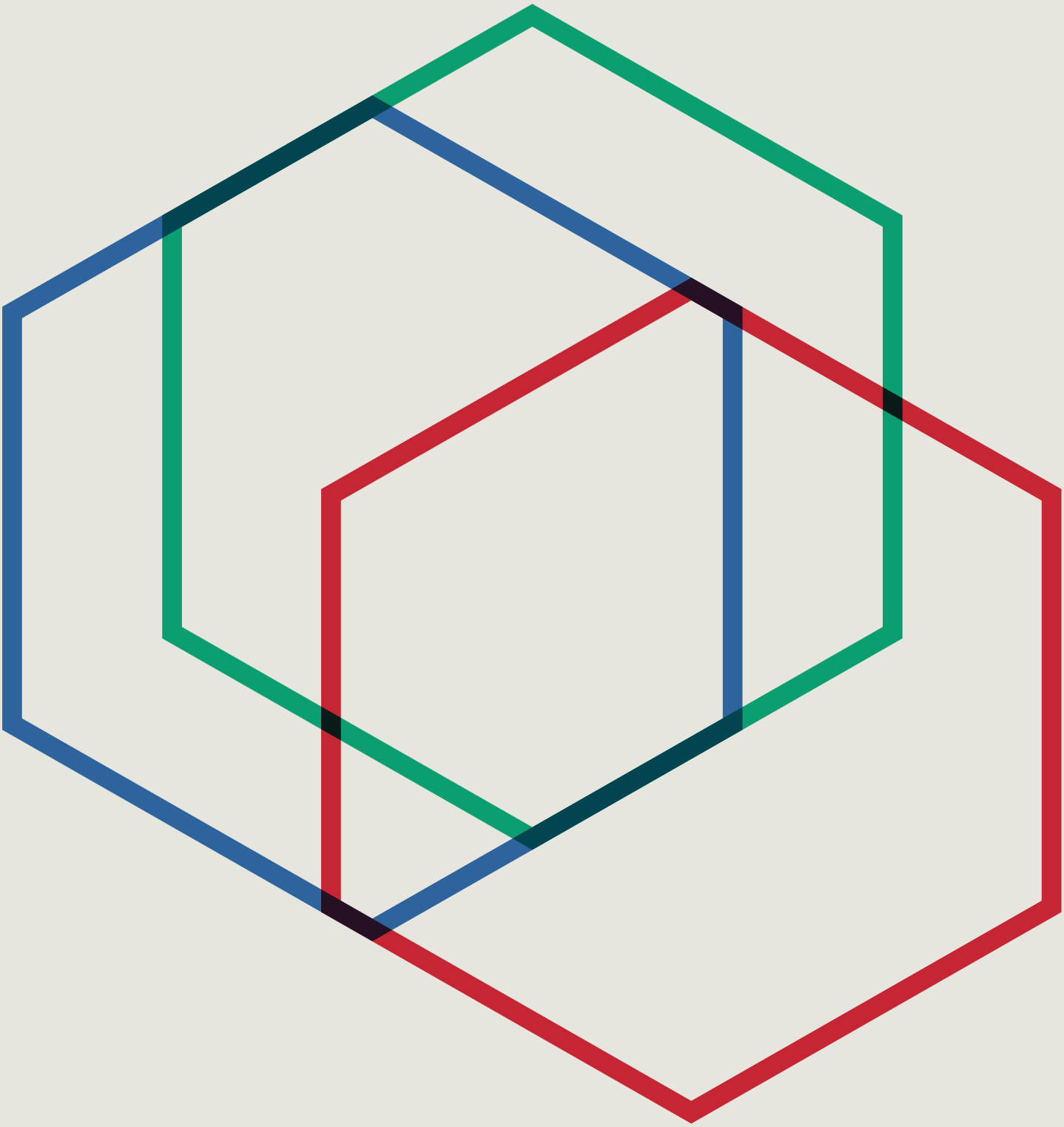
Research at IOCB Prague 2019

ÚOCHB AV ČR
IOCB PRAGUE



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Management

Institute Director:
Dr. Zdeněk Hostomský

Vice-director for Research:
Dr. Iva Pichová

Vice-director for Strategic Development:
Prof. Martin Fusek

IOCB Prague – excellence in basic research and successful applications

IOCB Prague is one of the few institutions in Central and Eastern Europe to successfully transform into a prosperous research institute and achieve global competitiveness. We currently have approximately 840 employees, of which more than 180 are foreigners. Our scientists work in 49 research and service groups. More than 160 PhD students make up an essential part of the IOCB community, and we constantly seek new talents to join us.

IOCB was founded in 1953 by Prof. František Šorm (1913–1980) as the Institute of Organic Chemistry, later renamed the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences (1960–1992) and, since 1993, of the Czech Academy of Sciences. From the very beginning, Prof. Šorm established IOCB as an interdisciplinary institute at the interface of chemistry, biology, and medicine with a combination of chemical and biological groups and teams working in the same field. He identified key areas of research such as nucleosides and nucleic acids, peptides and proteins, and terpenoids and steroids as well as a methodology-driven organic synthesis, to which IOCB has made significant contributions by pioneering cutting-edge research.

Drug discovery at IOCB – success story and legacy of Antonín Holý

In addition to excellence in basic research, IOCB has always been active and successful in applied research and practical applications, particularly in medicinal chemistry. The tradition started in 1969 with an ointment called Dermazulen, which was followed by the development of several human peptide hormones and their analogues.

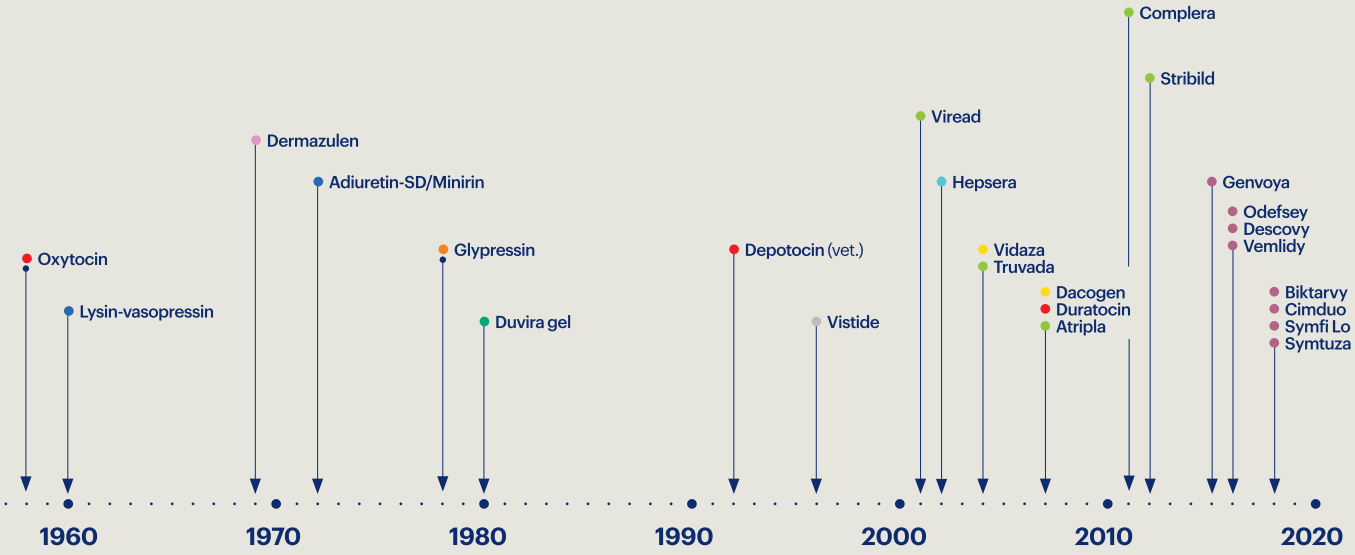
From a global perspective, the most significant contributions were acyclic nucleotide phosphonate antivirals (especially tenofovir as a component of Truvada, Atripla, and other anti-HIV and anti-HBV drugs) discovered by Prof. Antonín Holý at IOCB and later developed and marketed by Gilead Sciences, Inc.

Prof. Antonín Holý (1936–2012) was the most famous and successful scientist in the history of IOCB thanks to his groundbreaking basic research in the synthetic and medicinal chemistry of modified nucleosides and nucleotides and also to the discovery of antivirals used clinically in the treatment of viral diseases. Since 1976, he collaborated on the development of antiretroviral drugs with Prof. Erik De Clercq of the Rega Institute for Medical Research at the Catholic University of Leuven (Belgium) and John C. Martin, former CEO of Gilead Sciences (US).

Besides this well-known antiviral drug story, several other nucleoside compounds developed at IOCB became approved drugs. These include Decitabine, which is used in the treatment of acute myeloid leukemia, Azacytidine, which targets myelodysplastic syndrome (both discovered by Holý's peer Dr. Alois Píškala), and 9-(2,3-dihydroxypropyl)adenine (DHPA), an acyclic nucleoside analogue discovered by A. Holý and used clinically in anti-herpes ointments.

The legacy of A. Holý in the chemistry of nucleic acids components is continued by several IOCB groups active in the areas of nucleotide chemistry and nucleic acid research. Other groups in medicinal chemistry focus on different approaches to tackle cancer and diseases of viral, bacterial, and fungal origin.

Registered drugs with active compounds developed at IOCB



Bridging the past and present

The commercial success of these drugs and a significant income from patent royalties enabled IOCB to grow substantially and convert its campus into a modern institute with cutting-edge equipment. In January 2007, under the leadership of then director Zdeněk Havlas, IOCB changed its legal form to become a public research institution, and was restructured with all group leader positions open to international competition. Since then, IOCB has implemented an ambitious policy of rigorous and regular evaluations of the research groups by an International Advisory Board and a tenure-track program for the establishment of independent junior research groups. The current IOCB director, Zdeněk Hostomský, further promotes out-of-the-box thinking in the sense of crossing barriers and exploring new paths. He emphasizes excellence in basic research together with support for technology transfer and capitalization of potential applications.

These new policies and strategies have transformed IOCB into an internationally recognized institute. With English as the working language, scientists at IOCB (including group leaders) come from dozens of countries around the globe. The traditional portfolio of research fields covering classical organic, bioorganic and medicinal chemistry, and biochemistry has expanded to encompass theoretical and physical chemistry, materials science, bioconjugate chemistry, chemical biology, nanotechnology, and other related areas.

Current research

Embracing a number of different perspectives and approaches in organic chemistry and biochemistry, including insights from biology, physics, and mathematics, better reflects the complexity of living systems and grapples with big questions in the life sciences. Research at IOCB covers three major clusters of interconnected disciplines: CHEM, BIO and PHYS.

The CHEM cluster includes organic synthesis, medicinal chemistry, natural products chemistry, chemical biology, bioconjugate chemistry, drug design and discovery, photochemistry materials chemistry, and nanochemistry. In organic chemistry, groups focus on development of organic synthesis methodology, total synthesis of natural products, synthesis of fluorinated compounds, extended aromatic systems, and helicenes as well as on synthesis of modified derivatives and analogues of nucleosides, nucleotides, oligonucleotides, steroids, and peptides. In medicinal chemistry, groups specialize in development of antivirals (against hepatitis B and other emerging viruses), cytostatic agents against leukemia and different types of cancer, compounds targeting neuropathic pain and inflammation, antimicrobial agents, and antiparasitic compounds against malaria. In bioorganic chemistry and chemical biology, different aspects of nucleic acids research, the study of protein-DNA interactions, development of new bioconjugation reagents and reactions, novel fluorescent probes, and bioimaging reagents and techniques are investigated. In materials chemistry, projects include synthesis of functional molecules for preparation of nanomaterials, modified surfaces and materials for molecular electronics, the study of singlet fission, the study of molecules and reactions on metal surfaces, and the design and synthesis of modified nanodiamonds and molecular machines.

The BIO cluster includes biochemistry, molecular, structural and cell biology, virology, biochemical pharmacology, physiology, chemical ecology, diagnostic tools, and bioinformatics, etc. Biochemical groups perform multidisciplinary research focused on detailed characterization of human pathogens, such as HIV, HBV, influenza, Zika virus, *Mycobacterium tuberculosis*, interaction of key pathogenic proteins with cellular machineries, RNA modifications of viral and bacterial RNAs, analysis of regulatory processes affecting cancer growth, metabolic disorders (diabetes and obesity), and neurodegenerative processes. Structural biology and biochemical characterization of proteases, viral polymerases, phosphatidylinositol kinases, carbonic anhydrases, intramembrane proteases, membrane receptors and channels, and human transcription factors as well as their complexes and interactions with cellular partners and inhibitors are studied in order not only to better understand the corresponding biological processes but also to identify novel therapeutic targets. Biological activity screening (cytostatic and antiviral activity), the mechanism of action of bioactive compounds synthetized in medicinal chemistry groups, and development of original diagnostic methods contribute to the successful identification of specific inhibitors. Investigations of chemical ecology and molecular mechanisms of pheromone biosynthesis and the search for pheromone components of pest insect species are used in characterizing social insect communication and in subsequent application in mating disruption.

The PHYS cluster includes two main branches. The theoretical and computational chemistry groups focus on the application of modern quantum chemical and molecular modeling methods to study problems of high chemical and biological relevance. The spectroscopy/analytical chemistry groups, also partially serving to support the CHEM and BIO clusters, include molecular spectroscopy, analytical chemistry, separation science, electrochemistry, advanced microscopy, mass spectrometry, and NMR/EPR spectroscopy. More specifically, theoretical chemistry groups use quantum chemistry and molecular simulations to predict the structure, reactivity, and properties of organic molecules and biomolecules as well as to study biomolecular interactions and systems of increasing complexity (such as biological membranes), investigate electron transfer processes and mechanisms of organic and enzymatic reactions, and perform rational *in silico* design of ligands or inhibitors of biomolecular targets. Many of the studies are further supported by bioinformatics; IOCB hosts one of the nodes of the pan-European ELIXIR cluster. The spectroscopy groups perform organic, bioinorganic, and bioorganic structure determination by physical and spectroscopic methods and examine the relationship between structure and physical properties; they also carry out theoretical calculations to predict spectra. The technical development of methods for separation of biomolecules (such as capillary electrophoresis) is also being pursued.

Behind the research

IOCB Development Center
The IOCB Development Center (dc.uochb.cz) develops unique tools, instruments, and novel technologies and also provides repairs and maintenance of instrumentation in laboratories in order to support researchers at IOCB. Part of the activities are focused on commercial collaboration with other academic and industrial research laboratories.

IOCB Compound Library
The IOCB Compound Library preserves original compounds synthesized at IOCB Prague. In addition to a solid-state library, DMSO solutions in 384-well plates are prepared for screening by biochemists with emphasis on a low expenditure of substances and sufficiently functioning assays. The solutions are available in very small quantities for direct screening without any additional pipetting, which saves both time and the precious substances.

Beyond the research – technology transfer and applications

In applied research, the IOCB's long tradition of translating results of basic research into products that help people live better lives continues to this day. We have established a dedicated applied research infrastructure that consists of several internal spin-offs.

