation and growth: A mechanistic study	2017	2019
17-04034S	GA ČR	Principal signaling pathways regulating NG2 glia proliferation and differentiation following brain injuries	2017	2019
17-04719S	GA ČR	Influence of the transcriptional regulation on the neurosensory development and function of the auditory systém	2017	2019
17-07635S	GA ČR	Mechanisms of IFNgamma-induced cellular senescence and phenotypic plasticity	2017	2019
17-12496Y	GA ČR	The role of protein friction in the adaptive regulation of microtubule depolymerization and rescue	2017	2019
17-20904S	GA ČR	Mitochondrial respiratory complex II deficiency in cancer development	2017	2019
17-24441S	GA ČR	Molecular mechanisms of proliferation during tumor progression and wound healing studied by profiling on single cell level	2017	2019
17-30138A	AZV	OXPHOS Addiction as a New Hallmark in Cancer: Its Use for Development of Novel, Efficient Cancer Therapy	2017	2020
17-32727A	AZV	Innovative strategies for personalized medicine: molecular approaches targeting the impact of inherited metabolic diseases caused by PPO mutations	2017	2020
CZ.02.1.01/0.0/0.0/ 16_013/0001776	MŠMT	Czech Infrastructure for integrative structural biology for human health	2017	2021
CZ.02.1.01/0.0/0.0/ 16_013/0001777	MŠMT	ELIXIR-CZ: Capacity building	2017	2021
CZ.02.2.69/0.0/0.0/ 16_027/0008353	MŠMT	International mobility of researchers of the Institute of Biotechnologies of IBT	2018	2019
18-02550S	GA ČR	Specific elimination of senescent cells using mitochondria-targeted compounds	2018	2020
18-04790S	GA ČR	Engineered antibodies as platforms for cancer imaging and therapy	2018	2020
18-08304S	GA ČR	Reconstitution of mitochondrial trasport system in vitro	2018	2020
18-10687S	GA ČR	New ligands for old receptors of human natural killer cells: structure, assembly within the immune synapse and potential for therapy	2018	2020
18-10832S	GA ČR	Molecular mechanism of mitochondrial movement between cells	2018	2020
18-11275S	GA ČR	Monitoring of protein network dynamics during sperm-egg membrane interaction	2018	2020
18-13103S	GA ČR	Efficient killing of cancer cells via mitochondrial targeting of iron chelators	2018	2020

18-14167S	GA ČR	Orthologs of glutamate carboxypeptidase 2 in model organisms – search for physiological roles and therapeutic potential of the enigmatic enzyme	2018	2020
18-14325S	GA ČR	The genetic basis of species origin: What can we learn from organisms with female heterogamety?	2018	2020
18-19705S	GA ČR	High-fidelity fast tracking of protein motion mechanisms	2018	2020
18-21942S	GA ČR	MicroRNA in central nervous system injury: potential roles and therapeutic implications	2018	2020
18-24753Y	GA ČR	Properties of horizontal mitochondrial transfer in cancer	2018	2020
CZ.02.1.01/0.0/0.0/ 16_013/0007397	MŠMT	Centre for recombinant biotechnologies and immunotherapeutics	2018	2022
19-02046S	GA ČR	Glial cells – the key players in the progression of amyotrophic lateral sclerosis	2019	2021
19-07378S	GA ČR	Interplay between ISLET1 and NEUROD1 in pancreatic development and disease	2019	2021
19-08772S	GA ČR	Dissecting a contribution of BCL-2 family proteins to mitochondrial bioenergetics	2019	2021
19-11313S	GA ČR	Interspecies comparison of RNA localization within oocytes to elucidate regulation of early development and asymetric cell division	2019	2021
19-17398S	GA ČR	De novo development of bivalent protein binders mimicking the function of interferons lambda	2019	2021
19-20553S	GA ČR	Composition and Function of CII-low, an Alternative Assembly Form of Respiratory Complex II	2019	2021
19-22269Y	GA ČR	Development of non-canonical inhibitors of glutamate carboxypeptidase II: structure-activity relationship studies and biological activity	2019	2021
19-27477X	GA ČR	Cytoskeletal mechanics of the growth cone steering	2019	2023
GJ17-12496Y	GA ČR	The role of protein friction in the adaptive regulation of microtubule depolymerization and rescue	2019	2019
LTAUSA18196	MŠMT	Recombinant antibody molecules for in vivo imaging and therapy of prostate cancer	2019	2022
LTAUSA18197	MŠMT	Design, development, and testing of bioinformatic tools for validation of experimental and computer molecular models in structural biology, biotechnology and pharmacy	2019	2022
TJ02000219	TA ČR	Novel tools for diagnostics and improvement of fertilization ability of sperm	2019	2020



