

MILESTONES IN IPHYS HISTORY 1954-2024

•	1954	IPHYS founded – three Departments: Neuromuscular Physiology (E. Gutmann), Developmental Physiology and Pathology (J. Křeček), and Excitability of Central Nervous System (Z. Servít)
•	1956	IPHYS journal Physiologia Bohemoslovaca (since 1991 Physiological Research) is published in English
•	1961	The Department of Physiology and Pathophysiology of Metabolism is added (O. Poupa)
•	1964—1965	IPHYS is moved to the new campus of biological institutes of the Czech Academy of Sciences in Prague - Krč
•	1980—1989	Four Sectors are established: Neurophysiology (T. Radil), Developmental Physiology (J. Jelínek), Biological and Experimental Models (P. Klír), and Cellular and Molecular Physiology (J. Houštěk)
•	1990	IPHYS under democracy: The Scientific Council voted for the first time for the director of IPHYS Twenty-one scientific departments are established Beginning of the scientometric evaluation of research activities: IPHYS is one of the best institutes of the Czech Academy of Sciences
•	2001—2005	H. Illnerová (IPHYS) becomes the President of the Czech Academy of Sciences
•	2009	Opening of the new building (A2 wing) of IPHYS
	2014	The first junior research group established
•	2016	Opening of OFF-campus laboratories in BIOCEV (European Scientific Centre of Excellence in Biotechnology and Biomedicine in Vestec)
•	2019	IPHYS is awarded the prestigious European HR Excellence in Research Award
•	2020	International Advisory Board of IPHYS is established
•	2021—2024	Reconstruction of Animal facility
	2024	Three research fields: Neuroscience, Cardiovascular Research, and Metabolic Research Twenty-one scientific laboratories and one junior research group

General aim: the characterization of basic biological mechanisms to improve the prevention, diagnosis and treatment of serious non-communicable diseases

70 YEARS OF SCIENCE AT IPHYS 1954-2024 FOR RELATED ARTICLES, SEE PAGE 89



					Metabolomics, proteomics, bi	ioinformatics	
					Molecular physiology of	of the bone	_
				Therape	utic lithium-induced alteration of	rat brain	
METADOLIC DEGEADOLI					Metabolism of bioactive lipids	S	
				Unique drugs for obesity type 2	Molecular lieuropiology	1	_
CARDIOVASCULAR RESEARCH			Cardiao	sischemic tolerance, systemic hyr	ertension and heart failure		
			3D superresolution mic	roscopy of mitochondria and mtD	NA nucleoids		
NEUROSCIENCE			*	Circadian rhythms in physiologic	al functions		
			Redox signallin	g and mitochondrial phospholipas	se l		
INTERDISCIPLINARY RESEARCH			Effe	cts of omega 3 fatty acids on healt	h		_
			Nitric oxide-deficient or angio	tensin-dependent hypertension			
			P2X re	ceptors, structure and function			
			Morphine-induced alteration	on of opioid- and TRH-receptors			_
			Mitochondrial	liseases - cytochrome c oxidase			
			Structural	biology of signalling proteins			_
			Neuropathic	pain and neuroinflammation			
		Influe	nce of lipid-based diets on the progre	ession of Alzheimer's disease			
			Animal models of	t neuropsychiatric disorders			
		01	Bone and si	kin tissue engineering			_
		Struct	ure and function of transient recepto	or potential channels			
			Vascular ussue el				
		Agonist	biomathematics - mag				_
		Svetamic	affacts of white adinose tissue meta	bolism			
		Nitric oxid	e and glutamate at neuromuscular in	inction			
		There only	Mitochondrial diseases - ATP su	nthase			
		Age-related mechanism	s of epileptic seizures and epileptoge	enesis			
		Muscarinic receptors. a	allosteric modulators and signalling	bias			_
		GAE	A, receptors and synaptic transmiss	ion			
			Circadian rhythms in huma	ins			
		Genetics of sp	oontaneous hypertension				
		Excitatory	y synaptic transmission				
		Melatonin receptors and intrace	llular signalling				
		Ion and nutrient transport in eul	xaryotic cells				
		Epithelial transport and intestina	l functions				
	Myocare	dial sensitivity to hypoxia – sex diff	erences				_
		Vascular cell p	bhysiology				
	Fatty acid cycling mechanin	ns of mitochondrial uncoupling pr	oteins				
		Memory, spatial learni	ng				_
		Computational neuroscience	e				
		s and Na'/K'-Al Pase in the brain					
	Developmental neuropnarma	Acology of antieplieptic drugs					
	Electrogenic Na /	Rota adronorgia recontors					
Non-gu	antal release of acetylcholine and neuromus	scular transmission					
1011 qu	Altered control of vascular tone in hy	nertension					_
Ion-selective microelec	trodes and K ⁺ concentrations in muscle and	brain					
Brown adipose tis	sue development and its thermogenic functi	on					_
Periodizatio	n of early postnatal development in the rat						
Acetylcholine synthesis and	celease in nervous and non-nervous tissues						
Developmenta	al models of epileptic seizures and epilepsy						
	Circadian rhythms in brain						_
	Pain mechanisms						_
	Ionotropic glutamate receptors						_
Protect	ive and toxic effects of selenium						
Chromatographic methods	– collagen and elastin studies						
Mechanisms of age	-dependent salt hypertension						
Cardioprotec	tive effect of chronic hypoxia						_
Cardi	otoxicity of catecholamines						
Acetylcholine receptors	at neuromuscular junction						
	Cell cultures						
	Neurocytology						
Mitochondrial calcium and glycerol-3-phosp	hate dehydrogenase						
Cardiac development and se	insitivity to hypoxia						
Epilepsy and brain m	etabolism						
Ontogeny of animal be	shaviour						
Lipid metabolism – Cholesterol tra	nsport						
Higher brain fund	110NS						
Clinical and translational epileptolog	/						
IOXIC EFFECTS OF MERCUry and cadmium							
r and electrolyte metabolism, body huids, ion transport							
Spreading depression							
Neurotrophic effects in skeletel musels							
Musele physiology							
Critical periods of development peripatal programming							
stated periods of development, permatal programming			1001				
1954	1964	1974	1984	1994	2004	2014	

SCIENTISTS INVOLVED

Čajka, Kuda, Vrbacký encerová ošahlíková, Roubalová, Brejchová, Svoboda Balaštík uneš, Maletínská eckář, Kolář, Hlaváčková ežek, Dlasková umová, Sládek zek, Plecitá-Hlavatá, Jabůrek Copecký, Flachs, Rossmeisl, Kuda, Janovská, Bardová, Horáková uneš, Vaněčková, Zicha emková, Vávra, Bhattacharya jčíková, Roubalová, Svoboda ouštěk, Pecina)bšilová, Obšil, Košek aleček, Špicarová oležal, Jakubík, Janíčková aleš, Stuchlík ačáková, Brož yklický Sr., Vlachová, Teisinger ačáková, Filová ubínová, Janáček, Hadraba woboda, Novotný, Brejchová, Vošahlíková opecký, Flachs, Rossmeisl, Janovská, Bardová yskočil Jouštěk, Mráček, Klement, Ješina ubová, Jiruška uček, Doležal, Jakubik, Randáková emková, Krůšek lnerová, Sumová ravenec yklický, Vlachová, Krůšek, Smejkalová, Kořínek aněček, Zemková, Balík, Svobodová otyk, Horák, Sychrová, Zimmermannová apek, Pácha, Kolínská, Horáková)šťádal, Kolář, Pelouch, Ošťádalová ačáková, Lisá, Mareš V žek, Jabůrek Bureš, Burešová, Fenton, Stuchlík ánský, Košťál, Zápotocký voboda, Teisinger Aareš P, Kubová, Velíšek vskočil, Zemková-Dlouhá, Teissinger, Svoboda voboda yskočil, Zemková, Doležal lbrecht, Zicha, Kuneš, Behuliak, Vaněčková vskočil, Hník, Kříž Jahn, Skála, Houštěk, Drahota, Kopecký, Svoboda, Ježek, Rossmeisl, Zouhar)šťádalová, Babický, Pařízek 'uček, Doležal /lareš P, Kubová llnerová Vaněček Sumová yklický Sr, Vlachová, Paleček, Špicarová yklický, Vlachová, Krůšek, Smejkalová, Hrčka Krausová, Balík, Kořínek)šťádalová, Pařízek evl, Macek, Mikšík elínek, Kuneš, Zicha, Vaněčková oupa, Ošťádal, Pelouch, Kolář, Neckář, Hlaváčková oupa, Ošťádal, Faltová eránek Vyskočil olečková, Michl, Baudyšová, Tolar, Mareš V odin, Mareš V)rahota, Houštěk, Mráček oupa, Ošťádal, Kolář, Ošťádalová olbergrová, Kubová, Otáhal át, Nováková, Šterc, Martínek lahn, Koldovský, Dobiášová, Drahota adil, Bohdanecký, Indra, Mates ervít, Mareš P, Jiruška Yřeček, Jelínek, Dlouhá, Kuneš, Zicha Bureš, Burešová, Křivánek elená, Hník, Hudlická, Jirmanová, Soukup, Vejsada utmann, Žák, Vrbová, Beránek, Hník, Syrový, Vejsada, Paleček utmann, Hanzlíková, Hník, Bass, Syrový, Soukup lahn, Křeček, Koldovský, Houštěk, Kopecký



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



This year, we celebrate 70 years of the Institute of Physiology (IPHYS) of the Czech (former Czechoslovak) Academy of Sciences (CAS). True to its name, IPHYS has been systematically dedicated to research in the field of normal and pathological physiology, with a special focus on biomedical research. Three main, closely interconnected research directions have gradually crystallized, which IPHYS continues to pursue today: research in the fields of neuroscience, cardiovascular physiology, and metabolism.

Over the last seven decades, our society has grown considerably older and fatter, and obesity rates have tripled. Modern medicine is thus facing new challenges in the form of an increased onslaught of so-called lifestyle (also civilization) diseases. The cost of their treatment represents a major burden on healthcare systems worldwide. The main current goal of IPHYS is to characterize the causes of these non-communicable diseases associated with obesity and aging. We are characterizing the basic biological mechanisms in order to improve the prevention, diagnosis, and treatment of pathological conditions:

1. affecting the nervous system, such as Alzheimer's disease, epilepsy, and chronic pain;

2. linked to obesity, such as cardiovascular disease and diabetes; and

3. inherited diseases, especially those affecting mitochondrial energy metabolism.

Our research is also focused on developmental aspects, reflecting the notion that susceptibility to lifestyle diseases depends in part on various factors impacting pregnancy and birth.

IPHYS is well-equipped for biomedical research. The fundamental reconstruction of our animal facility was finished in the spring of 2024. IPHYS's instrumentation provides probably the best opportunities in the Czech Republic for the whole-body phenotyping of animal models of various diseases, including analyses of metabolism, body composition, blood pressure, cardiac functions, and animal behavior. Instruments for various imaging applications are available thanks to IPHYS's involvement in the CzechBioimaging infrastructure. High-throughput analytical methods are routinely performed in the service laboratories of Metabolomics (established in 2017) and Proteomics (established in 2020). Bioinformatics is being introduced to interpret all of these data, however the experience and knowledge of the researchers are the keys to understanding complex relationships.

We combine experiments on laboratory animals and cell models with clinical research. This is facilitated by IPHYS's participation in research consortia supported by the National Recovery Plan (2022-2025), i.e. in the National Institute for Metabolic and Cardiovascular Disease Research (CarDia; www. cardia.ikem.cz) and in the National Institute for Neurological Research (NPO-NEURO-D; www.ninr.cz). Thus, IPHYS collaborates with leading centers of clinical and academic research in our country, and also numerous partners in Europe and worldwide. Special partnerships with Czech universities provide IPHYS with the opportunity to serve as an important place for pre- and postgraduate education.

This brochure updates the information provided in the previous one, released in 2020. 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 summer of 2024.