Since 2009, technology transfer, applications, and IP protection have been coordinated by IOCB Tech and later also by i&i Prague. These IOCB subsidiary companies are recognized throughout Czechia as leading commercialization experts for biotech projects and have successfully attracted local and global investment groups and funds largely thanks to the current vice-director for strategic development, Prof. Martin Fusek, founder of technology transfer at IOCB.

IOCB Tech

IOCB Tech (www.iocbtech.cz) is a technology transfer office and subsidiary company of IOCB Prague. The company, which is wholly owned by IOCB Prague, helps translate the results of basic research carried out at IOCB by scientists in the fields of medicinal chemistry, material sciences, biology, and other areas related to chemistry. The primary goal is to make those results available for human use.

IOCB Tech has been involved in and arranged for the signing of more than ten key license agreements with major pharma partners such as Gilead Sciences, Merck, Novo Nordisk, and SHINE Medical Technologies. In 2018, the IOCB's income from these licenses exceeded 60 million USD. The current portfolio features projects focused on CNS (epilepsy and neuropathic pain), inflammation, cancer, microbial resistance, separation methods, and research tools.

i&i Prague

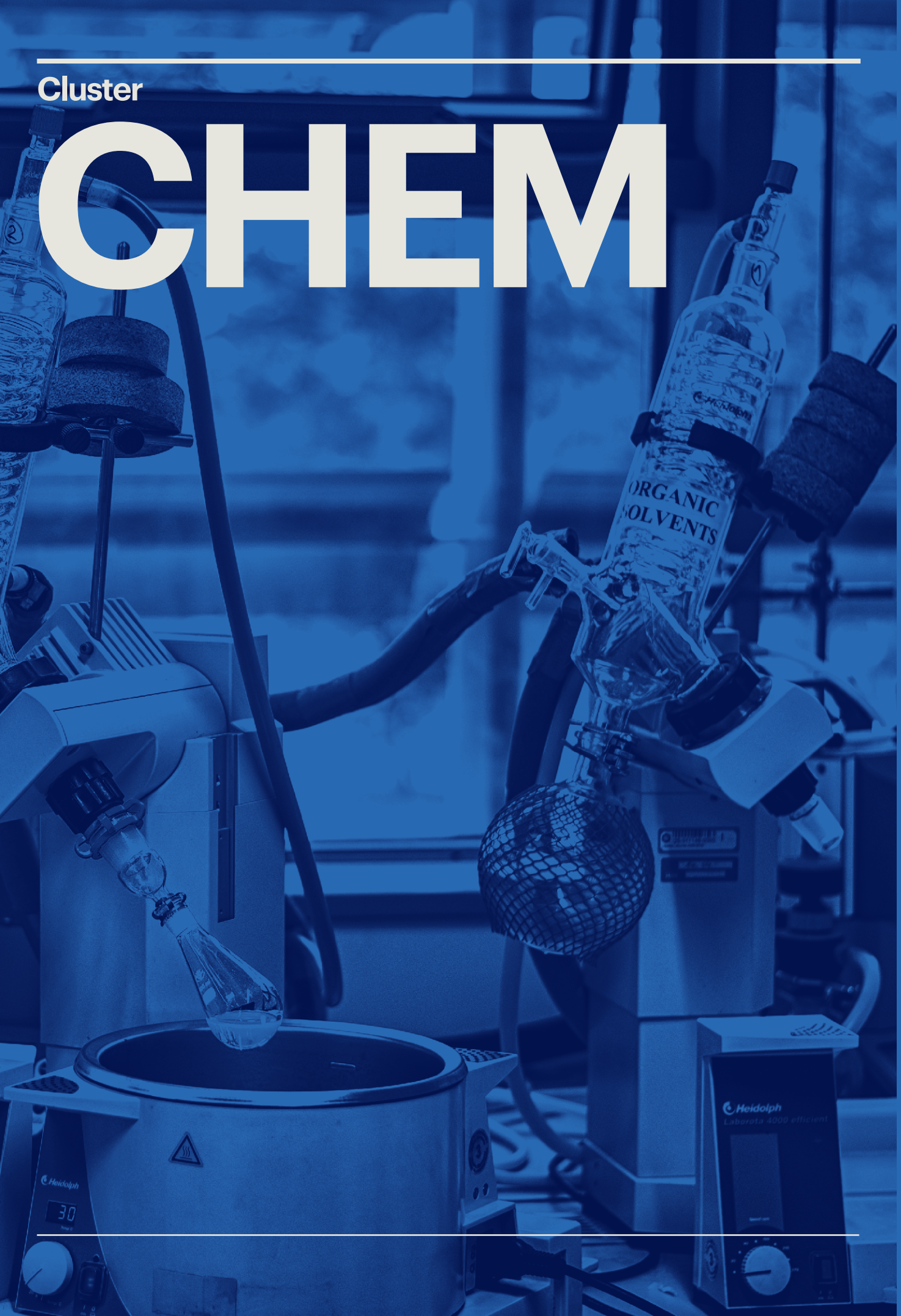
i&i Prague (www.iniprague.com) was founded in 2017 with the aim of representing the institute in all spin-offs arising from IOCB but also to scout for projects with innovative potential outside IOCB. The company provides pre-seed financing for such projects as well as commercial expertise and assistance in their development.

The IOCB story goes on...

The long-term success of IOCB Prague can be described on several levels, but in general the institute thrives thanks to its ability to connect, fuse, and find new opportunities in the right combinations. Excellent basic research at the interface of chemical and biological sciences, the translation of results from basic research into applications and commercial assets, the combination of tradition, expertise, and knowledge with cutting-edge technologies, the pursuit of experimental and theoretical disciplines, collaboration with world-class partners from both the clinical field and the pharma industry, the opening of transparent calls for new junior group leaders while supporting productive senior groups, attracting the best PhD students from Czech universities and abroad, and promoting collaboration across groups within the institute in addition to stimulating healthy competition with other institutions are a few good examples. Diversity bolsters IOCB Prague as a whole and makes it more resilient, versatile, and progressive. Our ultimate goal is to continue to contribute to world-class science and to enable humanity to benefit from our discoveries and applications.

Cluster

CHEM



Petr Beier Group (Organic Chemistry of Fluorine and Main Group Elements)
Petr Cígler Group (Synthetic Nanochemistry)
Michal Hocek Group (Bioorganic and Medicinal Chemistry of Nucleic Acids)
Ullrich Jahn Group (Chemistry of Natural Products)
Zlatko Janeba Group (Medicinal Chemistry of Nucleotide Analogues)
Jiří Kaleta Group (Molecular Devices)
Eva Kudová Group (Neurosteroids)
Josef Michl Group (Organic Chemistry)
Radim Nencka Group (Drug Design and Medicinal Chemistry)
Miloslav Polášek Group (Coordination Chemistry)
Dominik Rejman Group (Antimicrobial Compounds)
Ivan Rosenberg Group (Nucleotides and Oligonucleotides)
Tomáš Slanina Group (Redox Photochemistry)
Ivo Starý Group (Chemistry of Functional Molecules)
Milan Vrábel Group (Chemistry of Bioconjugates)
Dmytro Yushchenko Group (Chemical Biology)

Drug Discovery (Pavel Majer)
Synthesis of Radiolabeled Compounds (Aleš Marek)

Petr Beier Group

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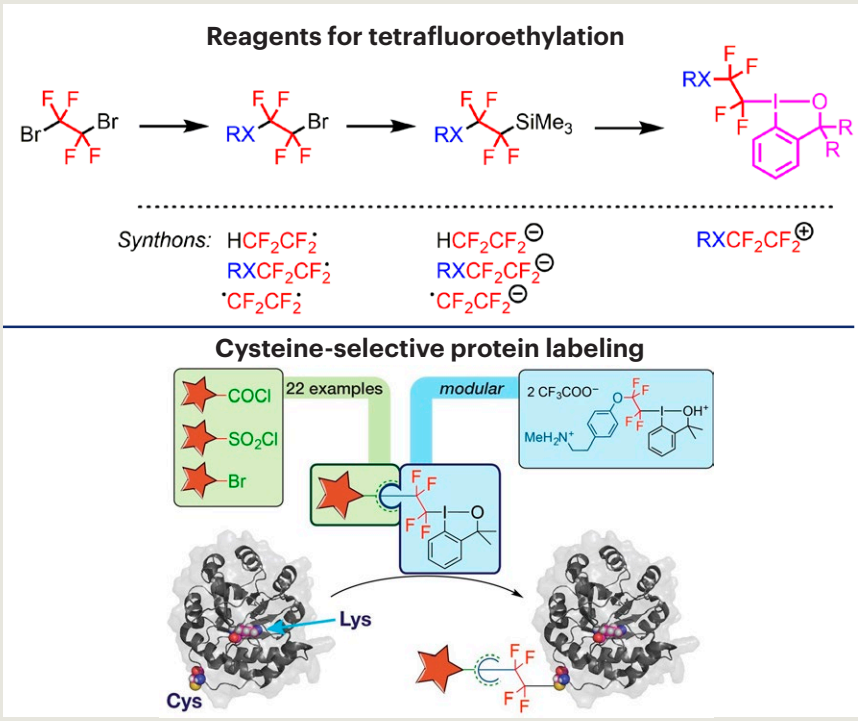
Senior Research Group

fluorine, sulfur, silicon, iodine, phosphorus, fluoroalkylation, bioconjugation, hypervalent iodine, sulfur pentafluorides



Research topics

Our research is focused on the development of new synthetic methodologies and reagents in organofluorine chemistry. We utilize the rich chemistry of main group elements such as phosphorus, sulfur, silicon, and iodine to unravel new chemical transformations and apply them in the synthesis of selectively fluorinated molecules.

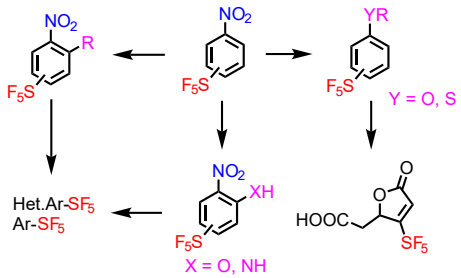
New methods for fluoroalkyl group transfer are in high demand in chemical synthesis and in the pharmaceutical and materials industries. We have designed and utilized new silicon-, sulfur-, and hypervalent iodine-based reagents for radical, nucleophilic, and electrophilic transfer of CF_2CF_2 groups. The iodine reagents are currently being investigated for bioconjugation of thiols and electron-rich amino acid residues.

Pentafluorosulfanyl group (SF_5) is a relatively undeveloped functionality with an interesting combination of physicochemical properties. Our research is focused on the development of new methods and reactions for the synthesis and transformation of SF_5-substituted aromatic, heteroaromatic, and aliphatic compounds.

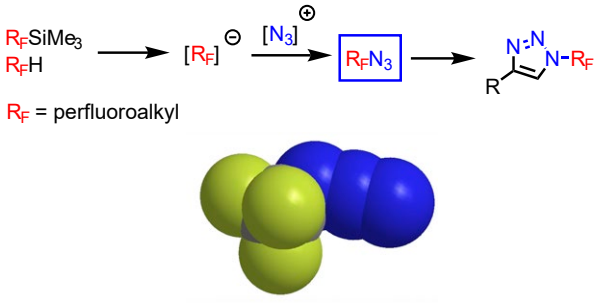
We have devised a new process for the synthesis of a new class of compounds—azidoperfluoroalkanes. Their synthetic applications are under investigation. Azidoperfluoroalkanes represent key building blocks for the synthesis of a range of new and synthetically useful vinyl triflates, fluorinated imidazoles, pyrroles, oxazoles, azepines, and other heterocycles.

Alfa-fluorinated phosphonates are important mimics of ubiquitous biological phosphates. We have prepared various phosphonates and used them as important fluorinated C1 synthons in the synthesis of new fluoroalkenes and fluorinated phosphonates.

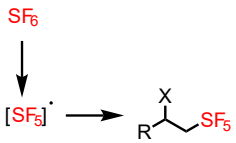
SF_5 compounds



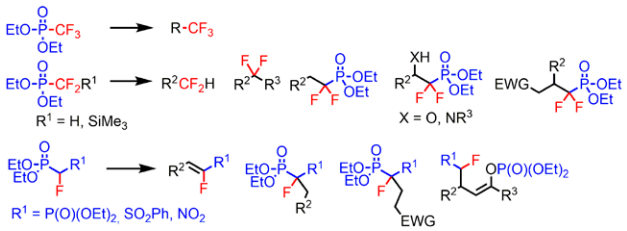
Azidoperfluoroalkanes



S-F activation of SF_6



Fluorinated phosphonates



Group members

Group leader Petr Beier
Scientists Martin Pošta, David Tichý, Svatava Voltrová
Ph.D. students Javier Ajenjo, Olga Bakhanovich, Viktor Khutoryanskiy, Iveta Klimánková, Athanasios Markos, Kheironnesae Rahimidashaghoul
Students Josef Filgas, Vojtěch Košťál

Selected papers

Motornov, V.; Beier, P. Chemoselective aza-[4+3]-annulation of N-perfluoroalkyl-1,2,3-triazoles with 1,3-dienes: Access to N-perfluoroalkyl-substituted azepines. *J. Org. Chem.* **2018**, 83, 15195–15201.

Motornov, V.; Markos, A.; Beier, P. Rhodium-catalyzed transannulation of N-(per)fluoroalkyl-1,2,3-triazoles in microwave conditions—a general route to N-(per)fluoroalkyl-substituted five-membered heterocycles. *Chem. Commun.* **2018**, 54, 3258–3261.

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Blastik, Z.E.; Voltrová, S.; Matoušek, V.; Jurásek, B.; Manley, D.; Klepetářová, B.; Beier, P. Azidoperfluoroalkanes: Synthesis and Application in Copper(I)-Catalyzed Azide-Alkyne Cycloaddition. *Angew. Chem. Int. Ed.* **2017**, 56, 346–349.

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Khutorianskyi, V.V.; Sonawane, M.; Pošta, M.; Klepetářová, B.; Beier, P. Oxidative nucleophilic aromatic amination of nitrobenzenes. *Chem. Commun.* **2016**, 52, 7237–7240.

Financial support

Synthesis and reactivity of N-fluoroalkylated compounds. Ministry of Education, Youth and Sports (MŠMT), INTERACTION LTAUSA18, 2019–2022.

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Development of fluoroalkylated hypervalent iodine reagents for thiol bioconjugations. Czech Science Foundation (GA ČR), No. 17-00598S, 2017–2019.

