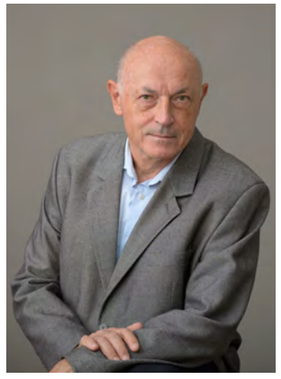

PREVENTION
TREATMENT
EPILEPSY
ALZHEIMER'S DISEASE
CHANNELOPATHIES
SCHIZOPHRENIA
OBESITY AND METABOLIC SYNDROME
INHERITED METABOLIC DISEASES
NEURODEGENERATION
AUTISM
CANCER
PHYSIOLOGY
BIOMEDICINE
INFECTIONS BY YEASTS
DIABETES MELLITUS TYPE 2
DISEASES OF THE INTESTINE
DISORDER OF BIORHYTHMS
DIAGNOSIS
KNOWLEDGE
CHRONIC KIDNEY FAILURE
HYPERTENSION
INBORN COGNITIVE DEFECTS
CHRONIC HEART FAILURE
INSTITUTE
OF PHYSIOLOGY
OF THE CZECH ACADEMY OF SCIENCES
ISCHEMIC HEART DISEASE
HEART ARRHYTHMIAS
NEUROPATHIC PAIN
DEPRESSION

2020

FOREWORD

WELCOME TO THE INSTITUTE OF PHYSIOLOGY OF THE CZECH ACADEMY OF SCIENCES



Since its foundation in 1954, the Institute of Physiology (IPHYS) of the Czech Academy of Sciences (CAS) has been a leading national research institution in the field of normal and pathological physiology, with a special focus on biomedical research. Our mission is to characterize basic biological mechanisms and use our findings to improve prevention, diagnosis and treatment of serious non-communicable diseases:

1. pathological conditions affecting the brain and the nervous system, such as Alzheimer's disease, epilepsy, and chronic pain;
2. diseases linked to obesity (more than half of the Czech adult population is overweight or obese), such as cardiovascular diseases (these account for half of all deaths in the Czech Republic), and diabetes (nearly 10 % of the Czech population currently suffers from type 2 diabetes);
3. inherited diseases, especially those affecting mitochondrial energy metabolism.

Most of these diseases are associated with ageing. The cost of their treatment represents a major burden on health care systems worldwide.

The pages that follow highlight the most important achievements our scientific laboratories accomplished over the past three years. We also introduced innovative methodologies, which are available at the Department of Metabolomics (established in 2017) and the Department of Proteomics (established in 2020; in collaboration with the Institute of Molecular Genetics of the CAS). Finally, we are at the beginning of fundamental reconstruction of our animal facility to be finished in 2022. The rebuilt animal house will provide an ideal environment for our novel studies using experimental mouse and rat models.

About two-thirds of the total funding of IPHYS (approximately 400 million CZK each year) depends on the grant system. During the past years, we introduced a new internal economy system that gives us better ways to administer the Institute's financing. In key decisions, we will receive help from the International Advisory Board of IPHYS, which was established in 2020.

IPHYS hosts excellent, globally recognized teams that collaborate within the Czech Republic with leading clinical centres (e.g. the National Institute of Mental Health, and the Institute of Experimental and Clinical Medicine), other institutes of the CAS (especially the Institute of Organic Chemistry and Biochemistry) and numerous laboratories in Europe and worldwide. A special partnership with Czech universities (namely Charles University and the University of Chemistry and Technology in Prague) provides IPHYS with the opportunity to serve as an important place for pre- and postgraduate education. Importantly, IPHYS is involved in consortia of leading scientific institutes that were recently established in order to support biomedical research (www.epirec.cz and www.mediaim.cz). We are also looking forward to more intense collaboration within the campus of biomedical research institutes of the CAS in Prague, Krč (www.biomed.cas.cz).

This brochure updates the information provided in the previous one, which was released in 2017. Of course, in contrast to the existing and continuously updated IPHYS website (www.fgu.cas.cz), the brochure can only mirror the current situation at the time of its release, i.e. the autumn of 2020.

I am looking forward to serving as the Director of IPHYS for my second term (2020 – 2025). I would like to take this opportunity to extend my appreciation to all of my colleagues, who are responsible for the friendly and enthusiastic atmosphere at IPHYS that helps to make it an excellent scientific institution. I believe the future is bright for IPHYS.

Jan Kopecký
director of IPHYS

IPHYS

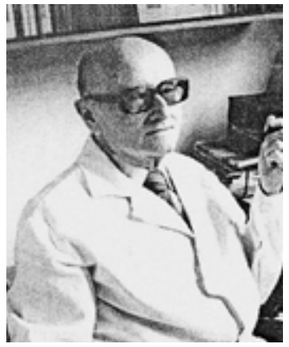
IPHYS IS THE LEADING RESEARCH INSTITUTION IN THE FIELD OF NORMAL AND PATHOLOGICAL PHYSIOLOGY.

Its mission is to improve our fundamental knowledge on the physiological and pathological processes associated with the function of the nervous system, cardiovascular system, and specific areas of metabolism, and thus pave the way to novel prevention, diagnostic and therapeutic procedures for combating serious human diseases. All these activities emphasize the Institute's prominent role in biomedical research in the Czech Republic.

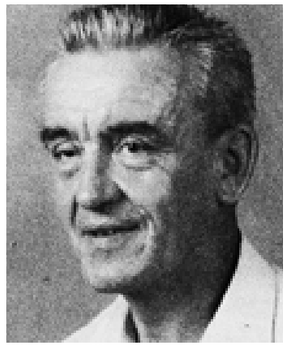
WHAT IS THERE TO KNOW ABOUT IPHYS?

HISTORY OF IPHYS

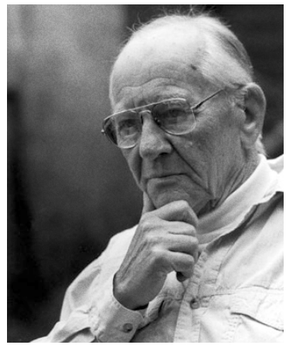
Zdeněk Servít



Arnošt Gutmann



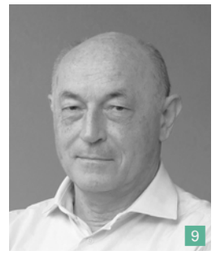
Jiří Křeček

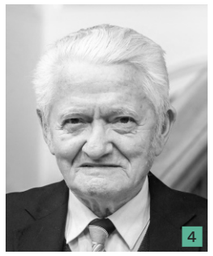


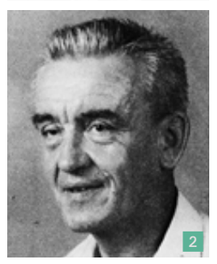
Otakar Poupa

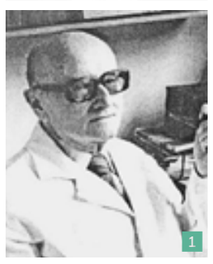
The origin of the current IPHYS is traced back to 1950 when two outstanding personalities, **Prof. Zdeněk Servít** (1913–1986) and **Prof. Arnošt Gutmann** (1910–1977), met at the Department of Neurophysiology within the Central Biological Institutes. In 1952, the Czechoslovak Academy of Sciences (CSAV) was founded. Servít´s laboratory (epileptology) and Gutmann´s laboratory (neuromuscular function) joined a group interested in critical periods of ontogenetic development headed by **Prof. Jiří Křeček** (1923–2014) to form a section of the new Biological Institute. On the basis of successful research and acceptance at home as well as abroad, IPHYS was officially founded on January 1, 1954 and consisted of these three laboratories. In 1956, a fourth group led by **Prof. Otakar Poupa** (1916–1999), who studied the adaptation of the organism to its environment, joined the Institute. The outstanding contribution of these scientists in the fields of neurophysiology, muscle regeneration, heart adaptation to hypoxia and late effects of early interventions was subsequently enriched by their students and follower scientists at IPHYS.

DIRECTORS OF THE INSTITUTE





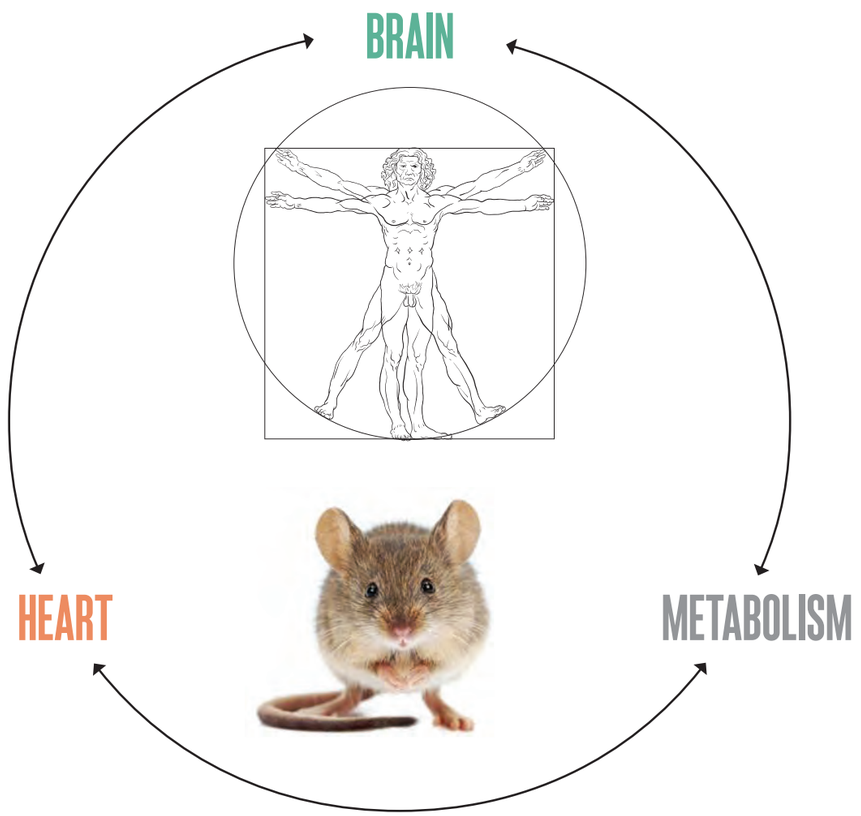




since 2015	9 MUDr. Jan KOPECKÝ, DrSc.
2010–2015	8 RNDr. Lucie KUBÍNOVÁ, CSc.
2003–2010	7 RNDr. Jaroslav KUNEŠ, DrSc.
1995–2003	6 Prof. MUDr. Pavel MAREŠ, DrSc.
1990–1995	5 Prof. MUDr. Bohuslav OŠŤÁDAL, DrSc.
1980–1989	4 RNDr. Zdeněk DRAHOTA, DrSc.
1970–1980	3 MUDr. Ladislav VYKLICKÝ, DrSc.
1970	2 Prof. MUDr. Jiří KŘEČEK, DrSc.
1954–1969	1 Prof. MUDr. Zdeněk SERVÍT, DrSc.

RESEARCH STRATEGY

THE OVERALL RESEARCH STRATEGY AT IPHYS COMBINES COMPLEMENTARY EFFORTS IN SEVERAL FIELDS. BOTH ANIMAL AND HUMAN STUDIES ARE PERFORMED.



MAIN RESEARCH FIELDS

NEUROSCIENCE

Neuroscience research covers studies aimed at understanding basic physiological and pathological processes related to human neurological and psychiatric diseases. Investigations at the system level study development and integrative functions of the central nervous system that include cognitive functions (memory, spatial orientation or learning), chronic and neuropathic pain, and epilepsy. At the cellular level, circadian rhythms (i.e. processes repeated rhythmically during a 24-hour period) and pathophysiological mechanisms of drug addictions and side effects are investigated. Studies at the molecular level are aimed at revealing the biochemical principles of neuron growth and guidance, signal transduction and transmission from one cell to another, structural and functional correlations of neurotransmitter receptor activation and their modulation by biological and pharmacological compounds. Aspects of neural signalling are studied *in vivo*, *in vitro* as well as theoretically using computer simulations and modelling.

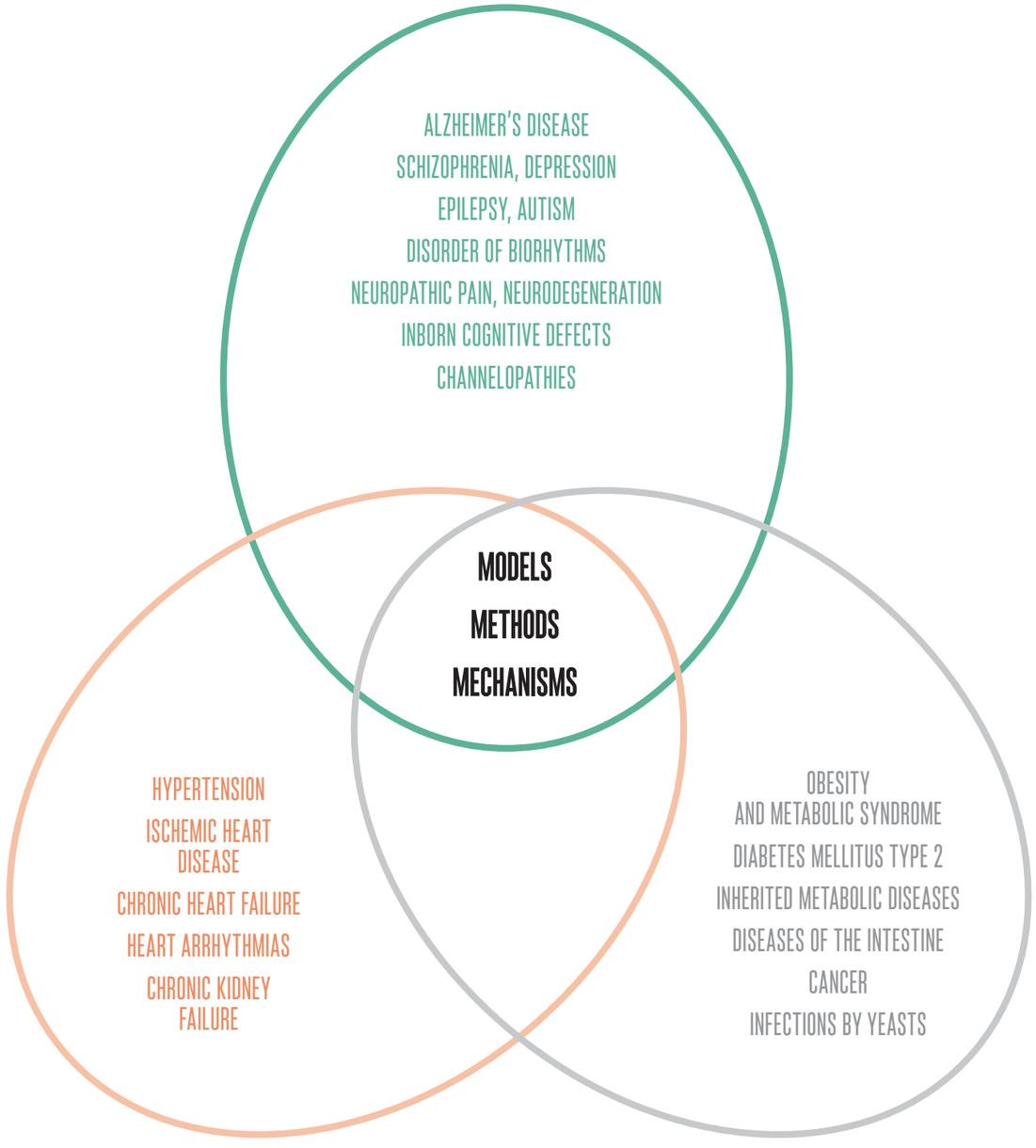
CARDIOVASCULAR RESEARCH

Research in the cardiovascular field is focused on the mechanisms of the development, therapy, and prevention of serious cardiovascular diseases, such as ischemic heart disease, hypertension, and chronic heart and kidney failure. Particular attention is paid to the development of cardiac adaptation to oxygen deprivation and to the mechanisms of cardiac protection against ischemic injury. Studies on the mechanisms of blood pressure regulation, the vascular contraction, and development of the conductive system represent a basis for new therapeutic approaches to hypertension and cardiac arrhythmias. The genetic approach deals with the modifications or defects of selected genes responsible for cardiovascular diseases. Work is also done on the development of new biomaterials that may be suitable for vascular and heart valve replacements, based on synthetic and biological scaffolds seeded with stem cells.

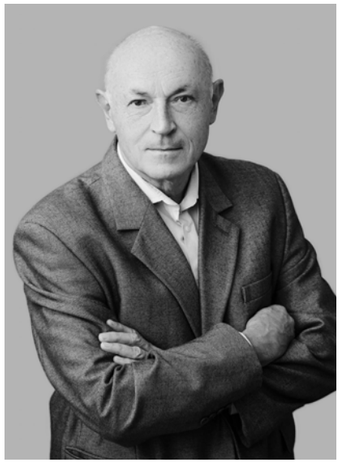
METABOLIC RESEARCH

Studies in this field cover specific aspects of metabolism from the cellular to whole-body level. The research is focused on characterisation of transport systems in cell membranes, specific signalling pathways affecting metabolism, the function of mitochondria and the impact of mitochondrial dysfunction on health, interactions between nutrition and the immune system that affect metabolism, circadian control of metabolism, genetic basis of obesity-related diseases as well as the ontogenic aspects and the role of ageing in metabolic health.

DISEASES IN FOCUS



IPHYS MANAGEMENT



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Deputy Director for Education and Science Support
Prof. RNDr. Jiří Pácha, DrSc.

Deputy Director for Administration
Ing. Petra Janečková

Chairperson Board of IPHYS
Doc. PharmDr. Alena Sumová, DSc.

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Charles University, Prague

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Institute of Organic Chemistry and Biochemistry, CAS

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Institute of Molecular Genetics, CAS

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Faculty of Medicine of Charles University, Hradec Králové

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Institute for Clinical and Experimental Medicine, Prague

Secretary
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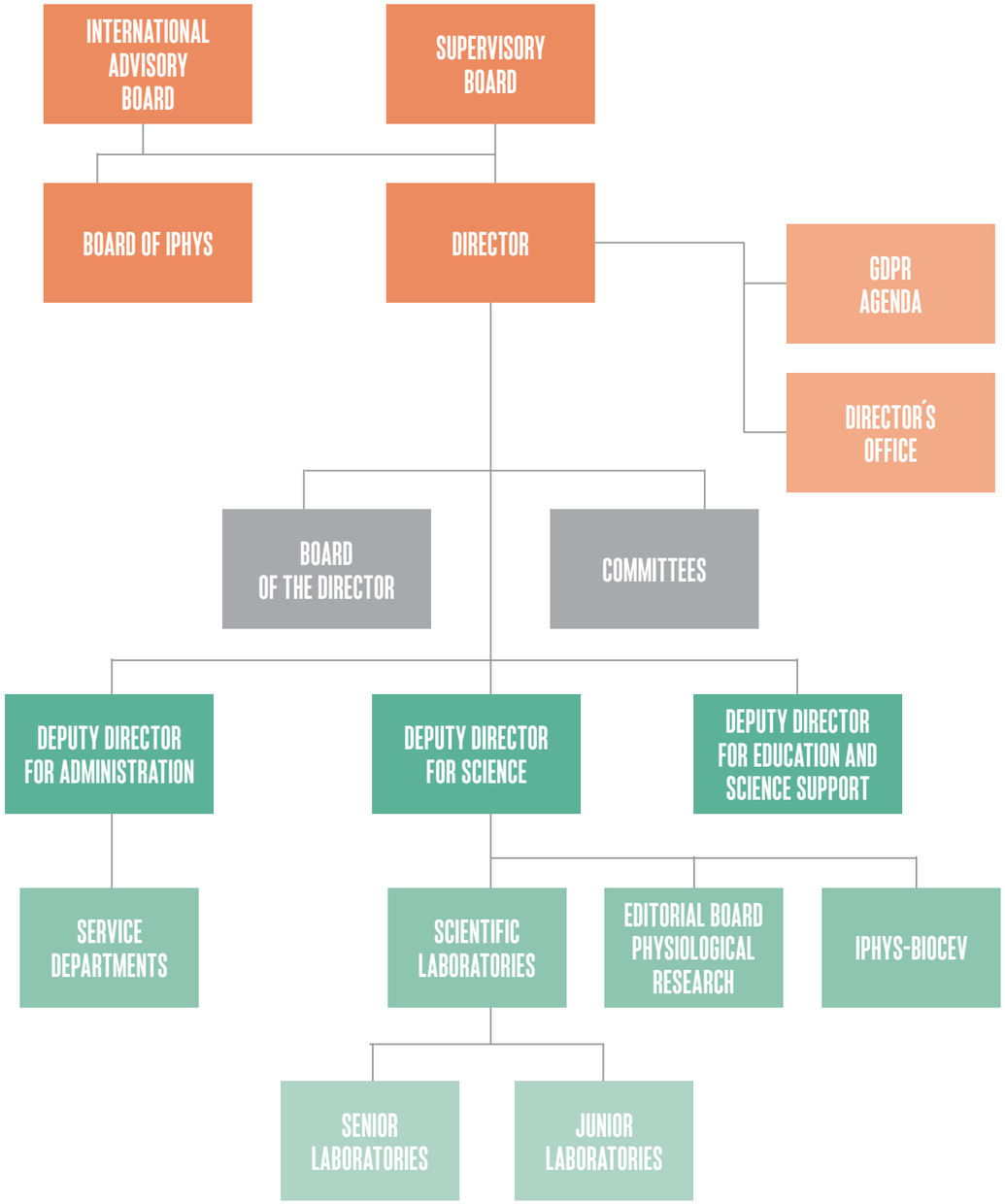
Professor at the Department of Medical Cell Biology, University of Uppsala, Sweden

Prof. Dr. Matthias Blüher
Director of the Helmholtz Institute for Metabolic, Obesity and Vascular Research, Leipzig, Germany

Prof. Dr. med. Pontus Persson
Director of the Institute of Vegetative Physiology, Editor in Chief of Acta Physiologica, Berlin, Germany

Prof. Marianne Schultzberg, PhD
Professor of clinical neuroscience, Karolinska Institutet, Sweden

ORGANIZATIONAL STRUCTURE



SCIENTIFIC LABORATORIES

*KEEP SILENCE
IT IS NECESSARY FOR EXPERIMENTS

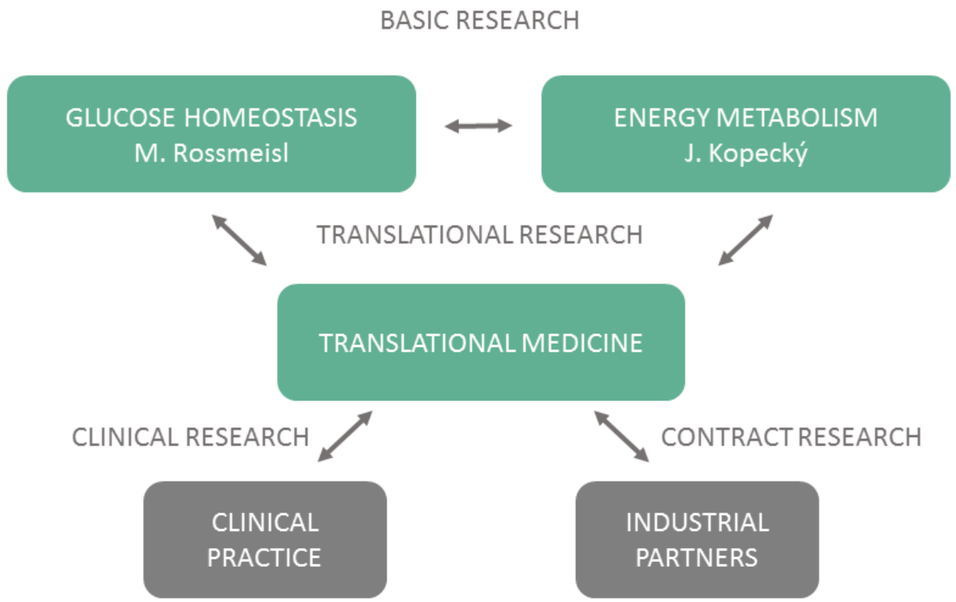
ADIPOSE TISSUE BIOLOGY

head **MUDr. Martin Rossmeisl, Ph.D.** 1 martin.rossmeisl@fgu.cas.cz
key researchers Kristina Bardová, Olga Horáková 2 Petra Janovská 3
Jan Kopecký 4 Petr Zouhar 5 PhD students Kateřina Adamcová 6
Jiří Funda 7 Illariia Irodenko 8 Veronika Kalendová 9 Lucie Leňková,
Marko Mitrovič 10 Gabriella Sistilli 11 Sara Stanić technicians Soňa Hornová 12
Jana Jahelková 13 Adéla Krejcárková 14 Karolína Seďová 15 Daniela Šálková 16

We study the physiological regulation of metabolism and its disturbance in obesity and related diseases (i.e. **METABOLIC SYNDROME**), with the main focus on adipose tissue, the liver, skeletal muscle, and the gut. In this context, we examine the influence of drugs, diet, and natural substances, namely n-3 polyunsaturated fatty acids of marine origin (**OMEGA-3S**), as well as their combinations. Our results emphasize the key role of **ADIPOSE TISSUE METABOLISM** in the development of obesity-related diseases as well as their treatment. Our methodological repertoire includes gene expression screens using RNA sequencing, gene transfer using viral vectors, metabolomics, histology, as well as whole-body phenotyping of energy metabolism, body composition, and insulin sensitivity in mice. By combining experiments on mice and cell models with clinical studies, we try to apply new insights in clinical medicine.