I am looking forward to continuing to serve as the Director of IPHYS to the end of 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 that the future is bright for IPHYS.

Jan Kopecký director of IPHYS

Kopecky

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?

- IPHYS has a more than 70-year tradition (6-7)
- Research at IPHYS includes three main topics: neuroscience, cardiovascular research, and metabolic research (9–11)
- IPHYS is supervised by the director and the IPHYS Boards (12-14)
- IPHYS consists of 22 scientific laboratories and includes off-campus laboratories in BIOCEV within an excellent joint project of six institutes of the CAS and Charles University (15-60)
- Necessary services at IPHYS are provided by 10 service departments, including the Centre for Preclinical Testing (61–71)
- IPHYS publishes the peer-reviewed journal Physiological Research 🚯
- A new facility for research animals was constructed at IPHYS (72–73)
- The European Commission awarded IPHYS the prestigious European HR Excellence in Research Award protecting also intellectual property of IPHYS (74)
- IPHYS has almost 410 employees with 60 principal investigators (75)
- Most of IPHYS research is conducted within the framework of national and international collaborations (76-78)
- IPHYS is a member of two European infrastructures Czech Bioimaging and EPTRI (79)
- More than 120 scientific articles are published per year by scientists of IPHYS (80-81)
- IPHYS employs world-renowned experts awarded major domestic and foreign prizes for their scientific work (82–83)
- Dozens of bachelor's, master's and PhD students are trained at IPHYS in collaboration with universities (84–85)
- Results obtained at IPHYS are actively disseminated to the scientific community as well as to the general public (86–87)
- More than 75 research topics have been studied at IPHYS since 1954 (89-107)

HISTORY OF IPHYS

DIRECTORS OF THE INSTITUTE



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 (ČSAV) 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.







since 2015	9 MUDr
2010-2015	⁸ RNDr.
2003-2010	7 RNDr.
1995-2003	6 Prof. N
1990-1995	5 Prof. N
1980-1989	4 RNDr.
1970-1980	3 MUDr
1970	2 Prof. N
1954-1969	1 Prof. N

. Jan KOPECKÝ, DrSc. Lucie KUBÍNOVÁ, CSc. Jaroslav KUNEŠ, DrSc. MUDr. Pavel MAREŠ, DrSc. MUDr. Bohuslav OŠŤÁDAL, DrSc. Zdeněk DRAHOTA, DrSc. . Ladislav VYKLICKÝ, DrSc. MUDr. Jiří KŘEČEK, DrSc. 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

DISEASES IN FOCUS

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.



OBESITY AND METABOLIC SYNDROME DIABETES MELLITUS TYPE 2 INHERITED METABOLIC DISEASES **DISEASES OF THE INTESTINE** CANCER **INFECTIONS BY YEASTS** OSTEOPOROSIS

IPHYS MANAGEMENT



Director MUDr. Jan Kopecký, DrSc.



Deputy Director for Science MUDr. Jiří Paleček, CSc.



Deputy Director for Administration Ing. Petra Janečková



Chairman **Board of IPHYS** RNDr. Ondřej Kuda, Ph.D.

BOARD OF INSTITUTE OF IPHYS

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Internal Members Mgr. Martin Balaštík, Ph.D. Mgr. Jan Jakubík, Ph.D. Prof. RNDr. František Kolář, CSc. RNDr. Ivana Vaněčková, DSc.

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BIOCEV Secretary

Mgr. Adéla Bocková, Ph.D.

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Prof. MUDr. Vojtěch Melenovský, CSc. Institute for Clinical and Experimental Medicine, Prague

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Members

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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 ZACHOVEJTE TICHO JE NEZBYTNÉ K POKUSÚM Laboratory of Adipose Tissue Biology (16) Laboratory of Bioenergetics (18) Laboratory of Biological Rhythms (20) Laboratory of Biomaterials and Tissue Engineering (22) Laboratory of Biomathematics (24) Laboratory of Cellular Neurophysiology (26) Laboratory of Computational Neuroscience (28) Laboratory of Developmental Cardiology (30) Laboratory of Developmental Epileptology (32) Laboratory of Experimental Hypertension (34) Laboratory of Genetics of Model Diseases (36) Laboratory of Membrane Transport (38) Laboratory of Metabolism of Bioactive Lipids (40) Laboratory of Mitochondrial Physiology (42) Laboratory of Molecular Neurobiology (44) Laboratory of Molecular Physiology of Bone (46) Laboratory of Neurochemistry (48) Laboratory of Neurophysiology of the Memory (50) Laboratory of Pain Research (52) Laboratory of Structural Biology of Signalling Proteins (54) Laboratory of Translational Metabolism (56) BIOCEV (58) - Junior Research Group: Laboratory of Pancreatic Islet Research (60) *KEEP SILENCE It is necessary for experiments





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We study the physiological regulation of metabolism and its disturbances in obesity and related diseases (i.e. METABOLIC SYNDROME), focusing mainly on adipose tissue, the liver, skeletal muscle and intestine. In this context, we investigate the effects of drugs, experimental diets and natural substances such as n-3 polyunsaturated fatty acids of marine origin (OMEGA-3S), as well as the metabolic benefits of exercise. Our results emphasize the key role of ADIPOSE TISSUE METABOLISM in the development as well as treatment of obesity-related diseases. Our advanced methodological repertoire includes gene expression screening by RNA sequencing, gene transfer by viral vectors, metabolomics, proteomics, histological analysis, as well as the *in vivo* phenotyping of energy metabolism, body composition and insulin sensitivity in mice. By combining experiments in mice and cell models with clinical studies, we aim to apply new findings in clinical medicine.

CURRENT PROJECTS

BASIC RESEARCH



Basic research in the Laboratory is conducted by two Research units with complementary focus, which closely collaborate and are engaged in translational research carried out jointly with clinical centres as well as industrial partners from the Czech Republic and Norway.

SELECTED OUTPUTS

- The differential induction of lipid cycling in white fat and fatty acid release from the tissue (Flachs et al. (2017) Int | Obes 41:372-380) correlate with non-shivering thermogenesis in skeletal muscle (Janovska et al. (2023) Mol Metabolism 69:101683) and a genetically determined propensity to obesity in mice; the muscle phenotype could be imprinted early after birth (Buresova et al. (2020) Int J Obes 44:235-244).
- 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).
- Metformin inhibits intestinal glucose transport to acutely lower blood glucose (Horakova et al. (2019) Sci Rep 9:6156).
- Muscle 11:1614-1627).
- Exercise training induces PAHSA lipokines in adipose tissue of humans (Brezinova et al. (2020) BBA Mol Cell Biol Lipids 1865:158576).

Dysregulation of adipose tissue metabolism in cardiac patients with cachexia (Janovska et al. (2020) J Cachexia Sarcopenia



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We study the physiology of **MITOCHONDRIA**, cell organelles responsible for most of the energy production at the molecular level. We have a long track record in mitochondrial diseases due to deficiencies in F1Fo ATP synthase. Our laboratory 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 animal as well as cell-derived models to study biochemical changes associated with 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



(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 c15orf61 signal with mitochondria in HEK293 cells.

SELECTED OUTPUTS

- Markovic et al.: Genetic Complementation of ATP synthase deficiency due to dysfunction of TMEM70 assembly factor in rat (2022) Biomedicines 10.(2):276.
- Cunatova et al.: Loss of COX4I1 leads to combined respiratory chain deficiency and impaired mitochondrial protein synthesis (2021) Cells 10.(2):369.
- the rotor structure of the enzyme (2019) FASEB J 33(12):14103-14117.
- 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.

• Kovalciková J. et al.: TMEM70 facilitates biogenesis of mammalian ATP synthase by promoting subunit c incorporation into



BIOLOGICAI RHYTHMS

head Prof. PharmDr. Alena Sumová, DSc. 1 alena.sumova@fgu.cas.cz key researchers Helena Illnerová – emeritus, Martin Sládek 2 PhD students Tereza Dočkal 3 Milica Drapšin, Dmytro Semenovykh 4 Kateryna Semenovykh 5 technicians Pavel Houdek 6 Eva Suchanová 7

Our focus of interest is the endogenous time-keeping system, the CIRCADIAN CLOCKS, of mammals, including humans. The system anticipates regular changes in the environment and temporally regulates physiological processes, so that they take place at the proper time of day in synchrony with external time and relative to each other, resulting in tissue-specific BIOLOGICAL RHYTHMS. A failure of this temporal regulation has a negative impact on HUMAN HEALTH. Using in vivo and in vitro models and diverse approaches including animal behavior analysis, time-resolved transcriptomics or real-time monitoring of gene expression in cultured organotypic tissue explants, we study the MOLECULAR MECHANISMS of the circadian clocks, their development and means of regulation. We also investigate the consequences of circadian disruption on human health and collaborate on the development of novel chronopharmacological compounds.

CURRENT PROJECTS

- Ontogenesis of the circadian clock investigating mechanisms of how the biological rhythms develop,
- with focus on the central clock in the suprachiasmatic nucleus of the hypothalamus (SCN)
- roid plexus, and other peripheral tissues are synchronized with signals from the external environment and within our body
- Human circadian system studying the association between the circadian system and health in the general population and in cohorts of patients suffering from disorders associated with disrupted sleep



Multilevel circadian organization from the gene levels to studies of human populations. From left: rhythmically expressed genes in mouse choroid plexus; neurons in hippocampal region CA1 labeled with phosphorylated GSK3b; time-series of PER2 protein levels in suprachiasmatic nuclei from newborn mice visualizing oscillation over 3 days ex vivo; amplitude of PER2 rhythm in individual cells from mouse choroid plexus ex vivo; polar phase plot of rhythmic metabolites in rat plasma; actogram of locomotor activity of mouse before and after SCN lesion; correlation between components of social jetlag; word cloud of keywords from our recent publications.

SELECTED OUTPUTS

- Sládek M., Klusáček J., Hamplová D., Sumová A.: Population-representative study reveals cardiovascular and metabolic disease biomarkers associated with misaligned sleep schedules (2023) Sleep 46(6):zsad037 - The first study showing an association between social jetlag, chronotype and cardio-metabolic health in a representative Czech population.
- Liška K., Dočkal T., Houdek P., Sládek M., Lužná V., Semenovykh K., Drapšin M., Sumová A.: Lithium affects the circadian clock in the choroid plexus - A new role for an old mechanism (2023) Biomedicine & Pharmacotherapy 159:114292 - We showed that lithium affects the circadian clock in the choroid plexus independently of GSK3.
- Greiner P., Houdek P., Sládek M., Sumová A.: Early rhythmicity in the fetal suprachiasmatic nuclei in response to maternal signals detected by omics approach (2022) PLOS Biology 20(5):e3001637 - Using a unique approach, our results indicate the importance of a well-functioning maternal biological clock in providing a rhythmic environment during fetal brain development.
- Honzlová P., Novosadová Z., Houdek P., Sládek M., Sumová A.: Misaligned feeding schedule elicits divergent circadian reorganizations in endo- and exocrine pancreas clocks (2022) Cell Mol Life Sci 79(6):318 - The first evidence in rats and mice that whereas the clock in the endocrine pancreas shifts according to mealtime, the clock in the exocrine pancreas can be severely impaired by incorrect meal timing.
- Nováková M., Praško J., Látalová K., Sládek M., Sumová A.: The circadian system of patients with bipolar disorder differs in episodes of mania and depression (2015) Bipolar Disorders 17:303 - The first evidence for changes in the functional state of the circadian system during episodes of mania and depression.