Petr Cígler Group

Synthetic Nanochemistry
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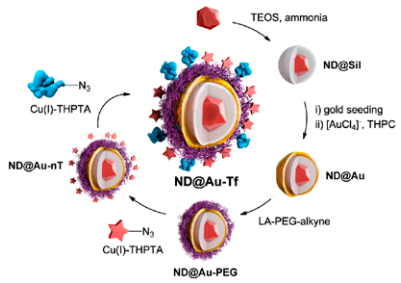
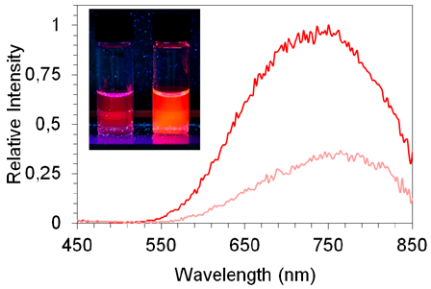
Senior Research Group
nanoparticles, bioimaging, sensing, fluorescence,
nanodiamond, virus-like particle, theranostics, plasmonics

NANOPARTICLES FOR BIOIMAGING, DIAGNOSTICS AND THERAPY

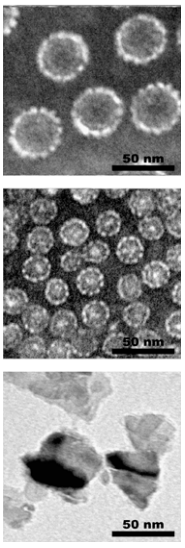
Advanced synthetic protocols



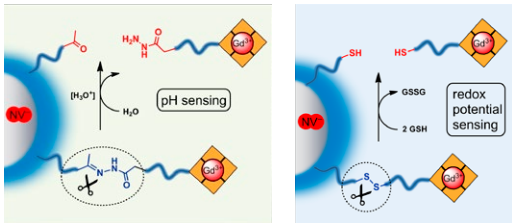
Near-infrared nanoprobes



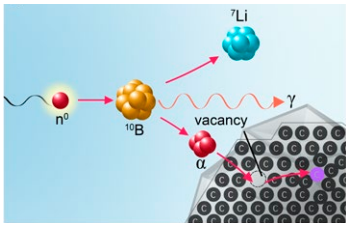
Inorganic and bioorganic nanoparticles



New sensing schemes—quantum detection



Creation of luminescent centers



Research topics

We investigate interactions of nanoparticles with a biological environment and find new approaches for their synthesis. Currently, we are working on either inorganic or bioorganic structures. Using these nanoparticles, we construct targeted multimodal imaging nanoprobes and particles for diagnostics, therapy, or so-called theranostics (THERApeutics and diagNOSTICS from one particle).

Our important type core structure is fluorescent nanodiamond, a material with a unique electronic structure enabling optical readout of magnetic and electric fields. It is a non-photobleachable near-infrared emitting fluorophore. Using a complex synthetic approach, we build up new molecular architectures on its surface enabling the use of the particles as fluorescent nanolabels and multimodal nanosensors. In collaboration with other teams, we develop novel quantum detection technologies based on nanodiamonds.

Another type of particles we study are virus-like capsides—a versatile biomaterial inspired by nature. The proteins of capsides spontaneously self-assemble into compact pseudospheric particles. These building nanoblocks can be easily modified chemically. With atomic precision, we attach new molecularly designed architectures to the surfaces or inner space of capsides. Viral capsides serve as a platform for a polyvalent display of ligands that can target cancer cells and, at the same time, deliver therapeutic molecules to the right place. Polyvalency brings us a new quality: strong co-operativity of ligands, which cannot be reached with small molecules.

We also study near-infrared emitting gold nanoclusters, plasmonic gold nanoshells, particles for gene therapy delivering siRNA and mRNA, and another nano-sized systems. For all the projects, we design and synthesize novel linkers, fluorescent dyes, ligands, polymers, and chemically modified proteins.

Group members

Group leader Petr Cígler
Scientists Goutam Pramanik, Ivan Řehoř, Hana Španielová, Václav Vaněk
Postdocs Jana Kovalčíková, Jitka Neburková, Chandra Prakash Epperla, Jiří Schimer
Research assistants Zuzana Chumová, Miroslava Guricová
Ph.D. students Jan Bartoň, Marek Kindermann, Klaudia Kvaková, Helena Raabová
Students Jakub Čopák, Alžběta Runová
Technician Petra Typoldová

Selected papers

Havlik, J.; Petrakova, V.; Kucka, J.; Raabova, H.; Panek, D.; Stepan, V.; Zlamalova Cilova, Z.; Reineck, P.; Stursa, J.; Kucera, J.; Hruby, M.; Cigler, P. Extremely rapid isotropic irradiation of nanoparticles with ions generated in situ by a nuclear reaction. *Nat. Commun.* **2018**, 9, 4467.

Vavra, J.; Rehor, I.; Rendler, T.; Jani, M.; Bednar, J.; Baksh, M.M.; Zappe, A.; Wrachtrup, J.; Cigler, P. Supported Lipid Bilayers on Fluorescent Nanodiamonds: A Structurally Defined and Versatile Coating for Bioapplications. *Adv. Funct. Mater.* **2018**, 28, 1803406.

Balek, L.; Buchtova, M.; Kunova Bosakova, M.; Varecha, M.; Foldynova-Trantirkova, S.; Gudernova, I.; Vesela, I.; Havlik, J.; Neburkova, J.; Turner, S.; Krzyscik, M. A.; Zakrzewska, M.; Klimaschewski, L.; Claus, P.; Trantirek, L.; Cigler, P.; Krejci, P. Nanodiamonds as "artificial proteins": Regulation of a cell signalling system using low nanomolar solutions of inorganic nanocrystals. *Biomaterials* **2018**, 176, 106–121.

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Financial support

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Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022, Cígler, P. (co-PI)

Uncovering Structure-Cytotoxicity Relationship of α-Synuclein Aggregates. IOCB Collaborative Interdisciplinary Program, 2018–2020, Cígler, P. (co-PI)

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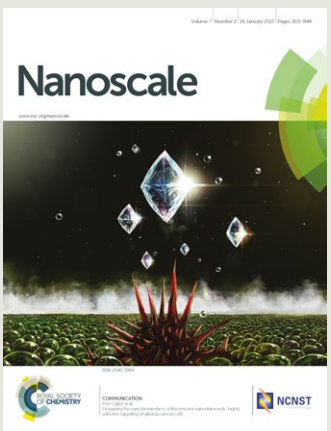
Spin-based nanolytics—Turning today's quantum technology research frontier into tomorrow's diagnostic devices (NanoSpin). ERA-NET/QuantERA Project, 2018–2020, Cígler, P. (co-PI)

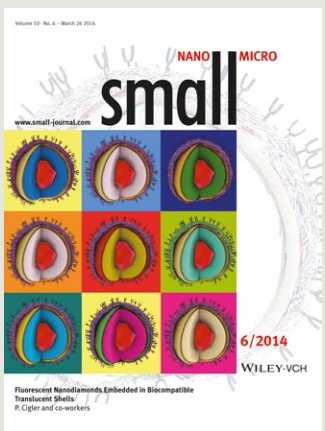
Use of plasmonic nanoparticles for in vitro diagnostics. Ministry of Industry and Trade (MPO), No. FV10755, 2016–2020, Cígler, P.

Visualization of the invisible—a novel way to detection of individual miRNA molecules in living cells. Neuron Impuls Grant, 2018–2019, Cígler, P.

Quantum detection technologies: nanodiamond for sensing in intracellular environment. Czech Science Foundation (GA ČR), No. 16-16336S, 2016–2018, Cígler, P.

Nanofiber drug carriers for controlled release of wound healing substances based on the encapsulation of functionalized nanodiamond particles. Czech Health Research Council (AZV ČR), No. 15-33094A, 2015–2018, Cígler, P. (co-PI)





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Senior Research Group

nucleosides, nucleotides, oligonucleotides, nucleic acids, DNA, RNA, polymerases

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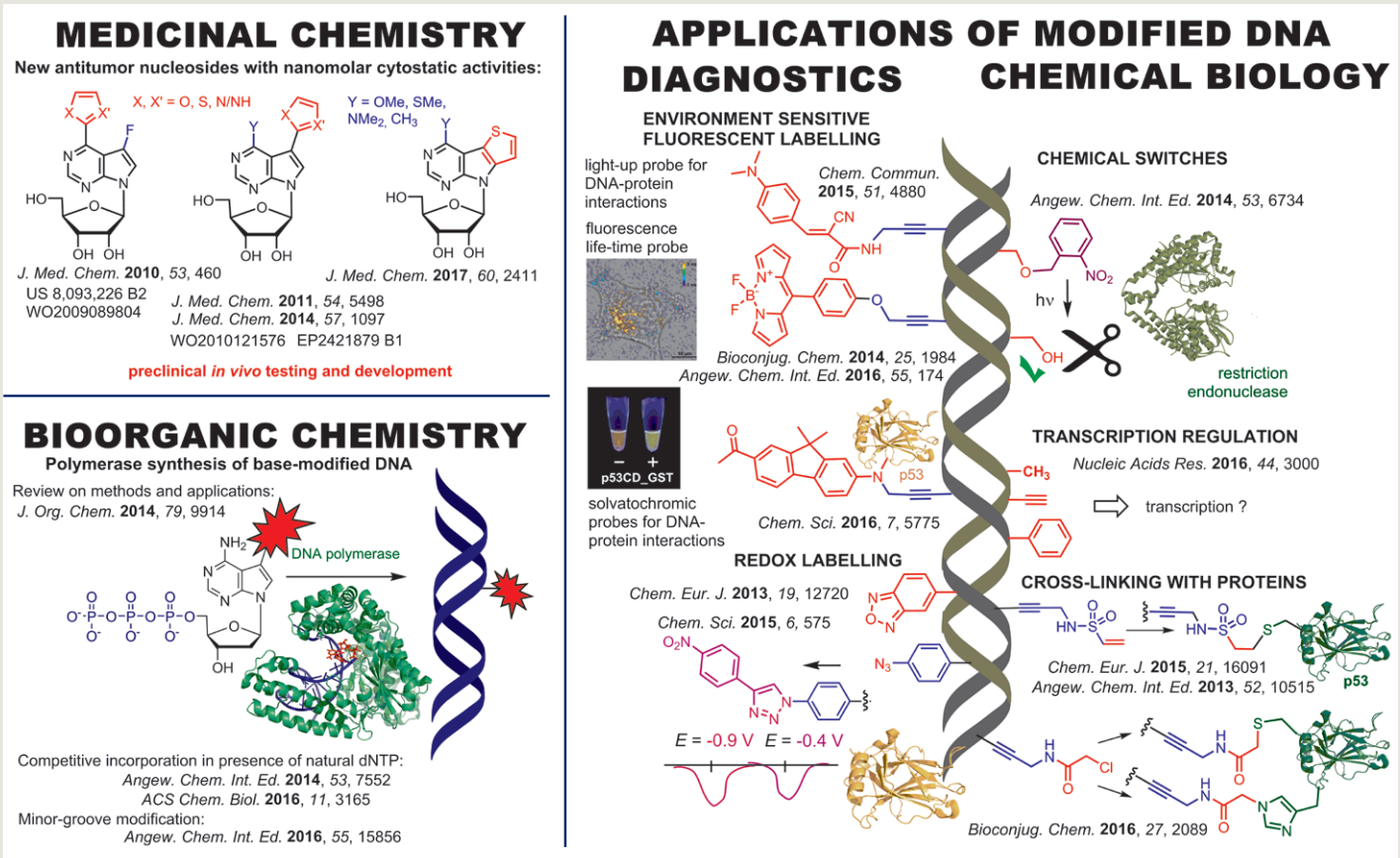

Research topics

The group designs and prepares novel types of modified derivatives and analogues of nucleobases, nucleosides, nucleotides, and nucleic acids for applications in all areas of biomedicinal sciences. Developments of synthetic methodology rely on cross-coupling and C-H arylation reactions as well as glycosylations and phosphorylations. In medicinal chemistry, rational design and the systematic biological activity screening of libraries of modified nucleobases and nucleosides have led to the discovery of several new types of potent nucleoside antivirals and cytostatics. Selected aryl-7-deazapurine nucleosides undergo preclinical study of the mechanism of action, pharmacokinetics, and *in vivo* antitumor activity. Several methods of polymerase construction of functionalized nucleic acids bearing diverse useful substituents have been developed, and their applications are pursued in bioanalysis (e.g. redox labeling for electrochemical detection in diagnostics of mutations of DNA, or environment-sensitive fluorescent labeling for sensing protein-DNA interactions) and in chemical biology (reactive labeling for bioconjugations and cross-linking with proteins, or bioorthogonal reactions in the major groove of DNA for the switching of interactions with proteins or regulation of transcription).

Group members

Group leader Michal Hocek
Scientists Tomáš Kraus, Pavla Perlíková, Veronika Sýkorová, Michal Tichý
Postdocs Anna Krajczyk, Olena Mayboroda, Catherine Mulholland
Ph.D. students Aswathi Chakrapani, Marianne Fleuti, Filip Gracias, Pedro Güixens-Gallardo, Vojtěch Havlíček, Ivana Ivancová, David Kodr, Matouš Krömer, Miroslav Kuba, Denise-Liu Leone, Ján Matyašovský, Nemanja Milisavljević, Agata Olszewska, Marek Ondruš, Alessandro Panattoni, Ambra Spampinato, Zuzana Vaníková, Lucia Veselovská, Marek Vician, Chao Yang
Technician Tereza Schröpferová

Selected papers

Tokarenko, A.; Lišková, B.; Smoleň, S.; Táborská, N.; Tichý, M.; Gurská, S.; Perlíková, P.; Frydrych, I.; Tloušťová, E.; Znojek, P.; Mertlíková-Kaiserová, H.; Poštová Slavětínská, L.; Pohl, R.; Klepetářová, B.; Khalid, N.-U.-A.; Wenren, Y.; Laposa, R. R.; Džubák, P.; Hajdúch, M.; Hocek, M. Synthesis and Cytotoxic and Antiviral Profiling of Pyrrolo- and Furo-fused 7-Deazapurine Ribonucleosides. *J. Med. Chem.* **2018**, 61, 9347–9359.

Güixens-Gallardo, P.; Zawada, Z.; Matyasovsky, J.; Dziuba, D.; Pohl, R.; Kraus, T.; Hocek, M. Brightly Fluorescent 2′-Deoxyribonucleoside Triphosphates Bearing Methylated Bodipy Fluorophore for in cellulo Incorporation to DNA, Imaging and Flow Cytometry. *Bioconjug. Chem.* **2018**, 29, 3906–3912.

Slavíčková, M.; Janoušková, M.; Šimonová, A.; Cahová, H.; Kambová, M.; Šanderová, H.; Krásný, L.; Hocek, M. Turning off transcription with bacterial RNA polymerase through CuAAC click reactions of DNA containing 5-ethynyluracil. *Chem. Eur. J.* **2018**, 24, 8311–8314.

Panattoni, A.; Pohl, R.; Hocek, M. Flexible Alkyne-Linked Thymidine Phosphoramidites and Triphosphates for Chemical or Polymerase Synthesis and Fast Post-Synthetic DNA Functionalization through Copper-Catalyzed Alkyne–Azide 1,3-Dipolar Cycloaddition. *Org. Lett.* **2018**, 20, 3962–3965.

Janoušková, M.; Vaníková, Z.; Nici, F.; Boháčová, S.; Vítovská, D.; Šanderová, H.; Hocek, M.; Krásný, L. 5-(Hydroxymethyl)uracil and -cytosine as potential epigenetic marks enhancing or inhibiting transcription with bacterial RNA polymerase. *Chem. Commun.* **2017**, 53, 13253–13255.