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Patents

Patents granted 2015 – 2019

Maly, P., Krizova, L., Kuchar, M., Petrokova, H. Polypeptides for the treatment of autoimmune diseases based on blocking the p19 subunit of the IL-23 human cytokine.

Maly, P., Sebo, P., Kuchar, M., Vankova, L., Petrokova, H., Osicka, R. Polypeptide antagonists of human IL-23 receptor for treatment of autoimmune diseases.

Neuzil, J., Stursa, J., Werner, L. Tamoxifen derivatives for treatment of neoplastic diseases, especially with high HER2 protein level.

Neuzil, J., Werner, L., Stursa, J. Biguanide triphenylphosphonium analogs, process of their preparation and their use as a medicament.

Skerra, A., Richter, A., Morath, V., Barinka, C., Ptacek, J. PSMA-specific binding proteins.

New patent applications 2015 – 2019

Barinka, C., Pomper, M., Novakova, Z., Foss, C. Development of new monoclonal antibodies recignizing human prostate-specific membrane antigen (PSMA).

Hubackova, S., Werner, L., Stursa, J., Neuzil, J. Compounds for treatment of senescence-related disorders.

Maly, P., Raska, M., Kuchar, M., Kosztyu, P., Turanek, J., Petrokova, H. Polypeptides mimicking epitope of VRC01 broadly neutralizing antibody as antigens for development of a vaccine against HIV-1 infection.

Truksa, J., Werner, L., Stursa, J. Deferoxamine derivatives as medicaments.

Truksa, J., Werner, L., Stursa, J., Sandoval-Acuna, C., Blazkova, K. 3,5-bis(phenyl)-1H-heteroaryl derivatives as medicaments.


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Collaboration with Application Sphere

During its brief existence, the Institute has already achieved a number of remarkable results, which by their nature are directed to the application sphere and have their use in the diagnosis and therapy of human and veterinary diseases.

Our most significant achievement in this field is the innovative approach to cancer treatment through use of mitochondrially targeted agents. One of them, mitochondrially targeted tamoxifen, is now in phase 1 clinical trials. The basis and necessary prerequisite for such translational success is cooperation with a strategic partner an investor, which in this case are Smart Brain s. r. o. and KKCG a. s. Without their participation, the transfer of even ground-breaking research results to clinical practice would not be conceivable.