CURRENT PROJECTS

- The (patho)physiology of adipose tissue plasticity and its relation to obesity development and metabolic health; enhancing the lipid-buffering capacity of adipose tissue by various interventions (e.g. omega-3s, calorie restriction, cold exposure, exercise)
- Omega-3s in the prevention/treatment of NAFLD
- The role of the endocannabinoid system in the insulin-sensitizing effects of omega-3s given as marine phospholipids
- The role of the intestine in the metabolic effects of various lipid forms of omega-3s
- The perinatal regulation of metabolism in mice and humans



Basic research in our laboratory is conducted by two research units with complementary focus, which closely collaborate and are engaged in translational research conducted together with clinical centres as well as industrial partners from the Czech Republic and Norway. Within IPHYS, the most important cooperating partner is the Laboratory of Metabolism of Bioactive Lipids (headed by O. Kuda).

SELECTED OUTPUTS

- Omega-3s stimulate adiponectin secretion in mice (Flachs et al. (2006) Diabetologia 49, 394–397), reduce hepatic fat accumulation depending on AMPK (Jelenik et al. (2010) Diabetes 59, 2737–2746), prevent the proliferation of fat cells (Adamcova et al. (2018) Marine Drugs 16, 515) and serve as a precursor of novel anti-inflammatory lipid mediators (Kuda et al. (2016) Diabetes 65, 2580–2590).
- The induction of lipogenesis in white fat during cold exposure is linked to leanness (Flachs et al. (2017) Int J Obes 41, 372–380).
- Omega-3s differentially modulate endocannabinoids in the adipose tissue of obese mice and diabetic patients (Rossmeisl et al. (2018) BBA - Mol Cell Biol Lipids 1863, 712–725).
- Obesity resistance is linked to the postnatal induction of fatty acid oxidation in skeletal muscle (Buresova et al. (2020) Int J Obes 44, 235-244).
- Metformin inhibits intestinal glucose transport to acutely lower blood glucose (Horakova et al. (2019) Sci Rep 9, 6156).
- Dysregulation of epicardial adipose tissue in cachexia due to heart failure: the role of natriuretic peptides and cardiolipin (Janovska et al. (2020) J Cachexia Sarcopenia and Muscle, in press).

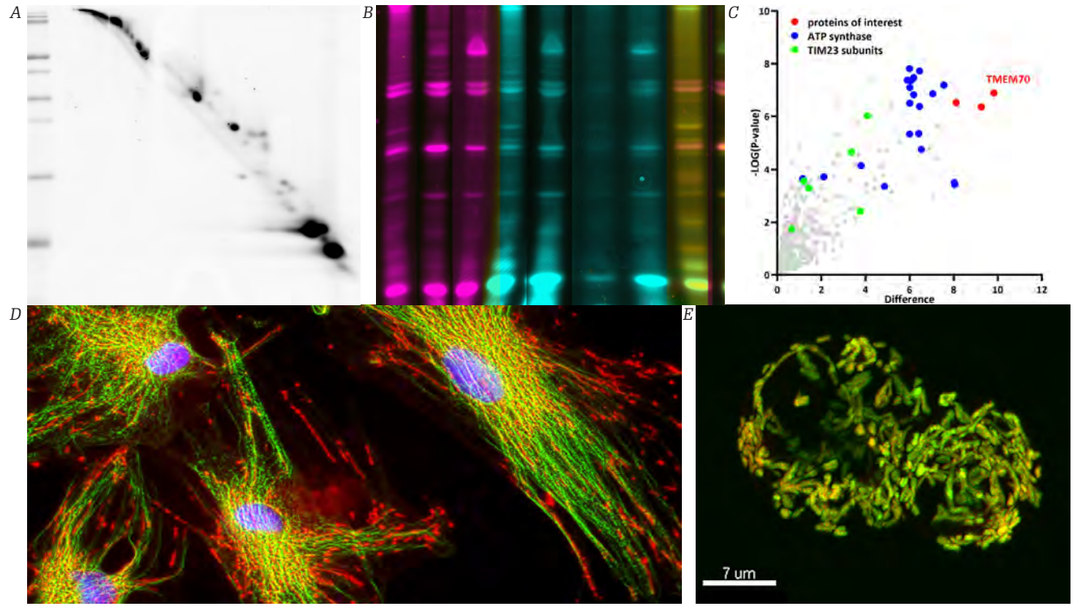
BIOENERGETICS

head RNDr. Tomáš Mráček, Ph.D. 1 tomas.mracek@fgu.cas.cz
key researchers Lukáš Alán, Zdeněk Drahota 2 Josef Houštěk 3 Vilma Kaplanová 4 Eliška Koňaříková 5 Petr Pecina 6 Alena Pecinová 7 Kateřina Tauchmannová 8 Marek Vrbacký PhD students Kristýna Čunátová 9 Zuzana Drašnarová, Aleksandra Markovic 10 Guillermo Puertas 11 Michal Zima, technicians Vladimíra Brožková 12

We study the physiology of **MITOCHONDRIA**, the cell organelles responsible for the majority of energy production at the molecular level. We have a long track record on mitochondrial diseases due to deficiencies in F1Fo ATP synthase. Our department described the first patient with ATP synthase deficiency of nuclear origin back in 1999 and later discovered the disease-causing gene to be **TMEM70**. We use both animal models and cells derived from patients harbouring various mitochondrial disorders. Our research is focused mainly on (1) the assembly of **MITOCHONDRIAL RESPIRATORY CHAIN COMPLEXES** and supercomplexes and protein factors involved in this process; (2) human diseases caused by mutations in genes involved in mitochondrial energy provision – **MITOPATHIES**; (3) identifying new mitochondrial genes that play a causal role in **METABOLIC SYNDROME AND HEART FAILURE**; (4) interactions between mitochondrial and nuclear genomes; and (5) the role of **mtDNA** haplotypes in the development of complex metabolic phenotypes.

CURRENT PROJECTS

- Mitochondrial myopathies – identification and validation of disease-causing genes
- Mitochondrial ATP synthase – characterization of enzyme biogenesis, identification of new assembly factors
- Cytochrome c oxidase – tissue specific isoforms of supernumerary subunits, their role in enzyme biogenesis and modulation of biochemical function
- Mitochondrial proteomics – shotgun and targeted approaches to evaluating mitoproteome changes in disease models
- New diagnostic approaches to mitochondrial diseases – the development of protocols using leukocytes for frontline diagnostics of suspected patients



(A, B) *Analysis of subunit composition of ATP synthase.* ***(C)*** *Affinity enrichment of ATP5G interactors.* ***(D)*** *Mitochondrial reticulum (red) in fibroblasts from patient with mitochondrial disorder.* ***(E)*** *Co-localization of c15 or f61 signal with mitochondria in HEK293 cells.*

SELECTED OUTPUTS

- Kovalciková J et al.: TMEM70 facilitates biogenesis of mammalian ATP synthase by promoting subunit c incorporation into the rotor structure of the enzyme. (2019) FASEB J 33(12), 14103-14117.
- Pecina et al.: Role of the mitochondrial ATP synthase central stalk subunits γ and δ in the activity and assembly of the mammalian enzyme. (2018) Biochim Biophys Acta-Bioenerg 1859(5), 374-381.
- Melenovsky et al.: Myocardial iron content and mitochondrial function in human heart failure: a direct tissue analysis. (2017) Eur J Heart Fail 19(4), 522-530.
- Hartmannova et al.: Acadian variant of Fanconi syndrome is caused by mitochondrial respiratory chain complex I deficiency due to a non-coding mutation in complex I assembly factor NDUFAF6. (2016) Hum Mol Genet 25(18), 4062-4079.
- Cizkova et al.: TMEM70 mutations cause isolated ATP synthase deficiency and neonatal mitochondrial encephalocardiomyopathy. (2008) Nat Genet 40(11), 1288-1290.

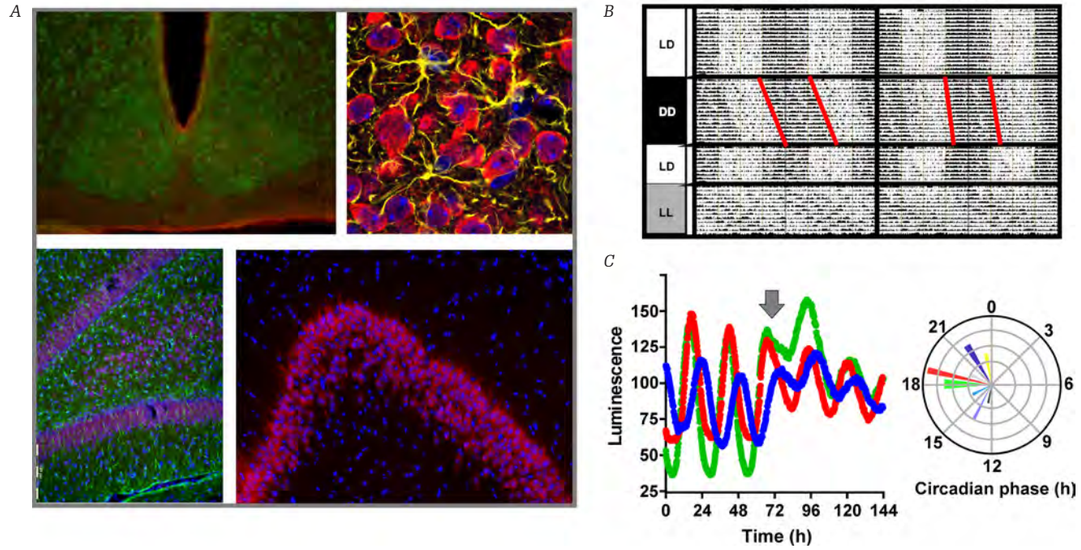
BIOLOGICAL RHYTHMS

head **Doc. PharmDr. Alena Sumová, DSc.** 1 alena.sumova@fgu.cas.cz
key researchers Martin Sládek 2 Lenka Polidarová, Helena Illnerová – emeritus
PhD students Vendula Čečmanová, Karolína Šuchmanová 3 Petra Hozlová
Kateřina Semenovykh 4 Mllica Drapsin 5 technicians Pavel Houdek 6
Eva Suchanová 7

Our focus of interest is the endogenous timing-keeping system, the **BIOLOGICAL (CIRCADIAN) CLOCKS**, of mammals, including humans. The system temporally regulates physiological processes in our body so that they take place at the proper time of day in synchrony with external time and relative to each other. A failure of this temporal regulation has a negative impact on **HUMAN HEALTH**. Using *in vivo* and *in vitro* models, we study the **MOLECULAR MECHANISMS** of how the circadian clocks are regulated, how these clocks control processes in our body, and what the consequences of disrupting these regulation systems are for human health over our lifespan.

CURRENT PROJECTS

- The ontogenesis of the biological clock, investigating mechanisms of how the circadian clocks develop and how they are entrained
- Entrainment of the circadian clocks, exploring the mechanisms of how the clocks are synchronized with signals from the external environment and within our body, using various *in vivo* and *in vitro* models
- The circadian system in patients with various disorders, studying the circadian system in patients suffering from disorders associated with a disrupted sleep pattern to find connections between the functional state of the timing system and those disorders



(A) *Immunohistochemical detection of proteins in neurons and glia of suprachiasmatic nuclei of the hypothalamus (SCN) (upper photo) and hippocampal neurons (lower photo).* ***(B)*** *Demonstration of rat locomotor activity under different light conditions (LD – light/dark, DD – constant darkness, LL – constant light) and its changes in Alzheimer's disease model – McGill (published in Petrásek et al., 2018)* ***(C)*** *Circadian expression of clock gene PER2 in organotypic explants of SCN measured by bioluminescence and its modulation (arrow). Graphical representation of its phase.*

SELECTED OUTPUTS

- Novakova M., Prasko J., Latalova K., Sladek M., Sumova A.: The circadian system of patients with bipolar disorder differs in episodes of mania and depression. (2015) Bipolar Disorders 17, 303-314 – The first evidence for changes in functional state of the circadian during episodes of mania and depression.
- Olejnikova L, Polidarova L, Behuliak M, Sladek M, Sumova A: Circadian alignment in a foster mother improves the offspring's pathological phenotype. (2018) J Physiol (London) 596(23), 5757-5775 – The evidence for importance of maternal clock for health of the offspring.
- Novosadova Z., Polidarova L., Sladek M., Sumova A.: Alteration in glucose homeostasis and persistence of the pancreatic clock in aged mPer2Luc mice. (2018) Sci Rep 8 (1), 11668 - The evidence for resilience of pancreatic clock to aging.
- Cecmanova V., Houdek P., Suchmanova K., Sladek M., Sumova A.: Development and entrainment of the fetal clock in the suprachiasmatic nuclei: The role of glucocorticoids. (2019) J Biol Rhythms 34(3), 307-322 – The first evidence that glucocorticoids synchronize the SCN clock in fetuses.

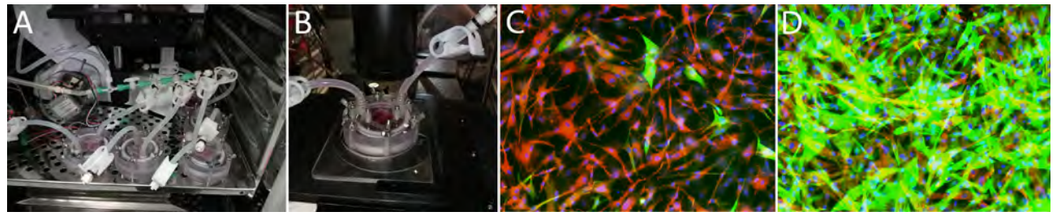
BIOMATERIALS AND TISSUE ENGINEERING

head **Doc. MUDr. Lucie Bačáková, CSc.** 1 lucie.bacakova@fgu.cas.cz
key researchers Andreu Blanquer, Antonín Brož 2 Elena Filová 3
Ivana Němčáková 4 Jarmila Knitlová 5 Jana Racková, Roman Matějka, Jana Musílková,
Lubica Staňková, Marta Vandrovcová, Jana Zárubová, Markéta Zikmundová
PhD students Martina Doubková 6 Julia Pajorová, Šimon Pražák 7 Antonín Sedlář 8
Marie Steinerová, Mária Tomková 9 Martina Trávníčková 10 Jana Štěpanovská
technicians Věra Lisá, Jana Voborníková 11 Ivana Zajanová 12

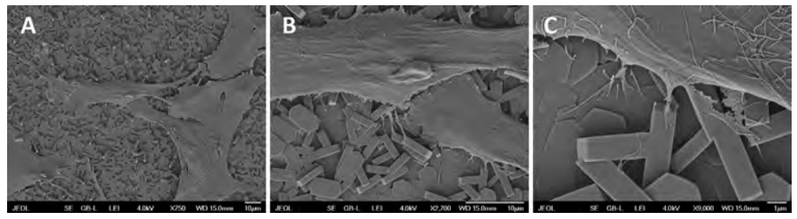
The Laboratory is subdivided into three research groups: **VASCULAR TISSUE ENGINEERING, BONE TISSUE ENGINEERING**, and **SKIN TISSUE ENGINEERING**. Within each group, the main tasks are (1) to improve currently-used tissue replacements by introducing cell and other biological components, and (2) to construct completely new replacements on the basis of biomaterials (synthetic and nature-derived) and cells. In order to achieve these goals, we carry out studies on the molecular mechanisms of cell behavior on synthetic and nature-derived materials, such as the adhesion, growth, differentiation, potential damage, and immune activation of cells. We use differentiated cells (animal cells or commercially available human cells) or human stem cells (derived from adipose tissue, bone marrow, or Wharton jelly) as the cell component of these constructs. Phenotypic maturation of these cells is accelerated by mechanical stimulation in dynamic cell culture systems. Promising cell-material constructs are tested *in vivo* in rat, rabbit, or pig models.

CURRENT PROJECTS

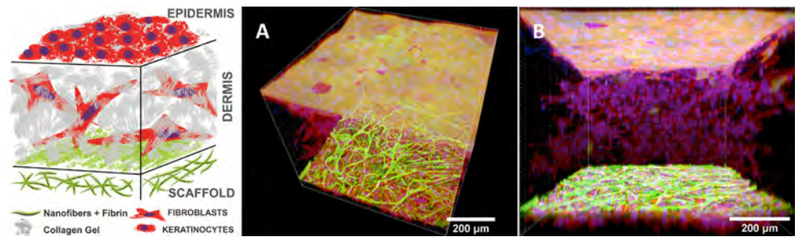
- Self-endothelialization of novel bioactive surfaces of decellularized vascular grafts
- New materials for cardiovascular surgery based on modified decellularized tissues
- Bioartificial cardiovascular patches and vessels from porcine collagen reinforced with nano/microfibers using stem cells and dynamic culture
- Rational development of a smart prosthetic material: silicalite-1 coating on TiAlV alloy
- Improved growth of human skin cells on biomimetic nanofibrous matrices for active wound healing



Example of vascular tissue engineering. ***(A)*** *Dynamic cell culture system generating pulse pressure stress used for mechanical stimulation of adipose tissue-derived stem cells (ASCs).* ***(B)*** *Detail of a chamber of this system with microscopic live-cell imaging.* ***(C, D)*** *Immunofluorescence staining of SM α-actin (red) and calponin (green), i.e. markers of differentiation towards vascular smooth muscle cells, in ASCs cultured for 7 days in a fibrin gel on glass in a medium with TGF-β1 and BMP-4 under static conditions* ***(C)*** *and under dynamic conditions* ***(D)***.



Example of bone tissue engineering. Human osteoblast-like MG 63 cells on day 1 after seeding on silicalite-1 films for potential bioactive coating of metallic bone implants. Scanning electron microscopy, original magnification 750x ***(A)****, 2700x* ***(B)****, and 9000x* ***(C)***.



Example of skin tissue engineering. Developing a bilayer construct of keratinocytes and fibroblasts on a PLLA nanofibrous membrane modified with fibrin and collagen gel. Left: schematic design; right ***(A, B)*** *actual construct.*

SELECTED OUTPUTS

- Bacakova M et al. A two-layer skin construct consisting of a collagen hydrogel reinforced by a fibrin-coated polylactide nanofibrous membrane. (2019) Int J Nanomedicine 14, 5033–5050.
- Liskova J et al. Heat-treated carbon coatings on poly (L-lactide) foils for tissue engineering. (2019) Mater Sci Eng C Mater Biol Appl 100, 117-128.
- Jirka I et al. The photodynamic properties and the genotoxicity of heat-treated silicalite-1 films. (2019) Materials (Basel) 12(4), 567.
- Bacakova L et al. Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells - a review. (2018) Biotechnology Advances 36(4), 1111-1126.
- Bacakova L et al. Vascular smooth muscle cells (VSMCs) in blood vessel tissue engineering: the use of differentiated cells or stem cells as VSMC precursors. In: Muscle Cell and Tissue, Ed. Kunihiro Sakuma. IntechOpen, London, United Kingdom, chapter 14, pages 289-308 (2018). ISBN 978-953-51-6092-2.
- Matejka R et al. Cultivation chamber for optical-electrical monitoring of biological cultures *in-vitro* with optical-transparent diamond electrodes. Utility model, approved on 18. 05. 2017 under No. UV 30691.

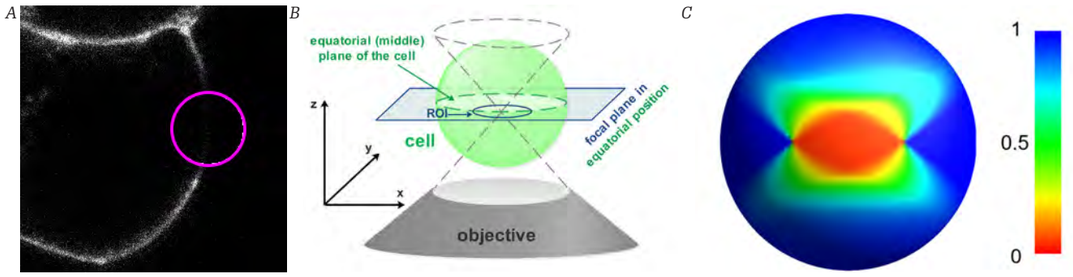
BIOMATHEMATICS

head RNDr. Jiří Janáček, Ph.D. 1 jiri.janacek@fgu.cas.cz
key researchers Jana Brejchová, Martin Čapek 12 Daniel Hadraba,
Petr Karen, Lucie Kubínová 2 Barbora Radochová 3 Lenka Roubalová 4
Petr Svoboda, Hana Ujčíková 6 František Vostárek 7 Miroslava Vošahlíková
PhD students Kristína Cechová, David Kala, Zuzana Kubínová 8
technicians Jitka Čočková 9 Pavla Chotěborská, Diana Siswartonová 10
Ivana Švandová, David Vondrášek 11

The Laboratory consists of two research groups. The **BIOIMAGING AND IMAGE ANALYSIS GROUP** conducts research into 3D micro-anatomical aspects of physiological phenomena at the mesoscopic, microscopic, and ultrastructural level. It is engaged in a range of collaborative projects across the campus and beyond. The research of the **BIOCHEMISTRY OF MEMBRANE RECEPTORS GROUP** is primarily focused on analysis of the cellular and molecular mechanisms of the desensitization of hormone response mediated by **G-PROTEIN-COUPLED RECEPTORS** (GPCRs), the transducers of signals into the cell interior. GPCRs play a key role in many physiological functions and are targets of the majority of therapeutic agents. Operating mainly at the *in situ* and *in vitro* levels, respectively, the two groups complement each other when studying phenomena confined to the cell membrane.