Tichý, M.; Smoleň, S.; Tloušťová, E.; Pohl, R.; Oždian, T.; Hejtmánková, K.; Lišková, B.; Gurská, S.; Džubák, P.; Hajdúch, M.; Hocek, M. Synthesis and Cytostatic and Antiviral Profiling of Thieno-fused 7-Deazapurine Ribonucleosides. *J. Med. Chem.* **2017**, 60, 2411–2424.

Downey, A. M.; Pohl, R.; Roithová, J.; Hocek, M. Synthesis of nucleosides through direct glycosylation of nucleobases with 5-O-mono-protected or 5-modified ribose. Improved protocol, scope and mechanism. *Chem. Eur. J.* **2017**, 23, 3910–3917.

Matyašovský, J.; Perlíková, P.; Malnuit, V.; Pohl, R.; Hocek, M. 2-Substituted dATP derivatives as building blocks for polymerase synthesis of DNA modified in minor groove. *Angew. Chem. Int. Ed.* **2016**, 55, 15856–15859.

Dziuba, D.; Pospíšil, P.; Matyašovský, J.; Brynda, J.; Nachtigallová, D.; Rulíšek, L.; Pohl, R.; Hof, M.; Hocek, M. Solvatochromic Fluorene-Linked Nucleoside and DNA as Color-Changing Fluorescent Probes for Sensing Interactions. *Chem. Sci.* **2016**, 7, 5775–5785.

Perlíková, P.; Rylová, G.; Nauš, P.; Elbert, T.; Tloušťová, E.; Bourderioux, A.; Poštová Slavětínská, L.; Motyka, K.; Doležal, D.; Znojek, P.; Nová, A.; Harvanová, M.; Džubák, P.; Šiller, M.; Hlaváč, J.; Hajdúch, M.; Hocek, M. 7-(2-Thienyl)-7-deazaadenosine (AB61), a new potent nucleoside cytostatic with a complex mode of action. *Mol. Cancer Ther.* **2016**, 15, 922–937.

Raindlová, V.; Janoušková, M.; Slavíčková, M.; Perlíková, P.; Boháčová, S.; Milisavljevic, N.; Šanderová, H.; Benda, M.; Barvík, I.; Krasný, L.; Hocek, M. Influence of major-groove chemical modifications of DNA on transcription by bacterial RNA polymerases. *Nucleic Acids Res.* **2016**, 44, 3000–3012.

Dziuba, D.; Jurkiewicz, P.; Cebecauer, M.; Hof, M.; Hocek, M. A Rotational Bodipy-Nucleotide: An Environment-Sensitive Fluorescence-Lifetime Probe for DNA Interactions and Applications in Live-Cell Microscopy. *Angew. Chem. Int. Ed.* **2016**, 55, 174–178.

Financial support

Gilead Sciences & IOCB Research Center, 2006–2021.

Praemium Academiae to M. Hocek, Czech Academy of Sciences, 2016–2021.

Chemical biology for development of new therapies. European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022.

Cytostatic hetero-fused 7-deazapurine nucleosides, pharmacology, metabolism and mechanism of action. Czech Science Foundation (GA ČR), No. 19-08124S, 2019–2021.

Bioconjugation reactions for cross-linking of proteins to DNA. Czech Science Foundation (GA ČR), No. 18-03305S, 2018–2020.

Artificial epigenetics: Development of a eukaryotic bioorthogonal transcription system for gene expression manipulation in the cell (with L. Krásný group). Czech Science Foundation (GA ČR), No. 17-03419S, 2017–2019.

Click Chemistry for Future Gene Therapies to Benefit Citizens, Researchers and Industry (CLICKGENE). International Training Network, European Commission (Horizon 2020), 2015–2019.

Awards—Michal Hocek

Praemium Academiae, scientific excellence, Czech Academy of Sciences, 2015

Elected member of the Learned Society of the Czech Republic, 2017

Ullrich Jahn Group

Chemistry of Natural Products
ullrich.jahn@uochb.cas.cz
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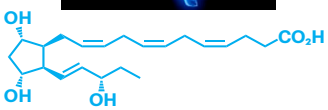
Senior Research Group

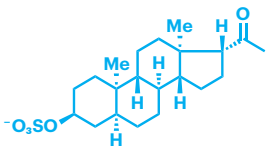
total synthesis, natural products, radicals, electron transfer, alkaloids, lipids, terpenes

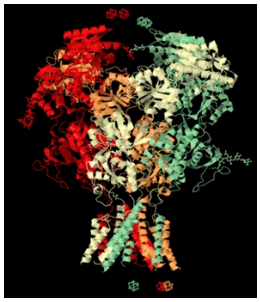
Phytoprostanes

Neuroprostanes

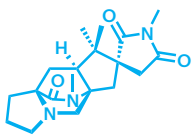


Neuroprotective Steroids



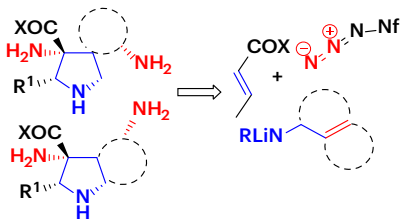


Diketopiperazines Asperparaline C

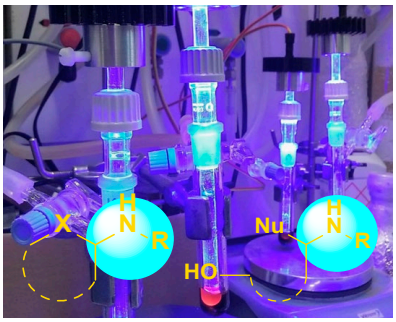


Insect Pheromones

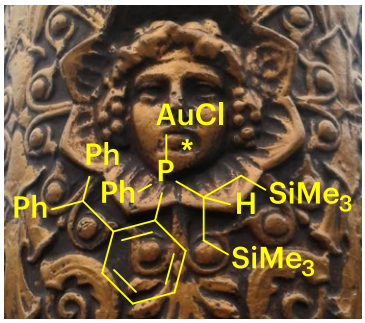
Unnatural amino acids for new peptide architectures



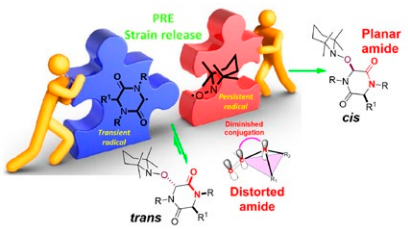
Photocatalysis C(sp³)-H & C(sp²)-H Amination Reactions



P-Chiral Gold Catalysts



Free Radical Chemistry



Research topics

The group's interests focus to a large extent on the total synthesis of natural products and their biological investigation. One the one hand, the establishment and confirmation of the structures of natural products, and on the other hand innovative approaches to accessing them in reasonable amounts for biological investigations are pursued. Interest spans from complex indole and bridged diketopiperazine alkaloids via terpenoid and steroid natural products to lipid metabolites, such as autoxidatively formed prostanes or pheromones, which are important for signaling pathways in humans, plants, and insects respectively. The group provides expertise in selected medicinal chemistry topics using bioinspired synthetic approaches. An equally important area of focus is curiosity-driven research, where we are exploring new pathways in transition metal catalysis using unconventional ligand architectures, photochemistry and photocatalysis, radical reactions, the chemistry of reactive intermediates, and electron transfer chemistry.

Group members

Group leader Ullrich Jahn
Scientist Emanuela Jahn
Postdocs Jakub Smrček
Ph.D. students Maria Aurelia Bosi, Victor Golubev, Denisa Hidasová, Trong Nguyen Phan Huu, David Just, Mikhail Klychnikov, Radka Kucherková, Tomáš Mašek, Tereza Pavlíčková, Chiranan Pramthaisong, Michal Šimek, Navyasree Venugopal, Ilaria Vespoli
Technician Anna Hlavačková
Student Václav Chmela

Selected papers

Dokli, I.; Pohl, R.; Klepetářová, B.; Jahn, U. First Total Synthesis of ent-Asperparaline C and Assignment of the Absolute Configuration of Asperparaline C. *Chem. Commun.* **2019**, 55, 3931–3934.

Kapras, V.; Vyklicky, V.; Budesinsky, M.; Cisarova, I.; Vyklicky, L.; Chodounska, H.; Jahn, U. Total Synthesis of ent-Pregnanolone Sulfate and Its Biological Investigation at the NMDA Receptor. *Org. Lett.* **2018**, 20, 946–949.

Mahamulkar, S.G.; Císařová, I.; Jahn, U. New Phosphine Ligand Architectures Lead to Efficient Gold Catalysts Enabling Cycloisomerization Reactions at Very Low Loading. *Adv. Synth. Catal.* **2018**, 360, 4215–4224.

Amatov, T.; Jangra, H.; Pohl, R.; Císařová, I.; Zipse, H.; Jahn. U. Unique stereoselective homolytic C-O bond activation in diketopiperazine-derived alkoxyamines via amide pyramidalization. *Chem. Eur. J.* **2018**, 24, 15336–15345.

Amatov, T.; Pohl, R.; Císařová, I.; Jahn, U. Synthesis of Bridged Diketopiperazines by Using the Persistent Radical Effect and a Formal Synthesis of Bicyclomycin. *Angew. Chem. Int. Ed.* **2015**, 54, 12153–12157.

Jagtap, P.R.; Ford, L.; Deister, E.; Pohl, R.; Císařová, I.; Hodek, J.; Weber, J.; Mackman, R.; Bahador, G.; Jahn, U. Highly Functionalized and Potent Antiviral Cyclopentane Derivatives Formed by a Tandem Process Consisting of Organometallic, Transition-Metal-Catalyzed, and Radical Reaction Steps. *Chem. Eur. J.* **2014**, 20, 10298–10304.

Kafka, F.; Holan, M.; Hidasová, D.; Pohl, R.; Císařová, I.; Klepetářová, B.; Jahn, U. Oxidative Catalysis Using the Stoichiometric Oxidant as a Reagent: An Efficient Strategy for Single-Electron-Transfer Induced Tandem Anion-Radical Reactions. *Angew. Chem., Int. Ed.* **2014**, 53, 9944–9948.

Vazdar, K.; Kunetskiy, R.; Saame, J.; Kaupmees, K.; Leito, I.; Jahn, U. Very Strong Organosuperbases Formed by Combining Imidazole and Guanidine Bases: Synthesis, Structure, and Basicity. *Angew. Chem. Int. Ed.* **2014**, 53, 1435–1438.

Lagoutte, R.; Šebesta, P.; Jiroš, P.; Kalinová, B.; Jirošová, A.; Straka, J.; Černá, K.; Šobotník, J.; Cvačka, J.; Jahn, U. Total Synthesis, Proof of Absolute Configuration, and Biosynthetic Origin of Stylopsal, the First Isolated Sex Pheromone of *Strepsiptera*. *Chem. Eur. J.* **2013**, 19, 8515–8524.

Financial support

Gilead Sciences & IOCB Research Center, 2016–2021

Chemical biology for development of new therapies. European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022.

Photochemical and photocatalyzed amination reactions. Czech Science Foundation (GA ČR), 2017–2019.

New phosphine ligand architectures and their application in catalysis. Czech Science Foundation (GA ČR), 2018–2020.

Polycyclic phenolic natural products. Czech Science Foundation (GA ČR), 2019–2021.

Collaboration

Dr. Thierry Durand (Univ. of Montpellier/Institut Biomolculaire Max Mousseron Montpellier): Total synthesis and biological investigation of autoxidatively formed lipid metabolites

Prof. Burkhard König (Univ. Regensburg): Photoredox chemistry with enolates

Gilead Sciences: Bioinspired potentially antiviral compounds

Dr. Iva Pichová (IOCB Prague): Elucidation of desaturase enzymes

Zlatko Janeba Group

Medicinal Chemistry of Nucleotide Analogues
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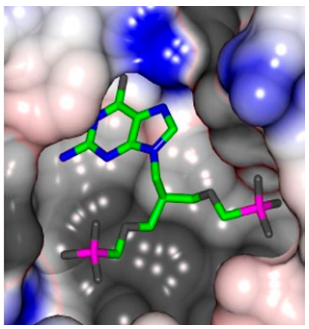
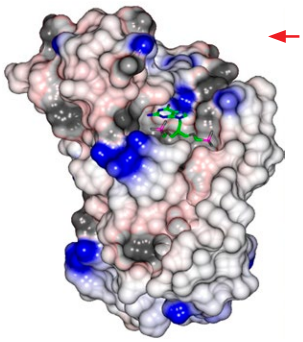
Senior Research Group

organic synthesis, medicinal chemistry, drug discovery, drug delivery, nucleotide analogues

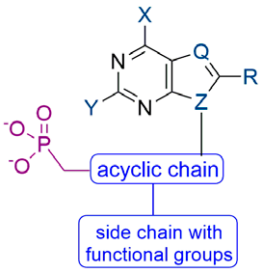
Inhibitors of phosphoribosyltransferases



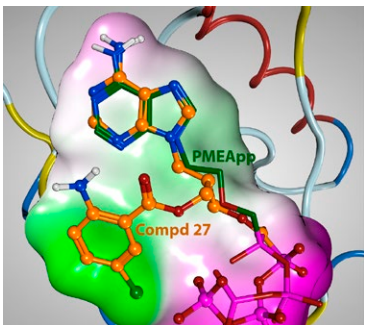


J. Med. Chem. **2013**, 2513 / *J. Med. Chem.* **2013**, 6967
J. Med. Chem. **2015**, 827 / *J. Med. Chem.* **2015**, 4822

Acyclic nucleoside phosphonates (ANPs)



Inhibitors of adenylate cyclases

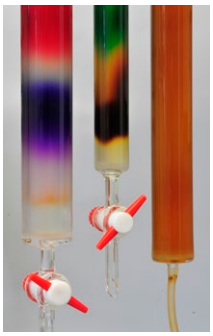


Antimicrob. Agents Chem. **2014**, 664
ChemMedChem **2015**, 1351 / *ChemMedChem* **2016**, 2534

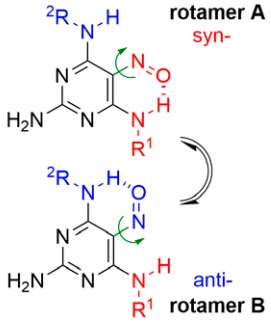
Antivirals

Bioorg. Med. Chem. **2013**, 1199 / *Med. Res. Reviews* **2015**, 1175
Eur. J. Med. Chem. **2016**, 185 / *Vet. Microbiol.* **2016**, 84

Intramolecular hydrogen bonding

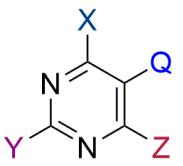


separation at RT

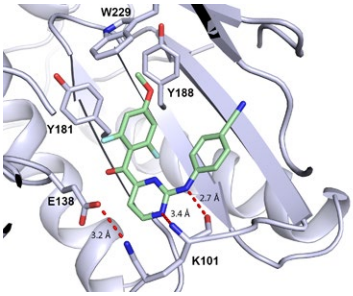


J. Org. Chem. **2013**, 10121 / *Chem.Commun.* **2014**, 14892
Chem.Commun. **2015**, 13986 / *J. Org. Chem.* **2016**, 3780

Polysubstituted pyrimidines



Anti-inflammatory agents



Med. Chem. Res. **2014**, 4482 / *Med. Chem. Res.* **2015**, 2154
Nitric oxide **2016**, 48

Research topics

We are engaged in the design, development, and synthesis of biologically active antimetabolites, especially analogues of nucleic acid components, which are able to act as potent inhibitors of various enzymes of nucleoside and nucleotide metabolism (e.g. purine nucleoside phosphorylases, adenylate cyclases, polymerases, and phosphoribosyltransferases). Acyclic nucleoside phosphonates (ANPs) represent a key class of antimetabolites for their antiviral, cytostatic, and antiparasitic properties. We develop efficient methods for the synthesis of novel types of ANPs and their prodrugs and study their biological properties. We also focus on bisphosphonate analogues, a special class of ANPs containing a second phosphonate moiety in the acyclic part of the molecule, which were shown to be potent inhibitors of purine salvage pathway phosphoribosyltransferases, essential enzymes for many parasites and bacteria (e.g. *Plasmodium falciparum*, *Trypanosoma brucei*, and *Mycobacterium tuberculosis*). Substantial effort is directed at the design of non-nucleoside reverse transcriptase inhibitors with potent antiviral activity and at the development of pyrimidines with significant anti-inflammatory properties for potential treatment of ulcerative colitis, rheumatoid arthritis, and colon cancer. We also study physico-chemical properties of substituted 5-phenylazopyrimidines (molecular switches).