• Entrainment of the circadian clock - exploring the mechanisms of how the clocks in the SCN, in the cho-

Time (h)



BIOMATERIALS AND TISSUE ENGINEER

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The Laboratory is subdivided into three research groups: VASCULAR TISSUE ENGINEERING, SKIN TISSUE ENGINEERING and CONNECTIVE TISSUE ENGINEERING (e.g. bone, cartilage). Within each group, the main tasks are (1) to improve currently-used tissue replacements by introducing cell and other biological components, (2) to construct completely new replacements on the basis of biomaterials and cells, and (3) to create **3D TISSUE MODELS** in vitro in order to replace laboratory animals in modern science according to the 3R principle. Our detached part of the laboratory at BIOCEV in Vestec near Prague, deals with the creation of tissue models based on SPHEROIDS AND ORGANOIDS, such as the in vitro model of glioblastoma. We use differentiated cells or STEM CELLS (derived from adipose tissue, bone marrow and Wharton jelly, or induced pluripotent stem cells) as the cell component of our constructs. The phenotypic maturation of cells is accelerated by mechanical stimulation in DYNAMIC BIOREACTORS. We are also developing the **3D BIOPRINTING** of various matrices together with cells.

CURRENT PROJECTS

- "Praemium Academiae" a large project focused on vascular, skin and bone tissue engineering including creating tissue models
- decellularized matrices
- "Center for Regenerative Medicine" a large OP JAK project focused on vascular and skin tissue engineering and wound healing
- New functionalized plasmon-based sensors as tools for cell monitoring and advanced tissue engineering



Examples of vascular tissue engineering (A-D), skin tissue engineering (E, F) and connective tissue engineering (G, H). Porcine pericardium before (A) and after (B) decellularization, and after recellularization with adipose tissue-derived stem cells and endothelial cells (top view, C) and with endothelial cells stained in brown (cross-section, D). Vascularized Dermal-epidermal skin construct (E) with detail of capillary-like structures (F). 3D bioprinter in laminar flow box (G) and samples of 3D-bioprinted collagen matrix with fibroblasts.

SELECTED OUTPUTS

- We created a decellularized and electron beam-irradiated porcine pericardium matrix as a scaffold for human adiposederived cells, differentiating vascular smooth muscle cells from adipocytes (Filova E. et al. Recellularized pericardium for cardiovascular replacements, utility model No. 36181, 2022)
- We created a dermal-epidermal skin construct as a potential skin replacement or skin model in vitro (Bacakova M. et al. (2019) Int J Nanomedicine 14:5033), further improved by introducing capillary-like structures based on endothelial cells and adipose tissue-derived stem cells (Tomšů J, PhD thesis "Interactions of Skin and Stem Cells with Polymer Nanofibers for Construction of Skin Substitutes")
- We participated in developing various novel bioactive coatings for metallic bone implants that modulate the adhesion, growth and osteogenic differentiation of human bone-derived cells, including stem cells (Brož et al. (2022) Mater Des 224:111373; Gabor et al. (2022) Mater Des 219:110811; Nemcakova et al. (2022) Sci Rep 12:5264; Vandrovcova et al. (2021) Coatings 11:210).

• A novel tissue-engineered *in vitro* model for studying the pathogenesis and treatment of hypertrophic



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CURRENT PROJECTS

• The correlative biomechanics of biomedical materials and tissue





Measurement of capillaries in skeletal muscle. Images from confocal microscope (a). Data are edited using desktop virtual reality with a haptic device (b). Model (c) is used for the calculation of length, directionality and tortuosity.

The Laboratory conducts research into 3D micro-anatomical aspects of physiological phenomena at the mesoscopic, microscopic, and ultrastructural level. We are engaged in a range of collaborative projects across the campus and beyond.

We measure quantitative geometric characteristics of various biological structures based on microscopic methods (3D SHG, CLSM, CARS) using original STEREOLOGICAL METHODS, image processing and virtual reality.

We are currently expanding our focus to include LABEL-FREE IMAGING and imaging methods that capture physiological events at a microscopic scale (FLIM-FRET, PLIM), and are moving towards the microscopic imaging of events in vivo, on 3D constructs and organoids under as close to physiological conditions as possible.

SELECTED OUTPUTS

- We visualized the structure and mechanical properties of tissue obtained from relapsed clubfoot during surgery. Label-free microscopy, AFM and image analysis were done at IPHYS. Vondráček et al. (2023) Microscopy and Microanalysis 29(1): Cover image of the Journal issue.
- Obese insulin-resistant mice increased capillarization selectively around small predominantly intermediate muscle fibres. We developed analytical methods and software and we also participated in the conception and design of the study. Umek et al. (2019) Histochem Cell Biol 152(5):323-331.
- Olejníčková V., Šaňková B., Sedmera D., Janáček J.: Trabecular architecture determines impulse propagation through the early embryonic mouse heart (2019) Front Physiol 9(8):1876.
- Janáček J., Jirák D.: Variance of the isotropic uniform systematic sampling (2019) Image Anal Stereol 38(3):261-267.



CFI I III AR NEUROPHYSIOLOGY

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We study the functional and pharmacological properties of ion channels. We use advanced electrophysiology methods, primarily the **PATCH-CLAMP TECHNIQUE**, combined with analytical techniques, MOLECULAR BIOLOGY, BIOCHEMISTRY, IMMUNOHISTOCHEMISTRY, MICROSCOPY AND MICROFLUOROMETRIC 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 structural, functional, and pharmacological consequences of mutations in genes encoding NMDA receptors associated with neuropsychiatric disorders
- A study of the molecular mechanisms of the positive and negative allosteric modulatory action of ster-
- Investigation of the molecular basis of thermosensitive TRP channel regulation and the role of these channels in the mechanisms of acute and chronic pain



The study of structure, function, and pathophysiology of ionotropic glutamate receptors and TRP ion channels using molecular biology, patchclamp electrophysiology, and behavioral assessment of mouse and zebrafish animal models.

SELECTED OUTPUTS

- In the field of NMDA receptors, we have studied (1) the conformational rearrangement of the NMDA receptor amino-terminal domain during receptor activation, (2) the palmitoylation of NMDA receptors, which controls receptor function and steroid sensitivity, (3) the potentiation of presynaptic glutamate release by pregnanolone and pregnanolone sulfate, (4) the modulation of NMDA receptors by novel pregnane-based steroids, which may compensate for the loss-of-function of mutated NMDA receptors found in patients with neuropsychiatric disorders, and (5) the multiple roles of plasma membrane cholesterol in glutamatergic synaptic transmission. (Vyklicky et al. (2021) Nat Comun 12:2697; Hrcka Krausova et al. (2020) J Neurosci 40(31):5922-5936; Hirschfeldova et al. (2021) J Pers Med 11:1250; Korinek et al. (2020) Sci Rep 10:12651; Hubalkova et al. (2021) | Neurosci 41:2119-2134; Holubova et al. (2021) Biomolecules 11:1026; Smejkalova et al. (2021) Br J Pharmacol 178:3888-3904; Štefková-Mazochová et al. (2022) Br J Pharmacol 179:65-83; Kysilov et al. (2022) Br J Pharmacol 179:3970-3990: Abramova et al. (2023) ACS Chem Neurosci 14:1870-1883).
- We have clarified the structural basis underlying 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 that mediates EGFR-induced sensitization signaling pathways involved in regulating skin homeostasis (Zimova et al. (2020) Front Phys 11:189; Nadezdhin et al. (2021) Nat Struct Mol Biol 28(7):564-572; Sinica et al. (2021) Physiol Res 70:363-381; Zimova et al. (2022) Biomed Pharmacother 152:113262; Ptakova et al. (2022) J Cell Physiol 237:3614-3626; Moparthi et al. (2022) Nat Commun 13:6113; Zhang et al. (2022) Nat Commun 13:7483).



COMPLITA NEUROSCIENCE

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CURRENT PROJECTS

- stimulus encoding schemes
- complexity on neuronal coding efficiency
- during development



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.

The Laboratory of Computational Neuroscience investigates the fundamental MECHANISMS OF INFOR-MATION 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 ACTIV-ITY, 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 (biennial Neural Coding meetings, OCNS workshops).

SELECTED OUTPUTS

- Barta, Kostal: The effect of inhibition on rate code efficiency indicators (2019) PLoS Comput Biol 15:e1007545.
- Levakova et al.: Moth olfactory receptor neurons adjust their encoding efficiency to temporal statistics of pheromone fluctuations (2018) PLoS Comput Biol 14:e1006586.
- Rajdl et al.: Entropy factor for randomness quantification in neuronal data (2017) Neural Networks 95:57-65.
- Smit et al.: Axon tension regulates fasciculation/defasciculation through the control of axon shaft zippering (2017) eLife 6:e19907.
- 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.

• The analysis of stochastic neuronal models and estimation of key biophysical parameters under various • The biophysical modelling of neural connectivity and its dependence on the guided growth of axons



DEVELOPMENTAL CARDIOLOGY

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ISCHEMIC HEART DISEASE is a leading cause of mortality globally. Our research delves into the tolerance of the heart to injuries stemming from acute OXYGEN DEPRIVATION, encompassing examinations from the molecular level to the entire organism using animal models. Our primary focus lies in investigating three fundamental aspects: i) understanding the mechanisms that support robust cardiac tolerance during **EARLY ONTOGENY**, ii) unveiling the enhanced cardiac tolerance achieved through adaptations to CHRONIC HYPOXIA, regular exercise training, and other unconventional interventions, and iii) exploring the modifications in cardiac tolerance that manifest in association with various PATHOLOGICAL CONDITIONS. Furthermore, our research efforts include an investigation into the pathogenetic mechanisms at play in the initiation and progression of cardiomyopathy and HEART FAILURE, spanning various causes. We pay particular attention to the influence of METABOLIC RISK FACTORS and comorbidities, aiming to pave the way for innovative THERAPEUTIC strategies.

CURRENT PROJECTS

- Molecular mechanisms of increased cardiac tolerance to oxygen deprivation.
- Role of hypoxia-inducible factor-1a in the pathophysiology of cardiovascular diseases. • Epitranscriptomic regulations in heart development and disease.
- Development and maintenance of arrhythmogenic substrate in the failing 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

- Alánová P., Alán L., Opletalová B., Buhuslavová R., Abaffy P., Matějková K., Holzerová K., Benák D., Kaludercic N., Menabo R., Di Lisa F., Ošťádal B., Kolář F., Pavlínková G.: HIF-1a limits myocardial infarction by promoting mitophagy in mouse hearts adapted to chronic hypoxia (2024) Acta Physiologica in press:e14202.
- Benák D., Holzerová K., Hrdlička J., Kolář F., Olsen M., Karelson M., Hlaváčková M.: Epitranscriptomic regulation in fasting hearts: implications for cardiac health (2024) RNA biology 21:1-14.
- Olejníčková V., Hamor P.U., Janaček J., Bartoš M., Zábrodská E., Saňková B., Kvasilová A., Kolesová H., Sedmera D.: Development of ventricular trabeculae affects electrical conduction in the early endothermic heart (2024) Developmental dynamics 253:78-90.
- Benák D., Kolář F., Zhang L., Devaux Y., Hlaváčková M.: RNA modification m(6)Am: the role in cardiac biology (2023) Epigenetics 18:2218771.
- Neckář J., Alánová P., Olejníčková V., Papoušek F., Hejnová L., Šilhavý J., Behuliak M., Bencze M., Hrdlička J., Vecka M., Jarkovská D., Švíglerová J., Mistrová E., Štengl M., Novotný J., Oštádal B., Pravenec M., Kolář F.: Excess ischemic tachyarrhythmias trigger protection against myocardial infarction in hypertensive rats (2021) Clinical science 135:2143-2163.
- Oštádal B., Oštádal P.: Sex-based differences in cardiac ischaemic injury and protection: therapeutic implications (2014) British Journal of Pharmacology 171:541-554.

- Pathogenetic mechanisms and novel experimental therapy of heart failure of various etiology.