CURRENT PROJECTS

- The development of new approaches to the quantitative analysis of tubular structures in order to study the vascular bed in the developing heart and the conduction system in ventricles
- The effect of nanosecond electric pulses on microtubule morphology and dynamics
- The morphology of the Langerhans islets isolated for therapeutic transplantations
- The correlative biomechanics of biomedical materials and tissue
- The effect of lithium on Na^+/K^+-ATPase activity and functional consequences of oxidative stress; from animal model to bipolar patients
- The consequences of sustained morphine treatment and withdrawal on the rat brain: proteomic and functional studies
- The selection of diagnostic markers of the long-term effect of multifunctional peptide agonists and antagonists targeting μ-, δ- and κ-opioid receptors – the search for new possibilities for the treatment of chronic pain
- Alterations of δ-opioid receptor mobility and function by depleting the plasma membrane cholesterol content of live cells



The mobility of δ-opioid receptors was determined by the new method of FRAP analysis which may be applied for studies of other GPCRs. ***(A)*** *Microscopic image* ***(B)*** *Schematic representation of the microscope setup* ***(C)*** *Mathematical model of fluorophore concentration*

SELECTED OUTPUTS

- The volume of the islets of Langerhans can be estimated from single 2D images using regression-based methods, which often perform significantly better than the methods currently used in clinical practice (Dvorak et al. (2018) Image Anal Stereol 37, 191-204).
- Optical Projection Tomography reveals the inner structure of the peripheral nerve fascicles, opening up a new path for research into the microstructure of the inner contents of fascicular nerve groups and their spatial distribution within the nerve, including their interconnections (Prats-Galino et al. (2018) Clinical Anatomy 31, 424-431).
- The effect of a therapeutic concentration of lithium on living HEK293 cells results in an increase in Na^+/K^+-ATPase, decrease in plasma membrane hydration and changes in overall protein composition (Vosahlikova et al. (2017) BBA General Subjects 1861, 1099-1112).
- Characteristics of μ-, δ- and κ-opioid receptors in the forebrain cortex of rats addicted to morphine and in animals after morphine withdrawal (Ujcikova et al. (2017) PLoS ONE doi.org/10.1371/journal.pone.0186797).
- The induction of oxidative stress by the long-term treatment of live HEK293 cells with a therapeutic concentration of lithium is associated with down-regulation of the δ-opioid receptor amount and function (Vosahlikova et al. (2018) Biochem Pharmacol 154, 452-463).
- The mobility of δ-opioid receptor molecules in the plasma membrane of live cells decreases after cholesterol depletion (Janacek et al. (2019) BBA Biomembranes 1861, 1346-1354).

CELLULAR AND MOLECULAR NEUROENDOCRINOLGY

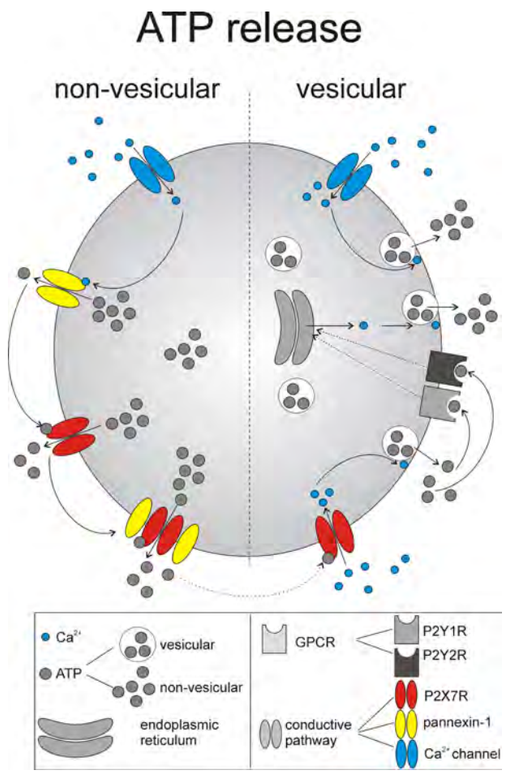
The Laboratory is the part of Laboratory of Pain Research from 2020.

head RNDr. Hana Zemková, CSc. 1 hana.zemkova@fgu.cas.cz
key researchers Anirban Bhattacharyya 2 Irena Svobodová 3
PhD students Milorad Ivetič 4 Marian Rupert 5 Sonja Sivčev 6
technicians Hana Janoušková 7 Irina Kalová 8

The laboratory is focused on the research of **ION CHANNELS** and **MEMBRANE RECEPTORS IN NEUROENDOCRINE CELLS**, with a special emphasis on the **PITUITARY** and **HYPOTHALAMUS**. We investigate interactions between plasma membrane electrical events and receptor-controlled pathways at the cellular and molecular level, determine the manner in which hormones and neurotransmitters utilize calcium and cyclic nucleotides as intracellular messengers, and characterize **ION CHANNELS** involved in **HORMONE SECRETION** and **SYNAPTIC TRANSMISSION**. We also address how the structural features of receptor channels relate to their functions. To achieve this, we investigate both native and recombinant channels that are involved in the activity of pituitary cells and hypothalamic neurons. Our current work is focused on **ATP-GATED P2X RECEPTORS**, mechanisms of **ATP RELEASE** in hypothalamus, and understanding the physiological meaning of the purinergic modulation of synaptic transmission in magnocellular **OXYTOCIN** and **VASOPRESSIN** neurons.

CURRENT PROJECTS

- The mechanism of ATP release and function of purinergic P2X receptors in hypothalamic supraoptic and suprachiasmatic nuclei
- The electrical excitability of anterior pituitary cells
- The relationship between the molecular structure and function of recombinant purinergic P2X receptor-channels



Schematic summary of identified mechanism underlying ATP release from hypothalamic cells. The initial non-vesicular ATP release (predominantly Ca^{2+}-independent) further stimulates P2X7 and P2Y receptors that evoke Ca^{2+}-dependent vesicular release.

SELECTED OUTPUTS

- Jelinkova et al.: Identification of P2X4 receptor transmembrane residues contributing to channel gating and interaction with ivermectin. (2008) Pflug Arch-Europ J Physiol 456, 939-950.
- Vavra et al: Facilitation of glutamate and GABA release by P2X receptor activation in supraoptic neurons from freshly isolated rat brain slices. (2011) Neuroscience 188, 1-12.
- Bhattacharya et al.: Potentiation of inhibitory synaptic transmission by extracellular ATP in rat suprachiasmatic nuclei. (2013) J Neurosci 33, 8035-8044.
- Zemkova et al.: Spontaneous and CRH-induced excitability and calcium signaling in mice corticotrophs involves sodium, calcium, and cation-conducting channels. (2016) Endocrinology 157, 1576-89.
- Svobodova et al.: Circadian ATP release in organotypic cultures of the rat suprachiasmatic nucleus is dependent on P2X7 and P2Y receptors. (2018) Front Pharmacol 9, article 192.
- Sivcev et al.: Synthetic testosterone derivatives modulate rat P2X2 and P2X4 receptor channel gating. (2019) J Neurochem 150, 28-43; doi: 10.1111/jnc.14718.

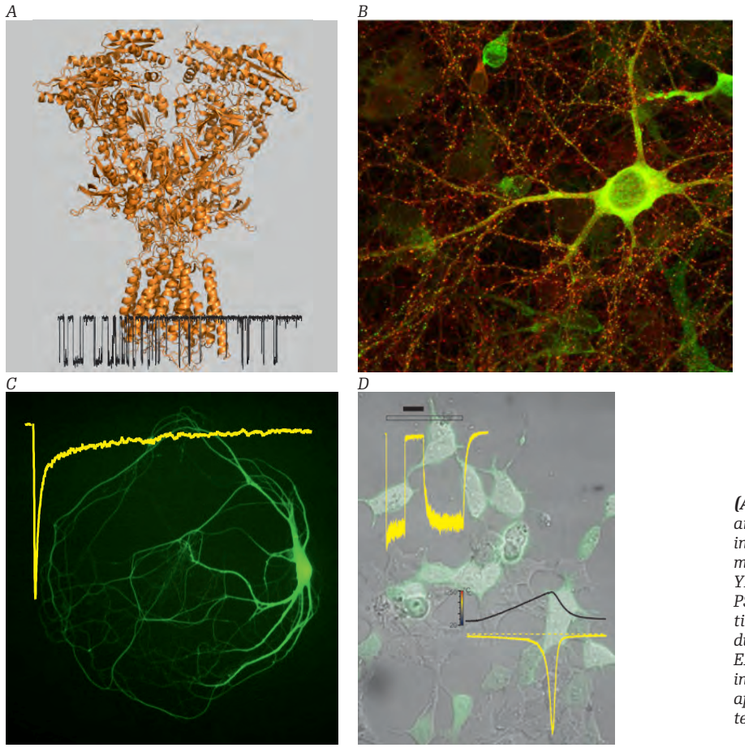
CELLULAR NEUROPHYSIOLOGY

head **Prof. MUDr. Ladislav Vyklický, DrSc.** 1 ladislav.vyklicky@fgu.cas.cz
key researchers Aleš Balík 2 Jiří Černý 3 Ivan Dittert, Miloslav Kořínek 4 Martin Horák 5 Jan Krůšek 6 Tereza Smejkalová 7 Viktorie Vlachová 8 Lenka Vyklická 9 Vojtěch Vyklický, František Vyskočil 10 Lucie Zímová 11 Barbora Krausová 12
PhD students Kristýna Barvíková 13 Pavla Hubálková 14 Margarita Kolecheva 15 Štěpán Kortus 16 Viktor Kuchtiak 17 Bohdan Kysilov 18 Marek Ladislav, Lucie Máčiková 19 Anna Misiachna 20 Viktor Synytsya 21 Kristýna Skřenková 22 Lenka Strnadová 23 Dragana Hajduković 24 technicians Miloslava Kuldová 25 Magda Kuntošová 26

We study the functional and pharmacological properties of ion channels. We use advanced electrophysiology methods, primarily the **PATCH-CLAMP TECHNIQUE**, combined with analytical techniques, **MOLE-CULAR BIOLOGY**, **BIOCHEMISTRY**, **IMMUNOHISTOCHEMISTRY**, microscopy, and **MICRO-FLUO-ROMETRIC METHODS**. We focus on ionotropic glutamate receptors, specifically the **NMDA RECEPTOR** subtype, which plays an essential role in normal physiology but under certain pathological conditions can participate in the development of serious **PSYCHIATRIC AND NEUROLOGICAL DISORDERS**. Through the detailed study of NMDA receptor structure, **PHARMACOLOGY**, and trafficking, we aim to identify potential treatments for diseases associated with the dysfunction of the glutamate system. We also investigate the molecular and biophysical properties and the physiological significance of a specific subclass of **TRP ION CHANNELS** that are involved in the detection of noxious thermal, mechanical, and chemical stimuli.

CURRENT PROJECTS

- A study of the molecular mechanisms of the positive and negative allosteric modulatory action of steroids at NMDA receptors and the influence of these compounds on synaptic transmission
- A study of the surface expression, function, and pharmacology of disease-associated mutations of the human NMDA receptor
- Investigation of the molecular basis of thermosensitive TRP channel regulation and the role of these channels in the mechanisms of acute and chronic pain



(A) *Model of NMDAR structure (gold) and NMDAR single-channel recording.* ***(B)*** *Confocal micrograph of a primary hippocampal neuron expressing YFP-GluN1 (yellow) immunostained for PSD95 (red).* ***(C)*** *GFP-expressing autaptic hippocampal neuron, inset shows a dual AMPAR/NMDAR-mediated evoked EPSC.* ***(D)*** *GFP-expressing HEK293 cells, insets show NMDAR response to agonist application (top) and TRPV1 response to temperature ramp (bottom).*

SELECTED OUTPUTS

- We have studied the effects of steroids on NMDARs and found that (1) the site of action for the steroids is at the membrane domain of the receptor; (2) some newly synthesized steroids (e.g. pregnanolone hemipimelate) have no effect on NMDARs activated during synaptic transmission but are potent inhibitors of tonically activated NMDARs; (3) the probability of opening of NMDA receptors is controlled by membrane cholesterol; and (4) steroids can rectify the consequences of disease-associated mutations of the human NMDA receptor. (Korinek et al. (2015) J Physiol 593, 2279-2293; Vyklicky et al. (2015) Sci Rep 5, 10935; Slavikova et al. (2016) J Med Chem 59, 4724-4739; Vyklicky et al. (2016) J Neurosci 36, 2161–2175; Petrovic et al. (2017) Nat Neurosci 20, 529-539; Vyklicky et al. (2018) Front Mol Neurosci 11, 110; Kapras et al. (2018) Org Lett 20, 946-949; Krausova et al. (2018) J Med Chem 61, 4505-4516; Ladislav et al. (2018) Front Mol Neurosci 11, 113; Cerny et al. (2019) Biomolecules 9(10), 546; Hrcka Krausova (2020) J Neurosci 40(31), 5922-5936).
- We have clarified the structural basis underlying the TRPA1-channelopathy-associated pain syndrome and discovered that evolutionarily highly conserved N-terminal structural motifs critically, and each in a different way, contribute to the conformational stability of this channel. We have functionally and structurally characterized two regulatory sites through which TRPA1 interacts with annular and regulatory lipids. Moreover, we have identified Thr264 in the TRPV3 channel to be a key ERK phosphorylation site mediating EGFR-induced sensitization signalling pathways involved in regulating skin homeostasis (Zima et al. (2015) Neuropharmacology 93, 294-307; Hynkova et al. (2016) Sci Rep 6, 28700; Vyklicka et al. (2017) J Biol Chem 292, 21083-21091; Zimova et al. (2018) Sci Signal 11(514), pii: eaan8621; Macikova et al. (2019) FEBS J 286(18), 3664-3683); Zimova et al. (2020) Front Phys 11,189).

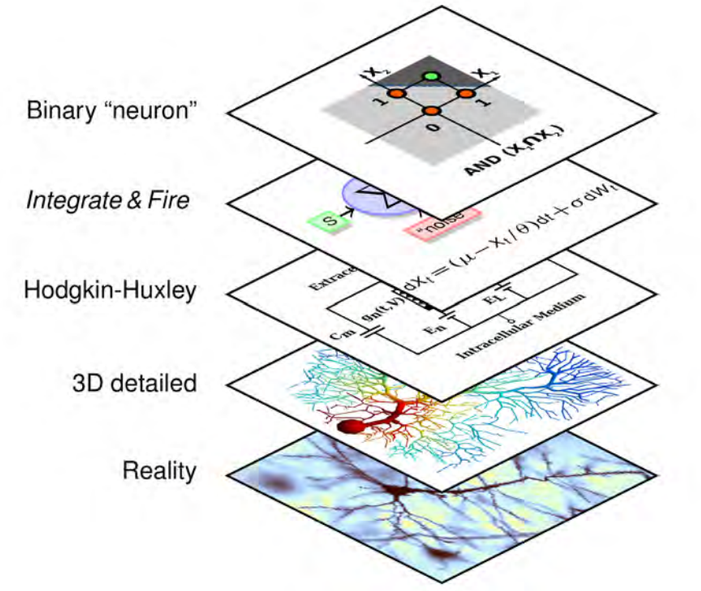
COMPUTATIONAL NEUROSCIENCE

head Mgr. Lubomír Košťál, Ph.D. 1 lubomir.kostal@fgu.cas.cz
key researchers Petr Lánský 2 Martin Zápotocký 3 Marie Leváková
PhD students Tomáš Bárta 4 Rimjhim Tomar 5

The Laboratory of Computational Neuroscience investigates the fundamental **MECHANISMS OF INFORMATION REPRESENTATION AND PROCESSING IN THE BRAIN**. **STOCHASTIC PROCESSES**, information theory, and statistical estimation theory methods are employed to analyse the **NEURONAL CODE**. Of particular interest is the **EFFICIENT CODING** hypothesis for **SENSORY NEURONS** and the role of **NOISE** and **ENERGETIC CONSTRAINTS** in the decoding process. The group proposes novel analytical and numerical modelling techniques to explore the properties and the function of **NEURAL ACTIVITY, CONTROL, AND DEVELOPMENT**. **BIOPHYSICS**, nonlinear dynamics, **CYBERNETICS**, and mathematical statistics methods provide the tools for both simulated and experimental data analysis. The group is also active in the organization of international conferences and workshops (biennal *Neural Coding* meetings, *OCNS* workshops).

CURRENT PROJECTS

- The analysis of stochastic neuronal models and estimation of key biophysical parameters under various stimulus encoding schemes
- The impact of different forms of noise together with metabolic energy consumption and decoding complexity on neuronal coding efficiency
- The biophysical modelling of neural connectivity and its dependence on the guided growth of axons during development
- Models and analysis of neural oscillations, both of physiological and pathophysiological origin



Models can range from detailed biophysical models, describing processes that take place in different parts of the neuron, through models neglecting the space structure of the neuron or the time course of action potentials, to binary neurons acting as logical units.

SELECTED OUTPUTS

- Levakova et al.: Moth olfactory receptor neurons adjust their encoding efficiency to temporal statistics of pheromone fluctuations. (2018) PLoS Comput Biol 14, e1006586.
- Smit et al.: Axon tension regulates fasciculation/defasciculation through the control of axon shaft zippering. (2017) eLife 6, e19907.
- Rajdl et al.: Entropy factor for randomness quantification in neuronal data. (2017) Neural Networks 95, 57-65.
- Kostal et al.: Performance breakdown in optimal stimulus decoding. (2015) J Neural Eng 12, 036012.
- Kostal et al.: Measures of statistical dispersion based on Shannon and Fisher information concepts. (2013) Inform Sci 235, 214-223.
- Bartussek et al.: Limit-cycle-based control of the myogenic wingbeat rhythm in the fruit fly Drosophila. (2013) J Roy Soc Interface 10, 20121013.

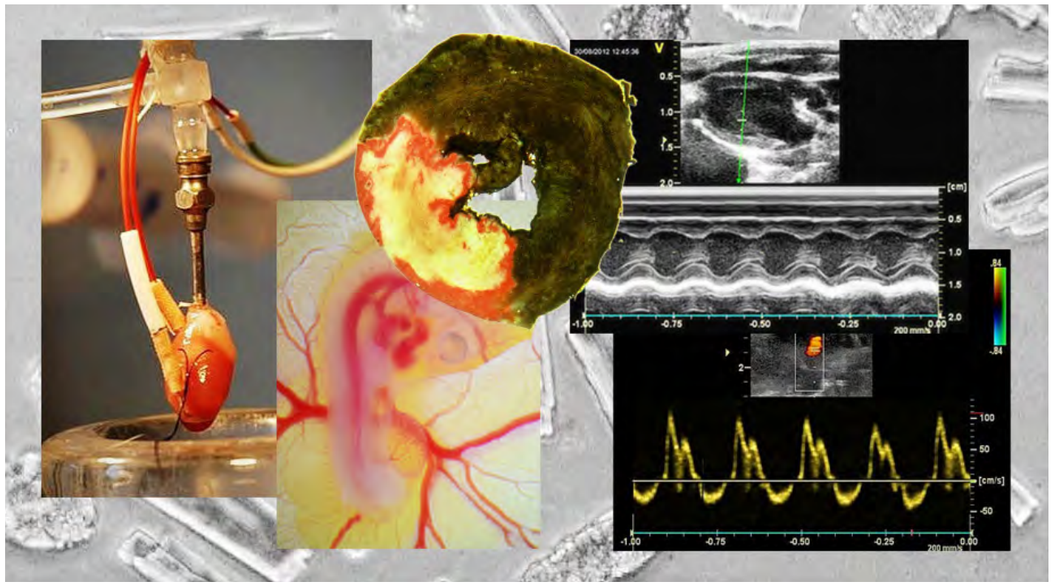
DEVELOPMENTAL CARDIOLOGY

head RNDr. Jan Neckář, Ph.D. 1 jan.neckar@fgu.cas.cz
key researchers Petra Alánová, Martina Gregorovičová 2 Markéta Hlaváčková, Kristýna Holzerová 3 Hana Kolesová, František Kolář 4 Olga Nováková 5 Veronika Olejníčková 6 Bohuslav Ošťádal, Ivana Ošťádalová, David Sedmera 7
PhD students Daniel Benák 8 Michaela Cyprová 9 Jaroslav Hrdlička, Lenka Sedláková 10 Dmytro Semenovykh, Šárka Škutová 11 technicians Miloslava Marková 12 František Papoušek 13 Milana Pešková 14 Jarmila Svatůňková 15

ISCHEMIC HEART DISEASE is the main cause of mortality worldwide. We study the cardiac tolerance to injury caused by acute **OXYGEN DEPRIVATION** from the molecular level to the whole organism using animal models. Our research is focused mainly on the study of mechanisms that underlie (1) high cardiac tolerance to injury during **EARLY ONTOGENY**, (2) increased cardiac tolerance induced by adaptation to **CHRONIC HYPOXIA** and regular **EXERCISE** training, and (3) altered cardiac tolerance associated with various pathological states. **CONGENITAL HEART DISEASE** affects between 0.5-1 % of all newborns. We study the mechanisms of the pathogenesis of congenital heart malformations to better understand their causes and therefore enable their primary prevention. Using chick and mouse embryos as models, we focus on the physiology of the developing heart and the formation of its **VASCULATURE** and **CONDUCTION SYSTEM**, as proper heart function is crucial for embryonic/fetal survival and normal development. We also use poikilotherm models to better understand the evolution of cardiac regenerative potential.

CURRENT PROJECTS

- The molecular mechanisms underlying the cardioprotective effects of chronic hypoxia and regular exercise on acute ischemia/reperfusion injury and postinfarction heart failure
- The influence of various types of systemic hypertension and dyslipidemia on cardiac ischemic tolerance and postinfarction remodelling
- Developmental aspects of cardiac ischemic tolerance
- The role of epigenetic mechanisms in the control of heart function and metabolism
- The phylogenesis of the cardiac conduction system in vertebrates
- Regeneration capacity of the developing and poikilotherm heart



Main experimental models and techniques used in the Laboratory of the Developmental Cardiology to study protective mechanisms against cardiac ischemia/reperfusion injury and heart failure, and the development of cardiac conduction system.

SELECTED OUTPUTS

- Inflammatory cytokine TNF-α plays a key role in the induction of the ischemia-resistant cardiac phenotype of chronically hypoxic rats via its receptor TNFR2 and the NF-κB-dependent activation of protective redox signalling with increased antioxidant defense (Chytilová et al. (2015) Acta Physiol 214, 97-108).
- Selective replacement of mitochondrial DNA increases the cardioprotective effect of chronic continuous hypoxia in spontaneously hypertensive rats (Neckář et al. (2017) Clin Sci 131, 865-881).
- Myocardial ischemic tolerance in rats subjected to endurance exercise training during adaptation to chronic hypoxia (Alánová et al. (2017) J Appl Physiol 122, 1452-1461).
- Trabecular architecture determines impulse propagation through the early embryonic mouse heart (Olejníčková et al. (2019) Front Physiol 9, 1876).
- Epoxyeicosatrienoic acid analog EET-B attenuates post-myocardial infarction remodelling in spontaneously hypertensive rats (Neckář et al. (2019) Clin Sci 133, 936-951).
- HIF-1α is required for the development of the sympathetic nervous system (Bohuslavová et al. (2019) Proc Natl Acad Sci USA 116, 13414-13423).