Group members

Group leader Zlatko Janeba
Scientists Dana Hocková (deputy), Michal Česnek
Postdocs Alejandro Martin Carnero, Martin Klečka, Viktor Kolman, Petr Špaček
Ph.D. students Lucie Čechová, Jan Frydrych, Filip Kalčic, Tomáš Klejch, Jan Skácel
Students Artem Chayka, Pavel Kraina, Ladislav Prener
Secretary Barbara Česneková

Selected papers

Procházková, E.; Navrátil, R.; Janeba, Z.; Roithová, J.; Baszczyňski, O. Reactive cyclic intermediates in the ProTide prodrug activation: trapping the elusive pentavalent phosphorane. *Org. Biomol. Chem.* **2019**, 17, 315–320.

Procházková, E.; Čechová, L.; Kind, J.; Janeba, Z.; Thiele, C.M.; Dračínský, M. Photoswitchable intramolecular hydrogen bonds in 5-phenylazopyrimidines revealed by in situ irradiation NMR spectroscopy. *Chem. – Eur. J.* **2018**, 24, 492–498.

Doleželová, E.; Teran, D.; Gahura, O.; Kotrbová, Z.; Procházková, M.; Keough, D.; Špaček, P.; Hocková, D.; Guddat, L.; Zíková, A. Evaluation of the *Trypanosoma brucei* 6-oxopurine salvage pathway as a potential target for drug discovery. *PLoS Negl. Trop. Dis.* **2018**, 12(2): e0006301.

Špaček, P; Keough, D.T.; Chavchich, M.; Dračínský, M.; Janeba, Z.; Naesens, L.; Edstein, M.D.; Guddat, L.W.; Hocková, D. Synthesis and Evaluation of Asymmetric Acyclic Nucleoside Bisphosphonates as Inhibitors of *Plasmodium falciparum* and Human Hypoxanthine-Guanine-(Xanthine) Phosphoribosyltransferase. *J. Med. Chem.* **2017**, 60, 7539–7554.

Procházková, E.; Čechová, L.; Tarábek, J.; Janeba, Z.; Dračínský, M. Tunable Push–Pull Interactions in 5-Nitrosopyrimidines. *J. Org. Chem.* **2016**, 81, 3780–3789.

Břehová, P.; Šmídková, M.; Skácel, J.; Dračínský, M.; Mertlíková-Kaiserová, H.; Soto Velasquez, M.P.; Watts, V.J.; Janeba, Z. Design and synthesis of fluorescent acyclic nucleoside phosphonates as potent inhibitors of bacterial adenylate cyclases. *ChemMedChem* **2016**, 11, 2534–2546.

Eng, W.S.; Hocková, D.; Špaček, P.; Janeba, Z.; West, N. P.; Woods, K.; Naesens, L.M.J.; Keough, D.T.; Guddat, L.W. The first crystal structures of Mycobacterium tuberculosis 6-oxopurine phosphoribosyltransferase: Complexes with GMP and pyrophosphate and with acyclic nucleoside phosphonates whose prodrugs have antituberculosis activity. *J. Med. Chem.* **2015**, 58, 4822–4838.

Janeba, Z. Development of small-molecule antivirals for Ebola. *Med. Res. Rev.* **2015**, 35, 1175–1194.

Dračínský, M.; Čechová, L.; Hodgkinson, P.; Procházková, E.; Janeba, Z. Resonance-assisted stabilisation of hydrogen bonds probed by NMR spectroscopy and path integral molecular dynamics in polysubstituted 5-nitrosopyrimidines. *Chem. Commun.* **2015**, 51, 13986–13989.

Keough, D.T.; Hocková, D.; Janeba, Z.; Wang, T.-H.; Naesens, L.; Edstein, M.D.; Chavchich, M.; Guddat, L.W. Aza-acyclic nucleoside phosphonates containing a second phosphonate group as inhibitors of the human, *Plasmodium falciparum* and *vivax* 6-oxopurine phosphoribosyltransferases and their prodrugs as antimalarial agents. *J. Med. Chem.* **2015**, 58, 827–846.

Čechová, L.; Procházková, E.; Císařová, I.; Dračínský, M.; Janeba, Z. Separation of planar rotamers through intramolecular hydrogen bonding in polysubstituted 5-nitrosopyrimidines. *Chem. Commun.* **2014**, 50, 14892–14895.

Baszczyňski, O.; Janeba, Z. Medicinal chemistry of fluorinated cyclic and acyclic nucleoside phosphonates. *Med. Res. Rev.* **2013**, 33, 1304–1344.

Financial support

Gilead Sciences & IOCB Research Center, 2006–2021.

Acyclic nucleoside phosphonates as potential inhibitors of adenine phosphoribosyltransferases in human trypanosomatid parasites. Czech Science Foundation (GA ČR), No. 19-07707S, 2019–2021, Hocková, D.

Inhibitors of hypoxanthine-guanine-xanthine phosphoribosyltransferase as versatile drugs to treat infectious diseases. National Health and Medical Research Council, Australia, No. 1147368, 2018–2020, Guddat, L.W. & Hocková, D.

Center for Development of Original Drugs. Technology Agency of the Czech Republic (TA ČR), No. TE01020028, 2012–2019.

Personalized medicine. Technology Agency of the Czech Republic (TA ČR), No. TN01000013, 2019–2020.

Design, synthesis and biological evaluation of potential modulators of human adenylate cyclases. Ministry of Education, Youth and Sports (MŠMT), Program INTER-EXCELLENCE, No. LTAUSA18086, 2019–2022, Janeba, Z.

Collaboration

- Weizmann Institute of Science, Rehovot, Israel
- School of Chemistry & Molecular Biosciences, The University of Queensland, Brisbane, Australia
- Department of Drug Evaluation, Army Malaria Institute, Enoggera, Australia
- Rega Institute for Medical Research, KU Leuven, Belgium
- Facultad de Ciencias e Ingeniería de Alimentos, Universidad Técnica de Ambato, Ecuador
- College of Pharmacy, Purdue University, West Lafayette, Indiana, USA
- University College London, United Kingdom
- Gilead Sciences, Inc., Foster City, California, USA
- Biology Centre of the CAS, České Budějovice, Czech Republic
- Institute of Experimental Medicine of the CAS, Prague, Czech Republic

Jiří Kaleta Group

Molecular Devices
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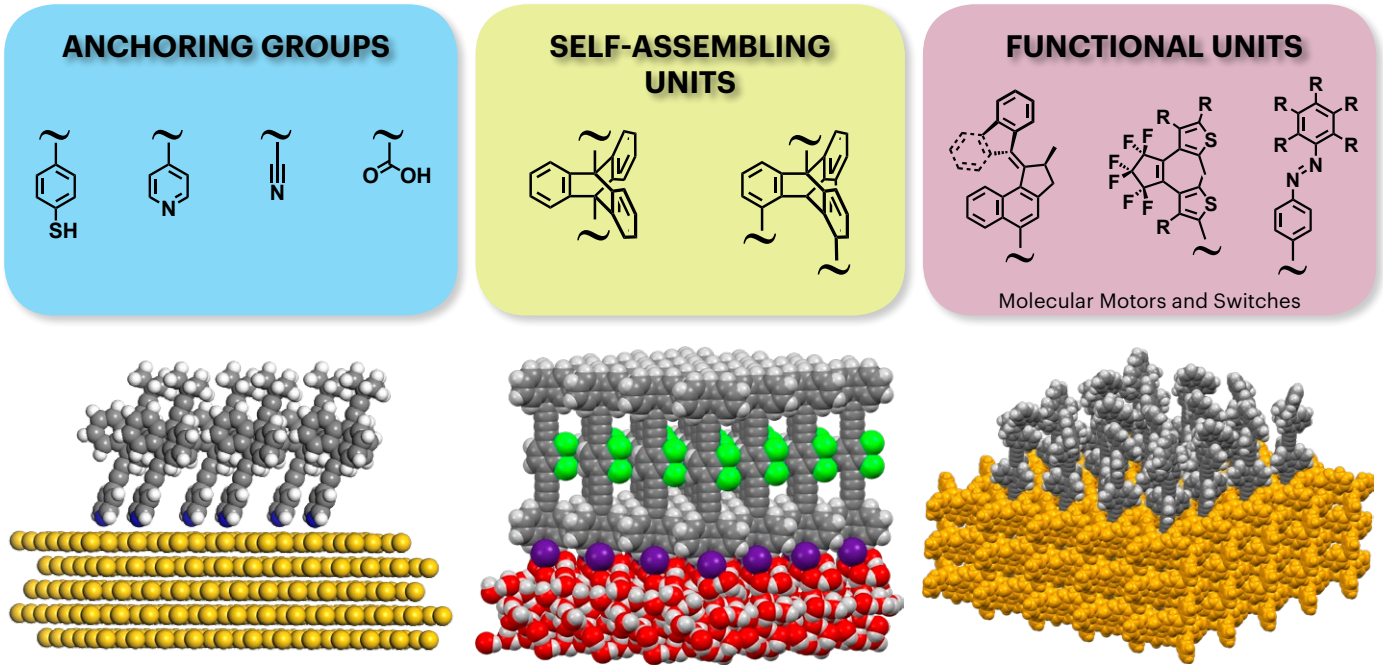
Junior Research Group
molecular-level devices, molecular machines, molecular switches, molecular motors, organic synthesis, supramolecular chemistry, smart materials, photochemistry



(Kaleta *et al. J. Org. Chem.* **2015**, 80, 10134-10150.)

(Kaleta *et al. PNAS* **2018**, 115, 9373-9378.)

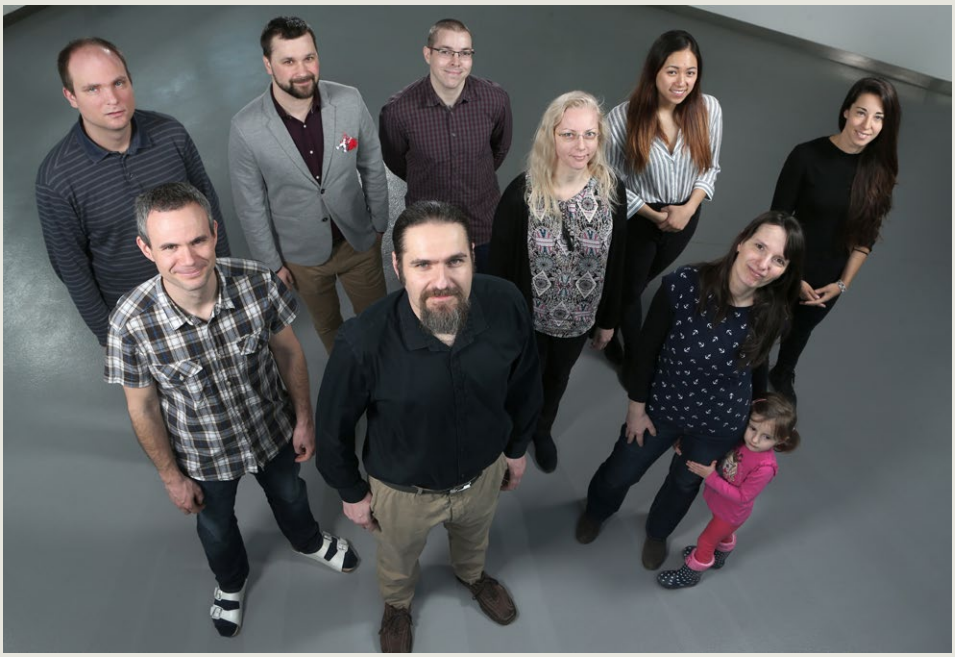
(Kaleta *et al. J. Am. Chem. Soc.* **2017**, 139, 10486-10498.)

Research topics

Our research is focused on the design, synthesis, and study of advanced molecular-level devices and their complex 2- or/and 3-dimensional assemblies. Organization of individual molecules into regular arrays should amplify their function and thus lead to new types of smart materials with potential application in nanoelectronics or as novel propulsion systems. This heavily interdisciplinary topic comprises organic chemistry (multistep synthesis of complex molecular machines is a crucial pillar of our research) with physical, material, surface, and theoretical chemistry.

Most of our molecular devices consist of several characteristic building blocks: (i) an anchoring group that holds them on various surfaces, (ii) a bulky unit that helps them organize into 2D or 3D structures, and (iii) various molecular switches (triggered either by light, heat, or a redox reaction) or light-driven molecular motors that act as the functional heart of each machine.

ARTIFICIAL PROPULSION SYSTEMS
Self-propelled synthetic devices that transform chemical energy into mechanical motion are examples of biomimetic nonequilibrium systems. They are of a great interest today, because of their potential applications in nanomachinery, chemical sensing, and nanoscale assembly. Controlled motion at the nano- and micro-scale is ubiquitous in nature. Evolution had hundreds of millions of years to optimize these extraordinary and extremely complex biological machines. Lacking the luxury of time, we would like to take inspiration in these biological systems and intelligently design novel transporting systems based on artificial molecular motors.



Group members

Group leader Jiří Kaleta
Postdocs Guillaume Bastien, Carina Santos Hurtado, Milan Mašát, Eva Kaletová, Igor Rončević, Lukáš Severa
Student Thị Phuong Lê
Secretary Kateřina Pokorná

Selected papers

Kaleta, J.; Rončević, I.; Císařová, I.; Dračínský, M.; Šolínová, V.; Kašička, V.; Michl, J. Bridge-Chlorinated Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acids. *J. Org. Chem.* **2019**, 84, 2448–2461.