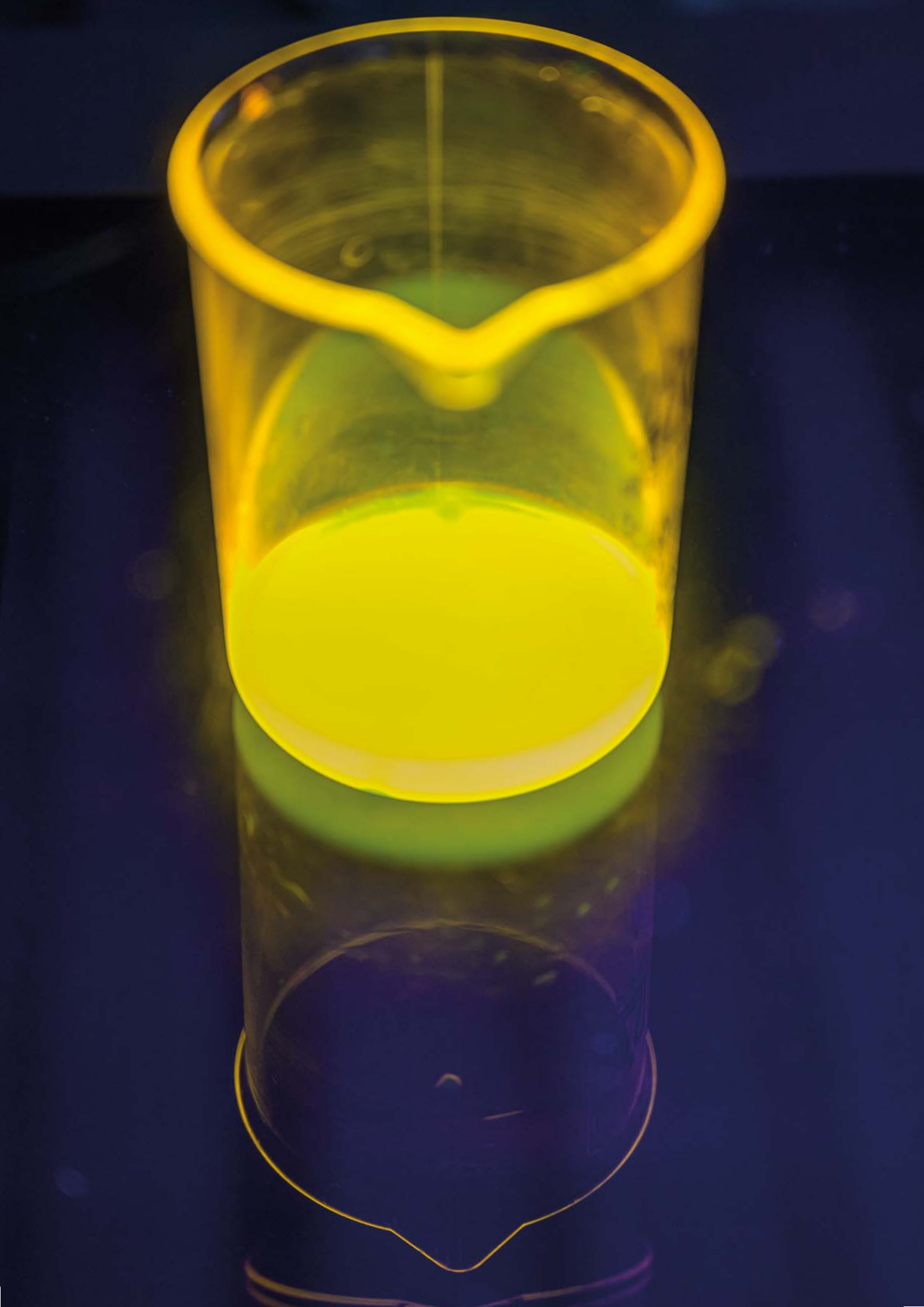
Another type of cooperation with the application sphere consists in joint projects where the application partner can directly apply the project results on their own development and production of new innovative products. In this way, in cooperation with Dyntec spol. s r. o., unique polyvalent veterinary vaccines against serious animal diseases have been developed and tested. In cooperation with PrimeCell Advanced Therapy, a. s. a different project is aimed to develop a unique technology for antibody-based separation of damaged sperm. This technology could have considerable potential for use in as-sisted reproduction in the human and veterinary field.

MitoTAM 25 mg

Dyntec

Finally, a number of collaborative projects exploit heterologous protein expression/purification and protein engineering platforms established in our Institute. Within this framework, we carry out on-demand production of target proteins for both large pharmaceutical companies (e.g., Merck, Bayer) and small and medium enterprises, we have licensed a host of expression clones to various vendors (Abcam, Exbio), and we also actively participate in the schemes aimed at the transfer of technologies from academia to enterprise sectors (e.g. Innovation vouchers of the Central Bohemian Region).

When bringing the research results into practice, the Institute also works with i&i Prague s.r.o. This cooperation helps us to identify and assess the application potential of our results and allows us to off er them at the international network of application partners.