NFVFI NPMFNTAI EPILEPTOLOGY

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Our long-term research goals are (1) to better understand the **PATHOPHYSIOLOGY OF EPILEPTIC** SEIZURE, EPILEPSY AND ITS COMORBIDITIES, PARTICULARLY IN THE DEVELOPING BRAIN, (2) to develop new approaches to the treatment of epilepsy and its psychiatric comorbidities, and (3) to improve the safety of anti-seizure drugs for the developing brain. To elucidate the molecular, 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 and chronic models of acquired epilepsy. In our research, we utilize modern electrophysiological, molecular, biochemical, pharmacological and behavioral techniques. Beyond basic research and close collaboration with clinical epilepsy centers, 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

- Age-specific molecular, cellular and structural mechanisms of ictogenesis, epileptogenesis and epilepsyrelated comorbidities
- The molecular, cellular, structural and functional consequences of early-life seizures • The long-term impact of early-life exposure to anti-seizure drugs on brain development and underlying

- The developmental pharmacology of classical and potential anti-seizure drugs, age-related differences





Changes in the expression of GABA_A receptor α 1 and γ 2 subunit mRNA in developing rats, 7 to 60 days old.

SELECTED OUTPUTS

- The first experimental study on the prophylaxis of post-traumatic epilepsy (Servít (1960) Nature 188:669-670).
- A new extraction procedure that enables the measurement of precise levels of labile brain metabolites in small samples of brain tissue (Folbergrova et al. (1969) J Neurochem 16:191-203). et al. (1992) Dev Brain Res 65:185-189). et al. (2001) J Neurosci 21:3593-3599).
- Age-specific, flexion seizures induced with a systemic administration of NMDA as a model of human infantile spasms (Mareš • Status epilepticus induces neuronal damage in the mediodorsal nucleus of the thalamus as early as at P12 in rats (Kubová • Postictal potentiation precedes postictal refractoriness during early postnatal development (Mareš and Kubová (2015)
- Epilepsia 56:e10-14).
- Transition to seizures, which has been thought to be random, is a relatively complex process that is characterized by the slow and progressive loss of neuronal network resilience (Chang et al. (2018) Nat Neurosci 21:1742-1752).



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Our department studies the mechanisms of **BLOOD PRESSURE** regulation and **END-ORGAN DAMAGE** in RATS with different types of experimental hypertension, chronic kidney and heart disease with special attention given to the **ONTOGENETIC FACTORS** involved in these processes. Our research is focused on studying i) the mechanisms of beneficial effects of EMPAGLIFLOZINS on cardiorenal damage; ii) the central mechanisms participating in **BLOOD PRESSURE REGULATION** - with special attention given to the role of **CENTRAL ANGIOTENSIN II**, nitric oxide and reactive oxygen species; iii) changes in SYMPATHETIC AND PARASYMPATHETIC TONE in the CONTROL OF THE BAROREFLEX; iv) the role of ENDOTHELIN system in heart failure models; and v) metabolic and cardiovascular effects of new analogs of NEUROPEPTIDES regulating FOOD INTAKE in rats with a special focus on NEU-**ROINFLAMMATION** (in cooperation with the Institute of Organic Chemistry and Biochemistry CAS in Prague).

CURRENT PROJECTS

- The mechanism of therapeutic effects of gliflozins in heart failure
- The role of the endothelin system in the pathophysiology of chronic heart failure
- ance in spontaneously hypertensive rats
- The possible role of prolactin-releasing peptide analogs in the treatment of obesity and hypertension with a special focus on neuroinflammation



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

- Hojná S., Rauchová H., Malínská H., Marková I., Hüttl M., Papoušek F., Behuliak M., Miklánková D., Vaňourková Z., Neckář J., Kadlecová M., Kujal P., Zicha J., Vaněčková I.: Antihypertensive and metabolic effects of empagliflozin in Ren-2 transgenic rats, an experimental non-diabetic model of hypertension (2021) Biomed Pharmacother 144:112246.
- Zicha J., Behuliak M., Vavřínová A., Dobešová Z., Kuneš J., Rauchová H., Vaněčková I.: Cooperation of augmented calcium sensitization and increased calcium entry contributes to high blood pressure in salt-sensitive Dahl rats (2021) Hypertens Res 44(9):1067-1078.
- Řezáčová L., Vaněčková I., Hojná S., Vavřínová A., Valovič P., Rauchová H., Behuliak M., Zicha J.: Both central sympathoexcitation and peripheral angiotensin II-dependent vasoconstriction contribute to hypertension development in immature heterozygous Ren-2 transgenic rats (2022) Hypertens Res 45(3):414-423.
- Mráziková L., Hojná S., Pačesová A., Hrubá L., Strnadová V., Neprašová B., Železná B., Kuneš J., Maletínská L.: Palmitoylated prolactin-releasing peptide treatment had neuroprotective but not anti-obesity effect in fa/fa rats with leptin signaling disturbances (2022) Nutr Diabetes 12(1):26.
- Mráziková L., Neprašová B., Mengr A., Popelová A., Strnadová V., Holá L., Železná B., Kuneš J., Maletínská L.: Lipidized prolactin-releasing peptide as a new potential tool to treat obesity and type 2 diabetes mellitus: preclinical studies in rodent models (2021) Front Pharmacol 12:779962.
- Kala P., Vaňourková Z., Škaroupková P., Kompanowska-Jezierska E., Sadowski J., Walkowska A., Veselka J., Táborský M., Maxová H., Vaněčková I., Červenka L.: Endothelin type A receptor blockade increases renoprotection in congestive Heart failure combined with chronic kidney disease: Studies in 5/6 nephrectomized rats with aorto-caval fistula (2023) Biomed Pharmacother 158:114157.
- Valovič P., Behuliak M., Vaněčková I., Zicha J.: Impaired vascular β-adrenergic relaxation in spontaneously hypertensive rats: The differences between conduit and resistance arteries (2023) Eur J Pharmacol 958:176045.

• The effects of acetylcholinesterase inhibition on the cardiovascular system and cardiac ischemic toler-



IFTICS OF MODEL DISEASES

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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 only identified 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. The **SPONTANEOUSLY HYPER**-TENSIVE RAT (SHR) is the most widely used animal model of essential hypertension and associated metabolic disturbances that are typical for metabolic syndrome. Although it cannot be expected that the individual predisposing genes themselves will 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

- Analysis of the hemodynamic mechanisms that initiate salt-sensitive hypertension in hyperaldosteronism Analysis of the molecular mechanisms underlying hemodynamic abnormalities that initiate the devel-• Linkage and correlation analyses of intermediary phenotypes to reveal candidate genes underlying
 - Low NaCl - Low NaCl

I ow NaCl

Mean arterial pressure, cardiac output, and systemic vascular resistance (SVR) during the administration of a low-NaCl diet (0.26% NaCl) and a high-NaCl diet (4% NaCl) in control rats infused with the vehicle and in rats infused with aldosterone.

SELECTED OUTPUTS

- The development of a model system for genetic and correlation analyses of cardiovascular and metabolic disturbances in spontaneously hypertensive rats (SHRs), HXB/BXH recombinant inbred strains derived from crosses of SHRs with Brown Norway rats (Hübner et al.: Integrated transcriptional profiling and linkage analysis for identification of genes underlying disease (2005) Nat Genet 37:243-253; www.genenetwork.org).
- Identification of the first blood pressure regulatory QTL at the molecular level in SHRs as a deletion variant of the Cd36 gene (Pravenec et al. (2008) Nat Genet 40:952-954) as well as a number of other QTLs associated with metabolic and cardiac traits (reviewed by Pravenec et al. (2014) Physiol Res 63:Suppl 1, S1-S8).
- Identification of hemodynamic mechanisms of salt-dependent hypertension in primary aldosteronism (Kurtz et al.: Hypertension in primary aldosteronism is initiated by salt-induced increases in vascular resistance with reductions in cardiac output (2023) Hypertension 80:1077-1091).

complex pathophysiological traits in the SHR strain using HXB/BXH recombinant inbred strains





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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 not only interested in the molecular characterisation of transporters in terms of their STRUCTURE/FUNCTION, SUBSTRATE SPECIFICITY AND **TRANSPORT MECHANISM**, but also in their biogenesis and degradation, posttranslational regulation and their role in EUKARYOTIC CELL PHYSIOLOGY. We specialise in transporters related to the INTRACELLULAR pH and CATION HOMEOSTASIS of lower eukaryotes and in TRANSPORTERS OF HIGHER EUKARYOTES RELATED TO HUMAN DISEASES.

CURRENT PROJECTS



Structural and functional characterization of human Na⁺/H⁺ antiporter NHA2 in Saccharomyces cerevisiae. (A) NHA2 was functionally expressed in the plasma membrane of the yeast S. cerevisiae and its activity improved the LiCl and NaCl tolerance of cells. (B) Several new features of NHA2 that are important for its transport activity were revealed. (C) The specific NHA2 inhibitor phloretin (in yellow) binds in the core of the protein close to the cation-binding site.

SELECTED OUTPUTS

- The involvement of Trk1 and Trk2 potassium uptake systems in Ca2⁺ signalling and stress survival has been described (Zimmermannova et al. (2021) FEMS Yeast Res 21:foab015; Duskova et al. (2021) Microbiology 167:001065).
- New mechanisms in the regulation of Nha1 and its role in yeast cell physiology have been elucidated (Albacar et al. (2021) J Fungi 7(12):1010; Papouskova et al. (2021) Mol Microbiol 15:41-57).
- Structural features contributing to the activity and affinity change of the Trk1 K⁺ importers have been elucidated (Masaryk and Sychrova (2022) J Fungi 8:432; Masaryk et al. (2023) Comput Struct Biotech J 21:2705-2716; Papouskova et al. (2023) Yeast 40:63-83).
- Various types of potential antifungal drugs have been tested in conventional, pathogenic and non-conventional yeast (Csáky et al. (2020) Yeast 37(1):45-62; Vaitkiene et al. (2020) Front Microbiol 11:2077; Kodedová et al. (2023) Microbiol Res 26:127303).
- New structural features of the human NHA2 antiporter have been described (Velazquez et al. (2022) Protein Sci 31:e4460).



d RNDr. Ondřej Kuda, Ph.D. 💶 ondrej kuda@fgu.cas.cz key researchers Kristyna Brejchová 2 Dovile Milonaityte 3 PhD students Martin Riečan 🔺 Michaela Vondráčková 🇉 ger Martina Rombaldová 💿 Jana Brejchová 🗾 students Monika Krakovková 🔳

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**, spatial metabolomics, transcriptomics, 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





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

SELECTED OUTPUTS

- Vondrackova M., Kopczynski D., Hoffmann N., Kuda O.: LORA, Lipid Over-Representation Analysis based on structural information (2023) Anal Chem 95(34):12600-12604.
- containing branched palmitic acid ester of hydroxystearic acid (PAHSA) are present in the breast milk and hydrolyzed by carboxyl ester lipase (2022) Food Chem 388:132983.
- Zechner R., Kuda O.: Distinct roles of adipose triglyceride lipase and hormone-sensitive lipase in the catabolism of triacylglycerol estolides (2021) PNAS 118(2):e2020999118.
- Lopes M., Brejchova K., Riecan M., Novakova M., Rossmeisl M., Cajka T., Kuda O.: Metabolomics atlas of oral 13C-glucose tolerance test in mice (2021) Cell Rep 37(2):109833.
- 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.

Brejchova K., Paluchova V., Brezinova M., Cajka T., Balas L., Durand T., Krizova M., Stranak Z., Kuda O.: Triacylglycerols

Brejchova K., Radner F.P.W., Balas L., Paluchova V., Cajka T., Chodounska H., Kudova E., Schratter M., Schreiber R., Durand T.,



head RNDr. Petr Ježek, DrSc. 💶 petr.jezek@fgu.cas.cz key researchers Andrea Dlasková 2 Hana Engstová 3 Martin Jabůrek 4 Eduardo Klöppel 🗉 Oleksandra Mozheitova 🙃 Katarína Smolková 🗾 Jitka Špačková 🔳 Tomáš Špaček 🔋 Jan Tauber 10 PhD students Kamila Baslarová 11 Bazila Bazila 12 Klára Gotvaldová 13 David Lorenc 14 Jiří Novotný 15 Vojtěch Pavluch, Pavla Průchová 16 technicians Jitka Smiková 17 Jana Vaicová 18

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



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).