Kaleta, J.; Bastien, G.; Císařová, I.; Batail, P.; Michl, J. Molecular Rods: Facile Desymmetrization of 1,4-Diethynylbicyclo[2.2.2]octane. *Eur. J. Org. Chem.* **2018**, 37, 5137–5142.

Kaleta, J.; Wen, J.; Magnera, T.F.; Dron, P.I.; Zhu, C.; Michl, J. Structure of a Monolayer of Molecular Rotors on Aqueous Subphase from Grazing-Incidence X-Ray Diffraction. *PNAS* **2018**, 115, 9373–9378.

Kaleta, J.; Chen, J.; Bastien, G.; Dračínský, M.; Mašát, M.; Rogers, C.T.; Feringa, B.L.; Michl, J. Surface Inclusion of Unidirectional Molecular Motors in Hexagonal Tris(*o*-phenylene)cyclotriphosphazene. *J. Am. Chem. Soc.* **2017**, 139, 10486–10498.

Kaleta, J.; Kaletová, E.; Císařová, I.; Teat, S.J.; Michl, J. Synthesis of Triptycene-Based Molecular Rotors for Langmuir-Blodgett Monolayers. *J. Org. Chem.* **2015**, 80, 10134–10150.

Kaleta, J.; Dron, P.I.; Zhao, K.; Shen, Y.; Císařová, I.; Rogers, C.T.; Michl, J. Arrays of Molecular Rotors with Triptycene Stoppers: Surface Inclusion in Hexagonal Tris(*o*-phenylenedioxy)cyclotriphosphazene. *J. Org. Chem.* **2015**, 80, 6173–6192.

Financial support

IOCB institutional support for junior research groups, 2019–2024.

Self-Assembled Arrays of Molecular Rotors and Motors, IOCB Bridging grant, 2018.

Collaboration

Prof. Eric Masson (Ohio University, Chemistry & Biochemistry, Athens, Ohio, USA)

Prof. Josef Michl, Prof. Charles T. Rogers (University of Colorado at Boulder, Department of Chemistry and Department of Physics, Boulder, Colorado, USA)

Prof. Jyh-Chiang Jiang (National Taiwan University of Science and Technology, Taipei, Taiwan)

Prof. Ben Feringa (University of Gröningen, Stratingh Institute for Chemistry, Gröningen, Netherlands)

Prof. Patrick Batail (University of Angers, Angers, France)

Martin Dračínský, Václav Kašička (IOCB Prague, Czech Republic)

Awards—Jiří Kaleta

The Alfred Bader Award for Organic Chemistry, 2016

The Coris Award for the best oral presentation—XIV. Conference of young biologists, biochemists and chemists, Czech Republic, 2014

Prix de Chimie—1st Prize, awarded by the French embassy and the Rhodia, 2010

Eva Kudová Group

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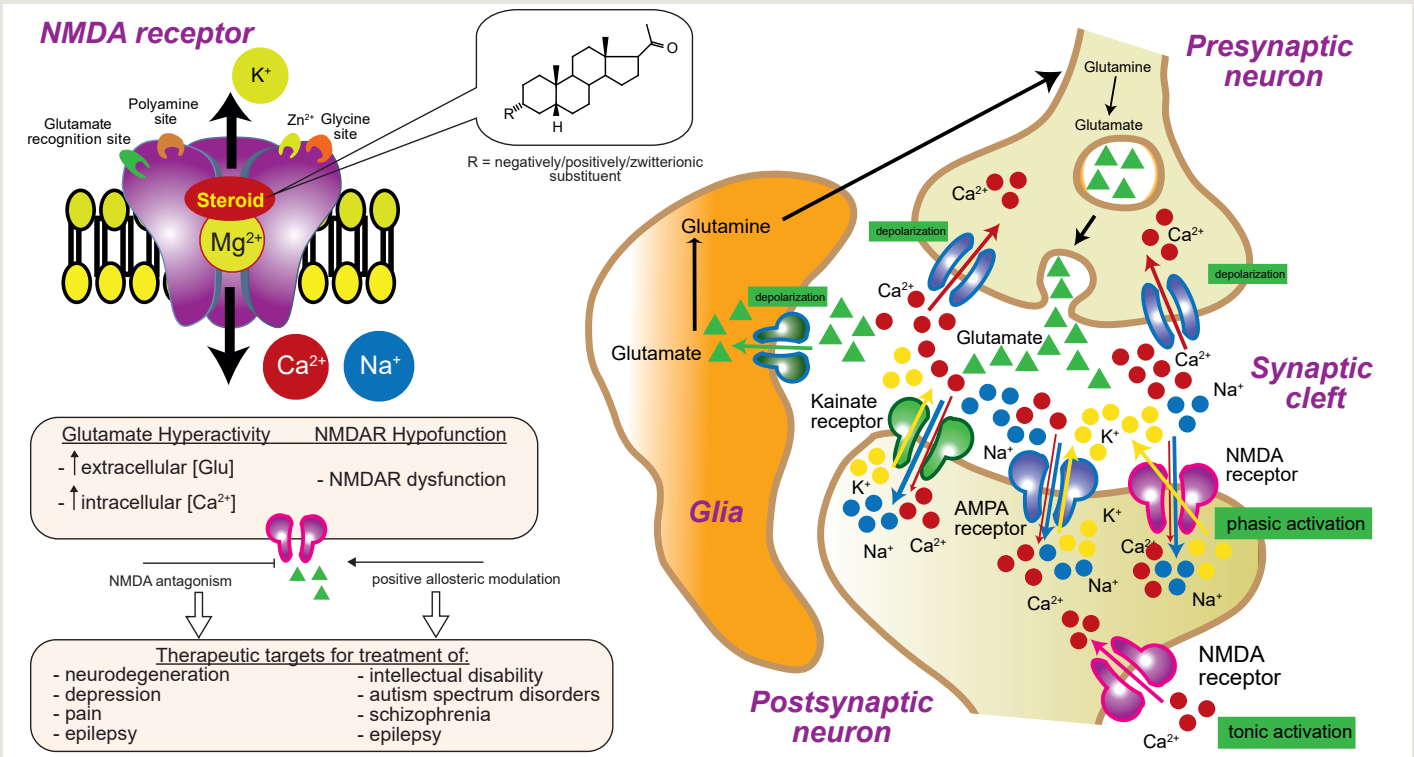
Targeted Research Group

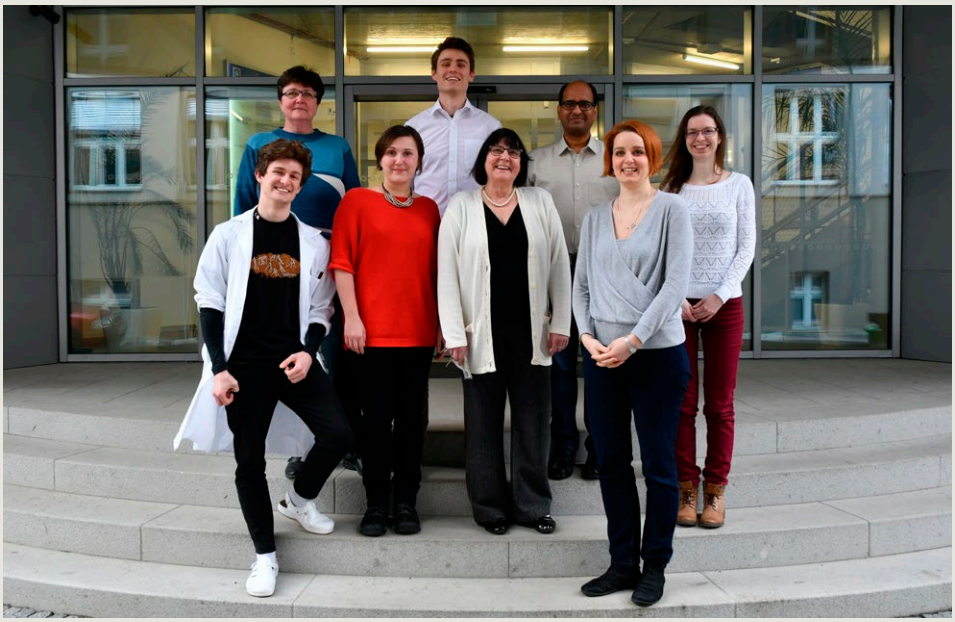
S.M.A.R.T. Steroids, NMDA receptor, GABA receptor, muscarinic receptor, purinergic receptor, NMDA hypofunction, epilepsy, neuropathic pain, excitotoxicity, neuroprotection



Research topics

Neurosteroids are endogenous steroids that are synthesized from cholesterol and produce rapid effects on neuronal excitability and synaptic function. Their synthetic analogues are called neuroactive steroids. The effects of neurosteroids and neuroactive steroids are mediated by interactions with ligand-gated ion channels such as glutamate, $GABA_A$, glycine, nicotinic acetylcholine receptors, etc. On the contrary, the neuroprotective mechanism of action of neurosteroids/neuroactive steroids is not yet fully understood; however, it may be realized by non-genomic mechanisms and moreover might involve regulation of the pro- and anti-apoptotic factors expression, intracellular signaling pathways, neurotransmission, and oxidative and inflammatory processes.

Multiple clinical studies have been conducted so far to show the efficacy of neurosteroids in the treatment of central and peripheral nervous system disorders. Identifying novel potentially beneficial drugs to treat neurological damage/neurodegeneration is one of the most investigated areas in contemporary pharmacology and neuroscience. Therefore, we design, synthesize, and screen **S.M.A.R.T.** steroids—Steroidal Molecules As Rapid-acting Therapeutics. Our research demonstrates that S.M.A.R.T. steroids have a neuroprotective effect, in both *in vitro* and *in vivo* models of neurodegeneration, and show neuroprotective properties and minimal side effects in animal models of several neurological diseases like epilepsy, neuropathic pain, ischemia, neuropsychiatric disorders, and others. To assay and show the possibilities of our S.M.A.R.T., we have built up a multidisciplinary network both within and outside the IOCB capable of analyzing biological effects on the molecular, cellular, and system levels.



Group members

Group leader Eva Kudová
Scientists Hana Chodounská, Martin Kotora
Postdocs Santosh Kumar Adla, Eszter Szánti Pintér
Research assistants Kateřina Kouřilová, Barbora Slavíková
Ph.D. student Miroslav Kašpar
Student Tomáš Svoboda

Selected papers

Sivcev, S.; Slavikova, B.; Rupert, M.; Ivetic, M.; Nekardova, M.; Kudova, E.; Zemkova, H. Synthetic testosterone derivatives modulate rat P2X2 and P2X4 receptor channel gating. *J. Neurochem.* **2019**, 150, 28–43.

Smidkova, M.; Hajek, M.; Adla, S.K.; Slavikova, B.; Chodounska, H.; Matousova, M.; Mertlikova-Kaiserova, H.; Kudova, E. Screening of Novel 3alpha5beta-Neurosteroids for Neuroprotective Activity against Glutamate- or NMDA-Induced Excitotoxicity. *J. Steroid Biochem. Mol. Biol.* **2019**, 189, 195–203.

Krausova, B.; Slavikova, B.; Nekardova, M.; Hubalkova, P.; Vyklicky, V.; Chodounska, H.; Vyklicky, L.; Kudova, E. Positive Modulators of the N-Methyl-D-Aspartate Receptor: Structure-Activity Relationship Study on Steroidal 3-Hemiesters. *J. Med. Chem.* **2018**, 61, 4505–4516.

Vyklicky, V.; Krausova, B.; Cerny, J.; Ladislav, M.; Smejkalova, T.; Kysilov, B.; Korinek, M.; Danacikova, S.; Horak, M.; Chodounska, H.; Kudova, E.; Vyklicky, L. Surface expression, function, and pharmacology of disease-associated mutations in the membrane domain of the human GluN2B subunit. *Front. Mol. Neurosci.* **2018**, 11, 110.

Kapras, V.; Vyklicky, V.; Budesinsky, M.; Cisarova, I.; Vyklicky, L.; Chodounska, H.; Jahn, U. Total Synthesis of ent-Pregnanolone Sulfate and Its Biological Investigation at the NMDA Receptor. *Org. Lett.* **2018**, 20, 946–949.

Bukanova, J.V.; Solntseva, E.I.; Kolbaev, S.N.; Kudova, E. Modulation of GABA and glycine receptors in rat pyramidal hippocampal neurons by 3α5β-pregnanolone derivatives. *Neurochem. Int.* **2018**, 118,145–151.

Vyklicky, V.; Smejkalova, T.; Krausova, B.; Balik, A.; Korinek, M.; Borovska, J.; Horak, M.; Chvojkova, M.; Kleteckova, L.; Vales, K.; Cerny, J.; Nekardova, M.; Chodounska, H.; Kudova, E.; Vyklicky, L. Preferential inhibition of tonically over phasically activated NMDA receptors by pregnane derivatives. *J. Neurosci.* **2016**, 36, 2161–2175.

Slavíková, B.; Chodounska, H.; Nekardova, M.; Vyklicky, V.; Marek, L.; Hubalkova, P.; Krausova, B.; Vyklicky, L.; Kudova, E. Neurosteroid-like Inhibitors of N-Methyl-D-aspartate Receptor: Substituted 2-Sulfates and 2-Hemisuccinates of Perhydrophenanthrene. *J. Med. Chem.* **2016**, 59, 4727–4739.

Kudova, E.; Chododounska, H.; Slavikova, B.; Budesinsky, M.; Nekardova, M.; Vyklicky, V.; Krausova, B.; Svehla, P.; Vyklicky, L. Jr. A New Class of Potent N-Methyl-D-Aspartate Receptor Inhibitors: Sulfated Neuroactive Steroids with Lipophilic D-Ring Modifications. *J. Med. Chem.* **2015**, 58, 5950–5966.

Financial support

Center for Development of Original Drugs. Technology Agency of the Czech Republic (TA ČR), No. TE01020028, 2012–2019.

Project PerMed: Personalized Medicine – Diagnostics and Therapy, National Centres of Competence 1. Technology Agency of the Czech Republic (TA ČR), No. TN01000013, 2019–2020.

Project PharmaBrain. Ministry of Education, Youth and Sports (MŠMT), European Structural and Investment Funds, OP RDE, No. CZ.02.1.01/0.0/0.0/16_025/0007444.

Molecular, cellular, and behavioral effects of NMDA receptor-modulating steroids. Czech Science Foundation (GA ČR), No. 17-02300S, 2017–2019.

Molecular mechanisms of allosteric modulation of muscarinic acetylcholine receptors by neurosteroids and cholesterol. Czech Science Foundation (GA ČR), No. 19-05318S, 2019–2021.

Identification of new molecules that are able to interact with allosteric binding sites on purinergic P2X receptors. Czech Science Foundation (GA ČR), No. 18-05413S, 2018–2020.

Patents

CZ 307648 (December 19, 2018)
Steroidal compounds for treatment of mental and neurological disorders
Vyklický, L.; Kudová, E.

AU 2015309371 (July 5, 2018); **US 10,017,535** (July 10, 2018); **JP6437636(B2)** (December 12, 2018)
Amphiphilic compounds with neuroprotective properties
Kudová, E.; Chodounská, H.; Kapras, V.; Vyklický, L.; Valeš, K.; Jahn, U.