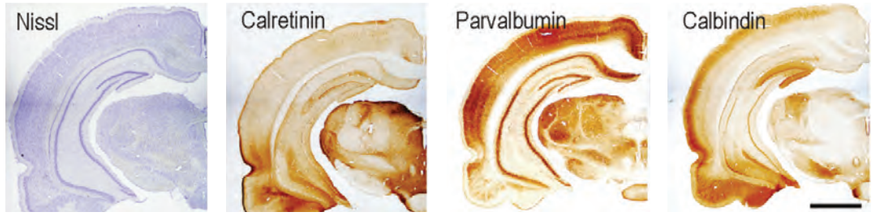
DEVELOPMENTAL EPILEPTOLOGY

head **Doc. PharmDr. Hana Kubová, DrSc.** 1 hana.kubova@fgu.cas.cz
key researchers Jaroslava Folbergrová 2 Přemysl Jiruška 3 Pavel Mareš 4
Anna Mikulecká 5 Jakub Otáhal 6 Antonín Pošusta, Šárka Růžičková 7
Grygoriy Tsenov PhD students Zina Ben Salem, Jan Chvojka 8 Šárka Danačíková 9
David Kala, Jan Kudláček 10 Jan Svoboda 11 technicians Blanka Čejková 12
Eva Lažková, Irinka Nešev 13 Ivana Rabasová 14

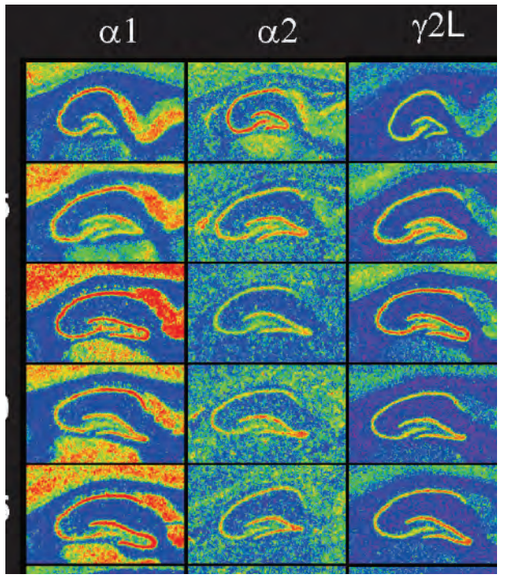
The research at our Laboratory focuses on the pathophysiology of **EPILEPSY** and epileptic seizures in adulthood and particularly in **THE DEVELOPING BRAIN**. In all age groups, we study the mechanisms of **ICTOGENESIS, EPILEPTOGENESIS**, and **EPILEPSY-RELATED COMORBIDITIES**. In our research, we utilize modern electrophysiological, imaging, biochemical, pharmacological, and advanced mathematical techniques. To elucidate the cellular and network mechanisms involved in epilepsy and to increase the translational potential of new observations, we make extensive use of various models of provoked seizures, chronic models of acquired epilepsy, and also genetic models. In close collaboration with clinical epilepsy centers, we work to develop new diagnostic techniques for epilepsy. Beyond basic research, we work to a limited extent with the pharmaceutical industry to search for age-specific anti-seizure drugs and to ameliorate the potential adverse side effects of these drugs.

CURRENT PROJECTS

- Mechanisms of ictogenesis, epileptogenesis and epilepsy-related comorbidities in the mature and immature brain
- The development of new diagnostic techniques for epilepsy
- The long-term impact of early pharmacological intervention in neurotransmitter systems on brain development
- The role of oxidative stress and metabolic alterations in the pathogenesis of epilepsy and seizures during the development of the brain
- Developmental pharmacology of classical and potential anti-seizure drugs



Representative low magnification photomicrographs illustrating the patterns of Nissl, calretinin, parvalbumin and calbindin staining in cerebral hemisphere of the rat brain.



Distribution of α1, α2, and γ2 subunits of GABAA receptor in the hippocampus at different postnatal (P) days in the rat.

Bar holding test in twelve (P12) and twenty-five (P25) days old rats.

SELECTED OUTPUTS

- The first description of the age-specific, flexion seizures induced by a systemic administration of NMDA in immature rats. The model was further validated as a model of human infantile spasms (Mareš et al. (1992) Dev Brain Res 65, 185-189).
- Status epilepticus induces neuronal damage in the mediodorsal nucleus of the thalamus as early as P12 in rats (Kubová et al. (2001) J Neurosci 21, 3593-3599).
- Transition to seizures, which has been considered to be random, is instead a complex process that is characterized by the slow and progressive loss of neuronal network resilience (Chang et al. (2018) Nat Neurosci 21, 1742-1752).
- Epileptogenesis in the immature brain is associated with oxidative stress and mitochondrial dysfunction. Resveratrol provides a marked protective effect (Folbergrová et al. (2018) Mol Neurobiol 55, 7512-7522).
- Postictal potentiation in the immature brain is replaced by postictal refractoriness during development (Mareš and Kubová (2015) Epilepsia 56, e10-14).

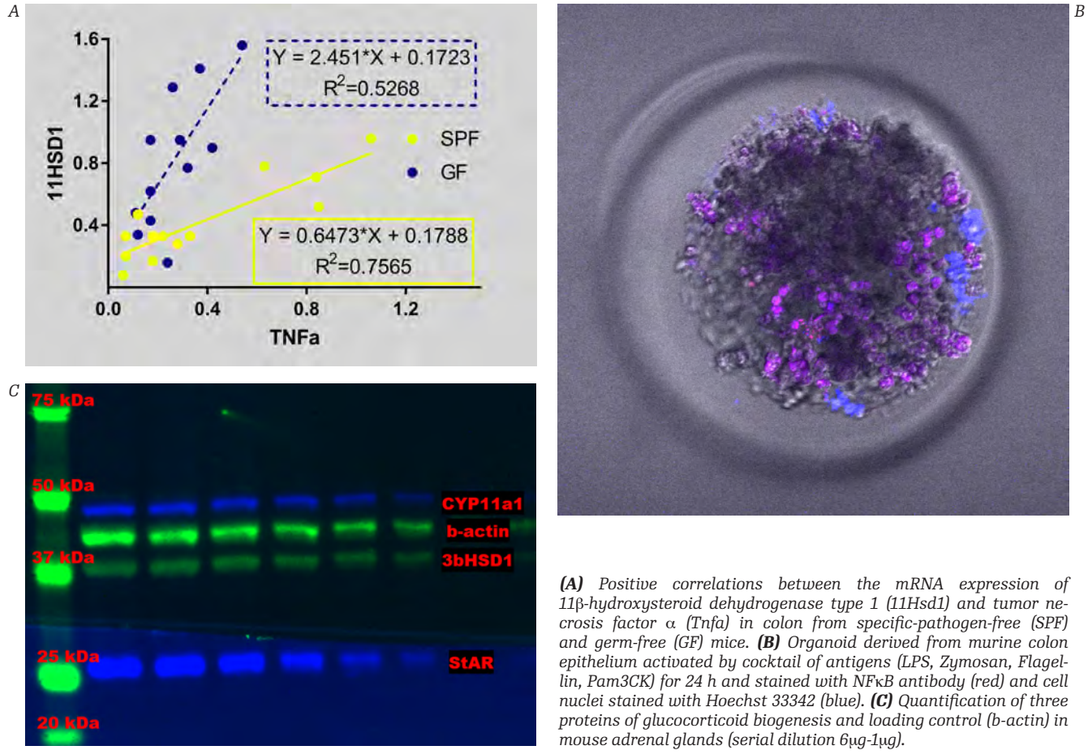
EPITHELIAL PHYSIOLOGY

head Prof. RNDr. Jiří Pácha, DrSc. 1 jiri.pacha@fgu.cas.cz
key researchers Peter Ergang 2 Petra Klusoňová 3 Karla Vagnerová 4
PhD students Kateřina Balounová 5 Martin Vodička technicians Ivana Muricová 6

This Laboratory´s research is focused on the **BIOLOGY, PHYSIOLOGY, AND PATHOPHYSIOLOGY OF THE INTESTINE** and the cellular and molecular **MECHANISMS OF CORTICOSTEROID REGULATION**. To achieve these aims, our group utilizes a wide range of experimental approaches including biochemical analysis (i.e. the determination of enzyme activities), gene expression analysis, proteomic techniques, microanatomy (laser microdissection), and electrophysiological techniques (voltage clamp). To elucidate the mechanisms operating under normal and pathological conditions, we use germ-free animals and animal models of psychosocial and inflammatory stress, colitis and allergy as well as different intestinal and adrenocortical cell lines. Our research focuses on the elucidation of (1) the role of local synthesis and metabolism of glucocorticoids in gut physiology and pathophysiology, (2) the effect of stress on neuroendocrine regulatory pathways, and (3) the regulation of intestinal transport in a healthy and diseased intestine.

CURRENT PROJECTS

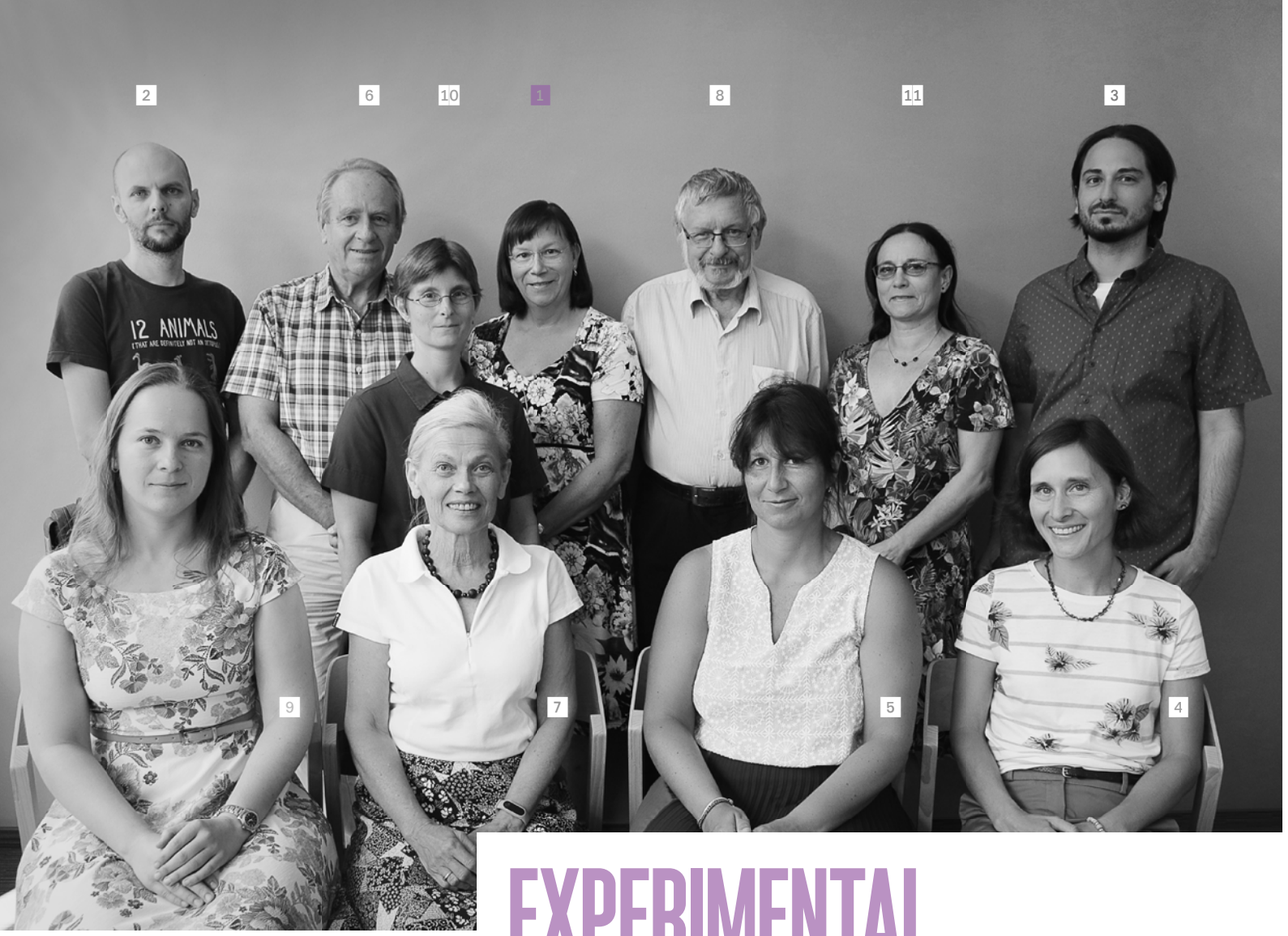
- The role of microbiota in the extraadrenal synthesis and metabolism of glucocorticoids in gut physiology
- The effect of gut microbiota on neuroendocrine regulatory pathways during stress
- The role of bacteria and butyrate in intestinal dysbiosis



(A) *Positive correlations between the mRNA expression of 11β-hydroxysteroid dehydrogenase type 1 (11Hsd1) and tumor necrosis factor α (Tnfa) in colon from specific-pathogen-free (SPF) and germ-free (GF) mice.* ***(B)*** *Organoid derived from murine colon epithelium activated by cocktail of antigens (LPS, Zymosan, Flagellin, Pam3CK) for 24 h and stained with NFκB antibody (red) and cell nuclei stained with Hoechst 33342 (blue).* ***(C)*** *Quantification of three proteins of glucocorticoid biogenesis and loading control (b-actin) in mouse adrenal glands (serial dilution 6μg-1μg).*

SELECTED OUTPUTS

- Ergang et al.: Differential impact of stress on hypothalamic-pituitary-adrenal axis: gene expression changes in Lewis and Fisher rats. (2015) Psychoneuroendocrinology 53, 49-59.
- Ergang et al.: Social defeat stimulates local glucocorticoid regeneration in lymphoid organs. (2018) Endocr Connect 7, 1389-1396.
- Vodicka et al. Microbiota affects the expression of genes involved in HPA axis regulation and local metabolism of glucocorticoids in chronic psychosocial stress. (2018) Brain Behav Immun 73, 615-624.
- Ergang et al. Inflammation regulates 11β-hydroxysteroid dehydrogenase type 1 differentially in specific compartments of the gut mucosal immune system. (2017) Steroids 126, 66-73.
- Sotak et al. Peripheral circadian clocks are diversely affected by adrenalectomy. (2016) Chronobiol Int 33, 520-529.
- Vagnerova et al. Interactions between gut microbiota and acute restraint stress in peripheral structures of the hypothalamic-pituitary-adrenal axis and the intestine of male mice. (2019) Front Immunol 10, 2655.



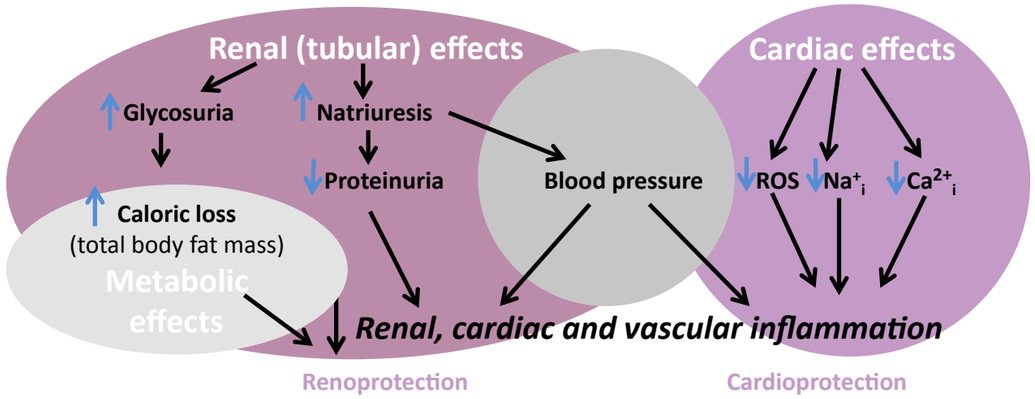
EXPERIMENTAL HYPERTENSION

head RNDr. Ivana Vaněčková, DSc. 1 ivana.vaneckova@fgu.cas.cz
key researchers Michal Behuliak 2 Michal Bencze 3 Milada Dobiášová, Silvie Hojná 4 Michaela Kadlecová 5 Jaroslav Kuneš 6 Hana Rauchová 7 Lenka Řezáčová, Josef Zicha 8 PhD students Anna Vavřínová 9
technicians Alena Charvátová 10 Zdeňka Kopecká 11

Our Laboratory studies the mechanisms of **BLOOD PRESSURE** regulation and **END-ORGAN DAMAGE** in **RATS** with different types of **EXPERIMENTAL HYPERTENSION**, with special attention given to the **ONTOGENETIC FACTORS** involved in these processes. Our research is focused on studying (1) the central mechanisms participating in **BLOOD PRESSURE REGULATION** – with special attention to the role of central angiotensin II, nitric oxide and reactive oxygen species, (2) the mechanisms of the beneficial effects of **EMPAGLIFLOZINS** on cardiorenal damage (in cooperation with the Institute of Experimental Medicine of the CAS), (3) changes in **SYMPATHETIC AND PARASYMPATHETIC TONE** in the baroreflex control, (4) **STRESS-INDUCED** cardiovascular and neuroendocrine responses, (5) the role of oxidative stress in these processes, and (6) metabolic and cardiovascular effects of new analogs of **NEUROPEPTIDES** regulating **FOOD INTAKE** in rats (in cooperation with the Institute of Organic Chemistry and Biochemistry of the CAS).

CURRENT PROJECTS

- Central and peripheral modulation of vascular tone and sodium excretion: the role of the brain and kidney in the pathophysiology of hypertension
- Complex analysis of protective actions of empagliflozin on metabolic parameters and cardiorenal damage in experimental non-diabetic hypertension
- Role of brain angiotensin II, nitric oxide, and reactive oxygen species in blood pressure control: their importance in contrasting forms of hypertension
- The possible role of stable analogs of prolactin-releasing peptide in the treatment of obesity and hypertension: studies in lean and obese rodents



New antidiabetics – gliflozins (inhibitors of sodium-glucose transporter 2) show many beneficial actions beyond their hypoglycemic effects. The underlying mechanisms of these additional cardiorenal protective effects are still not well understood, especially in hypertensive non-diabetic disease. Thus, we are interested in the mechanisms of beneficial effects empagliflozin on end-organ damage and metabolic parameters in different forms of experimental hypertension.

SELECTED OUTPUTS

- Behuliak M, Bencze M, Polgarova K, Kunes J, Vaneckova I, Zicha J. Hemodynamic response to gabapentin in conscious spontaneously hypertensive rats. (2018) Hypertension 72(3), 676-685.
- Bencze M, Behuliak M, Vavrinova A, Zicha J. Altered contractile responses of arteries from spontaneously hypertensive rat: The role of endogenous mediators and membrane depolarization. (2016) Life Sci 166, 46-53.
- Kunes J, Prazienkova V, Popelova A, Mikulaskova B, Zemenova J, Maletinska L. Prolactin-releasing peptide: a new tool for obesity treatment. (2016) J Endocrinol 230(2), R51-8.
- Rezacova L, Hojna S, Kopkan L, Rauchova H, Kadlecova M, Zicha J, Vaneckova I. Role of angiotensin II in chronic blood pressure control of heterozygous Ren-2 transgenic rats: Peripheral vasoconstriction versus central sympathoexcitation. (2019) Biomed Pharmacother 116, 108996.
- Vaneckova I, Hojna S, Vernerova Z, Kadlecova M, Rauchova H, Kompanowska-Jezierska E, Vanourkova Z, Cervenka L, Zicha J: Renoprotection provided by additional diuretic treatment in partially nephrectomized Ren-2 transgenic rats subjected to the combined RAS and ETA blockade. (2019) Front Physiol 18(10), 1145.
- Vavrinova A, Behuliak M, Bencze M, Vaneckova I, Zicha J. Which sympathoadrenal abnormalities of adult spontaneously hypertensive rats can be traced to a prehypertensive stage? (2019) Hypertens Res 42(7), 949-959.

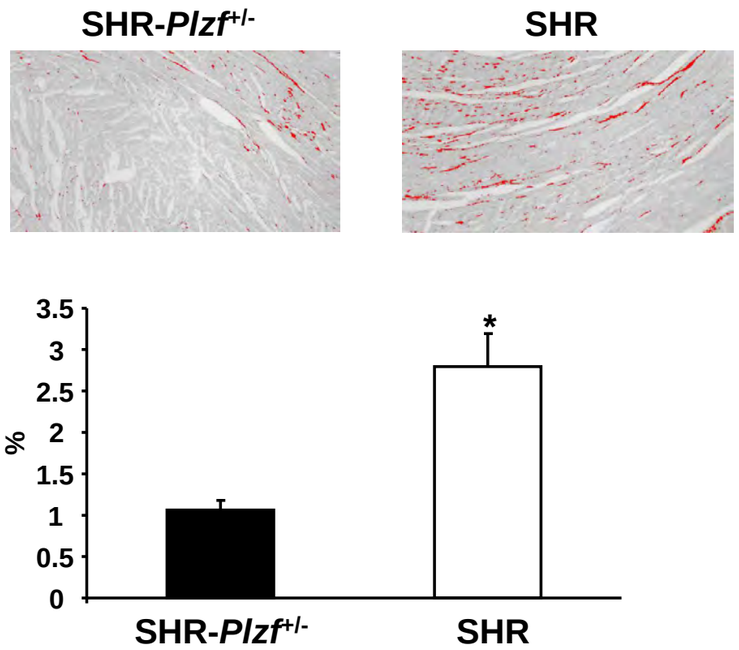
GENETICS OF MODEL DISEASES

head Ing. Michal Pravenec, DrSc. 1 michal.pravenec@fgu.cas.cz
key researchers Jan Šilhavý 2 Miroslava Šimáková 3 Petr Mlejnek 4
František Liška 5 technicians Alena Musilová 6

METABOLIC SYNDROME is a cluster of several risk factors for type 2 diabetes and cardiovascular disease, including obesity, hypertension, insulin resistance, and dyslipidemia. Genome-wide association studies in humans identified only a minor proportion of the total heritability of such complex traits so far. Studies in **ANIMAL MODELS OF HUMAN COMPLEX DISEASES** can provide a useful alternative. Experiments with rat models can control for both genetic background and environmental effects as well as enable the **GENETIC MANIPULATION** of experimental animals. Systems genetics analyses use intermediate molecular phenotypes, such as transcript, protein, or metabolite abundance, to bridge DNA variation with complex traits. Although it is unrealistic to expect the individual predisposing genes themselves to be conserved between rats and humans, it is likely that the networks and pathways of genes leading to disease susceptibility will be conserved across species.

CURRENT PROJECTS

- The identification of genes and pathways that regulate hemodynamic, cardiac, and metabolic traits in animal models
- The analysis of molecular-based biochemical and hemodynamic mechanisms of salt-dependent hypertension



Identification of Plzf (Promyelocytic leukemia zinc finger) gene as a genetic determinant that predisposes spontaneously hypertensive rats (SHR) to cardiac fibrosis. Interstitial fibrosis is clearly discernible in a section stained with Sirius Red in SHR and much less pronounced in SHR-Plzf+/– rats with targeted Plzf gene.