SFI FCTFD OUTPUTS

- Revisited the mechanism of insulin secretion in pancreatic β-cells: Plecitá-Hlavatá et al. Glucose-stimulated insulin secretion fundamentally requires H₂O₂ signaling by NADPH oxidase 4. (2020) Diabetes 69:1341–1354. The article introduces a revolutionary new concept of ATP plus redox signaling being required for insulin secretion in pancreatic β -cells stimulated by glucose (H₂O₂ signaling produced by the NADPH oxidase isoform 4, NOX4) or branched-chain keto acids and fatty acids (H₂O₂, signaling by mitochondria). This discovery will have a great impact on future translational research on antidiabetic drugs and nutritional guidance to prevent type 2 diabetes.
- Review: Ježek et al.: Contribution of mitochondria to insulin secretion by various secretagogues (2022) Antioxid Redox Signal 36.920-952
- Clinical study of 2-hydroxyglutarate in breast cancer Špačková et al.: Biochemical background in mitochondria affects 2HG production by IDH2 and ADHFE1 in breast carcinoma (2021) Cancers 13:1709.
- Mitochondrial phospholipase participates in cardiolipin remodeling Průchová et al.: Antioxidant role and cardiolipin remodeling by redox-activated mitochondrial Ca²⁺-independent phospholipase A2 γ in the brain (2022) Antioxidants 11:198.
- Magnetic resonance imaging of pancreatic islets Shapoval et al.: Poly(4-styrenesulfonic acid-co-maleic anhydride)-coated NaGdF4:Yb,Tb,Nd nanoparticles with luminescence and magnetic properties for imaging of pancreatic islets and β -cells (2022) ACS Appl Mater Interfaces 14:18233-18247.
- Multiple mtDNA copies in a single nucleoid Pavluch et al. Possible frequent multiple mitochondrial DNA copies in a single nucleoid in HeLa cells (2023) Sci Rep 13:5788.
- Review: Ježek et al.: Mitochondrial cristae morphology reflecting metabolism, superoxide formation, redox homeostasis, and pathology (2023) Antioxid Redox Signal 39 (10-12):635-683.



MOLECULAR NEUROBIOLOGY

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CURRENT PROJECTS

- The TRAK protein family in axonal transport and neural development
- Human variants of microtubule-associated proteins and their role in the pathogenesis of epilepsy and spastic paraplegia



A. Microtubule regulation in neural development and disease.

B. Axon growth in microfluidic chambers (tyrosinated tubulin red, detyrosinated tubulin green).

C. Tracing of diolistically-labeled cortical neuron den dritic spines.

The Laboratory of Molecular Neurobiology studies the regulation of microtubules during BRAIN DEVELOPMENT and in NEURODEVELOPMENTAL DISORDERS. We focuse on MICROTUBULE-ASSOCIATED PROTEINS and their role in microtubule dynamics, axon guidance, synapse formation and refinement. The activity of microtubule-associated proteins is tightly regulated on multiple levels. We analyze how posttranslational modifications and conformational changes of microtubule-associated proteins control their function in vitro and in neurons, and what is their impact on brain development using mouse models. Finally, we test how deregulation of microtubule-associated proteins contributes to pathogenesis of neurodevelopmental disorders - in particular autism spectrum disorder, epilepsy, or schizophrenia.

SELECTED OUTPUTS

- Ziak et al.: CRMP2 mediates Sema3F-dependent axon pruning and dendritic spine remodeling (2020) EMBO Rep 21(3):e48512.
- Maimon et al.: A CRMP4-dependent retrograde axon-to-soma death signal in amyotrophic lateral sclerosis (2021) EMBO J 40(17):e107586.
- Balaštík et al.: Prolyl isomerase Pin1 regulates axon guidance by stabilizing CRMP2A selectively in distal axons (2015) Cell Rep 13(4):812-828.

• Analysis of the isoform-specific role of Collapsin response mediator protein 2 in microtubule polymeriza-





I Fr.II **PHYSIOLOGY OF BONE**

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In obesity, the inability of adipose tissue to store excess calories leads to ectopic fat accumulation in the liver, muscles 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 bone fragility fractures, an overlooked complication affecting the quality of life in patients with metabolic complications. However, there is limited information on the physiological role of **BMAT** in relation to bone and whole-body energy metabolism, and we focus on this topic. Our 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 an international collaboration in Europe and the USA. The department was newly established in 2019, based on a 5-year "Start Up Research Program" financed by IPHYS.

CURRENT PROJECTS



Representative images of Hexabrix-stained bone marrow adipocytes (BMAds) in the tibia of mice fed with a high-fat diet (HFD) (A) and HFD supplemented with omega-3 polyunsaturated fatty acids (HFD+F) (B).

SELECTED OUTPUTS

- Beňová A., Ferenčáková M., Bardová K., Funda J., Procházka J., Špoutil F., Čajka T., Džubanová M., Balcaen T., Kerckhofs G., Willekens W., van Lenthe G.H., Alquicer G., Pecinová A., Mráček T., Horáková O., Rossmeisl M., Kopecký J., Tencerová M.: Novel thiazolidinedione analog reduces a negative impact on bone and mesenchymal stem cell properties in obese mice compared to classical thiazolidinediones (2022) Mol Metabol 65:101598.
- Beňová A., Tencerová M.: Obesity-induced changes in bone marrow homeostasis (2020) Front Endocrinol 11:294.
- Tencerová M., Ferenčáková M., Kassem M.: Bone marrow adipose tissue: Role in bone remodeling and energy metabolism (2021) Best Pract Res Clin Endocrinol Metabol 35(4):101545.
- Beňová A., Ferenčáková M., Bardová K., Funda J., Procházka J., Špoutil F., Čajka T., Džubanova M., Balcaen T., Kerckhofs G., Willekens W., van Lenthe G.H., Charyyeva A., Alquicer G., Pecinová A., Mráček T., Horáková O., Coupeau R., Svarer Hansen M., Rossmeisl M., Kopecký J., Tencerova M.: Omega-3 PUFAs prevent bone impairment and bone marrow adiposity in mouse model of obesity (2023) Commun Biol 6(1):1043.





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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
- 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



Upon Ca²⁺ 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

- Urushadze et al.: Timed Sequence Task: A new paradigm to study motor learning and flexibility in mice (2023) eNeuro 10:ENEURO.0145-23. • Abbondanza et al.: Nicotinic acetylcholine receptors expressed by striatal interneurons inhibit striatal activity and control striatal-dependent behaviors (2022) J Neurosci 42:2786-2803. - Randakova et al.: Fusion with promiscuous Gα16 subunit reveals signaling bias at muscarinic receptors (2021) Int J Mol Sci 22:10089. • Randakova et al.: Novel M2-selective, Gi-biased agonists of muscarinic acetylcholine receptors (2020) Br J Pharmacol 177:2073-2089. - Jakubik et al.: The operational model of allosteric modulation of pharmacological agonism (2020) Sci Rep 10:14421.

- Janickova 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.
- Randakova et al.: Novel long-acting antagonists of muscarinic ACh receptors (2018) Br J Pharmacol 175:1731-1743.
- Randakova et al.: Role of membrane cholesterol in differential sensitivity of muscarinic receptor subtypes to persistentlybound xanomeline (2018) Neuropharmacol 133:129-144.



NEUROPHYSIOLOGY **OF MEMORY**

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Our laboratory explores how we LEARN, REMEMBER, and ACT. We study SPATIAL NAVIGATION, which is analogous to remembering facts, events, and places. Conditions such as ALZHEIMER'S, SCHIZOPHRENIA, and other brain issues affect these areas. We don't fully understand these conditions, so current treatments only address symptoms. Lately, we have dived deeper into the science behind LEARNING AND MEMORY in both HEALTHY and UNHEALTHY BRAINS. To study behavior, we use cutting-edge tools such as special behavioral tests, light control of neuronal activity, and detailed brain scans.

CURRENT PROJECTS

- Understanding the hippocampus, an ancient part of human brain which is connected to a number of other parts, such as the Cornu Ammonis, dentate gyrus, and subicular complex. These parts work together in a large network.
- repeated thoughts, feelings, or behaviors. It is similar to having a song stuck in your head, but it is a thought or action that the affected individual cannot stop repeating. We are studying it by looking at experience OCD in their lifetime.
- Rats and their amazing sense of direction: It is commonly known that rats have a very good sense of
- in a new city without a map, how do we find our way. We are studying the tricks our brain uses to navigate and remember places.
- How drugs affect our brain: We are performing in-depth studies on how certain medications impact our
- the brain are active.



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

SELECTED OUTPUTS

- Patrono E., Hrůzova K., Svoboda J., Stuchlík A.: The role of optogenetic stimulations of parvalbumin-positive interneurons in the prefrontal cortex and the ventral hippocampus on an acute MK-801 model of schizophrenia-like cognitive inflexibility (2023) Schizophr Res 252:198-205. This study discovered the role of GABAergic transmission in an animal model of psychosis. We are the first to use a complex cognitive task, the attentional set-shifting task. To our knowledge, no one has used a cognitive behavioral task in rats coupled with the optogenetic stimulation of PV+ interneurons to reverse cognitive impairments. Moreover, this work shows optogenetics to be a potential method of active exploration in models of schizophrenia. The entire study was conducted in our laboratory.
- Vojtěchová I., Macháček T., Krištofíková Z., Stuchlík A., Petrásek T.: Infectious origin of Alzheimer's disease: Amyloid beta as a component of brain antimicrobial immunity (2022) PLoS Pathogens 18(11):e1010929. The amyloid cascade hypothesis, focusing on pathological protein aggregation, did not reveal the underlying cause of Alzheimer's disease. This article reviews evidence from the current literature that amyloid beta, traditionally considered pathological, also acts as an antimicrobial peptide that protects the brain from pathogens. We discuss these new findings in terms of the AD infection hypothesis and offer suggestions for future research. The authors of this article are three members of the laboratory.
- Žiak J., Weissová R., Jeřábková K., Janíková M., Maimon R., Petrásek T., Pukajová B., Kleisnerová M., Wang M., Brill M.S., Kasparek P., Zhou X., Alvarez-Bolado G., Sedláček R., Misgeld T., Stuchlík A., Perlson E., Balaštík M.: CRMP2 mediates Sema3Fdependent axon pruning and dendritic spine remodeling (2020) EMBO Rep 21(3):e48512. The regulation of axon guidance and pruning of inappropriate synapses by class 3 semaphorins are critical for neural circuit development. This collaborative paper demonstrated that CRMP2 Sema3F-dependent synapse pruning and its dysfunction share histological and behavioral features with neurodevelopmental disorders. Our team were responsible for the behavioral results. The study was a broad collaboration of several laboratories from the Czech Republic and abroad, including two laboratories from IPHYS.

• What is Obsessive-Compulsive Disorder (OCD)? OCD is a condition where people have unwanted and

• Studying how humans navigate: We are also curious about how humans find their way around. When

• Using advanced techniques to see inside the brain: We utilise sophisticated tools to see which parts of



PAIN RESEARCH

head MUDr. Jiří Paleček, CSc. 💶 jiri.palecek@fgu.cas.cz key researchers Anirban Bhattacharyya, Mário Heleš 💶 Diana Špicarová 🔳 Hana Zemková 🖪 PhD students Jana Čiháková, Monica Pontearso 🇉 Marian Rupert, Jakub Slepička 💿 Daniel Vasconcelos 🗾 students Varsamia Vasiliki Manolopoulou 🔹 technicians Hana Janoušková 🗉 Kateřina Krämerová 10

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 center 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 TRPV1, P2X and other receptors, neuroinflammation and glial cells in this process. In our research, we mainly use electrophysiological, optogenetic, immunohistochemical, and behavioral methods.