Popularization

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TÝDEN VĚDY A TECHNIKY
AKADEMIE VĚD ČR

One of the biggest popularization events in which the Institute regularly participates is the Week of Science and Technology organized by the Academy of Sciences of the Czech Republic. It is the most extensive science festival in the Czech Republic. It includes lectures, exhibitions, workplace events, and other activities in all scientific disciplines across the country.

Within the Week of Science and Technology the Institute staff presented a series of popular science lectures in the building of the Academy. The Institute organizes an annual open day. Students, teachers, and the public can enjoy a rich programme, which includes not only lectures, but also excursions to laboratories and demonstrations of scientific work. Each year we welcome an increasing number of visitors.

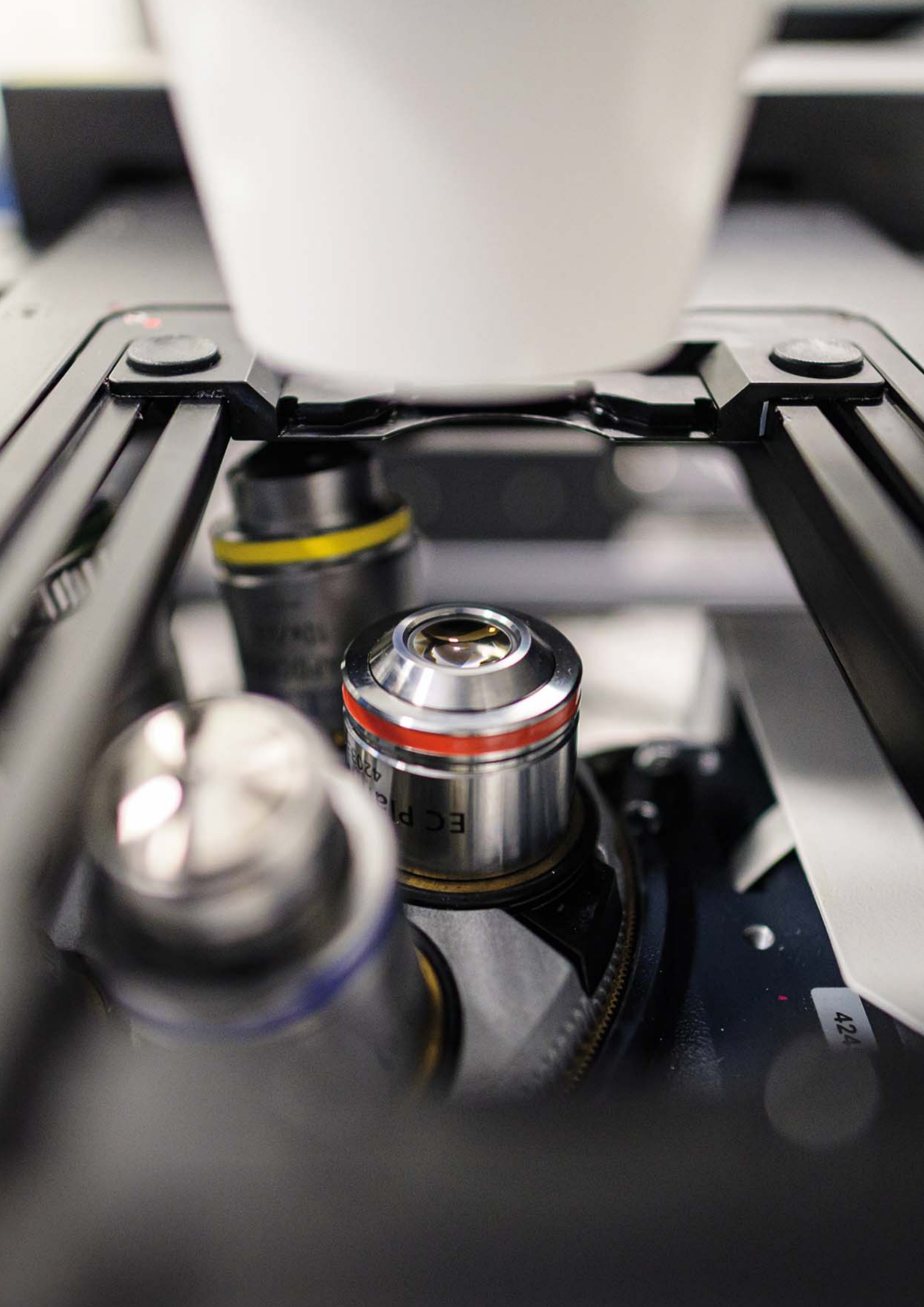
We have also actively participated in the Science Fair, which takes place every year at the Letňany Exhibition Center and brings news from the world of