SELECTED OUTPUTS

- The development of a model system for genetic analyses of cardiovascular and metabolic traits, the BXH/HXB recombinant inbred (RI) strains derived from crosses of spontaneously hypertensive rats (SHR) with Brown Norway (BN) rats (www.genenetwork.org).
- The identification of the first quantitative trait loci (QTLs) at the molecular level in the SHR, including mutated *Cd36, Ogn, Endog, Ebi2, Wars2, Folr1, Gstm1, Srebf1, Wwp2,* and other genes as determinants of metabolic, hemodynamic or cardiac traits using systems genetics analyses in RI strains and *in vivo* functional studies.
- The proposal of a new theory of molecular-based hemodynamic mechanisms of salt-dependent hypertension.
- Evidence that small amounts of inorganic nitrate or beetroot provide substantial protection from salt-induced increases in blood pressure.

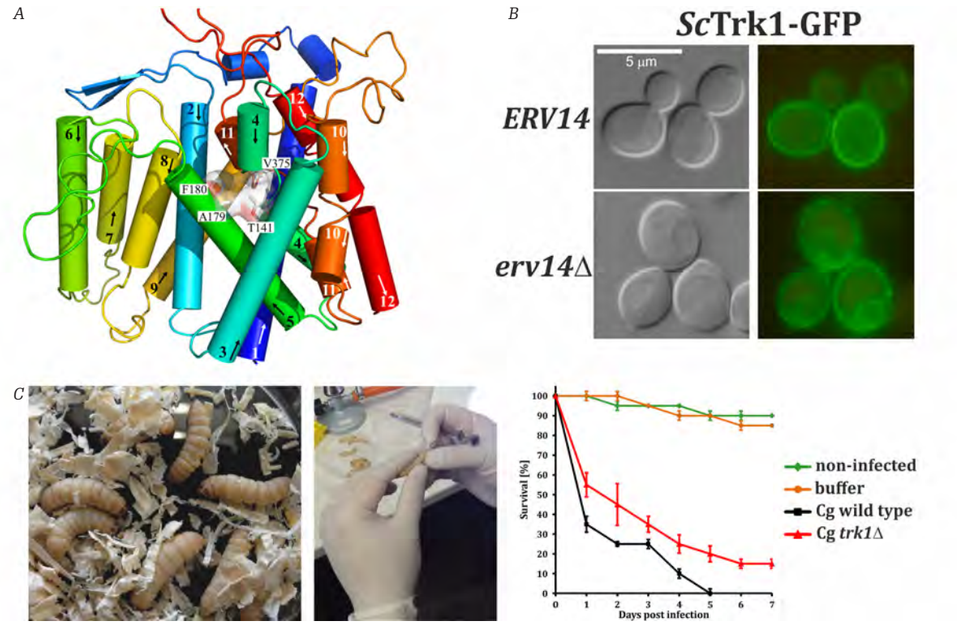
MEMBRANE TRANSPORT

head **RNDr. Hana Sychrová, DrSc.** 1 hana.sychrova@fgu.cas.cz
key researchers Michala Dušková 2 Marie Kodedová, Klára Papoušková 3
Diego Vélazquez Sánchez, Olga Zimmermannová 4 PhD students Jakub Masaryk 5
technicians Pavla Herynková 6 students Lenka Lasoňová

We study the proteins that transport compounds and signals across cell membranes. These proteins, called **TRANSPORTERS**, ensure the uptake of nutrients into cells, the efflux of waste compounds from cells, and communication with the environment. We are interested not only in the molecular characterization of transporters in terms of their **STRUCTURE/FUNCTION, SUBSTRATE SPECIFICITY, AND TRANSPORT MECHANISM**, but also in their biogenesis and degradation, posttranslational regulation, and in their role in **EUKARYOTIC CELL PHYSIOLOGY**. We specialize in transporters related to **INTRACELLULAR pH AND POTASSIUM HOMEOSTASIS**, or involved in the **OSMOTOLERANCE** and **SALT TOLERANCE** of lower eukaryotes, as well as in **TRANSPORTERS FROM HIGHER EUKARYOTES RELATED EITHER TO HUMAN DISEASES** or to the effective production of crops.

CURRENT PROJECTS

- Molecular characterization of cation transporters – relationship between their protein structure, substrate specificity and affinity, transport capacity, and biogenesis
- Characterization of non-transporting proteins involved in the maintenance of cation and pH homeostasis via their interaction with transporters
- Yeast as a tool to study transport processes in animal and plant cells
- Transporters in pathogenic yeasts as potential antifungal drug targets
- Specific transporters of non-conventional yeast species and their application in biotechnology



Membrane transporters *– from structure to function* ***(A)*** *3D model of a yeast plasma membrane Na^+/H^+ antiporter.* ***(B)*** *The targeting of the Trk1 K^+ importer to the plasma membrane depends on the Erv14 cargo receptor. Nomarski (left) and fluorescence (right) micrograph of Saccharomyces cerevisiae cells with or without the ERV14 gene expressing GFP-tagged Trk1.* ***(C)*** *Lack of the Trk1 K^+ importer renders pathogenic Candida glabrata cells less virulent for Galleria mellonella larvae (left). Larvae are injected with wild-type or Trk-less yeast cultures (middle) and larvae survival over time is monitored (right).*

SELECTED OUTPUTS

- A 3D model was created of a yeast Na^+/H^+ antiporter with experimentally verified residues important for cation recognition and activity regulation (e.g. 14-3-3 binding) (Kinclova-Zimmermannova et al. (2015) J Mol Biol 427, 1691-1694; Smidova et al. (2019) BBA 1866(12), 118534).
- Several transporters have been found to be interaction partners of the Erv14 cargo receptor in COPII vesicles (Rosas- Santiago et al. (2016) BBA – Biomembr 1858, 67–74; Rosas-Santiago et al. (2017) BBA – Mol Cell Res 1864, 1809-1818; Zimmermannova et al. (2019) BBA – Mol Cell Res 1866, 1376–1388; Papouskova et al. (2020) Mol Microbiol, in press).
- Glycerol transporters of non-conventional yeasts were characterized and their role in the osmotolerance, the regulation of intracellular pH and anhydrobiosis survival were described (Duskova et al. (2015) Mol Microbiol 97, 541-559; Duskova et al. (2015) FEMS Microbiol Lett 362, fnu041; Zemancikova et al. (2018) FEMS Microbiol Lett 365, fny020; Dibalova-Čulakova et al. (2018) Int J Food Microbiol 268, 27-34).
- Candida K^+ transporters were described, together with their role in virulence and pathogenicity (e.g. Llopis-Torregrosa et al. (2016) PLoS ONE 11, e0153374; Elicharova et al. (2016) FEMS Yeast Res 16, fow039; Elicharova et al. (2019) Yeast 36(7), 439-448; Llopis-Torregrosa et al. (2019) Sci Rep 9, 7529), and with characterization of new potential antifungal drugs (Kodedova et al. (2019) Cell Microbiol 21(12), e13093; Kodedova et al. (2020) Frontiers in Microbiol, in press).

METABOLISM OF BIOACTIVE LIPIDS

head **RNDr. Ondřej Kuda, Ph.D.** 1 ondrej.kuda@fgu.cas.cz
key researchers Kristyna Brejchová 2 Magno A. Lopes 3
PhD students Veronika Paluchová 4 Marina Oseeva 5

The original **METABOLOMICS** laboratory became an independent Laboratory in 2019 within the Laboratory of Adipose Tissue Biology when Dr. Kuda was awarded the Lumina Quaeruntur 2018 praemium by the Academy Council of the Czech Academy of Sciences to support outstanding promising researchers in setting up new scientific teams. The Laboratory focuses on the analysis of **LIPID MEDIATORS** (eicosanoids, docosanoids, endocannabinoids), in particular for identifying the source of the production of various mediators and their effect on metabolism and immune cells (i.e. adipocytes vs. macrophages). Currently, the Laboratory is exploring new **ANTI-DIABETIC LIPIDS**, fatty acid esters of hydroxy fatty acids, and lipid-related metabolic **PATHWAYS** using **STABLE ISOTOPES**, metabolomics, and **LIPIDOMICS**. We combine biochemistry, analytical chemistry, and organic chemistry with animal physiology, molecular biology, and informatics. The Laboratory has a strong collaboration with the Laboratory of Adipose Tissue Biology and with the Laboratory of Metabolomics.

CURRENT PROJECTS

- The metabolism of branched fatty acid esters of hydroxy fatty acids (FAHFA), eicosanoids, docosanoids, and endocannabinoids
- The role of antioxidant defence in the synthesis of antidiabetic lipokines
- Anti-inflammatory effects of novel omega-3 FAHFA in obesity
- The role of epicardial fat, subclinical inflammation, and novel lipid signalling molecules in the onset and development of heart failure
- Metabolic flux analysis, dynamic metabolomics, and lipidomics

(A) *Cell culture work.* ***(B)*** *Fixation of cells and staining of lipid droplets.* ***(C)*** *Solid phase extraction of lipid mediators.*

SELECTED OUTPUTS

- Brejchova K, Balas L, Paluchova V, Brezinova M, Durand T, Kuda O. Understanding FAHFAs: From structure to metabolic regulation. (2020) Prog Lipid Res 79, 101053.
- Paluchova V, Vik A, Cajka T, Brezinova M, Brejchova K, Bugajev V et al. Triacylglycerol-rich oils of marine origin are optimal nutrients for induction of polyunsaturated docosahexaenoic acid ester of hydroxy linoleic acid (13-DHAHLA) with anti-inflammatory properties in mice. (2020) Mol Nutr Food Res 64(11), e1901238.
- Paluchova V, Oseeva M, Brezinova M, Cajka T, Bardova K, Adamcova K et al. Lipokine 5-PAHSA is regulated by adipose triglyceride lipase and primes adipocytes for *de novo* lipogenesis in mice. (2020) Diabetes 69(3), 300–312.
- Brezinova M, Cajka T, Oseeva M, Stepan M, Dadova K, Rossmeislova L et al. Exercise training induces insulin-sensitizing PAHSAs in adipose tissue of elderly women. (2020) BBA 1865(2), 158576.
- Oseeva M, Paluchova V, Zacek P, Janovska P, Mracek T, Rossmeisl M et al. Omega-3 index in the Czech Republic: No difference between urban and rural populations. (2019) Chem Phys Lipids 220, 23–27.

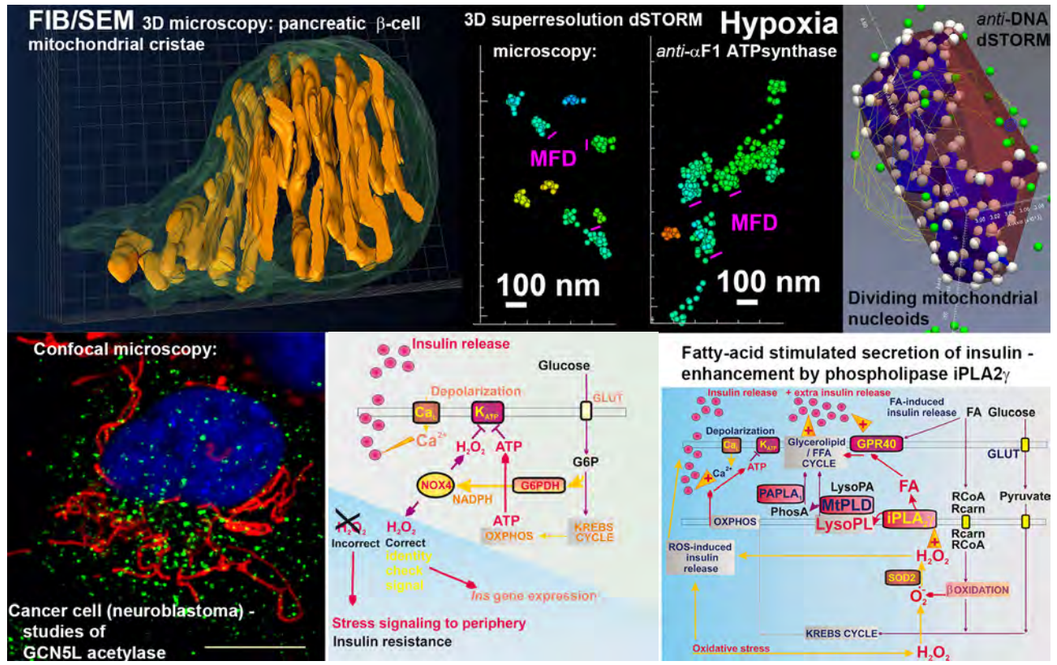
MITOCHONDRIAL PHYSIOLOGY

head RNDr. Petr Ježek, DrSc. 1 petr.jezek@fgu.cas.cz
key researchers Andrea Dlasková 2 Hana Engstová 3
Blanka Holendová 4 Martin Jabůrek 5 Jan Ježek, Alberto Andrés Leguina Ruzzi,
Lydie Plecitá 6 Katarína Smolková 7 Jitka Špačková 8 Jan Tauber 9
PhD students Vojtěch Pavluch, Anežka Kahancová 10 Pavla Průchová,
Klára Gotvaldová technicians Jitka Smiková, Ludmila Šimečková,
Jana Vaicová 11 students Štěpánka Tučková 12 Alexandra Urbančoková 13

MITOCHONDRIA, being the main source of cellular energy, ATP, and an essential metabolic hub and source of redox signalling in physiological and pathophysiological processes, are studied in cell and GMO mice models, likewise the **PRODUCTION OF REACTIVE OXYGEN** species that essentially initiate redox signals, e.g. in **HYPOXIC ADAPTATION** or **INSULIN RELEASE STIMULATION**, but in excess negatively impact cell function. Prolonged **OXIDATIVE STRESS** leads to cell death, but chronic moderate oxidative stress accompanies **PATHOPHYSIOLOGICAL DISORDERS** including neurodegenerations, type 2 diabetes, and pulmonary hypertension. Mitochondria possess their own DNA (mtDNA) organized with accessory proteins within nucleoids, the biology of which is studied by 3D superresolution microscopy. “Nanoscopy” is being developed to study mitochondrial **CRISTAE** morphology in relation to their functions. Finally, **MITOCHONDRIAL SIGNALLING** in cancer cells and **CANCER-SPECIFIC METABOLISM** are studied as being essential for future **ANTICANCER DRUG DEVELOPMENT**.

CURRENT PROJECTS

- Reactive oxygen species, redox regulations, redox signalling, and endogenous antioxidant mechanisms
- Nucleoids of mitochondrial DNA in relation to diabetes, nucleoid division, and ultrastructure by 3D super-resolution microscopy
- Novel cancer-related metabolites and mitochondrial metabolism, oxidative stress, or hypoxia
- Mechanisms of insulin release in pancreatic beta-cells
- Cristae morphology in relation to ATP-synthase oligomers and metabolic modes, including studies by FIB/SEM and 3D super-resolution fluorescence microscopy



FIB/SEM tomography of mitochondrial cristae (top left), 3D-superresolution microscopy of cristae (top middle), and mitochondrial DNA (top right), high resolution of cancer cell (bottom left and middle); discovered mechanism of insulin secretion stimulated fatty acids (bottom right).

SELECTED OUTPUTS

- To match physiological postprandial glucose concentrations to the sensitivity range of the glucose sensor in pancreatic β-cells, numerous factors delicately tune glucose-concentration dependence for the insulin release mechanism. We identified one of them, demonstrating that the ATP-synthase inhibitory factor IF1 slightly inhibits the synthesis of ATP *in vivo*, thus setting the range for the elevation of phosphorylating respiration and insulin release above 3 mM glucose, with half-activation at ~7 mM and saturation above 11 mM glucose. When this was largely cancelled by IF1 silencing, the elevation of respiration and OXPHOS occurred at a very low glucose concentration, approaching zero with a half-activation range of 0–2 mM glucose in INS-1E cells (Kahancová et al. Regulation of glucose-stimulated insulin secretion by ATPase Inhibitory Factor 1 (IF1). (2018) FEBS Lett 592, 999–1009).
- Cristae narrowing in glucose-stimulated INS-1E cells (Dlasková et al. 3D super-resolution microscopy reflects mitochondrial cristae alternations and mtDNA nucleoid size and distribution. (2018) Biochim Biophys Acta 1859, 829-844) and upon increased Krebs cycle substrate load in hypoxia-adapted Hep-G2 cells (Dlasková et al. Mitochondrial cristae narrowing upon higher 2-oxoglutarate load. (2019) Biochim Biophys Acta 1860, 659-678) pointed to a common mechanism of how a putative redox signalling and/or fuel sensing control cristae morphology to ensure efficient oxidative phosphorylation.
- Revisited mechanism of insulin secretion in pancreatic β-cells: Plecitá-Hlavatá et al. Glucose-stimulated insulin secretion fundamentally requires H_2O_2 signaling by NADPH oxidase 4. (2020) Diabetes, pii. db191130).

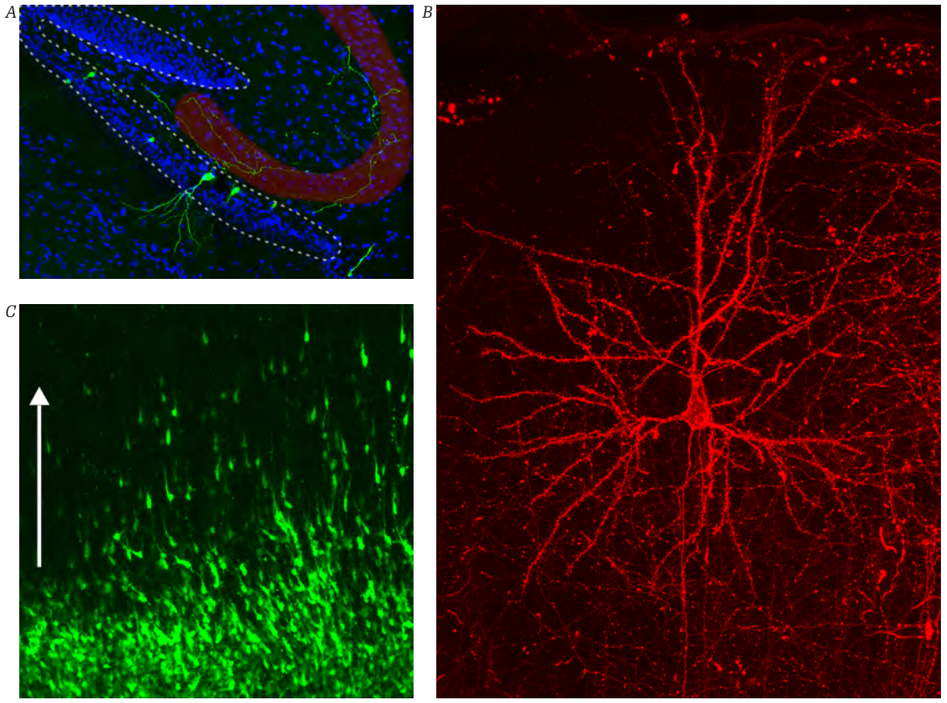
MOLECULAR NEUROBIOLOGY

head **Mgr. Martin Balaštík, Ph.D.** 1 martin.balastik@fgu.cas.cz
key researchers Jakub Žiak 4 Djamel Eddine Chafai PhD students Peter Búran 2
Barbora Pukajová, Michaela Rusková 5 Romana Weissová 3

During the development of the human brain, 86 billion neurons guide their processes, some of which can be a meter-long, to form over 10^{14} connections (synapses) with exceptional precision. Axon guidance is tightly regulated, and its deregulation has been associated with multiple **NEURODEVELOPMENTAL DISORDERS** such as autism or epilepsy. We are analyzing genes and molecular mechanisms that control axon growth, guidance, and its postnatal pruning in gradients of extracellular guidance cues. Using multiple *in vitro* and *in vivo* models (neuron cultures, transgenic/knockout mice, *in utero* electroporations, etc.) and combinations of molecular biology, histology, and microscopy techniques, we characterize the role of **MICROTUBULE-ASSOCIATED PROTEINS** (MAPs) in neural development and their conformational regulation by **PROLYL ISOMERASES**. In addition, we analyze the combinatorial effect of **MAPs** and **TUBULIN POST-TRANSLATIONAL MODIFICATIONS (PTMs)** on neuron polarization, growth, and neurodevelopmental disorders.

CURRENT PROJECTS

- Molecular mechanisms of axon/dendrite growth, guidance, and pruning: the isoform-specific functions of the microtubule-associated CRMP protein family (Collapsin response mediator proteins) in the axon/dendrite specification, guidance and elimination in gradients of class 3 Semaphorins
- Prolyl isomerases in neural development and neurodegeneration - the conformational regulation of CRMPs by prolyl isomerases in neural development and Alzheimer's disease
- Analysis of the combinatorial effect of tubulin post-translational modifications and microtubule-associated proteins on the regulation of neuron polarization, migration, and pruning *in vitro/in vivo*



(A) *Axonal projections of dentate gyrus (dashed line) granule cells (green color) into the CA3 region of hippocampus proper (red label).* In utero *electroporation was used for sparse GFP labelling of granule cells.* ***(B)*** *3D reconstruction of a single, retrogradely-labelled cortical pyramidal neuron using fluorescent dye (DiI).* ***(C)*** *Migration of GFP-labelled pyramidal neurons in the developing mouse cortex.* In utero *electroporation was used for GFP-labelling of the pyramidal neurons.*

SELECTED OUTPUTS

- We showed that CRMP2 is an essential mediator of Semaphorin 3F-dependent axon pruning and dendritic spine remodelling in the early postnatal stages, linked to the pathogenesis of autism spectrum disorder (Ziak et al. (2020) EMBO Rep 21 (3), e48512).
- We showed that excessive tubulin polyglutamylation causes reactive astrocytosis and neurodegeneration in the cerebral cortex and perturbs neuronal transport in mouse models (Magiera et al. (2018) EMBO J 37, 23).
- We demonstrated a new mechanism regulating axon growth and guidance in the gradients of Semaphorin 3A guidance cue by prolyl isomerase Pin1 and CRMP2 (collapsing response mediator protein 2), the deregulation of which leads to neurodevelopmental defects in mice (Balastik et al. (2015) Cell Reports 13, 812-828).

NEUROCHEMISTRY

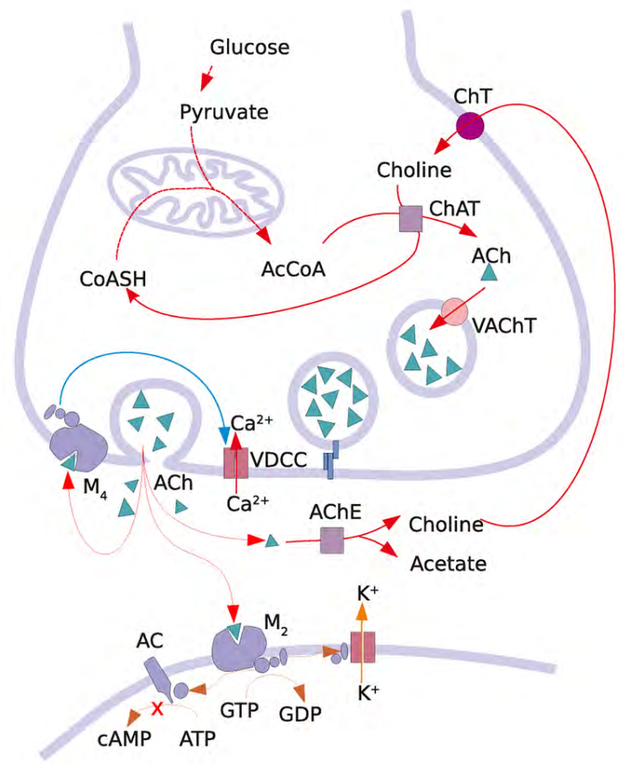
head **Mgr. Jan Jakubík, Ph.D.** 1 jan.jakubik@fgu.cas.cz
key researchers Eva Dolejší 2 Vladimír Doležal 3 Helena Janíčková 4
Alena Randáková 5 PhD students Alice Abbondanza 6 students Jana Bláhová 7
Dominik Nelic 8 Alexandra Tyshkevich 9 Jakub Danzig 11 Mark Revan Rangotis 12
Jigar Trisha Dhabalia, Mutale Jane Mulenga, Matyáš Smolík technicians Dana Ungerová 10

We study the physiology, biochemistry, and pharmacology of **CHOLINERGIC NEURONS** at the molecular level. In our studies we mainly employ cell lines, but also we use animal models. Our research is focused mainly on the following topics:

- The biochemical physiology and pharmacology of cholinergic neurons. The development and differentiation of cholinergic neurons. The synthesis, storage, and release of **ACETYLCHOLINE**. Presynaptic regulation of acetylcholine release.
- Cholinergic mechanisms in the pathogenesis of Alzheimer´s disease. The effects of β-amyloid on acetylcholine metabolism and muscarinic transmission.
- The molecular pharmacology of **MUSCARINIC RECEPTORS**. The allosteric modulation of receptor activation. The interaction of muscarinic receptors with G-proteins. The modelling of muscarinic receptor signal transduction.