EP 2675821 (April 18, 2018): DE, FR, GB
Pregnanolone derivatives substituted in 3alpha-position with the cationic group, method of their production, usage and pharmaceutical preparation involving them
Chodounská, H.; Vyklický, L.; Kapras, V.; Borovská, J.; Vyklický, V.; Valeš, K.; Stuchlík, A.; Rambousek, L.

US 8575376 (November 5, 2013); **EP 2435463** (October 12, 2016): DE, ES, FR, GB, IE, CH, DK, NL, SE, IT
Steroid anionic compounds, way of their production, their applications and pharmaceutical substances containing them
Chodounská, H.; Stastna, E.; Kapras, V.; Kohout, L.; Borovska, K.; Vyklický, L.; Valeš, K.; Cais, O.; Rambousek, L.; Stuchlik, A.; Bubeníková-Valešová, V.

Josef Michl Group

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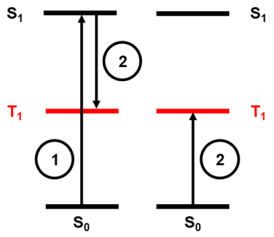
Distinguished Emeritus

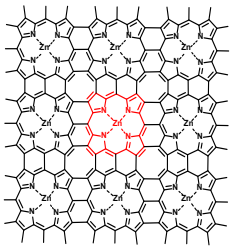
alkylation of gold surfaces, singlet fission, molecular rotors, carboranes, fluorination, porphene, electrochemical synthesis, two-dimensional polymers

Singlet Fission

(*Chem. Rev.* **2010**, 110, 6891)

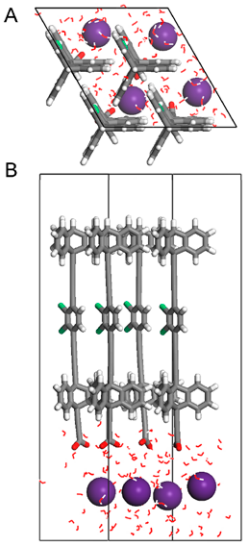


Electrochemical Synthesis



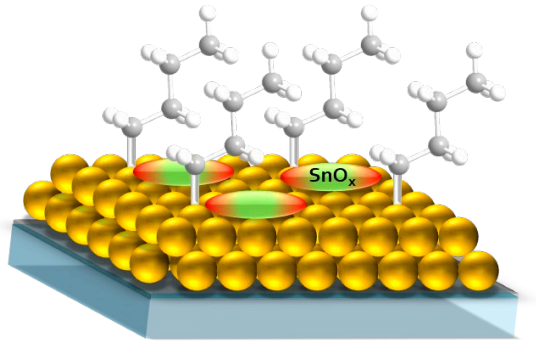
Molecular Rotors

(*PNAS* **2018**, 115, 9373)



New Ways to Molecular Surface Attachments

(*J. Am. Chem. Soc.* **2015**, 137, 12086)



Carborane Fluorination

Research topics

DIRECT ATTACHMENT OF ORGANIC MOLECULES TO GOLD SURFACE

The currently almost exclusively used alkanethiols have many advantages but also some disadvantages, such as sensitivity to oxidation and poor electrical contact to metal surfaces. We have found a simple way to attach alkyls to a gold surface directly through carbon-gold bonds.

SINGLET FISSION SENSITIZERS FOR SOLAR CELLS

Singlet fission is a usually inefficient process in which a molecular chromophore excited into its singlet state shares energy with a nearby ground-state chromophore, producing a pair of triplet-excited chromophores, at first coupled into an overall singlet. We are working on syntheses of efficient and sturdy compounds based on computational results of Dr. Zdeněk Havlas's group.

REGULAR ARRAYS OF ARTIFICIAL MOLECULAR ROTORS

We are interested in dipolar molecular rotors, which can be examined individually or in regular arrays of two or three dimensions. This strongly interdisciplinary project combining organic, physical, material, and computational chemistry should result in new materials with ferroelectric properties and possible application in the construction of new electronic devices.

FLUORINATION OF WEAKLY NUCLEOPHILIC ANIONS AND ELECTROCHEMISTRY IN LIQUID HF

A modular laboratory fluorine line permits synthesis of weakly nucleophilic anions with a high oxidation potential like 1H-$CB_{11}F_{11}$-, 1H-$CB_{11}F_6(CF_3)_5$-, and 1H-$CB_{11}F_5(CF_3)_6$-.

PORPHENE

The recent synthesis of porphene, a fully conjugated analog of graphene containing porphyrin instead of benzene rings provides access to a family of 2-dimensional polymers that can be arbitrarily functionalized by inserting metals with up to two ligands into the macrocyclic rings without taking any centers out of conjugation. Their properties and possible applications are under investigation.

Group members

Group leader Josef Michl
Scientists Miroslav Dudič, Shinjiro Kobayashi, Jan Plutnar, Lubomír Pospíšil
Postdocs Guillaume Bastien, Eva Kaletová, Yu Kitazawa, Milan Mašát, Igor Rončević, Katarina Varga
Ph.D. student Nikola Hofrová
Assistant Kateřina Pokorná

Selected papers

Kaleta, J.; Wen, J.; Magnera, T.F.; Dron, P.I.; Zhu, C.; Michl, J. Structure of a Monolayer of Molecular Rotors on Aqueous Subphase from Grazing-Incidence X-Ray Diffraction. *PNAS* **2018**, 115, 9373.

Wen, J.; Uto, T.; Chalupský, J.; Casher, D.L.; Raabe, G.; Fleischhauer, J.; Yanai, T.; Tsuji, H.; Komatsu, K.; Michl, J. Magnetic Circular Dichroism of an Unaromatic Planar [8]Annulene. *J. Phys. Org. Chem.* **2018**, 31, e3854.

Benkovičová, M.; Wen, D.; Plutnar, J.; Čížková, M.; Eychmüller, A.; Michl, J. Mechanism of Surface Alkylation of a Gold Aerogel with Tetra-*n*-butylstannane-d_{36}: Identification of Byproducts. *J. Phys. Chem. Lett.* **2017**, 8, 2339.

Buchanan, E.A.; Havlas, Z.; Michl, J. "Singlet Fission: Optimization of Chromophore Dimer Geometry", in: Advances in Quantum Chemistry: Ratner Volume, Volume 75; Sabin, J.R.; Brändas, E.J., Eds.; Elsevier: Cambridge, MA, **2017**, p. 175.

Šembera, F.; Plutnar, J.; Higelin, A.; Janoušek, Z.; Císařová, I.; Michl, J. Metal Complexes with Very Large Dipole Moments: the Anionic Carborane Nitriles 12-NC-$CB_{11}X_{11}$– (X = H, F, CH_3) as Ligands on Pt(II) and Pd(II). *Inorg. Chem.* **2016**, 55, 3797.

Cipolloni, M.; Kaleta, J.; Mašát, M.; Dron, P.I.; Yongqiang, S.; Zhao, K.; Rogers, C.T.; Shoemaker, R.K.; Michl, J. Time-Resolved Fluorescence Anisotropy of Bicyclo[1.1.1]pentane/Tolane-Based Molecular Rods Included in Tris(o-phenylenedioxy)cyclotriphosphazene (TPP). *J. Phys. Chem. C* **2015**, 119, 8805.

Kaletová, E.; Kohutová, A.; Hajduch, J.; Kaleta, J.; Bastl, Z.; Pospíšil, L.; Stibor, I.; Magnera, T.F.; Michl, J. The Scope of Direct Alkylation of Gold Surface with Solutions of C_1 - C_4 *n*-Alkylstannanes. *J. Am. Chem. Soc.* **2015**, 137, 12086.

Collaboration

Charles Roger (Dept. of Physics, Univ. Colorado, Boulder, CO, USA)

RNDr. Jiří Pfleger CSc. (Institute of Macromolecular Chemistry of the CAS)

RNDr. Zdeněk Bastl, CSc. (J. Heyrovský Institute of Physical Chemistry of the CAS)

Prof. RNDr. Jiří Ludvík, CSc. (J. Heyrovský Institute of Physical Chemistry of the CAS)

Financial support

Regular arrays of artificial surface-mounted dipolar molecular rotors. European Research Council (ERC), No. 2008-AdG 227756, 2009–2014, Michl, J.

New functionalization of gold surfaces. Czech Science Foundation (GA ČR), No. 14-2337S, 2014–2016, Michl, J.

Chemical modifications of graphene based materials: synthesis of graphene and halographene. Czech Science Foundation (GA ČR), No. 15-09001S, 2015–2017, Janoušek, Z. (co-PI)

Funkční materiály založené na bicyklo[1.1.1]pentanových rotorech: organizace a dynamika. Ministry of Education, Youth and Sports (MŠMT ČR), No. 7AMB16FR038, 2016–2017, Michl, J.

Singlet Fission: Redox and Photophysics of Captodative Biradicaloids. Czech Science Foundation (GA ČR), No. 19-22806S, 2019–2021, Michl, J.

Selected awards—Josef Michl

U.S. National Academy of Sciences, 1986
International Academy of Quantum Molecular Science, 1988
A. C. Cope Senior Scholar Award, 1993
Schrödinger Medal, 1993
Inter-American Photochemical Society Award, 1994
J. Heyrovský Gold Medal, 1994
Charles University Gold Medal, 1995
Czech Learned Society, Honorary Member, 1995
American Academy of Arts and Sciences, 1999
James Flack Norris Award, 2001
Porter Medal, 2002
Patria Award, 2005
Hammond Award, I-APS, 2015
Neuron Foundation Award, 2016

Honorary Doctorates:
Georgetown University, 1990
University of Pardubice, 1996
Masaryk University, 2004

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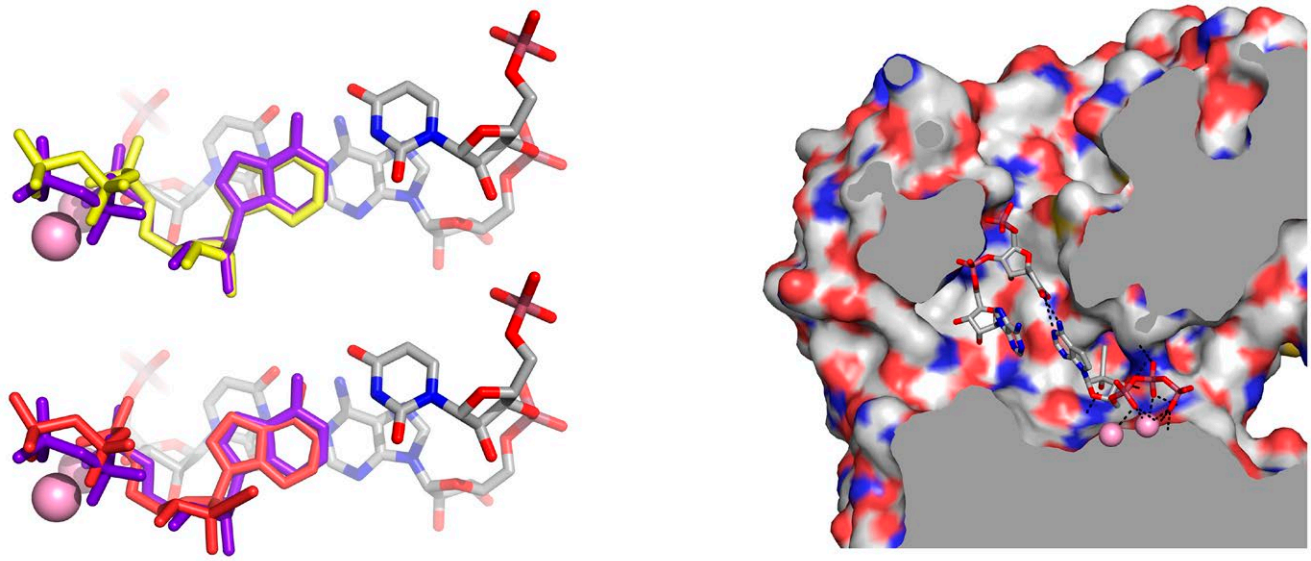
Senior Research Group

medicinal chemistry, chemical biology, enzyme inhibitors, phosphatidylinositol 4-kinase, nucleosides, nucleotides

The structural model of Zika virus RNA-dependent RNA polymerase in complex with RNA for the rational design of novel nucleotide inhibitors

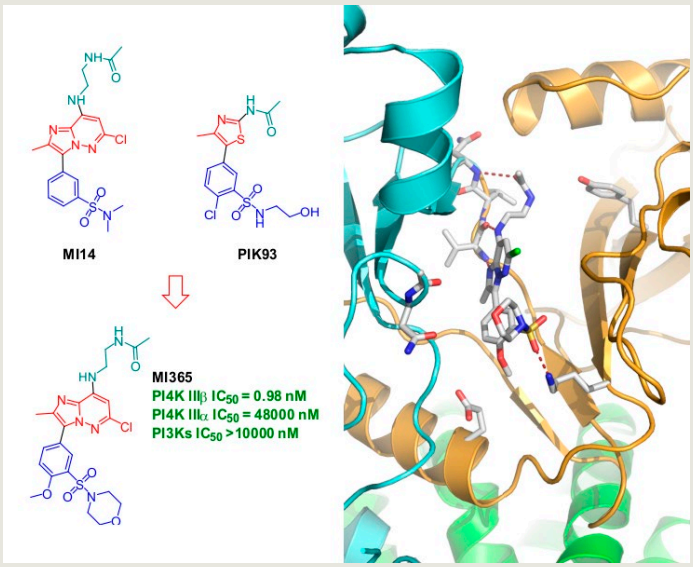


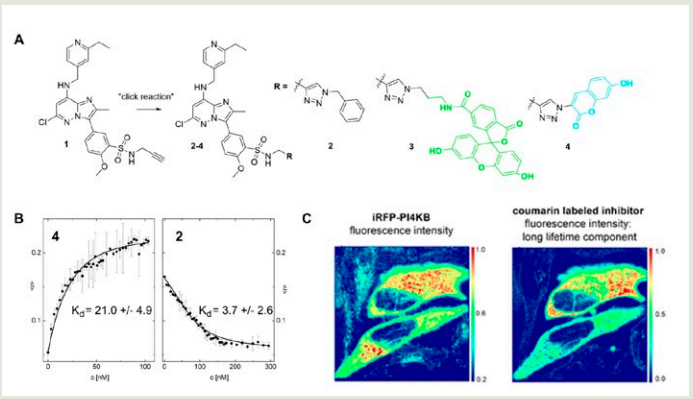
Research topics

The major focus of our group is modern medicinal chemistry and chemical biology. Our priority is to discover and develop novel therapeutic agents against selected diseases and prepare chemical tools that will facilitate understanding of pathological processes and provide clues for their effective treatment. We use state-of-the-art medicinal chemistry approaches, including fragment-based drug design and extensive molecular modeling, for identification and optimization of hit compounds.