CURRENT PROJECTS

- Mechanisms of chemotherapy-induced and diabetic neuropathic pain
- The role of neuroinflammation in chronic pain conditions
- The interaction of opioid and TRPV1 receptors with cytokines in analgesia
- The physiology, pharmacology and molecular structure of purinergic P2X receptor-channels
- [6] WT 21 Dav

We studied chemotherapy-induced neuropathic pain using different approaches (1) and showed that the inhibition of PI3K by the specific FDA approved inhibitor Duvelisib prevented Paclitaxel increased PI3K expression in DRG neurons (2), mechanical allodynia (3) and reduction of light-evoked inhibitory currents amplitude (4). Experiments targeting neuroinflammation showed that CCL2 prevented the inhibitory/analgesic effects of the opioid agonist DAMGO on evoked currents in the spinal cord (5).

SELECTED OUTPUTS

- The inhibition of synaptic transmission by anandamide precursor 20:4-NAPE is mediated by TRPV1 receptors under inflammatory conditions (Špicarová et al. (2023) Front Mol Neurosci 16:1188503).
- Neurosteroids as positive and negative allosteric modulators of ligand-gated ion channels: P2X receptor perspective (Sivčev et al. (2023) Neuropharmacology 234:109542).
- The dual PI3K_γ/δ inhibitor duvelisib prevents development of neuropathic pain in model of Paclitaxel-induced peripheral neuropathy (Adámek et al. (2022) J Neurosci 42(9):1864-1881).
- The chemokine CCL2 prevents opioid-induced inhibition of nociceptive synaptic transmission in spinal cord dorsal horn (Heleš et al. (2021) | Neuroinflammation 18:279).
- 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).
- The cancer chemotherapeutic Paclitaxel increases human and rodent sensory neuron responses to TRPV1 by activating TLR4 (Li et al. (2015) J Neurosci 35:13487-13500).

- The modulation of spinal cord synaptic transmission by endocannabinoids and neurosteroids





LLING P

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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 phosphothreoninecontaining 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 currently use include the expression of recombinant proteins and a range of biophysical methods to characterize INTERMOLECULAR INTERACTIONS and PROTEIN STRUCTURE, including cryo-EM, protein crystallography, NMR, SAXS and HDX-MS. All these methods enable us to better understand how the activity and function of protein-protein complexes is regulated.

CURRENT PROJECTS





(A) SAXS-based structural model of complex between Nedd4-2 and 14-3-3η protein. Black lines indicate intermolecular distance constraints assessed in chemical cross-linking experiments. The insets show the crystal structures of Nedd4-2 peptides containing the 14-3-3 binding motifs (PDB 6ZBT and 6ZC9). (B) Up, chemical shift perturbations obtained from ¹H-¹⁵N HSQC spectra of ¹⁵N-labeled FOXO4 in the presence of p53 mapped onto the crystal structure of the FOXO4 DBD:DNA complex. Down, fluorescence anisotropy measurements showing that the complex formation reduces the DNA-binding affinity of p53. (C) SAXS-based structural analysis of pCaMKK1: 14-3-3Y complex. Left, Experimental scattering curve of the complex superimposed with the calculated curve of the best-scoring CORAL AllosMod-FoXS model of the complex (shown in red). Right, ribbon representation of the best-scoring AllosMod-FoXS model of the complex.

SELECTED OUTPUTS

- Our findings provided the first structural glimpse into 14-3-3-mediated Nedd4-2 regulation and highlight the potential of the Nedd4-2:14-3-3 complex as a pharmacological target for Nedd4-2-associated diseases such as hypertension, epilepsy, kidney disease and cancer (Pohl et al. (2021) Comm Biology 4:899).
- We characterized the interaction between the transcription factors p53 and FOXO4. We showed that the interaction between p53 transactivation domain and the FOXO4 Forkhead domain is essential for the overall stability of the p53:FOXO4 complex (Mandal et al. (2022) Protein Sci 31:e4287).
- We structurally characterized CaMKK1:14-3-3 and CaMKK2:14-3-3 complexes and provided the structural basis for 14-3-3mediated CaMKK1 inhibition (Petrvalska et al. (2023) Protein Sci 32:e4805).



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Our research involves applying mass spectrometry-based technologies to perform **METABOLOMIC**, LIPIDOMIC AND PROTEOMIC ANALYSIS of various biological samples. This work covers the development and use of both liquid chromatography-mass spectrometry (LC-MS) and gas chromatographymass spectrometry (GC-MS) methods for the in-depth characterization and quantification of polar metabolites - METABOLOME, simple and complex lipids - LIPIDOME, 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 untargeted and targeted analysis of simple and 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 related to clubfoot pathogenesis.

CURRENT PROJECTS





(A) Processing of complex lipids in biofluids and tissues using MS-DIAL software (B) Visualization of interactive metabolomics/lipidomics atlas (web application) of 21 mouse tissues and biofluids in response to the metabolic challenge

SELECTED OUTPUTS

- biological and clinical research (2023) Trends Anal Chem 158:116825.
- Rakušanová S., Čajka T.: Current analytical methods to monitor type 2 diabetes medication in biological samples (2023) Trend Anal Chem 158:116831.
- Čajka et al.: Optimization of mobile phase modifiers for fast LC-MS-based untargeted metabolomics and lipidomics (2023) Int J Mol Sci 24:1987
- Lopes et al.: Metabolomics atlas of oral 13C-glucose tolerance test in mice (2021) Cell Rep 37:109833
- Tsugawa et al.: A lipidome atlas in MS-DIAL 4 (2020) Nat Biotechnol 38:1159-1163. • Eckhardt et al.: Novel contribution to clubfoot pathogenesis: The possible role of extracellular matrix proteins (2019) J Orthopaed Res 37:769-778.

Rakušanová S., Fiehn O., Čajka T.: Toward building mass spectrometry-based metabolomics and lipidomics atlases for





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 Krč 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. Six 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) 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



Průmyslová 595, 252 50 Vestec, Czech Republic tel: +420 325 873 140 e-mail: biocev@biocev.eu www.biocev.eu



JUNIOR RESEARCH

PANCREATIC ISLET RESEARCH

d RNDr. Lydie Plecitá, Ph.D. 💶 lydie.plecita@fgu.cas.cz key researchers Blanka Holendová Ph<mark>Ď students</mark> Štěpánka Benáková 💶 Monika Křivonosková 🔳 student Linda Stokičová 4

PANCREATIC β-CELLS constitute the majority of endocrine cells in the ISLETS OF LANGERHANS. They serve as glucose sensors and help maintain **GLUCOSE HOMEOSTASIS** in the body. Impairment of their function and quantity leads to the development of diabetes. Glucose homeostasis is regulated by **INSULIN**, which is secreted by β-cells. The main signaling pathways leading to the release of insulin granules have been described, but many details about the amplification of the pathways depending on the type of inducer are lacking. Our laboratory focuses on **REDOX SIGNALLING** as a key to regulating β-cell function. We study metabolites derived from glucose catabolism and redox signaling required for efficient insulin secretion. Its disruption and establishment of **OXIDATIVE STRESS** are the main triggers of the **DEVELOPMENT OF TYPE 2 DIABETES** in nutritional overload. In addition, β -cells are heterogeneous, and specific subpopulations are involved in the synchronized response of endocrine islet cells to glucose stimulation. We investigate the involvement of intracellular redox status in β-CELL HETEROGENEITY.

SERVICE DEPARTMENTS





METABOLOMICS

head Doc. Ing. Tomáš Čajka, Ph.D. 🔲 tomas.cajka@fgu.cas.cz team members Jiří Hricko 💶, Michaela Paučová 💷, Tatyana Kobets, Michaela Nováková 3. Aleksandra Shumilova

The Department provides fee-based services for LC-MS and GC-MS-based metabolomics and lipidomics analysis of biofluids (e.g., plasma, serum, urine), tissue (e.g., liver, heart, adipose tissue), and cells, as well as bioinformatics analysis of generated data sets. The Laboratory is equipped with Vanquish UHPLC System/Q Exactive Plus, Vanquish UHPLC System/Orbitrap Exploris 480, Ultimate 3000 RSLC System/QTRAP 5500, Agilent 8890 GC/Pegasus BT2 instrumentation, and Agilent Bravo for automated liquid handling. Platforms:

• LIMeX workflow (LIpids, Metabolites, and eXposome compounds) for the untargeted analysis of complex lipids, 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), metabolites labeled with stable isotopes (fluxomics), or pharmaceutical compounds for the ADME studies



LIMeX workflow for combined untargeted and targeted analysis

RADIOMETRY

head Roman Liška 🔲 roman.liska@fqu.cas.cz team member Karla Bohunová

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.



μCT scan of a shark heart using the contrast agent Lugol



PROTEOMICS SERVICE LABORATORY

head RNDr. Marek Vrbacký, Ph.D. marek.vrbacky@fgu.cas.cz team members (from the left) Elena Shcherbachenko, Rayyan Tariq Khan, Nadiia Prokopets

The proteomics service laboratory, also known as ProteoLab Krč (PLK), was jointly established by IPHYS and the Institute of Molecular Genetics of the CAS. It offers mass spectrometry-based bottom-up proteomic analyses to the research groups of both institutes, and also to other academic and non-academic subjects. The pay-persample service includes complete sample prep from various biological materials (e.g., cell lines, tissues, immunoprecipitation), untargeted or targeted LC-MS/MS of the resulting peptides and basic bioinformatic analysis. Prospective users should contact the lab to discuss the project, including the experimental design and statistical considerations. The laboratory is equipped with an Orbitrap Exploris 480 mass spectro-meter coupled to a nano UHPLC Ultimate 3000 liquid chromatograph.





ECONOMIC DEPARTMENT

head Kateřina Uhrová katerina.uhrova@fgu.cas.cz team members (bottom, from the left) Pavlína Hájková, Eva Hamalčíková, Lada Trčková, Lenka Nejedlá, Michaela Matějíčková, Michaela Trošková (above, from the left) Kamila Kohoutová, Dominika Šulcová, Gabriela Bartejsová, Běla Tobolová, Kateřina Rozsypalová, Jaroslava Králová, Lucie Němcová, Tereza Mádle, Dagmar Plzenská, Eva Syrová

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



ANIMAL FACILITY

head Ing. Martin Blažka • martin.blazka@fgu.cas.cz

team members (bottom, from the left) Kateřina Pavelková, Ilona Berková, Jana Lejčková, Hana Vančurová, Hana Ptáčková, Evelína Lavičková (above, from the left) Yelizaveta Plisko, Jan Krämer, Nikola Danitová, Petr Havlena, Pavel Štrof, Jana Perná

PROPERTY AND FACILITY DEPARTMENT

head Ladislav Krämer 🔲 ladislav.kramer@fgu.cas.cz team members (bottom, from the left) Irena Čechová, Agniezska Pelikán, Eva Půlová, Vladimíra Trůková, Jana Pechová (above, from the left) Helena Reimerová, Pavel Šuba, Ivan Slunéčko

The Department provides an environment 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.

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) Diana Moosová, Adéla Bocková, Petra Kubátová

INFORMATION TECHNOLOGY DEPARTMENT

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

LIBRARY

head Mgr. Lucie Trajhanová 🔲 lucie.trajhanova@fgu.cas.cz team members (from the left) Zuzana Nováková, Blanka Liberová

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 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. 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, Michal Růžička

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 2.103.

BIOLOGICAL CONTROLS

head Ing. Petr Mleinek, Ph.D. petr.mleinek@fgu.cas.cz team members (from the left) Renata Půtová, Lucie Heppnerová, Světlana Žufanová

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.cz). 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).

PRECLINICAL TESTING OF POTENTIAL PHARMACEUTICALS

In the period 2017 - 2023, thanks to the involvement of the IPHYS in the AV21 Strategy and the financial support received, we were able to develop a programme of Preclinical testing of potential pharmaceuticals. The programme reflected the need to use animal experiments as a key element in the development of new medicines, including tests and analyses carried out under GLP (GLP - Good Laboratory Practice) conditions. Laboratory animals are used exclusively for studies of potentially life-saving drugs and alternative methods are used where possible.