CURRENT PROJECTS

- Effects of membrane cholesterol on the function of muscarinic receptor with the aim to delineate how membrane cholesterol binds to a muscarinic receptor and how it slows down their activation
- Signalling bias at muscarinic receptor with the aim to delineate why some muscarinic agonists activate individual subtypes to a different extent and exhibit signalling bias
- Cholinergic modulation of striatum-based behaviour with the aim to determine how the cholinergic activation of striatal GABAergic interneurons modulates striatal signalling and striatum-based behaviour



Upon Ca^{2+} entry via voltage-dependent calcium channels (VDCC), acetylcholine (ACh) is released to synapse. Postsynaptically ACh regulates cAMP synthesis and K^+ flow via M2 receptors. Presynaptically it inhibits its own release via M4 receptors. AC – adenylyl cyclase, AcCoA – acetyl coenzyme A, ChAT – choline acetyl transferase, ChT – choline transporter, VAChT – vesicular acetylcholine transporter.

SELECTED OUTPUTS

- Randakova A et al.: Novel M2 -selective, Gi -biased agonists of muscarinic acetylcholine receptors. (2020) Br J Pharmacol 177, 2073–2089. Jakubik J et al.: The operational model of allosteric modulation of pharmacological agonism. (2020) Sci Rep 10, 14421.
- Janickova H et al.: Selective decrease of cholinergic signaling from pedunculopontine and laterodorsal tegmental nuclei has little impact on cognition but markedly increases susceptibility to stress. (2019) FASEB J 33, 7018–7036.
- Jakubik J et al.: Applications and limitations of fitting of the operational model to determine relative efficacies of agonists. (2019) Sci Rep 9, 4637.
- Randakova A et al.: Novel long-acting antagonists of muscarinic ACh receptors. (2018) Br J Pharmacol 175, 1731-1743.
- Randakova A et al.: Role of membrane cholesterol in differential sensitivity of muscarinic receptor subtypes to persistently-bound xanomeline. (2018) Neuropharmacology 133, 129–144.
- Janickova H, et al.: Deletion of the vesicular acetylcholine transporter from pedunculopontine/laterodorsal tegmental neurons modifies gait. (2017) J Neurochem 140, 787–798.

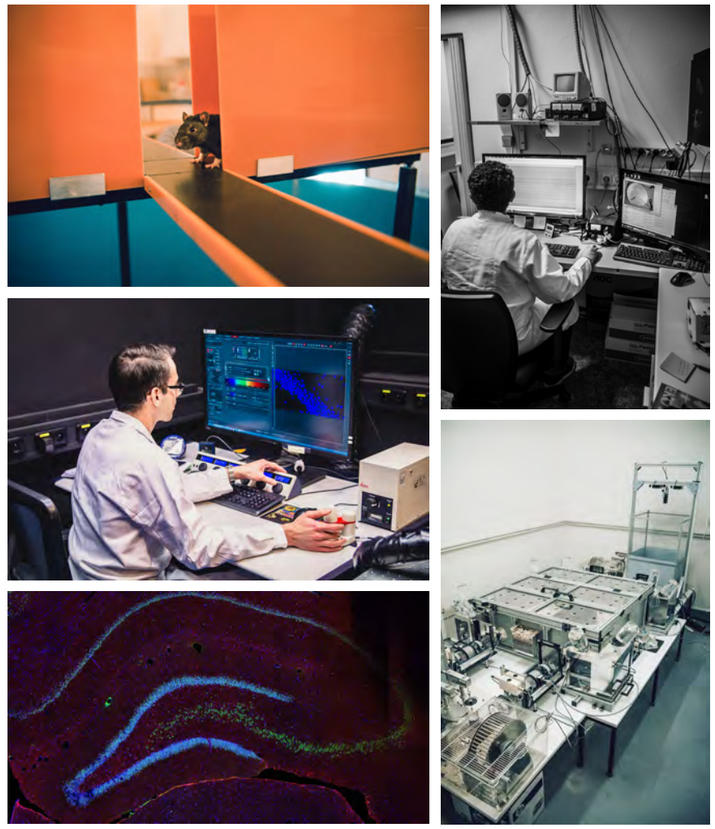
NEUROPHYSIOLOGY OF MEMORY

head **Prof. RNDr. Aleš Stuchlík, DSc.** 1 ales.stuchlik@fgu.cas.cz
key researchers Jan Svoboda 2 Štěpán Kubík 3 Kamil Vlček 4
Tomáš Petrásek, David Levčík 5 Enrico Patrono 6 PhD students Nikhil Ahuja,
Daniela Alexová 7 Hana Brožka 8 Helena Buchtová 9 Daniela Černotová 10
Lukáš Hejtmánek, Karolína Hrůzová 11 Martina Janíková 12 Kristýna Malenínská 13
Branislav Krajčovič 14 Dominika Radostová 15 Dominika Rišnovská 16
Gabriela Valigová 17 Iveta Vojtěchová technicians Michaela Radostná 18
Jindřich Kalvoda, Vladimíra Marková 19 Barbara Stuchlíková

Our Laboratory has focused on **LEARNING, MEMORY,** and **BEHAVIOUR** for several decades. **SPATIAL NAVIGATION** is a type of so-called **DECLARATIVE MEMORY** (the ability to remember facts, and events, and context). These domains are severely disrupted in **ALZHEIMER'S DISEASE** and other dementias, **SCHIZOPHRENIA**, and other neuropsychiatric disorders. We do not know the causes of these disorders, so we actually only treat their symptoms with current therapies. Our focus has recently extended to the **NEUROPHYSIOLOGICAL (CELLULAR, MOLECULAR, CIRCUIT-BASED) FOUNDATIONS OF LEARNING AND MEMORY BEHAVIOURS** in the **HEALTHY** and **DISEASED BRAIN**. We employ multiple modern techniques, including advanced phenotyping, viral vectors, optogenetics, and molecular imaging and combine them with neurobehavioural studies.

CURRENT PROJECTS

- The neurobiological foundation of memory traces: brain inactivations – *in vivo* imaging – neuropharmacology – phenotyping – adult neurogenesis – electrophysiology of cognition
- Mechanisms of behavioural deficits in brain disorders: animal models of brain disorders – transgenic models – pharmacology – cellular-resolution imaging
- High-resolution molecular imaging of network dynamics in the healthy and diseased brain: viral – vectors – optogenetics – molecular imaging – neuronal assemblies
- Relating brain activity to behavioural functions in humans: spatial navigation – strategies – the human mind – intracranial recordings – real and virtual mazes for humans



Selected neurobehavioural and molecular methods, setups, and outputs at the Laboratory of Neurophysiology of Memory.

SELECTED OUTPUTS

- Krajcovic et al. Neural and neuronal discoordination in schizophrenia: From ensembles through networks to symptoms. (2019) Acta Physiol 226(4), e13282.
- Nepovimova et al. Orexin supplementation in narcolepsy treatment: A review. (2019) Med Res Rev 39(3), 961-975.
- Petrasek et al. The McGill transgenic rat model of Alzheimer's disease displays cognitive and motor impairments, changes in anxiety and social behavior, and altered circadian activity. (2018) Front Aging Neurosci 10, 250.
- Fajnerova et al. A virtual reality task based on animal research – spatial learning and memory in patients after the first episode of schizophrenia. (2014) Front Behav Neurosci 27(8), 157.
- Hort et al.: Spatial navigation deficit in amnestic mild cognitive impairment. (2007) Proc Natl Acad Sci USA 104(10), 4042-4047.
- Telensky et al.: Functional inactivation of the rat hippocampus disrupts avoidance of a moving object. (2005) Proc Natl Acad Sci USA 108(13), 5414-5418.

PAIN RESEARCH

head MUDr. Jiří Paleček, CSc. 1 jiri.palecek@fgu.cas.cz
key researchers Diana Špicarová 2 Pavel Adámek 3 Petra Mrózková
Anirban Bhattacharyya 4 PhD students Mário Heleš 5 Jakub Slepička 6
technicians Kateřina Krämerová 7

The main research interest of the Laboratory is to study the **MECHANISMS OF PAIN** and to explore new possibilities for pain treatment, especially of chronic neuropathic states. Our experimental work is focused on the modulation of nociceptive information at the spinal cord level, which is the first relay centre between the periphery and the higher brain areas. **THE GOAL IS TO STUDY THESE MODULATORY MECHANISMS IN ORDER TO IMPROVE THERAPY FOR NEUROPATHIC, INFLAMMATORY, AND CANCER-RELATED PAIN.** The focus is on the role of transient receptor potential vanilloid 1 (TRPV1) and other receptors, inflammatory cytokines, and glial cells in this process. In our research, we use mainly electrophysiological, immunohistochemical, and behavioural methods.

CURRENT PROJECTS

- Modulation of spinal cord dorsal horn synaptic transmission by endocannabinoids
- Functional interaction between TLR4 and TRPV1 receptors in neuropathic pain
- The role of spinal inhibitory neurons in chronic pain conditions
- Interaction of opioid and TRPV1 receptors with cytokines in analgesia

Fig. 1

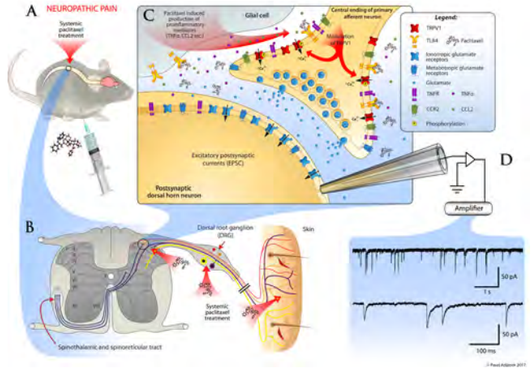


Fig. 2

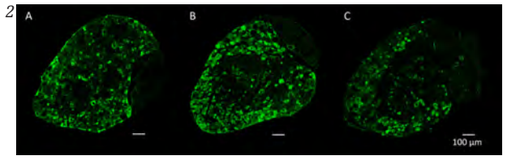


Fig. 3

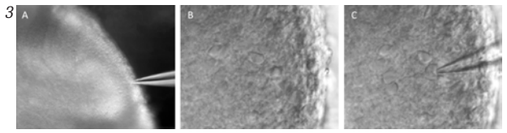
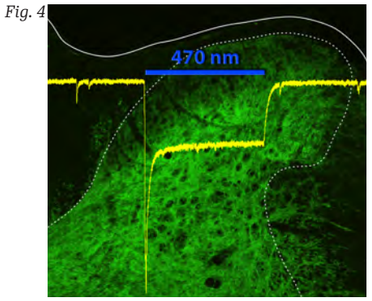
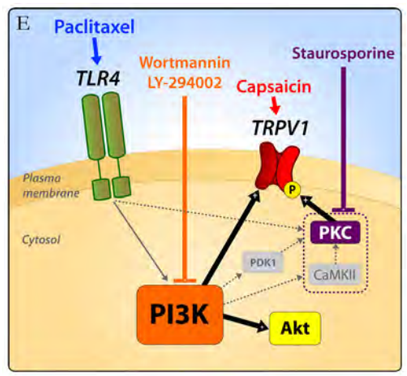


Fig. 4





(Fig. 1) *Proposed effect of chemotherapeutic drug paclitaxel (PTX) at spinal cord level. (A) Low concentration of PTX may penetrate through hematoencephalic-barrier. (B, C) In the spinal cord, PTX may activate TLR4 receptors and modulate TRPV1 receptors function. (D) These changes are studied by whole-cell patch-clamp recordings from superficial dorsal horn neurons. (E) The proposed scheme of PTX-induced signalling and TRPV1 modulation.* ***(Fig. 2)*** *Phospho-Akt kinase immunoreactivity in dorsal root ganglion (DRG) neurons (A, control situation) is increased after* in vivo *PTX application (B). This effect is significantly reduced by pretreatment with PI3K inhibitor wortmannin (C).* ***(Fig. 3a/b/c)*** *Electrophysiological technique patch-clamp is used to record postsynaptic currents from laminae I–II dorsal horn neurons in acute spinal cord slice.* ***(Fig. 4)*** *Optical stimulation (470 nm) leads to light-sensitive channelrhodopsin-2 (ChR2) mediated current (yellow trace) in inhibitory dorsal horn neurons recorded in transversal section of spinal cord from transgenic VGAT-ChR2-eYFP mice.*

SELECTED OUTPUTS

- Losartan attenuates neuroinflammation and neuropathic pain in paclitaxel-induced peripheral neuropathy. (Kalynovska et al. (2020) J Cell Mol Med 24, 7949-7958).
- Mechanical allodynia and enhanced responses to capsaicin are mediated by PI3K in a paclitaxel model of peripheral neuropathy. (Adamek et al. (2019) Neuropharmacology 146, 163-174).
- Peripheral inflammation affects the modulation of nociceptive synaptic transmission in the spinal cord induced by N-arachidonoylphosphatidylethanolamine. (Nerandzic et al. (2018) British J Pharmacol 175, 2322– 2336).
- Hypersensitivity induced by the activation of spinal cord PAR2 receptors is partially mediated by TRPV1 receptors (Mrozkova et al. (2016) PLoS One 11(10), e0163991).
- The cancer chemotherapeutic paclitaxel increases human and rodent sensory neuron responses to TRPV1 by activating TLR4 (Li et al. (2015) J Neurosci 35(39), 13487-13500).
- TRPV1 antagonist attenuates postoperative hypersensitivity by central and peripheral mechanisms (Uchytilova et al. (2014) Mol Pain 10(1), 67).
- TRPV1 receptor inhibition decreases CCL2-induced hyperalgesia. (Spicarova et al. (2014) Neuropharmacology 81, 75-84).

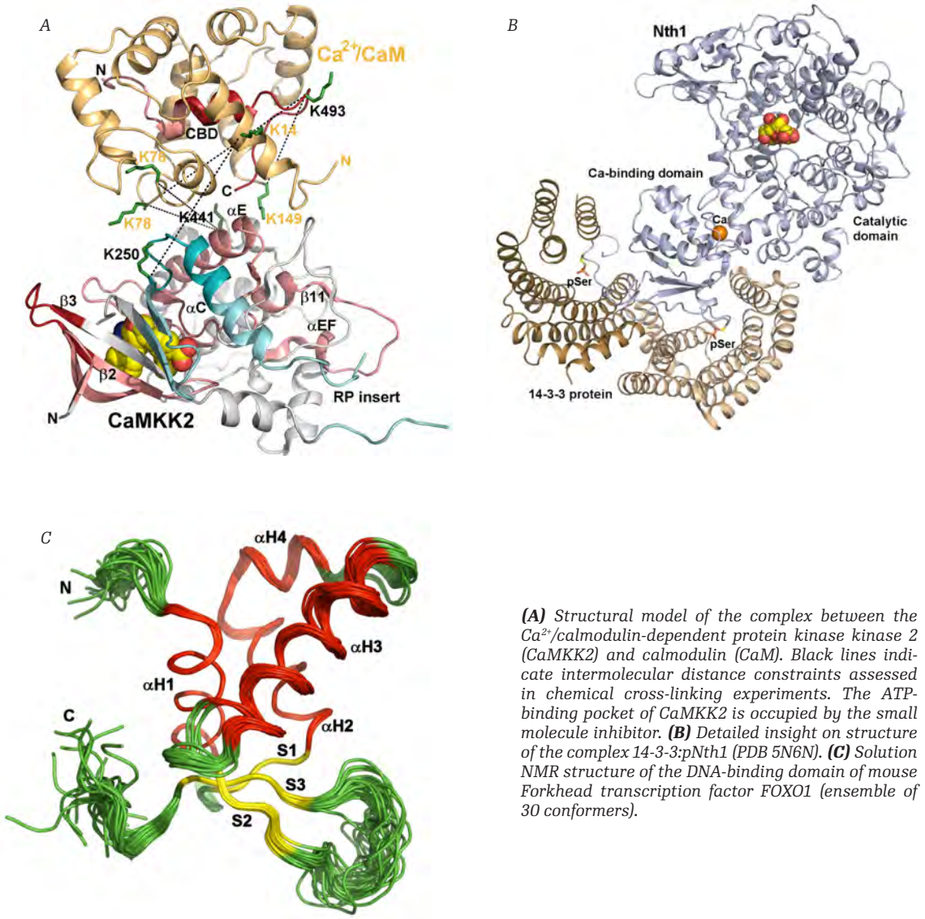
STRUCTURAL BIOLOGY OF SIGNALLING PROTEINS

head RNDr. Veronika Obšilová, Ph.D. 1 veronika.obsilova@fgu.cas.cz
key researchers Olívia Petrvalská 2 Aneta Šmídová 3 Tomáš Obšil 4
Matěj Horváth 5 PhD students Pavel Pohl 7 Rohit Joshi 8 Raju Mandal,
Domenico Lentini Santo, Karolína Honzejková 9 Klára Kohoutová 11
students Adéla Hofmanová 10 Nicola Koupilová 12 Martina Mikulů 13 Andrej Tekel 14
technicians Gabriela Kočárová, Dana Kalábová 6 Markéta Kolcunová 15

Our group is focused on **STRUCTURAL BIOLOGY** (the relationship between the structure and function of certain groups of proteins) in particular, we are interested in **14-3-3 PROTEINS AND THEIR COMPLEXES** with proteins involved in **APOPTOSIS, CANCER**, and **CALCIUM-TRIGGERED SIGNALLING PATHWAYS**. 14-3-3 proteins specifically bind to phosphoserine (or phosphothreonine)-containing motifs in a sequence-specific manner. Mechanistically, 14-3-3 proteins act as **ALLOSTERIC REGULATORS** and/or molecular scaffolds that constrain the conformation of the binding partner. Nonetheless, the underlying molecular mechanisms are only partially identified, mainly due to the **LACK OF STRUCTURAL DATA**. The methods we are currently using include recombinant protein expression, biophysical characterization and the study of intermolecular interactions, protein structure, and interaction surfaces. All these methods enable us to better understand how the activity and function of protein-protein complexes is regulated.

CURRENT PROJECTS

- Structural biology of 14-3-3 proteins and their complexes
- Mechanism of regulation of protein kinases CaMKK1, CaMKK2, and ASK1
- Study of the inhibition of protease caspase-2 in a 14-3-3 protein dependent manner
- Phosphorylation dependent regulation of human ubiquitin ligase NEDD4-2
- Molecular basis of interaction between FOXO Forkhead transcription factors and tumor suppressor p53
- Targeting senescence with small compounds against FOXO-TP53 interaction



(A) *Structural model of the complex between the Ca^{2+}/calmodulin-dependent protein kinase kinase 2 (CaMKK2) and calmodulin (CaM). Black lines indicate intermolecular distance constraints assessed in chemical cross-linking experiments. The ATP-binding pocket of CaMKK2 is occupied by the small molecule inhibitor.* ***(B)*** *Detailed insight on structure of the complex 14-3-3:pNth1 (PDB 5N6N).* ***(C)*** *Solution NMR structure of the DNA-binding domain of mouse Forkhead transcription factor FOXO1 (ensemble of 30 conformers).*

SELECTED OUTPUTS

- Solved atomic structure of the 14-3-3 protein complex with neutral trehalase Nth1 shows the ability of the 14-3-3 protein to modulate the conformation of the multidomain enzyme and function as an allosteric regulator (Alblova et al. (2017) Proc Natl Acad Sci USA 114, E9811-E9820).
- Our results show that 14-3-3 protein binding to caspase-2 may play a key role in regulating caspase-2 activation by masking the nuclear localization sequence of caspase-2 (Smidova et al. (2018) FEBS J 285, 4196-4213).
- Our results suggest that 14-3-3 protein directly interacts with the kinase domain of calcium/calmodulin-dependent protein kinase kinase (CaMKK2) and that the interaction might be stabilized by small-molecule compounds (Psenakova et al. Biochim Biophys Acta (2018) Gen Subj 1862, 1612-1625).
- CaMKK2 kinase domain interacts with the autoinhibitory region through the N-terminal lobe including the RP insert (Kylarova et al. (2018) Biochim Biophys Acta – Gen Subj 1862, 2304-2313).

TRANSLATIONAL METABOLISM

head **Doc. Ing. Tomáš Čajka, Ph.D.** 1 tomas.cajka@fgu.cas.cz
key researchers Ivan Mikšík 2 Adam Eckhardt 3 Jana Svobodová 4
PhD students Lucie Kulhavá 5 Marine Morvan 6
technicians Statis Pataridis 7 Armenuhi Kirakosjanová 8

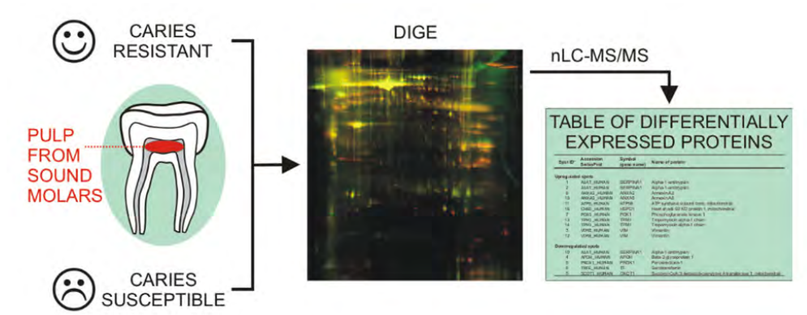
Our research involves applying mass spectrometry-based technologies to perform **METABOLOMIC AND PROTEOMIC ANALYSIS** of various biological samples. This work covers the development and use of both LC-MS and CE-MS methods for the in-depth characterization and quantification of complex lipids – **LIPIDOME**, polar metabolites – **METABOLOME**, various exogenous compounds such as drugs – **EXPOSOME**, and proteins – **PROTEOME**. We also focus on improving data processing, automated data curation, statistical methods, and the visualization of omics data. We have successfully integrated LC-MS methods for the targeted and untargeted analysis of complex lipids, polar metabolites, and exposome compounds (LIMeX) for a wide range of sample types and used them for studies focused on cardiovascular diseases, type 2 diabetes, lipogenesis, circadian rhythms, and drug adherence. We have also investigated the proteome of human teeth and saliva and their connection with tooth decay, including posttranslational modifications of proteins.