science and technology. It is designed for everyone interested in science; from students and teachers to top scientists.

To our great pleasure, our researchers have been repeatedly asked to appear on television programmess to share their expert opinions or results of their research. The nature of these appearances has been both serious reporting (ČT24, ČRo) and entertainment (Prima TV – Show Jana Krause).

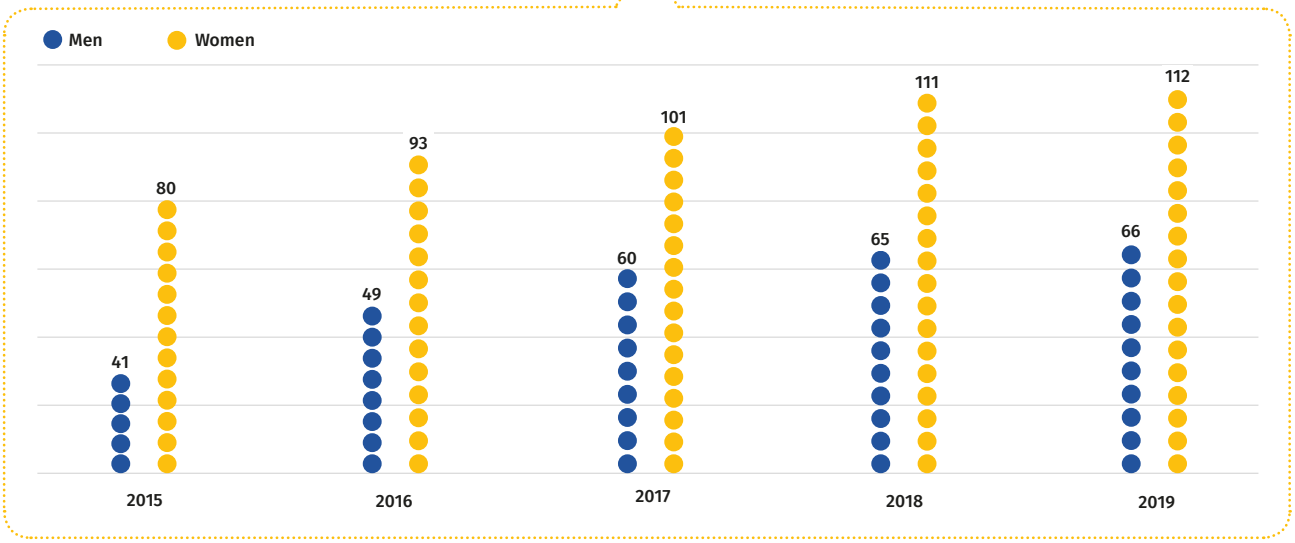
In 2016, Mladá Fronta published the book "Imunologie a imunopatologie lidské reprodukce – Vybrané kapitoly" (Immunology and Immunopathology of Human Reproduction – Selected Chapters), which was prepared in cooperation with the Institute researchers. Its success resulted in a second edition being published in 2020.

To increase the public awareness and to present our Institute in an audiovisual way we have commemorated its 10th anniversary by making a short video, which can be viewed on the Institute website in section "Institute".