Tested items:

newly developed potential medicinal substances, human and veterinary medicinal products, food supplements, medical devices

Test systems:

mouse, rat, guinea pig, rabbit, (mini-pig in collaboration with Pigmod centre).

The Programme resulted in the establishment and construction of the Preclinical Testing Centre.

Participating institutes:

 Institute of Molecular Genetics CAS, Czech Centre for Phenogenomics (CCP)

- Institute of Biotechnology CAS
- Institute of Animal Physiology and Genetics CAS, Pigmod Centre

CPT

The Preclinical Testing Centre offers and provides a range of testing and analysis and relies on long-term collaboration between institutions. IPHYS holds the certificate "Decision of SÚKL (sukls124283/2016) on the authorization to conduct GLP toxicological studies. Studies and testing can be conducted under GLP or non-GLP regime within the collaborating institutions.

Portfolio of services offered:

Acute toxicity studies, MTD studies

GLP / non-GLP

Repeated substance

treatment studies, DRF studies PK and ADME

GLP / non-GLP

GLP / non-GLP

(bio-distribution studies)

Study Proof of Concept (Pharmacology)

In vivo biocompatibility studies (for medical devices)

Toxicology tests - single or repeated administration of substances

Toxicokinetic testing - repeated, precisely timed blood draws

Pharmacological tests - testing the effects of substances

More information:

www.prekliniky.cz

DEVELOPMENT OF RESEARCH INFRASTRUCTION AND TECHNOLOGICAL ADAPTATION OF THE ANIMAL FACILITY

A basic and necessary condition for research activities in the field of biomedicine is the possibility of working on laboratory animals. In the 1960s, a central animal facility was built in Building G to produce laboratory animals and allow experiments on animal models. In order to work with laboratory animals to current standards, Building G required major refurbishment and the installation of new washing technology for the breeding vessels, as well as technology for the distribution of clean and dirty litter. The challenging structural refurbishment itself began in January 2020 and, while sustaining operations in partial wings of the menagerie throughout the refurbishment, was successfully completed with a certificate of occupancy in December 2023. This provided IPHYS with modern facilities for the breeding and housing of laboratory animals. From 2024, its capacity will gradually be used for experiments on laboratory mice and rats, mostly unique models of serious diseases. Modern equipment will enable the characterization of the mechanisms of origin of these diseases and their whole-body manifestations.

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.

During the implementation phase of the program, IPHYS focused on two main objectives through the proposed action plan (available on the IPHYS website): (1) the introduction of a recruitment process in accordance with OTM-R, which brings transparency and objectivity to the recruitment process, thereby promoting fairness and increasing applicants' trust, and (2) the enhancement of career development opportunities for researchers, particularly at the postdoctoral stage. As part of the program, IPHYS encouraged employees to gain scientific experience abroad, providing them with better opportunities for independent advancement in research, including the potential to establish their own research groups. In 2024, the HR Award will be renewed based on an evaluation of HR processes at IPHYS and an on-site visit by the European Commission. IPHYS is now preparing a new action plan for the future.

INTELLECTUAL PROPERTY

Significant discoveries achieved at IPHYS are protected by patents and utility models. Also, IPHYS strived for the effective transfer of research results into practice. Currently, 10 granted patents or patent portfolios and 12 registered utility models are being managed. In recent years, scientific teams have preferred to protect technical solutions with utility models because of the faster and more affordable option to protect their results. Most often, IPHYS protects its results together with research partners. In addition to other partners from the Czech Academy of Sciences, there is a clear increase in joint utility models with technical universities. After the end of the program HR Excellence in Research, IPHYS aims to continue to maintain the intellectual property protection agenda at the same level using the processes set up during the program.

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). Four valid patent portfolios are currently coregistered by these two Institutes. The patent portfolio protecting the result of Lipidated peptides lowering blood glucose levels 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 for a potential pharmaceutical product.

FUNDS AND EMPLOYEES IPHYS IS SUCCESSFUL IN ATTRACTING RESEARCH FUNDING AT BOTH THE NATIONAL AND INTERNATIONAL

FINANCING BY THE TYPE OF RESOURCES 2023

Grants (43%) Institutional (45%) Own resources (12%)

PROFESSIONAL **CATEGORY STRUCTURE OF EMPLOYEES** 2023

Scientific positions (199) Non-scientific positions (122) Student-doctorand (83)

NATIONAL COLLABORATIVE PROJECTS

MediAim A TRANSLATIONAL RESEARCH PROJECT 2015–ongoing

Vision:

Development of new therapeutic agents and strategies to fight certain non-communicable 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 non-communicable 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

www.mediaim.cz

funded by the participating organizations

CarDia

NATIONAL INSTITUTE FOR METABOLIC AND CARDIOVASCULAR DISEASE RESEARCH 2022–2025

Vision:

To gain a deeper understanding of the causes of lifestyle diseases, to develop new drugs and to make modern technologies more involved in treatment.

Mission:

We focus on experimental, preclinical, translational and clinical research in lifestyle diseases - diabetes, obesity and cardiovascular disease (CVD).

Participating organizations:

Institute of Clinical and Experimental Medicine; Institute of Physiology CAS; Institute of Organic Chemistry and Biochemistry CAS; Charles University; Masaryk University

Originated from the MediAim project, this National Institute CarDia project is focused on non-communicable diseases, namely CVD, heart failure, type 2 diabetes mellitus and obesity, which are the most common causes of morbidity and mortality in developed countries worldwide. The prevalence of cardiovascular disease and related mortality is higher in the Czech Republic than in most developed EU countries. The cost of treating these complex multifactorial lifestyle diseases and their complications places an extreme financial burden on the entire healthcare system. The combined efforts of the excellent and complementary participants of the CarDia project creates a comprehensive national research platform (institute) encompassing experimental, preclinical, translational and clinical research activities in the prevention and

treatment of CVD, its most common risk factors such as obesity and diabetes, and related chronic complications. This will ultimately help to prevent and treat these diseases more effectively by translating the knowledge gained from experimental research into new treatments and interventions.

More information:

www.cardia.ikem.cz

"Program for the Support of Excellent Research in Priority Areas of Public Interest in Healthcare - EXCELES", funded by the EU through the Recovery and Resilience Instrument - Next Generation EU; reg. no. LX22NPO5104

EPIREC EPILEPSY RESEARCH CENTRE PRAGUE 2019–ongoing

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 CAS; Second Faculty of Medicine, Charles University, Prague; Motol University Hospital, Prague; Faculty of Electrical Engineering, Czech Technical University, 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

Neur-IN National Institute for Neurological Research 2022–2025

Vision:

To support multidisciplinary research into neurological diseases in which neurodegeneration plays a significant role.

Mission:

We search the new discoveries about the brain and nervous system and to use them to reduce the burden of neurological diseases and improve the quality of life of the affected population.

Participating organizations

St. Anne's University Hospital, Brno; Masaryk University, Brno; Charles University, Prague; Palacký University, Olomouc; University of Ostrava, Ostrava; University of Technology, Brno; Czech Technical University, Prague; Institute of Physiology CAS, Prague; Institute of Experimental Medicine CAS, Prague; Institute of Biotechnology CAS, Prague; Institute of Scientific Instruments CAS, Brno

Neurological disorders are the most common cause of disability and the second most common cause of death. In connection with the aging of the population, there is also a worldwide increase in the incidence of neurodegenerative diseases. At the same time, the details of the causes and development of these diseases are often unknown and there is no preventive or causative therapy for them either. The health and economic impact of neurodegenerative diseases on our society will thus be likely increasing. Neur-IN responds to current needs and, through the integration of the efforts of top scientists, will contribute to mitigating the negative effects of neurodegeneration on society and the economy.

Over 250 preclinical and clinical researchers of eleven scientific research and clinical centres and universities are involved in Neur-IN participating in multidisciplinary research of neurodegeneration in a number of neurological diseases. In addition to the two notorious neurodegenerative diseases with a dramatically increasing prevalence of Alzheimer's and Parkinson's disease, Neur-IN also focusses on other neurological diseases in which neurodegeneration plays a significant role (for example, neurodevelopmental diseases, epilepsy, multiple sclerosis).

More information:

www.ninr.cz

"Program for the Support of Excellent Research in Priority Areas of Public Interest in Healthcare - EXCELES", funded by the EU through the Recovery and Resilience Instrument - Next Generation EU; reg. no LX22NPO5107

NATIONAL INSTITUTE FOR NEUROLOGY RESEARCH

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 2019 - 2024.

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 – LM2023050)

Ten partner institutions are involved in the project, providing open access to 16 leading imaging facilities in Prague, Vestec, Brno, České Budějovice and Olomouc. These core facilities cover all levels of biomedical imaging - from imaging of biomolecules and their interactions, structure and processes in cells and tissues to imaging of organs and whole organisms in both healthy and pathological conditions. The purpose of the project is to combine unique technological equipment for biomedical imaging accessible in the Czech Republic and to provide open access to a wide range of imaging technologies and expertise to national and international scientists from both the public and private sectors via a unified and coordinated logistic approach. The strength of the Czech-BioImaging is the unique combination of open access to top available equipment, extensive expertise in imaging, organisation of annual theoretical and practical courses and close cooperation with industry.

Scientific coordinator:

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

IPHYS Bioimaging facility provides service in the areas of image acquisition and image analysis. The facility operates nine high-end light microscopy and medical imaging systems. The facility excels in providing customised solutions to researches especially in labelfree microscopy, correlative microscopy, multiphoton microscopy and data analysis. The facility currently works on its modernisation as being included in followup OP JAK infrastructure project: Modernisation of the VVI Czech-BioImaging (CZ.02.01.01/00/23_015/ 0008205).

More information:

www.czech-bioimaging.cz

GFRMANV

Charité Universitätsmedizin Berlin

ITALY University of Padua

.IAPAN National Institute of Informatics

POLAND

Nencki Institute of Experimental Biology

SLOVAKIA

Centre of Experimental Medicine, SAS

SPAIN 🔶

IPHYS

University of Málaga

UNITED KINGDOM

University of Central Lancashire of Preston Medical Research Council

IIKRAINF

Kharkiv National Medical University

ASII

University of California University of Arizona University of Rochester Medical Center

EUROPEAN PEDIATRIC TRANSLATIONAL RESEARCH **INFRASTRUCTURE AISBL (EPTRI AISBL)**

PAN-EUROPEAN ORGANIZATION

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. The project involves 26 partners from 19 EU and associated countries. IPHYS is included in EPTRI as a top basic and translational medicine center 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, got status of AISBL, and applies for various calls from the European Commission.