CURRENT PROJECTS

- Simple, fast, and robust protocols for metabolomics and proteomics projects including data processing, data curation, statistical analysis, and visualization
- New separation methods (LC-MS, capillary electromigration techniques incl. CE-MS) for physiological research
- Metabolomics and proteomics for discovering new biomarkers of human health
- The predictive role of the proteomic composition of teeth and saliva in the etiology of tooth decay
- A correlative approach to extracellular matrix disorders: from proteins to tissue architecture at idiopathic pes equinovarus

A

B



(A) *Processing of complex lipids in human plasma and serum using MS-DIAL software*
(B) *Tooth proteomic comparison of caries-free and caries-positive people for detection of anti-caries compounds*

SELECTED OUTPUTS

- Tsugawa H, Satoh A, Uchino H, Cajka T, et al.: Mass spectrometry data repository enhances novel metabolite discoveries with advances in computational metabolomics. (2019) Metabolites 9, 119.
- Fan S, Kind T, Cajka T, et al.: Systematic error removal using random forest for normalizing large-scale untargeted lipidomics data. (2019) Anal Chem 91, 3590–3596.
- Cajka T: Towards merging targeted and untargeted analysis of the lipidome, metabolome and exposome. (2019) LC GC Europe 32, 314–316.
- Eckhardt A, et al.: Novel contribution to clubfoot pathogenesis: The possible role of extracellular matrix proteins. (2019) J Orthopaed Res 37, 769–778.
- Miksik I: Coupling of CE-MS for protein and peptide analysis. (2019) J Sep Sci 42, 385–397.

BIOCEV

EUROPEAN SCIENTIFIC CENTRE OF EXCELLENCE IN BIOTECHNOLOGY AND BIOMEDICINE

IPHYS is a founding member and partner in BIOCEV. This is a joint project of six institutes of the CAS (Institute of Biotechnology, Institute of Molecular Genetics, IPHYS, Institute of Microbiology, Institute of Experimental Medicine, Institute of Macromolecular Chemistry) and two faculties of Charles University in Prague (Faculty of Science and First Faculty of Medicine). The goal of the project is to establish a European Centre of Excellence in biomedicine and biotechnology. The new building of the research centre was constructed in Vestec, in close vicinity of the IPHYS Krc campus, with financial support from the European Structural Funds. BIOCEV focuses on detailed study of cellular mechanisms at the molecular level, research and development of novel therapeutic strategies, early diagnostics, biologically active agents including chemotherapeutics, protein engineering, and other innovative technologies. Seven IPHYS Laboratories participate in the BIOCEV project and have their laboratories at this centre since December of 2015.

RESEARCH PROGRAMMES:

The scientific scope of BIOCEV has been divided into five research programmes, each of them dealing with a number of separate research projects. Particular IPHYS projects in each programme are listed below. The programmes and projects have been designed to form a mutually integrated system of synergistic links inside BIOCEV:

1. Functional genomics
2. Cellular biology and virology
   - Mitochondrial structure and gene expression
     (Petr Ježek)
   - Transporters of potassium in regulation of the cell cycle,
     pH, and response to the stress of lower eukaryotes
     (Hana Sychrová)
   - Structure and function of membrane receptors
     (Ladislav Vyklický, Jiří Paleček, Hana Zemková)
3. Structural biology and protein engineering
   - Structural biology of signalling proteins
     (Veronika Obšilová)
4. Biomaterials and tissue engineering
   - Bioartificial structures for replacement and regeneration
     of damaged tissue
     (Lucie Bačáková)
5. Development of diagnostic and therapeutic procedures

AVAILABLE CORE FACILITIES

The implementation of complex projects requires a high-quality methodological basis concentrated in core facilities. All are open to external users to provide them with the following research services:

- Czech Centre for Phenogenomics
- Imaging Methods
- Centre of Molecular Structure
- Gene Core – Quantitative and Digital PCR
- OMICS – Proteomics and Genomics
- Cryobank

CONTACT

BIOCEV

Průmyslová 595, 252 50 Vestec, Czech Republic

tel: +420 325 873 140

e-mail: biocev@biocev.eu

www.biocev.eu

JUNIOR RESEARCH GROUP

MOLECULAR PHYSIOLOGY OF BONE

head Mgr. Michaela Tencerová, Ph.D. 1 michaela.tencerova@fgu.cas.cz
key researchers Glenda Paola Alquicer Barrera, Michaela Ferenčáková
PhD student Andrea Beňová 2

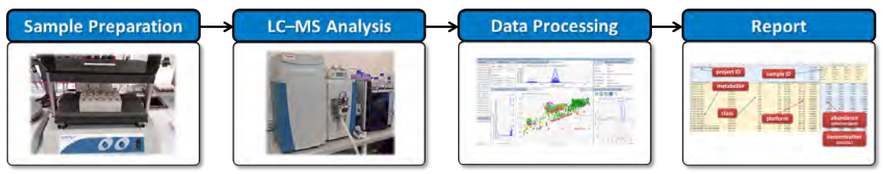
In obesity, the inability of adipose tissue to store excess calories leads to ectopic fat accumulation in the liver, muscle, or cardiovascular system and causes an impairment of glucose homeostasis. Recent studies have shown that bones are also affected by obesity, leading to enhanced adipocyte formation in bone marrow (**BMAT**). Higher BMAT volume is often associated with increased risk of **BONE FRACTURES**, an overlooked complication affecting the quality of life in patients with metabolic disorders. However, there is limited information on the physiological role of BMAT in relation to the **BONE** and whole-body **ENERGY METABOLISM**. The research projects employ murine and human cellular systems, mice biomodels, clinical studies and molecular, bioanalytical, and *in vivo* phenotyping techniques. The research is conducted as part of an international collaboration in Europe and the USA. This Laboratory was newly established in 2019, based on a 5-year "Start Up Research Program" financed by IPHYS.

SERVICE DEPARTMENTS

METABOLOMICS

head **Doc. Ing. Tomáš Čajka, Ph.D.** 1 tomas.cajka@fgu.cas.cz team members Jiří Hricko 2 Michaela Nováková 3 Michaela Paučová 4

The Department provides fee-based services for LC–MS-based metabolomic and lipidomic analysis in biological materials such as plasma/serum, tissue (e.g. liver, heart, lungs, muscle, adipose tissue), and cells. We use an LC–MS workflow LIMeX (LIpids, Metabolites, and eXposome compounds) for simultaneous extraction of complex lipids, polar metabolites, and exposome compounds. Targeted analysis is available for low-abundant metabolites. The Department is equipped with Vanquish UHPLC System / Q Exactive Plus and Ultimate 3000 RSLC System / QTRAP 5500 instrumentation.
Platforms:
- Combined untargeted and targeted analysis of complex lipids or polar metabolites and exposome compounds (food components and pharmaceutical drugs)
- Targeted analysis of specific low-abundant lipid mediators (eicosanoids, endocannabinoids, fatty acid esters of hydroxy fatty acids) and steroids, metabolites labelled with stable isotopes (fluxomics) or pharmaceutical compounds for the ADME studies

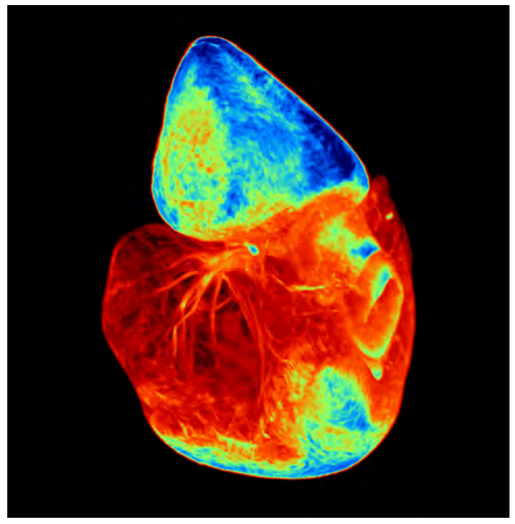


LIMeX workflow for combined untargeted and targeted analysis

RADIOMETRY

head **Roman Liška** 1 roman.liska@fgu.cas.cz team members Karla Bohunová 2 Pavla Smigolová

The Department provides services dealing with all types of work with radioactive materials. In addition, with Computerized Tomography (CT) and Positron Emission Tomography (PET), we can also provide *in vivo* anatomical and molecular imaging of small laboratory animals (mice and rats) for the quantitative 3D tomographic imaging of biodistributed radiotracers, bones, and various soft tissues, using the μCT/PET apparatus Albira. Radioactivity measurements of all kinds of radionuclides in different samples are carried out for researchers of other Laboratories of IPHYS, as well as of other Institutes of the CAS in the campus and BIOCEV. We also provide storage space, advice, and services in the manipulation of radioactive materials and the ordering and purchasing of radioactive preparations for more than a hundred radioisotopic laboratories from these Institutes.



μCT scan of a shark heart using the contrast agent Lugol

BIOLOGICAL CONTROLS

head **RNDr. Světlana Žufanová** 1 svetlana.zufanova@fgu.cas.cz
team members Lucie Heppnerová 2 Jaroslav Kalivoda 3 Jiří Marhan, Richard Pospíšil, Josef Prchal, Renáta Půtová 4 Lenka Řezáčová 5

We provide comprehensive preclinical and toxicological services in accordance with the principles of Good Laboratory Practice (GLP). We offer various biological and safety studies to our academic and business partners so as to fulfill their research and development goals, including studies under GLP regulations and in accordance with the OECD methods. We are an essential part of the newly established Centre for Preclinical Testing (CPT) within the CAS (www.prekliniky.en). Our vision is to enable better prospects for the commercialization of potentially therapeutically effective medicinal products to both institutes within the CAS and to other customers from the academic sector and the pharmaceutical industry.

Provided services:
- Preclinical *in vivo* toxicity research testing for safety evaluation of pharmaceutical, biopharmaceutical, and veterinary products (MTD, DRF, pilot studies).
- General safety drug development studies on small laboratory animals (mice, rats, guinea pigs, rabbits), all routes of administration, non-GLP and GLP studies.
- Other customized safety tests and studies on rodents.
- Biodistribution studies in small laboratory animals after single/repeated administration (biological part).

ANIMAL FACILITY

head **MVDr. Kristýna Bílková** 1 kristyna.bilkova@fgu.cas.cz
team members Josef Lachout, Jana Bártů 2 animal caretakers Ilona Berková 3 Monika Böhmová, Nikola Danitová 4 Evelina Lavičková, Jana Lejčková 5 Kateřina Pavelková 6 Hana Ptáčková 7 Jaroslava Quiquerez 8 Lucie Rosová 9 Hana Thierlová 10 Andrea Vališová 11 Hana Vančurová, Jitka Vyvadilová technicians Anna Fialová, Petr Havlena 12 Monika Humenná 13 Jan Krämer 14 Jana Perná 15 Lenka Vondrová

The Department provides an enviroment for *in vivo* research. The used animal models are laboratory rats, laboratory mice and zebra fish. The animal facility is conventional and the rodents are housed in open cages.

Provided services:
Breeding of various common and unique strains of laboratory rats and mice. Housing of animals in experiments. All necessary and related services. All procedures correspond to requirements of Act No 246/1992 Coll., on the protection of animals against cruelty, and Decree No 419/2012 Coll., on the protection of experimental animals. The facility runs under a continuous veterinary supervision.

ECONOMIC DEPARTMENT

head **Kateřina Uhrová** ■ katerina.uhrova@fgu.cas.cz
team members (from the left) Tereza Mádle, Lenka Kravčišinová, Lucie Dusilová, Kristýna Knězů, Lucie Čiperová, Běla Tobolová, Lada Trčková, Kamila Kohoutová, Eva Syrová, Viktor Kratochvíl, Dagmar Plzenská, Gabriela Bartejsová, Gabriela Trmalová, Jaroslava Králová, Lenka Nejedlá, (not in the photo) Eva Hamalčíková, Monika Kulhánková, Marcela Tomášková

The Economic Department is in charge of human resources, payroll and financial accounting, supply and the stocks, agenda of grants and operating programmes.

PROPERTY AND FACILITY DEPARTMENT

head **Ing. Jan Šilhavý, Ph.D.** ■ jan.silhavy@fgu.cas.cz
team members (from the left) Vladimíra Trůková, Irena Čechová, Ladislav Kramer, Helena Reimerová, Josef Uher, Pavlína Hájková, Stanislav Pečený, Eva Půlová, Vladimír Křehlík, Václava Jandová, Ivan Sluněčko, (not in the photo) Jana Pechová, Agniezska Pelikán, Eva Půlová

The Property and Facility Department provides all services related to the building maintenance and necessary health and safety rules. It also runs hostel rooms for IPHYS guests.

OFFICE OF THE DIRECTOR

head **Ing. Petra Janečková** ■ fgu@fgu.cas.cz
team members (from the left) Adéla Pecková, Petra Kubátová, Diana Moosová, Josef Prchal

The Office of the Director provides various administrative work of IPHYS. It organizes the events for the public and also the professional lectures. It ensures the popularization of the Institute to the media and the public. It records and manages the Institute´s intellectual property and coordinates activities of technology transfer.

INFORMATION TECHNOLOGY DEPARTMENT

head **Václav Pauločik** ■ vaclav.paulocik@fgu.cas.cz
team members (from the left) Ondřej Švanda, Tomáš Fišera, Martin Kantor, Jiří Vilím

Information Technology Department serves the whole campus with all services in the field of computer technology and traffic data network. It helps with the purchase, operation, and maintenance of hardware, data maintenance, and software upgrades.

LIBRARY

head **Mgr. Lucie Trajhanová** ■ lucie.trajhanova@fgu.cas.cz
team members (from the left) Blanka Liberová, Monika Stloukalová, Helena Sedláková, Zuzana Nováková

The Library provides access to both traditional paper-based and electronic resources for the whole campus. It provides information services based on the latest information technologies, national and international interlibrary loans, access to printed sources, specialised databases, and on-line journals. The supply of approximately 80,000 books and journals ranks the Library as one of the largest libraries of the scientific institutes of the CAS.

PHYSIOLOGICAL RESEARCH JOURNAL

editor-in-chief **RNDr. Jaroslav Kuneš, DrSc.** 1 jaroslav.kunes@fgu.cas.cz
managing editor **MUDr. Josef Zicha, DrSc.** 2 josef.zicha@fgu.cas.cz
team members Edita Balladová (left), Michal Růžička, Zdeňka Stádníková

Physiological Research is a scientific journal of IPHYS published bimonthly, containing articles on normal and pathological physiology, biochemistry, biophysics, pharmacology, and immunology. It was founded as Physiologia Bohemoslovaca in 1952. Since 1991, it has been published under the title Physiological Research. Its current impact factor is 1.701.

COLLABORATIONS

MOST OF IPHYS RESEARCH IS CONDUCTED IN THE FRAMEWORK OF DOMESTIC AND INTERNATIONAL COLLABORATION.

Among the principal Czech partners of IPHYS belong a number of institutes of the Czech Academy of Sciences, universities, hospitals, and other research institutions. Also, many research collaborations of individual IPHYS laboratories all around the world significantly increase the quality of research at IPHYS. The diagram shows only national and international partnerships based on formal agreements signed between 2015–2019.

ITALY
University of Padua

JAPAN
National Institute of Informatics

POLAND
Nencki Institute of Experimental Biology

SLOVAKIA
Centre of Experimental Medicine, SAS

UNITED KINGDOM
University of Central Lancashire of Preston

Medical Research Council

UKRAINE
Kharkiv National Medical University

USA
University of California
University of Arizona

IPHYS

ACADEMY OF SCIENCES
Biology Centre
Institute of Biotechnology
Institute of Physics
Institute of Microbiology
Institute of Experimental Botany
Institute of Experimental Medicine
Institute of Photonics and Electronics
J. Heyrovsky Institute of Physical Chemistry
Institute of Computer Science
Institute of Sociology
Institute of Molecular Genetics
Institute of Macromolecular Chemistry
Institute of Organic Chemistry and Biochemistry
Institute of Scientific Instruments
Institute of Rock Structure and Mechanics

HOSPITALS
University Hospital Hradec Králové
University Hospital Vinohrady
Motol University Hospital
Bulovka Hospital
General University Hospital in Prague
Institute of Clinical and Experimental Medicine
Institute of Endocrinology

UNIVERSITIES
Charles University
Masaryk University
Technical University of Liberec
Palacký University Olomouc
University of Chemistry and Technology
Food Research Institute Prague
Brno University of Technology
Jan Evangelista Purkyně University
Czech Technical University

OTHERS
IOCB Tech
Central European Institute of Technology
National Tissue Centre
National Institute of Mental Health

EUROPEAN PROJECTS

IPHYS PARTICIPATES IN TWO EUROPEAN INFRASTRUCTURES.

CZECH-BIOIMAGING

National research infrastructure for biological and medical imaging (MŠMT – LM2015062, LM2018129)

Nine partner institutions are involved in the project, providing open access to 13 leading imaging facilities. Czech-BioImaging is included in the Roadmap of Large Infrastructures for Research, Experimental Development, and Innovation of the Czech Republic for the years 2016–2022. The purpose of the project is to combine unique technological equipment for biomedical imaging accessible in the Czech Republic and to provide an open access to a wide range of imaging technologies and expertise to scientists in the Czech Republic and from abroad via a unified and coordinated logistic approach.

Scientific coordinator:
Ing. Daniel Hadraba, Ph.D.
(Laboratory of Biomathematics)

At present, eight instruments, mainly confocal and multiphoton microscopic systems and optical projection tomography tools are available at the IPHYS Bioimaging Facility. Training programmes, workshops, and consultations in advanced fluorescence microscopic techniques, image analysis and processing are provided. Follow-up OP VVV infrastructure project: Modernization of the national infrastructure for biological and medical imaging Czech-BioImaging (CZ.02 .1.01/0.0/0.0/18_046/0016045).
IPHYS is also a member of European Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences, Euro-BioImaging-ERIC, which is interlinked with the project Czech-BioImaging. Its goal is to attract new foreign users with interesting research projects and new options for cooperating in methodological research with top research facilities.

More information:
www.czech-bioimaging.cz

CZECH BIOIMAGING
Imaging principles of life

EUROPEAN PEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE (EPTRI)

European consortium coordinated by Consorzio per valutazioni biologiche e farmacologiche (funded within the Horizon 2020, INFRADEV-1)

Since developing human beings have very specific needs and there is a serious lack of medicines designed and developed specifically for children and the young in the EU and worldwide, the main aims of the EPTRI consortium are to build a research infrastructure dedicated to pediatric preclinical and translational research of new treatments for children. It focuses on developmental pharmacology, pediatric drug discovery, organ-on-a-chip, and other up-to-date fields of medicine dedicated to children. The work in EPTRI focuses on five domains: Human Development and Paediatric Medicine Discovery; Pediatric Biomarkers and Biosamples; Developmental Pharmacology; Paediatric Medicine Formulations and Medical Devices; Underpinning Medicine Development for Paediatric Clinical Studies.

Scientific coordinator:
Prof. RNDr. Aleš Stuchlík, DSc.
(Laboratory of Neurophysiology of Memory)

IPHYS Laboratories involved in EPTRI: Laboratory of the Neurophysiology of Memory, Laboratory of Developmental Epileptology, Laboratory of Metabolomics.
The project involves 26 partners from 19 EU and associated countries. IPHYS is included in EPTRI as a top basic and translational medicine centre in the Czech Republic. EPTRI has obtained support from the President of the Czech Academy of Sciences, signed Memoranda of Understanding with top-tier institutes in the Czech Republic, and applied for a support in INFRAIA call from the European Commission.

More information:
www.eptri.eu

ePTRI
European Paediatric Translational Research Infrastructure

NATIONAL COLLABORATIVE PROJECTS

MediAim
A TRANSLATIONAL RESEARCH PROJECT

Vision:
Development of new therapeutic agents and strategies to fight certain noncommunicable and viral diseases.

Mission:
We aim to understand the essence of diseases and to seek out new strategies for treating cardiovascular, viral, neurodegenerative, and oncologic diseases as well as diabetes and obesity.

Participating organizations
Institute of Physiology, CAS

Institute of Organic Chemistry and Biochemistry, CAS

Institute for Clinical and Experimental Medicine

The MediAim consortium comprises three distinguished Prague-based research institutes specializing in preclinical and clinical research. Collaboration focuses on experimental, preclinical, translational, and clinical research on the nervous and cardiovascular systems with selected aspects of metabolic research. The primary objectives are (1) the characterization of common mechanisms of pathogenesis associated with the occurrence of selected noncommunicable diseases, (2) the improvement of strategies to prevent, diagnose, and treat these diseases, and (3) the treatment of selected viral diseases. The MediAim project comprises a unique strong link between experimental and clinical research in the Czech Republic as it bridges the gap between basic and translational medical research by facilitating and bolstering multidisciplinary collaboration. The project's added value lies in its embrace of full drug development, from initial synthesis to patented drug candidates. Among first real successes of the research teams involved belong studies focusing on roles of lipidized peptides in weight loss, mitigation of the manifestations of diabetes, and significant slowing of neurodegenerative processes, currently in the stage of preclinical studies on experimental models with very good therapeutic potential for type 2 diabetes using new drugs.

More information:
www.mediaim.cz

EPIREC
EPILEPSY RESEARCH CENTRE PRAGUE

Vision:
Outstanding epilepsy research — paving the way to a seizure-free life

Mission:
We aim to transform the lives of people with epilepsy through high-quality research rapidly translated into patient welfare.

Participating organizations:
Institute of Physiology of the CAS

Second Faculty of Medicine,
Charles University in Prague

Motol University Hospital in Prague

Faculty of Electrical Engineering,
Czech Technical University in Prague

Epilepsy has been intensely studied for decades, but we still do not understand its mechanisms. New drugs are continually being introduced into clinical practice, but their impact is minimal and the proportion of patients with severe pharmacoresistant epilepsy remains unchanged. Hence, new and effective therapies for epilepsy are urgently needed. In epilepsy, the implementation of disruptive research technologies such as gene therapy, molecular pharmacology, and artificial intelligence could significantly change disease outcomes by improving diagnosis, identifying new causes and discovering novel treatments. The ultimate goal of recently established multidisciplinary epilepsy research center, EpiReC, is to pave the way for the development of new strategies to cure most severe and intractable epilepsies in adults and children and to ensure a rapid laboratory-to-patient journey for new discoveries.

More information:
www.epirec.cz

STRATEGY AV21

IPHYS IS THE COORDINATOR OF TWO LONG-TERM INTERDISCIPLINARY RESEARCH PROGRAMMES OF THE CZECH ACADEMY OF SCIENCES

QUALITAS
WELLBEING IN HEALTH AND DISEASE
(2015–2021)

Coordinator:
Doc. MUDr. Jakub Otáhal, Ph.D.
(IPHYS, Laboratory of Developmental Epileptology)

The programme **QUALITAS — Wellbeing in Health and Disease** integrates experts from various research disciplines (medicine, physics, engineering, social sciences, and the humanities). The main aim of the QUALITAS programme is to develop more effective strategies to prevent and treat lifestyle-choice related diseases. In addition to restoring health, these strategies should also enhance the successful social integration of disease sufferers, their re-employment and ultimately improve the wellbeing of patients and their careers.