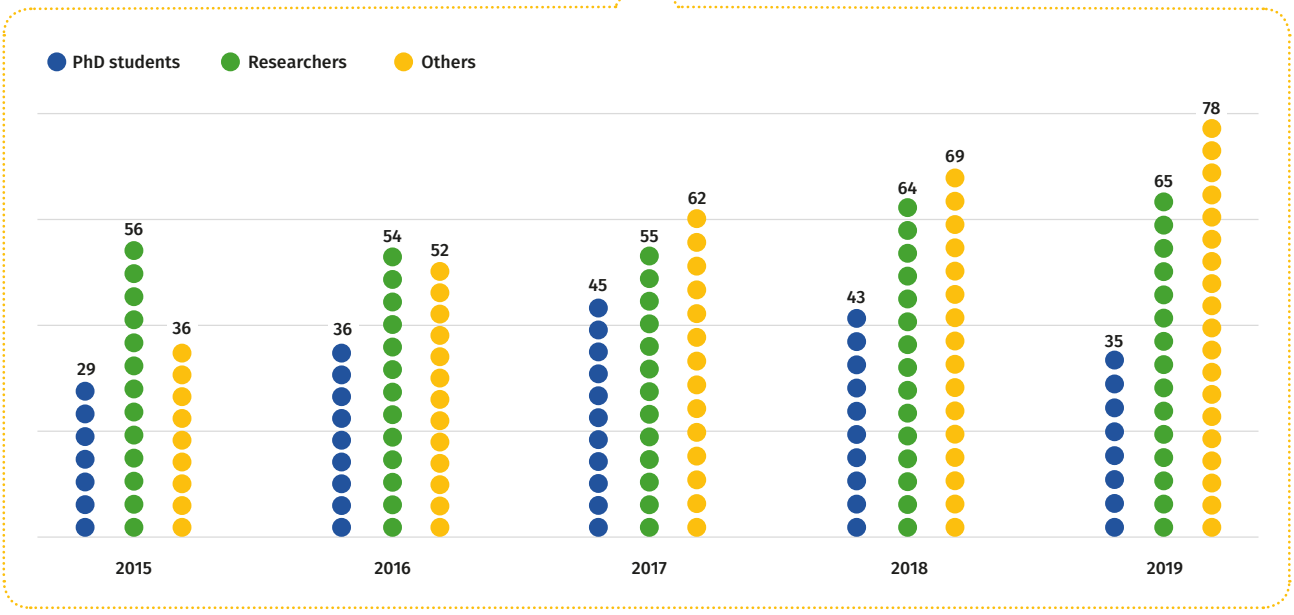
Institute staff

Institute staff – gender structure



The numbers in graphs represent both full time and part time employees through the years 2015-2019. The numbers show an increasing trend which corresponds with the overall development of the Institute. Apart from researchers and PhD students the graphs include technical and administrative workers.