More information: www.eptri.eu

PUBLICATIONS 2019–2023 PUBLICATIONS IN IMPACT FACTOR (IF) JOURNALS IN ASEP DATABASE

MOST CITED PAPERS – THE TOP TENS DATA VALID TO 15[™] APRIL 2024

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. Dobiášová M., Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein 588. No. of citations: 733
- Bačáková L., Filová E., Pařízek M., Ruml T., Švorčík V. Modulation of cell adhesion, proliferation and differentiation on 2. materials designed for body implants (2011) Biotechnology Advances 29(6):739-767. No. of citations: 730
- Iežek P., Hlavatá L. Mitochondria in homeostasis of reactive oxygen species in cell, tissues, and organism (2005) 3. International Journal of Biochemistry and Cell Biology 37(12):2478-2503. No. of citations: 578
- Vaněček J. Cellular mechanisms of melatonin action (1998) Physiological Reviews 78(3): 687-721. No. of citations: 483 4.
- Hubner N., Wallace C. A., Zimdahl H., Petretto E., Schulz H., Maciver F., Mueller M., Hummel O., Monti J., Zídek V., Musilová 5 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 (2005) Nature Genetics 37(3):243-253. No. of citations: 424
- 6. Pařízek J., Ošťádalová I. Protective effect of small amounts of selenite in sublimate intoxication (1967) Experientia 23(2):142-143. No. of citations: 404
- Vaněček J., Pavlík A., Illnerová H. Hypothalamic melatonin receptor sites revealed by autoradiography (1987) Brain 7. Research 435(1-2):359-362. No. of citations: 394
- Jiruška P., de Curtis M., Jefferys J. G. R., Schevon C. A., Schiff S. J., Schindler K. Synchronization and desynchronization in 8. epilepsy: controversies and hypotheses (2013) Journal of Physiology 591(4):787-797. No. of citations: 383
- 9. Vyskočil F., Bureš J., Kříž N. Potassium-selective microelectrodes used for measuring extracellular brain potassium during spreading depression and anoxic depolarization in rats (1972) Brain Research 39(1):255-259. No. of citations: 370
- 10. Gutmann E. Neurotrophic Relations (1976) Annual Review of Physiology 38:177-216. No. of citations: 314

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

- 1. Bačáková L., Zárubová J., Trávníčková M., Musílková J., Pajorová J., Slepička P., Kasálková-Slepičková N., Švorčík V., Kolská Z., Motarjemi H., Molitor M. 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. No. of citations: 303
- 2. Bačáková L., Pajorová J., Bačáková M., Skogberg A., Kallio P., Kolářová K., Švorčík V. Versatile application of nanocellulose: from industry to skin tissue engineering and wound healing (2019) Nanomaterials 9(2):164. No. of citations: 192
- Vyklický V., Kořínek M., Smejkalová T., Balík A., Krausová B., Kaniaková M., Lichnerová K., Černý J., Krůšek J., 3. Dittert I., Horák M., Vyklický ml. L. Structure, function, and pharmacology of NMDA receptor channels (2014) Physiological Research 63(Suppl.1):S191-S203. No. of citations: 188
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SELECTED AWARDS THE WORLD-RENOWNED IPHYS EXPERTS REGULARLY GAIN RECOGNITION FOR THEIR SCIENTIFIC WORK AND RECEIVE MAJOR DOMESTIC AND FOREIGN AWARDS.

2023

RNDr. Ondřej Kuda, Ph.D. 1

Prize of the Minister of Education for outstanding results in research, experimental development and innovation

2022

Ing. Veronika Palůchová	Josef Hlávka Prize
Prof. MUDr. Přemysl Jiruška, Ph.D.	Award of the Mini
Doc. MUDr. Lucie Bačáková, CSc. 2	Praemium Acaden
Ing. Michal Pravenec, DrSc. 3	G. J. Mendel Honor
Mgr. Dalibor Košek, Ph.D.	Otto Wichterle Pri
Prof. RNDr. František Vyskočil, DrSc.	Silver Medal of Ch
MUDr. Jan Kopecký, DrSc.	Jan Evangelista Pu sciences

2021

RNDr. Petr Ježek, Ph.D.	
Mgr. Michaela Tencerová, Ph.D.	
Prof. RNDr. Helena Illnerová, DrSc.	

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2020

MUDr. Josef Zicha, DrSc. RNDr. Zdeněk Drahota, DrSc. 5

Doc. PharmDr. Alena Sumová, DSc. 5

Jan Evangelista Purkinje Honorary Field Medal for merit in the biomedical sciences Jan Evangelista Purkinje Honorary Field Medal for merit in the biomedical sciences Vojtěch Náprstek Honorary Prize Medal for merit in the popularization of science

2019

F	Prof. MUDr. Ladislav Vyklický, DrSc. 4	Prize of the M development
F	Prof. RNDr. František Kolář, CSc.	Jan Evangelis sciences
F	NDr. Jaroslav Kuneš, DrSc.	G. J. Mendel H

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- ard of the Minister of Health for Health Research and Development nemium Academiae award for outstanding scientific contribution . Mendel Honorary Field Medal for merit in the biological sciences
- o Wichterle Prize for the scientific contribution in the field of life sciences
- ver Medal of Charles University
- Evangelista Purkinje Honorary Field Medal for merit in the biomedical

Prize of Minister of Education for an exceptional research findings, experimental evolution and innovation in the field of natural sciences 3rd prize in the project L'Oréal-UNESCO For Women in Science

Silver Medal of the President of the Senate

Prize of the Minister of Health for an exceptional result in research and developmentJan Evangelista Purkinje Honorary Field Medal for merit in the biomedical sciencesG. J. Mendel Honorary Field Medal for merit in the biological sciences

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 80 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.

Analytical Chemistry (1) Animal Physiology (21) Biochemistry (3) Developmental Biology (3) Microbiology (1) Molecular and Cell Biology, Genetics (4) Biochemistry and Pathobiochemistry (11) Medical Biophysics (2) Neuroscience (5) Biophysics and Chemical Physics (1) **Biomechanics** (1) Statistics and Mathematical Modelling (3)

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)
- English language courses
- modern campus with on-site accommodation
- **sports** facilities

• advancement report of the third year PhD students and the internal PhD thesis evaluation

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.

LECTURES FOR PROFESSIONAL PUBLIC (2019 - 2023)

Bureš's (2) International (25) National external (13) IPHYS (45) Methodological (13)

MEDIA COVERAGE OF IPHYS

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 were Michael Hastings (Great Britain) and Stefano Schiaffino (Italy) in 2023.

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.

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.

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.

SCIENCE EXPO IPHYS participates in the annual Science Expo, a large festival of the Czech Academy of Sciences (45 000 visitors each year). Annualy updated exhibition of IPHYS entitled "Research of diseases from a molecule to the whole body" covers most of IPHYS's research.

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.

 $\ensuremath{\mathsf{OPEN}}$ HOUSE DAY The Laboratories of IPHYS are opened to the public annually in November during the Week of the Czech Academy of Sciences.

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 and online on IPHYS website.

RESEARCH TOPICS STUDIED AT IPHYS (1954 - 2024)*ARTICLES OF IPHYS SCIENTISTS CREATED/PUBLISHED ABROAD

CRITICAL PERIODS OF DEVELOPMENT, PERINATAL PROGRAMMING, LATE EFFECTS OF EARLY INTERVENTIONS (1954-2024)

Hahn, Křeček, Koldovský, Houštěk, Kopecký

Hahn P, Křeček J, Křečková J. The development of thermoregulation. I. The development of thermoregulatory mechanisms in young rats. Physiol Bohemoslov 1956;5:283-290.

Nováková V, Faltin J, Flandera V, Hahn P, Koldovský O. Effect of early and late weaning on learning in adult rats. Nature 1962;193:280. Kraus M, Křeček J, Popp M. Development of corticosterone production by adrenal gland in normally and prematurely weaned rats. Physiol Bohemoslov 1967;16: 120-127.

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MUSCLE PHYSIOLOGY (1954–1979)

Gutmann, Hanzlíková, Hník, Bass, Syrový

Hník P, Jirmanová I, Vyklický L, Zelená J. Fast and slow muscles of the chick after nerve cross-union. J Physiol 1967;193:309-325. Syrový I, Gutmann E. Changes in speed of contraction and ATPase activity in striated muscle during old age. Exp Gerontol 1970;5:31-35. Gutmann E, Hanzlíková V, Vyskočil F. Age changes in cross striated muscle of the rat. J Physiol 1971;216:331-343. Gutmann E, Schiaffino S, Hanzliková V. Mechanism of compensatory hypertrophy in skeletal muscle of the rat. Exp Neurol 1971;31:451-464.

Carlson BM, Gutmann E. Development of contractile properties of minced muscle regenerates in the rat. Exp Neurol 1972;36:239-249. Bass A, Gutmann E, Hanzlíková V. Biochemical and histochemical changes in energy supply enzyme pattern of muscles of the rat during old age. Gerontologia 1975;21:31-45.

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NEUROTROPHIC EFFECTS IN SKELETAL MUSCLE (1954-1993)

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MECHANORECEPTORS DEVELOPMENT, MORPHOLOGY AND FUNCTION (1954-2016)

Zelená, Hník, Hudlická, Jirmanová, Soukup, Vejsada

Zelená J. The morphogenetic influence of innervation on the ontogenetic development of muscle spindles. J Embryol Exp Morphol 1957;5:283-292.

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Zelená J, Soukup T. Development of muscle spindles deprived of fusimotor innervation. Z Zellforsch Mikrosk Anat 1973;144:435-452.

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SPREADING DEPRESSION (1954–1999)

Bureš, Burešová, Křivánek

Bureš J, Burešová O. The use of Leao spreading depression in the study of interhemispheric transfer of memory traces. J Comp Physiol Psychol 1960;53: 558-563.

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WATER AND ELECTROLYTE METABOLISM. BODY FLUIDS. ION TRANSPORT (1954-2021)

Křeček, Jelínek, Dlouhá, Kuneš, Zicha

Čapek K, Jelínek J. The development of the control of water metabolism. I. The excretion of urine in young rats. Physiol Bohemoslov 1956;5:91-96.

Křeček J, Křečková J. The development of the regulation of water metabolism. III. The relation between water and milk intake in infant rats. Physiol Bohemoslov 1957;6: 26-34.

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TOXIC EFFECTS OF MERCURY AND CADMIUM (1956–1976)

Pařízek

Pařízek J, Záhoř Z. Effect of cadmium salts on testicular tissue. Nature 1956;177:1036.

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Pařízek J. Vascular changes at sites of oestrogen biosynthesis produced by parenteral injection of cadmium salts: the destruction of placenta by cadmium salts. J Reprod Fertil 1964;7:263-265.

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CLINICAL AND TRANSLATIONAL EPILEPTOLOGY (1958-2024)

Servít, Mareš P. Jiruška

- Servit Z. Prophylactic treatment of post-traumatic audiogenic epilepsy. Nature 1960;188:669-670. Servit Z, Machek J, Štercová A, Dudáš D, Krištof M, Červenková V. Reflex influences in the pathogenesis of epilepsy in the light of clinical statistics. Epilepsia 3: 315-322, 1962.
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HIGHER BRAIN FUNCTIONS (1958-2000)

Radil, Bohdanecký, Indra, Mates

Lánský P, Radil T. Statistical inference on spontaneous neuronal discharge patterns. I. Single neuron. Biol Cybern 1987;55:299-311. Paus T, Babenko V, Radil T. Development of an ability to maintain verbally instructed central gaze fixation studied in 8- to 10-yearold children. Int J Psychophysiol 1990;10:53-61.

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LIPID METABOLISM — CHOLESTEROL TRANSPORT (1959—2011)

Hahn, Koldovský, Dobiášová

Drahota Z, P Hahn P, Kleinzeller A, Kostolánská A: Acetoacetate formation by liver slices from adult and infant rats. Biochem /1964; 93:61-65.

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ONTOGENY OF ANIMAL BEHAVIOUR (1959-1987)

Lát, Nováková, Martínek

Nováková V, Faltin J, Flandera V, Hahn P, Koldovský O. Effect of early and late weaning on learning in adult rats. Nature 1962;193:280. Nováková V. Weaning of young rats: effect of time on behavior. Science 1966;151:475-476. Nováková V. Role of mother during suckling period of newborn rats on subsequent adult learning. Physiol Behav 1966;1: 219-221. Sandritter W, Nováková V, Pilny J, Kiefer G. Cytophotometrische Messungen des Nukleisäure und Proteingehaltes von Ganglienzellen der Ratte während der postnatalen Entwicklung und im Alter. Z Zellforsch Mikrosk Anat 1967;80:145-152.

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Folbergrová J, Passonneau JV, Lowry OH, Schulz DW. Glycogen, ammonia and related metabolities in the brain during seizures evoked by methionine sulphoximine. J Neurochem 1969;16:191-203.

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acid: the protective effect of NMDA and non-NMDA receptor antagonists. Exp Neurol 2000;161:336-345. Folbergrová J, Druga R, Otáhal J, Haugvicová R, Mareš P, Kubová H. Seizures induced in immature rats by homocysteic acid and the associated brain damage are prevented by group II metabotropic glutamate receptor agonist (2R,4R)-4-aminopyrrolidine-

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