Main Goals:
- Directly develop innovative diagnostic tools and therapies to prevent and treat diseases of modern civilization
- Minimize their consequences
- Promote faster recovery

Participating institutes:
- Institute of Physiology, CAS (three research studies)
- Institute of Experimental Medicine, CAS (two research studies)
- Institute of Molecular Genetics, CAS
- Institute of Biophysics, CAS
- Institute of Biotechnology, CAS
- Institute of Sociology, CAS
- Institute of Rock Structure and Mechanics, CAS

Collaborating partners:
IKEM, University Hospital Vinohrady, and others

More information:
www.fgu.cas.cz/qualitas

PRECLINICAL TESTING
OF POTENTIAL PHARMACEUTICALS
(2017–2021)

Coordinator:
MUDr. Jan Kopecký, DrSc.
(IPHYS, Director)

The programe **Preclinical Testing of Potential Pharmaceuticals** reflects the need to use experiments on animals as a key element in the development of new pharmaceuticals, including the tests and analyses performed under GLP conditions (GLP-Good Laboratory Practice). Laboratory animals are used exclusively for the studies of potentially life-saving therapeutics and where possible, alternative methods are used.

Main Goals:
- Coordination of research and development of potential pharmaceuticals and their comprehensive preclinical testing within the CAS institutes
- Facilitate introduction of potential pharmaceuticals into practice
- Foster collaboration between the academic sector and commercial entities

Participating institutes:
- Institute of Physiology, CAS
- Institute of Molecular Genetics, CAS, Czech Centre for Phenogenomics (CCP)
- Institute of Biotechnology, CAS
- Institute of Animal Physiology and Genetics, CAS, Pigmod Centre

These institutes form the **Centre for Preclinical Testing (CPT)**.

Collaborating partners:
Pharmakl, spol. s.r.o., and other commercial partners

More information:
www.prekliniky.cz

HR EXCELLENCE IN RESEARCH AWARD

In 2019, the European Commission awarded IPHYS the prestigious European HR Excellence in Research Award, guaranteed by Euraxess and financially supported by Operational Programme Research, Development, and Education. Hence IPHYS joined an exclusive group of research institutes and universities that have committed to improving their human resources strategy in accordance with the principles of the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers.

IPHYS is currently in the middle of the implementation phase of the programme, and its suggested Action Plan (available at the IPHYS webpage) is focused on two primary goals: (1) implementing an OTM-R compliant recruitment process consisting mainly of better documentation of current practice, and (2) improving the career development options of researchers, especially in the postdoctoral phase. Within the programme, IPHYS supports employees in gaining their scientific experience abroad and provides them with options for advancing their independence in research, including the possibility of starting their own laboratory.

INTELLECTUAL PROPERTY

Significant discoveries achieved at IPHYS are protected by patents and utility models. Also, IPHYS strives for the effective transfer of research results into practice. Currently, 15 granted patents or patent portfolios and 7 registered utility models are being managed. Nowadays, intellectual property at IPHYS is also protected by the program HR Excellence in Research Award, thanks to which the administration of the portfolio is coordinated more efficiently.

IPHYS – IOCB COLLABORATION

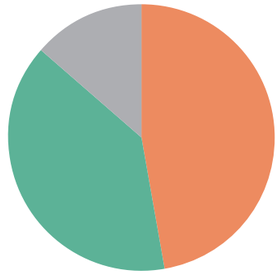
IPHYS co-owns the most significant patents or patent portfolios with the Institute of Organic Chemistry and Biochemistry of the CAS (IOCB). Currently, 7 valid patent portfolios and 1 filed patent application are co-registered by these two Institutes. The patent portfolio protecting the result *Lipidated peptides lowering blood glucose level* is one of the most successful research results of both Institutes. In 2017, the cooperating Institutes signed a research, collaboration, and license agreement with a leading global healthcare company, which is testing this result for a potential pharmaceutical product.

HR EXCELLENCE IN RESEARCH

FUNDS AND EMPLOYEES

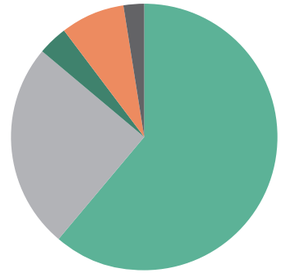
IPHYS IS SUCCESSFUL IN ATTRACTING RESEARCH FUNDING AT BOTH THE NATIONAL AND INTERNATIONAL LEVEL.

FINANCING BY THE TYPE OF RESOURCES
2019



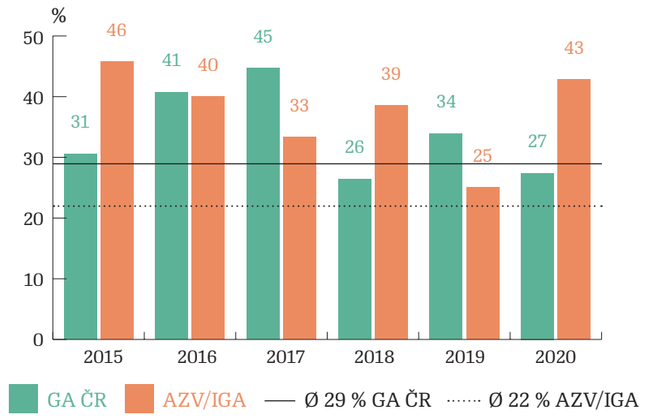
Grants (39 %)
Own resources (14 %)
Institutional (47 %)

FUND PROVIDERS
2019
(Number of projects)

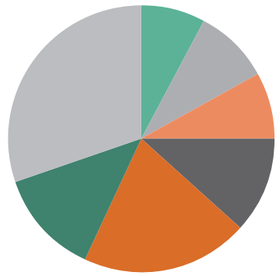


GA ČR (54)
AZV (22)
TA ČR (3)
MŠMT (7)
others EU (2)

SUCCESS RATES FOR GRANT FUNDING BY MAJOR DOMESTIC AGENCIES

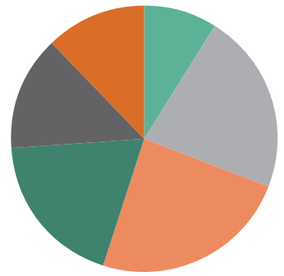


PROFESSIONAL CATEGORY STRUCTURE OF EMPLOYEES
2019



Senior scientist (35)
Junior scientist (41)
Postdoctoral fellow (35)
Research assistant (52)
PhD student (90)
Other scientific staff (57)
Others (133)

AGE STRUCTURE OF EMPLOYEES
2019

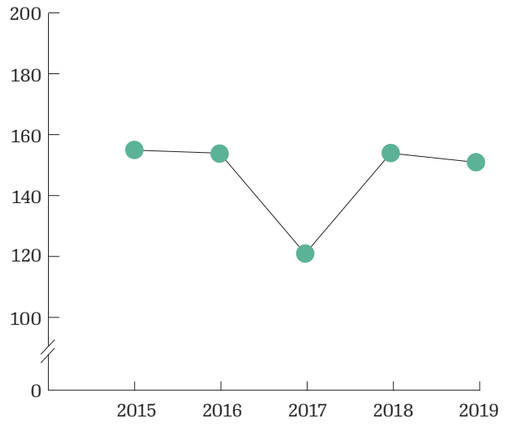


up to 25 years (9 %)
26–30 years (22 %)
31–40 years (24 %)
41–50 years (19 %)
51–60 years (14 %)
above 61 years (12 %)

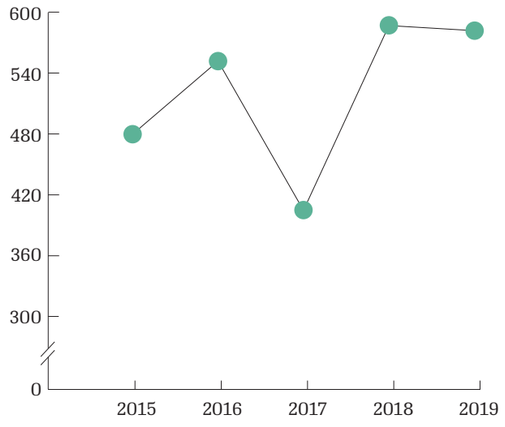
PUBLICATIONS 2015—2019

PUBLICATIONS IN IMPACT FACTOR (IF) JOURNALS IN ASEP DATABASE

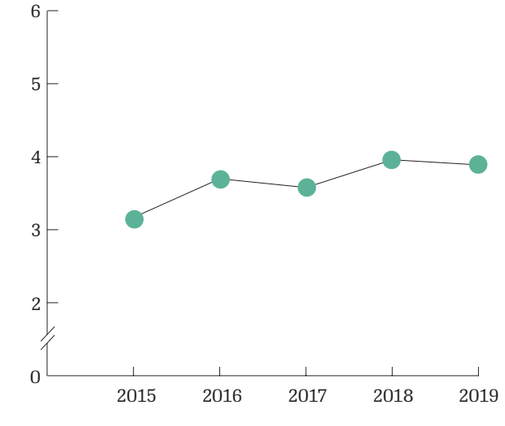
TOTAL NUMBER OF PUBLICATIONS



TOTAL IF



AVERAGE IF PER PUBLICATION



MOST CITED PAPERS THE TOP TENS

DATA VALID TO 31TH JUNE 2020

Only the publications with the first or corresponding author with the affiliation to IPHYS are listed.

Publications with the highest number of citations over the history of IPHYS:

1. **Ježek P.**, **Hlavatá L.**: Mitochondria in homeostasis of reactive oxygen species in cell, tissues, and organism. *Int J Biochem Cell Biol* 37(12), 2478–2503 (2005). No. of citations: 494
2. **Bačáková L.**, **Filová E.**, **Pařízek M.**, Ruml T., Švorčík V.: Modulation of cell adhesion, proliferation and differentiation on materials designed for body implants. *Biotechnology Advances* 29(6), 739-767 (2011). No. of citations: 476
3. **Dobiášová M.**, Frohlich J.: The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FERHDL). *Clin Biochem* 34(7), 583–588 (2001). No. of citations: 487
4. **Vaněček J.**: Cellular mechanisms of melatonin action. *Physiol Rev* 78(3), 687–721 (1998). No. of citations: 453
5. Hubner N., Wallace C. A., Zimdahl H., Petretto E., Schulz H., Maciver F., Mueller M., Hummel O., Monti J., **Zídek V.**, **Musilová A.**, **Křen V.**, Causton H., Game L., Born G., Schmidt S., Müller A., Cook S. A., Kurtz T. W., Whittaker J., **Pravenec M.**, Aitman T. J.: Integrated transcriptional profiling and linkage analysis for identification of genes underlying disease. *Nature Genet* 37(3), 243–253 (2005). No. of citations: 396
6. **Vaněček J.**, **Pavlík A.**, **Illnerová H.**: Hypothalamic melatonin receptor-sites revealed by autoradiography. *Brain Res* 435(1–2), 359–362 (1987). No. of citations: 385
7. Pařízek J., **Ošťádalová I.**: Protective effect of small amounts of selenite in sublimate intoxication. *Experientia* 23(2), 142–143 (1967). No. of citations: 368
8. **Vyskočil F.**, **Bureš J.**, Kříž N.: Potassium-selective microelectrodes used for measuring extracellular brain potassium during spreading depression and anoxic depolarization in rats. *Brain Res* 39(1), 255–259 (1972). No. of citations: 362
9. **Gutmann E.**: Neurotrophic relations. *Ann Rev Physiol* 38, 177–216 (1976). No. of citations: 313
10. **Tuček S.**: Regulation of acetylcholine synthesis in the brain. *J Neurochem* 44(1), 11–24 (1985). No. of citations: 258

Publications with the highest number of citations over the last 10 years:

1. **Bačáková L.**, **Filová E.**, **Pařízek M.**, Ruml T., Švorčík V.: Modulation of cell adhesion, proliferation and differentiation on materials designed for body implants. *Biotechnol Adv* 29(6), 739–767 (2011). No. of citations: 476
2. **Jiruška P.**, de Curtis M., Jefferys J. G. R., Schevon C. A., Schiff S. J., Schindler K.: Synchronization and desynchronization in epilepsy: controversies and hypotheses. *J Physiol* 591(4), 787–797 (2013). No. of citations: 207
3. **Ježek K.**, Henriksen E. J., Treves A., Moser E. I., Moser M. B.: Theta-paced flickering between place-cell maps in the hippocampus. *Nature* 478(7368), 246–249 (2011). No. of citations: 155
4. **Obšil T.**, **Obšilová V.**: Structure/function relationships underlying regulation of FOXO transcription factors. *Oncogene* 27(16), 2263–2275 (2008). No. of citations: 143
5. **Rossmeisl M.**, **Macek Jílková Z.**, **Kuda O.**, **Jeleník T.**, **Medříková D.**, Staňková B., Kristinsson B., Haraldsson G. G., Svensen H., Stoknes I., Sjövall P., Magnusson Y., Balvers M. G. J., Verhoeckx K. C. M., Tvrzická E., Bryhn M., **Kopecký J.**: Metabolic effects of n-3 PUFA as phospholipids are superior to triglycerides in mice fed a high-fat diet: Possible role of endocannabinoids. PLoS ONE 7(6), e38834 (2012). No. of citations: 136
6. **Mráček T.**, **Drahota Z.**, **Houštěk J.**: The function and the role of the mitochondrial glycerol-3-phosphate dehydrogenase in mammalian tissues. Biochim Biophys Acta-Bioenergetics 1827(3), 401-410 (2013). No. of citations: 131
7. **Smolková K.**, **Plecitá-Hlavatá L.**, Bellance N., Benard G., Rossignol R., **Ježek P.**: Waves of gene regulation suppress and then restore oxidative phosphorylation in cancer cells. Int J Biochem Cell Biol 43(7), 950-968 (2011). No. of citations: 127
8. Masoodi M., **Kuda O.**, **Rossmeisl M.**, **Flachs P.**, **Kopecký J.**: Lipid signalling in adipose tissue: Connecting inflammation & metabolism. Biochim Biophys Acta - Mol Cell Biol Lipids 185(4), 503-518 (2015). No. of citations: 116
9. **Vandrovcová M.**, **Bačáková L.**: Adhesion, growth and differentiation of osteoblasts on surface-modified materials developed for bone implants. Physiol Res 60(3), 403-417 (2011). No. of citations: 113
10. **Fenton A. A.**, Lytton W. W., Barry J. M., Lenck-Santini P. P., **Zinyuk L.**, **Kubík Š.**, **Bureš J.**, Poucet B., Muller R. U., **Olypher A. V.**: Attention-like modulation of hippocampus place cell discharge. J Neurosci 30(13), 4613-4625 (2010). No. of citations: 9

SELECTED AWARDS

THE WORLD-RENOWNED IPHYS EXPERTS REGULARLY GAIN RECOGNITION FOR THEIR SCIENTIFIC WORK AND RECEIVE MAJOR DOMESTIC AND FOREIGN AWARDS.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2020

RNDr. Zdeněk Drahota, DrSc. 6	Jan Evangelista Purkinje Honorary Field Medal for merit in the biomedical sciences
Doc. PharmDr. Alena Sumová, DSc. 6	Vojtěch Náprstek Honorary Prize Medal for merit in the popularization of science

2019

Prof. MUDr. Ladislav Vyklický, DrSc. 4	Prize of the Minister of Health for an exceptional result in research and development
Prof. RNDr. František Kolář, CSc.	Jan Evangelista Purkinje Honorary Field Medal for merit in the biomedical sciences
RNDr. Jaroslav Kuneš, DrSc. 2	G. J. Mendel Honorary Field Medal for merit in the biological sciences

2018

RNDr. Ondřej Kuda, Ph.D. 7	Lumina Quaeruntur – a prize for the prospective researchers
Prof. RNDr. František Vyskočil, DrSc. 5	Prize of the President of the Czech Academy of Sciences for the promotion and popularization of research, experimental development, and innovations

2017

Prof. RNDr. Helena Illnerová, DrSc.	Josef Hlávka Medal
MUDr. Josef Houštěk, DrSc. and his team	Prize of the Czech Academy of Sciences for the exceptional results in the field of energy metabolism and mechanisms behind mitochondrial diseases

2016

Prof. MUDr. Tomáš Radil, DrSc.	Award from Mensa Czech Republic for significant contribution to the nation's intelligence, promotion of intellectual culture, and spreading the good name of the Czech Republic in the world
Prof. RNDr. František Vyskočil, DrSc.	Medal of the Czech Learned Society for meritorious contributions to the advancement of science
Prof. MUDr. Bohuslav Ošťádal, DrSc. 1	G. J. Mendel Honorary Field Medal for merit in the biological sciences
Prof. MUDr. Pavel Mareš, DrSc.	Epileptology European Award 2016 for contributions to European epileptology

2015

Prof. RNDr. Helena Illnerová, DrSc. 3	Prize of the President of the Czech Academy of Sciences for the promotion and popularization of research, experimental development, and innovations
Ing. Michal Pravenec, DrSc. 8	Praemium Academiae award for outstanding scientific contribution
Prof. RNDr. Helena Illnerová, DrSc.	Ariens Kappers medal from European Biological Rhythms Society

STUDENTS AT IPHYS

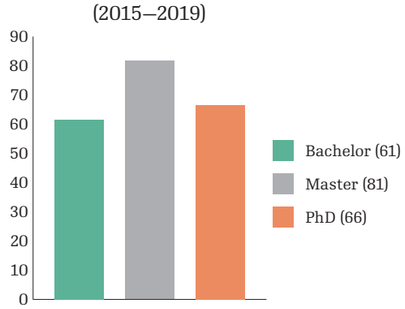
IPHYS PROVIDES TRAINING FOR STUDENTS OF BACHELOR'S, MASTER'S AND DOCTORAL DEGREE PROGRAMMES IN COOPERATION WITH A NUMBER OF CZECH UNIVERSITIES AND INTERNATIONAL INSTITUTIONS.

PhD PROGRAMME

Currently, around 70 PhD students are trained at IPHYS. PhD candidates enroll once per year in an open call with a deadline in March (the specific dates and deadlines are present at the IPHYS website). The candidates submit an online application form, in which they provide a detailed CV and research interests and choose up to three IPHYS research groups. The application is then evaluated by the principal investigators and the best candidates are selected to join the IPHYS PhD programme.

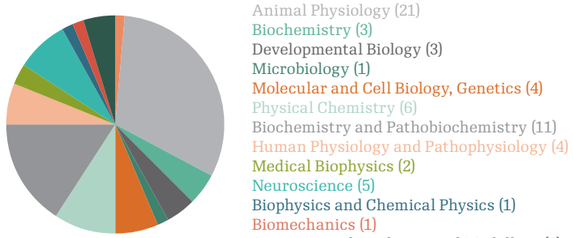
THESES DEFENDED

(2015–2019)



SCIENTIFIC FIELDS (PhD)

(Number of theses)
(2015–2019)



PhD STUDENTS ACTIVITIES AND BENEFITS

- **research** in the fields of neuroscience, cardiovascular physiology, and metabolism
- **use of up to date** physiological, biochemical, and molecular biology **methods**
- employment with up to the full time salary and **benefits**
- participation in **regular events** organized for PhD students (seminars, physiological methods course, biannual conference of IPHYS PhD students)
- **advancement report** of the third year PhD students and the **internal PhD thesis** evaluation
- **English** language courses
- modern **campus** with on-site accommodation
- **sports** facilities

OUTREACH ACTIVITIES

IPHYS ORGANIZES NUMBER OF EVENTS DURING ALL THE YEAR

ACTIVITIES FOR THE PROFESIONAL PUBLIC

Publicly accessible lectures of invited scientists from fields related to IPHYS research as well as those of IPHYS employees are organized weekly and include Bureš's lectures being delivered by first-class invited scientists.

ACTIVITIES FOR THE GENERAL PUBLIC

IPHYS research results are regularly presented at various science festivals organized by the Czech Academy of Sciences. In addition, several successful popular-science interactive programmes presenting the physiology of the human body and IPHYS research topics have been implemented recently.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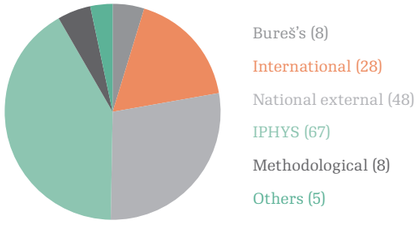
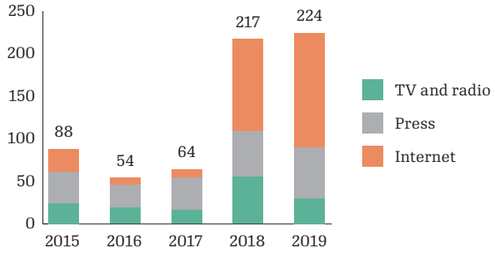
LECTURES FOR PROFESSIONAL PUBLIC

(2015–2019)



MEDIA COVERAGE OF IPHYS

(2015–2019)



1 BUREŠ'S LECTURE SERIES The lecture series was initiated in 2013 as part of the celebration of 60th anniversary of the establishment of IPHYS. The series is named in the honour of Jan Bureš (1926–2012), an outstanding neuroscientist (Laboratory of Neurophysiology of Memory), who worked at IPHYS from its foundation. Invited speakers between 2015–2019 were Stephan Herzig (Germany); Annamaria Vezzani (Italy); Masashi Yanagisawa (Japan); Philipp Scherer 1 (USA); Hana Antonicka (Canada); Victor Hruby (USA); Michael P. Czech (USA); Grant Pierce (Canada).

2 OPEN HOUSE DAY The Laboratories of IPHYS are opened to the public annually in November during the Week of Science and Technology.

3 PURKINJE CHAMBER OF PHYSIOLOGY An interactive exhibition, which is presented during Open House Day, explains biological clocks, the functioning of muscles, the significance of heartbeat frequency, and uncovers many other functions of the human body.

4 MEMORY PARK An interactive workshop with eleven unique psychological tests of memory and orientation skills, some of them developed at IPHYS (Laboratory of Neurophysiology of Memory) is offered to the public several times a year.

5 WEEK OF THE BRAIN IPHYS researchers participate every year in the Week of the Brain – a unique cycle of lectures on the newest discoveries and trends in brain research and neuroscience, which is a part of the worldwide Brain Awareness Week.

6 THE HUMAN BODY IN HEALTH AND DISEASE Joint presentations of IPHYS's researchers and clinicians presenting collaboration between experts from basic research and clinical specialists, essential for the development of novel diagnostic and therapeutic procedures, are organized twice a year.

7 SCIENCE EXPO IPHYS participates in the annual Science Expo, a large festival of the Czech Academy of Sciences (30 000 visitors in 2019). The new exhibition of IPHYS entitled "Research of diseases from a molecule to the whole body" covering most of the IPHYS's research was created in 2018.

8 OPEN SCIENCE The Czech Academy of Sciences offers student internships every year within the Open Science project, which allow high-school students to access scientific institutes and laboratories and motivate them to follow a career path in sciences. Students involved in the Open Science projects at IPHYS regularly achieve prestigious awards at the final Conference of Open-Science Students.

CONTACTS

DIRECTOR'S OFFICE

Petra Kubátová
petra.kubatova@fgu.cas.cz
+420 241 062 424

COMMUNICATIONS

Diana Moosová
diana.moosova@fgu.cas.cz
+420 241 062 413

HUMAN RESOURCES

Marcela Tomášková
marcela.tomaskova@fgu.cas.cz
+420 241 062 225

GRANT OFFICE

Ing. Kristýna Knězů
kristyna.knezu@fgu.cas.cz
+420 241 062 727

INSTITUTE OF PHYSIOLOGY OF THE CZECH ACADEMY OF SCIENCES

Vídeňská 1083
142 20 Prague 4-Krč

Tel.: +420 241 062 424

fgu@fgu.cas.cz
www.fgu.cas.cz
FyziologickyUstavAVCR

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Editors: MUDr. Jan Kopecký, DrSc., Ing. Olga Zimmermannová, Ph.D., Diana Moosová