Institute staff – involved in research and others



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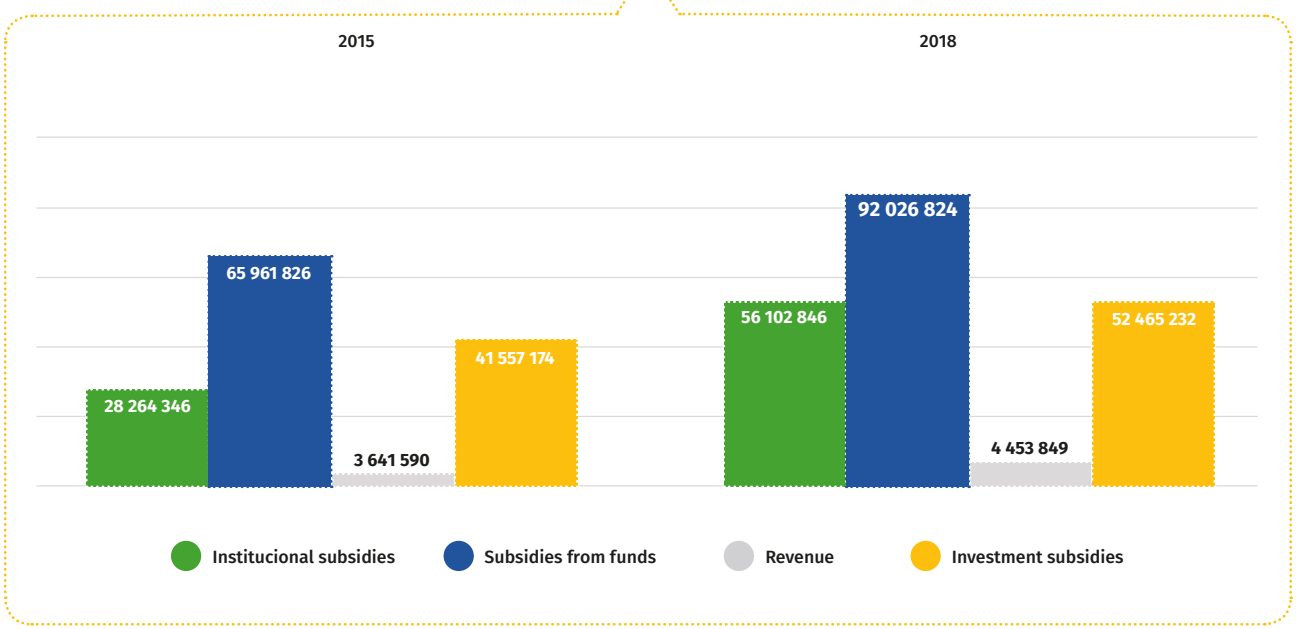
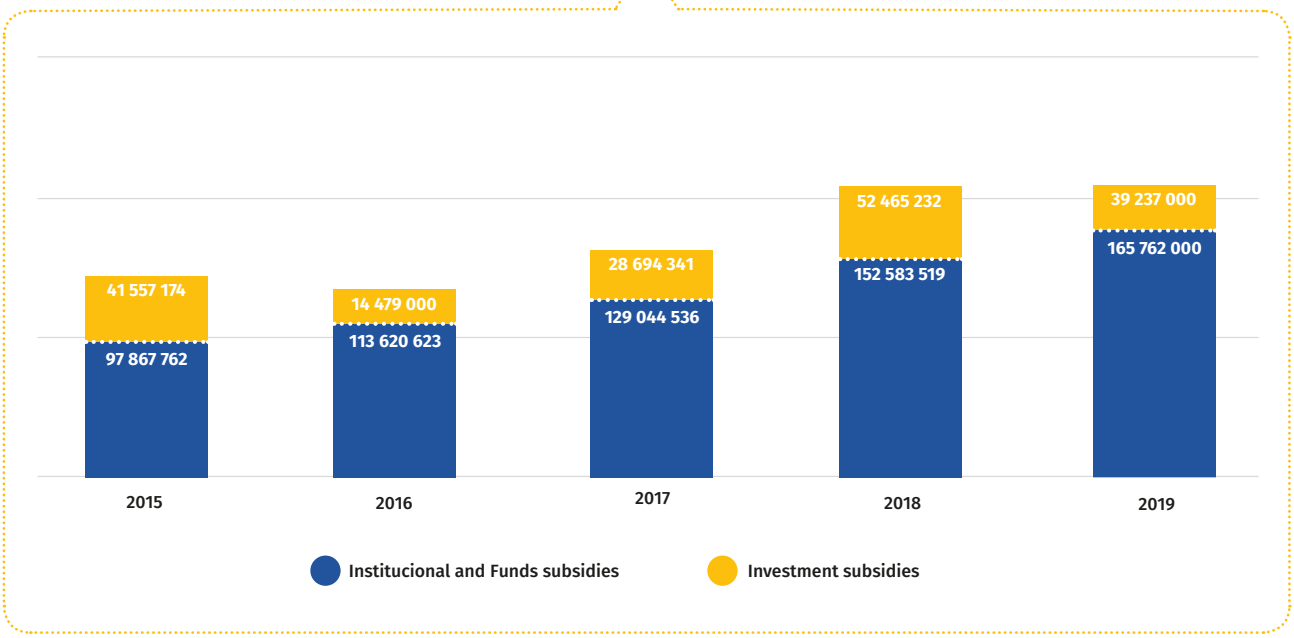
Institute's Budget

Total recources 2015 and 2018



Total recources – progress through the years

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