The major part of the research in our lab focuses on the development of novel means of deciphering biological processes connected with viral replication, including involvement of various viral proteins, host-virus interaction, and control of innate immunity related to viral infection. Our main targets are RNA viruses from the Flaviviridae, Picornaviridae, and Togaviridae families. We are a part of the team that discovered the first nucleoside derivatives active against Zika virus (Flaviviridae family). We have also prepared triphosphate derivatives of selected nucleosides and proved that they effectively inhibit RNA-dependent RNA polymerase of this dangerous human pathogen. In addition, we have invented highly selective chemical probes based on inhibition of phosphatidylinositol 4-kinase IIIβ that are capable of arresting replication of various important human pathogens by blockage of membrane remodeling initiated by these viruses.

Apart from viral diseases, our projects aim to discover novel inhibitors of enzymes involved in the pathology of neurodegenerative diseases, e.g. neutral sphinghomyelinase 2 (nSMase2). This enzyme plays an important role in exosome release. This is a cellular process strongly implicated in various neurodegenerative disorders such as Alzheimer disease as well as in the pathogenesis of several viruses, including HIV. Optimization of the HTS hit resulted in compound MS882, a potent, orally available, brain-penetrable nSMase2 inhibitor, which inhibits exosome release both *in vitro* and *in vivo*. We have performed a large study around this compound and demonstrated its efficacy in a mouse model of Alzheimer's disease.





(Left) Design of novel PI4KIIIβ inhibitors that are hybrids of MI14 and PIK93. (Up) A) Fluorescent inhibitors as chemical biology tools. B) Biochemical evaluation of fluorescent compound 4 and nonfluorescent analogue 2. C) Colocalization of fluorescent inhibitor 4 with transiently expressed iRFP-PI4KIIIβ in living HeLa cells.

Group members

Group leader Radim Nencka
Scientists Milan Dejmek, Hubert Hřebabecký, Michal Šála
Postdocs Jiří Böserle, Ján Kozic, Ivana Mejdrová
Research assistant Marcela Dvořáková
Ph.D. students Anthony Allan, Mbilo Misehe, Michaela Novotná, Tomáš Otava, Kryštof Škach, Milan Štefek
Technician Jaroslava Sklenářová
Student Ivana Dvořáková
Secretary Barbara Česneková

Selected papers

Mejdrová, I.; Chalupská, D.; Plačková, P.; Müller, C.; Šála, M.; Klíma, M.; Baumlová, A.; Hřebabecký, H.; Procházková, E.; Dejmek, M.; Strunin, D.; Weber, J.; Lee, G.; Matoušová, M.; Mertlíková-Kaiserová, H.; Ziebuhr, J.; Birkus, G.; Boura, E.; Nencka, R. Rational Design of Novel Highly Potent and Selective Phosphatidylinositol 4-Kinase IIIβ (PI4KB) Inhibitors as Broad-Spectrum Antiviral Agents and Tools for Chemical Biology. *J. Med. Chem.* **2017**, 60, 100–118.

Humpolickova, J.; Mejdrová, I.; Matousova, M.; Nencka, R.; Boura, E. Fluorescent Inhibitors as Tools To Characterize Enzymes: Case Study of the Lipid Kinase Phosphatidylinositol 4-Kinase IIIβ (PI4KB). *J. Med. Chem.* **2017**, 60, 119–127.

Hercík, K.; Kozak, J.; Šála, M.; Dejmek, M.; Hřebabecký, H.; Zborníková, E.; Smola, M.; Ruzek, D.; Nencka, R.; Boura, E. Adenosine triphosphate analogs can efficiently inhibit the Zika virus RNA-dependent RNA polymerase. *Antiviral Res.* **2017**, 137, 131–133.

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Financial support

Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022, Nencka, R.

Development and testing of novel perspective antivirals and their prodrug forms active against tick-borne encephalitis virus. Ministry of Health (MZ), No. 16-34238A, 2016–2019, Nencka, R.

Advanced studies on West Nile virus infection pathogenesis towards novel therapeutic strategies. Czech Science Foundation (GA ČR), No. 16-20054S, 2016–2018, Nencka, R.

Rational design of phosphatidylinositol 4-kinase IIα inhibitors as tools for chemical biology and potential therapeutics. Czech Science Foundation (GA ČR), No. 15-09310S, 2015–2017, Nencka, R.

Awards

Sanofi award for pharmacy (PI4KIIIβ project, Mejdrová, I.)

Shimadzu award for young scientist (PI4KIIIβ project, Mejdrová, I.)

The Czech Mind (Česká hlava)—Doctorandus in natural sciences (PI4KIIIβ project, Mejdrová, I.)

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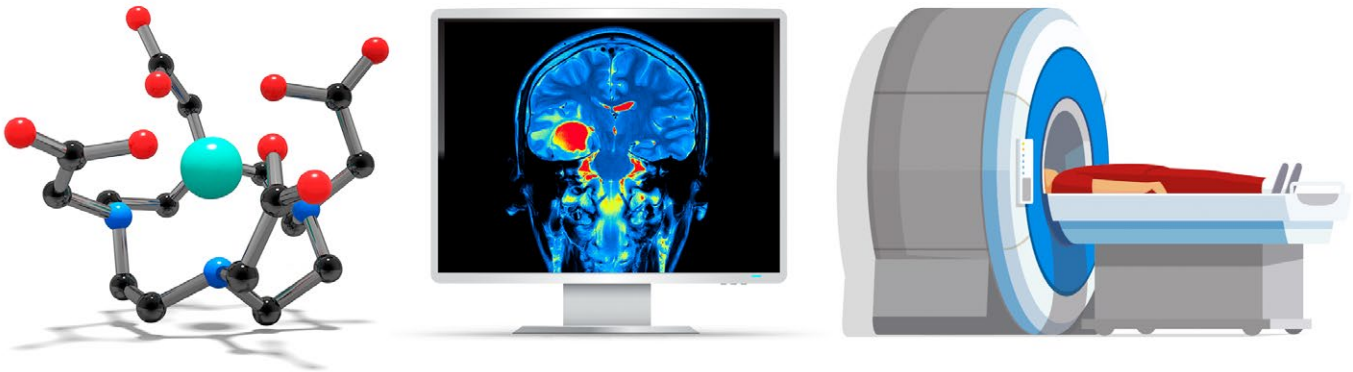
Targeted Research Group
metal chelates, molecular imaging, contrast agents, combinatorial chemistry, MRI, PET, nuclear medicine, cancer radiotherapy, bioconjugation

COORDINATION COMPOUNDS FOR MEDICAL IMAGING AND THERAPY

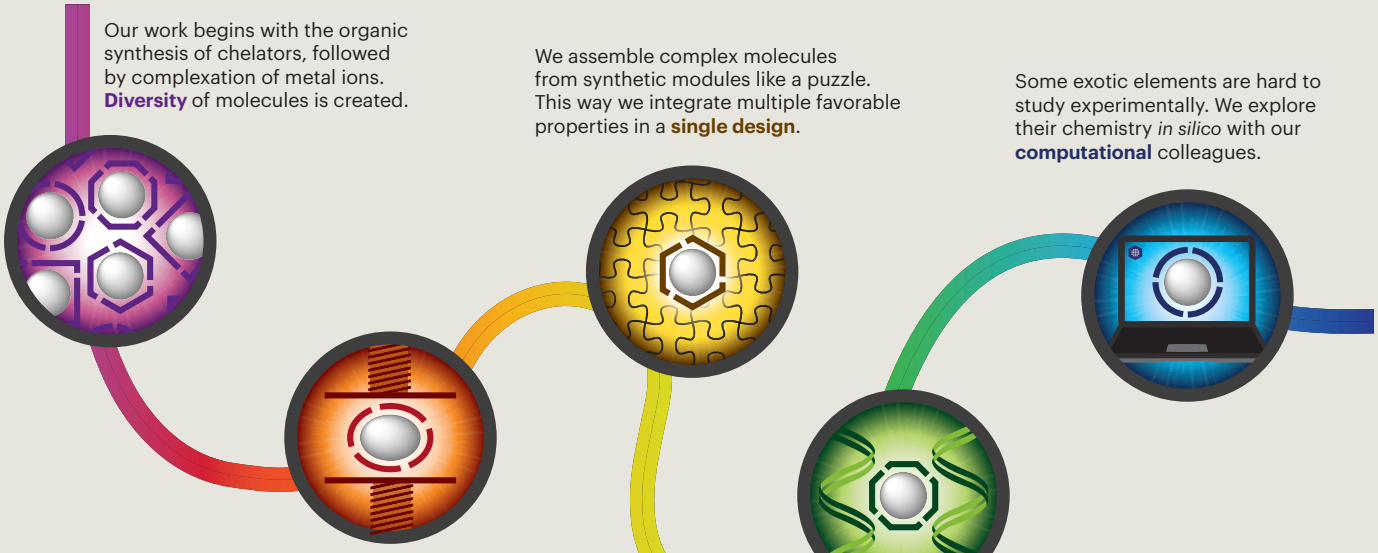


Research topics

METAL CHELATES
Our team is dedicated to advancing the fields of nuclear medicine and molecular imaging by providing new chemical tools. We design organic chelators that coat metal ions and form stable complexes. We integrate additional functionalities into these chelators, such as connectivity to (bio)molecules, or metal-selective behavior. The interplay between organic chemistry and metal coordination provides exciting possibilities for innovation. Depending on the metal, our molecules can serve as medical imaging probes or can be used in cancer radiotherapy. We mostly work with metals from the lanthanide series, but the whole periodic system is our laboratory. Being a targeted research group, we are committed to turning our research into practical applications, for which we actively seek industrial partners.

IMAGING PROBES
Humans naturally need to see things in order to understand them. Unfortunately, pathologies in our bodies start at the molecular level, which is obscured to us. Advanced imaging techniques and specialized molecular probes are about to change that. Our team is developing gadolinium-based probes for magnetic resonance imaging (MRI) that can recognize and report on specific biogenic molecules. We are working on new methodologies for synthesizing and testing vast libraries of such probes. We are also testing new principles of how these probes can report on molecular events. Last but not least, we are developing multimodal probes for combined imaging with hybrid MRI/PET scanners.

THERAPY
Radiotherapeutic agents are more efficient and require lower dosages to beat cancer than traditional chemotherapy. But because of relentless radioactive decay, it is critical that everything works smoothly all the way from synthesis to the patient's vein. We focus on advancing three crucial aspects of the chemistry behind radiotherapeutics: i) purification of metal radionuclides to extremely high purity; ii) binding metals in highly inert chelates; iii) strategies to connect metal chelates to biomolecules.



Group members

Group leader Miloslav Polášek
Postdoc Tomáš David
Ph.D. student Jan Kretschmer

Selected papers

David, T.; Hlinová, V.; Kubíček, V.; Bergmann, R.; Striese, F.; Berndt, N.; Szöllősi, D.; Kovács, T.; Máthé, D.; Bachmann, M.; Pietzsch, H.-J.; Hermann, P. Improved Conjugation, 64-Cu Radiolabeling, in Vivo Stability, and Imaging Using Nonprotected Bifunctional Macrocyclic Ligands: Bis(Phosphinate) Cyclam (BPC) Chelators. *J. Med. Chem.* **2018**, 61, 8774–8796.

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David, T.; Kubíček, V.; Gutten, O.; Lubal, P.; Kotek, J.; Pietzsch, H.-J.; Rulíšek, L.; Hermann, P. Cyclam Derivatives with a Bis(phosphinate) or a Phosphinato–Phosphonate Pendant Arm: Ligands for Fast and Efficient Copper(II) Complexation for Nuclear Medical Applications. *Inorg. Chem.* **2015**, 54, 11751–11766.

Polasek, M.; Caravan, P. Is Macrocycle a Synonym for Kinetic Inertness in Gd(III) Complexes? Effect of Coordinating and Noncoordinating Substituents on Inertness and Relaxivity of Gd(III) Chelates with DO3A-like Ligands. *Inorg. Chem.* **2013**, 52, 4084–4096.

Financial support

IOCB interdisciplinary grant, 2018–2020, PI: Polášek, M., co-PI: Straka, M.

Synthesis and screening of selective probes for magnetic resonance imaging. Czech Science Foundation (GA ČR), No. 17-22834Y, 2017–2019, Polášek, M.

CONCOORD: Controlled coordination for novel radiopharmaceuticals. Charles University Grant Agency (GA UK), No. 1608218, 2018–2019, Kretschmer, J.

Patents

- **EP17204972.8** (2017, pending)—Compounds for separation of rare earth elements, method of separation, and use thereof
- **PCT/EP2018/083215** (2018, pending)—Compounds for separation of rare earth elements and s-, p-, d- metals, method of separation, and use thereof
- **EP19178492.5** (2019, pending)—Compounds for chromatographic separation of rare earth elements and s-, p-, d- metals, method of separation, and use thereof
- **EP19182286.5** (2019, pending)—Cyclen-based compounds, coordination compounds, peptides, pharmaceutical preparation, and use thereof

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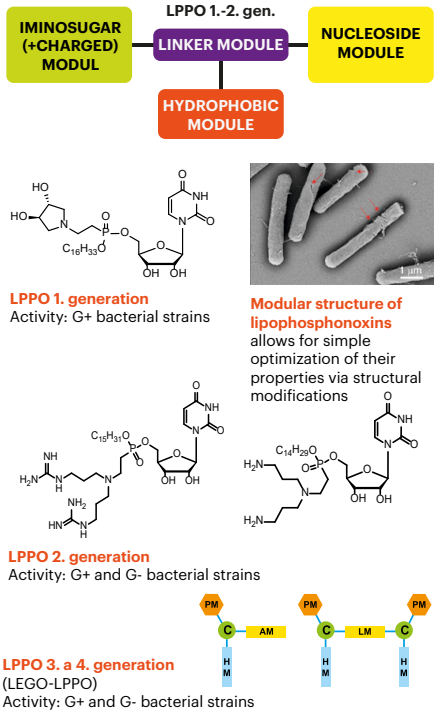
Targeted Research Group

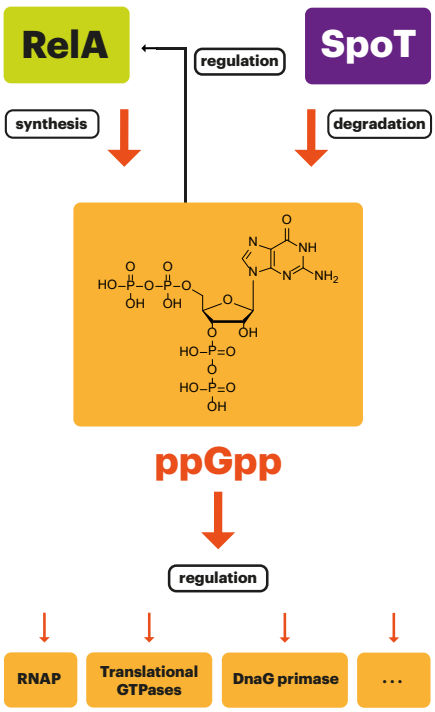
antimicrobial, antibiotic, bacteria, inhibitor, regulation, bacterial stringent response, nucleotide biosynthesis, salvage pathway

LIPOPHOSPHONOXINS

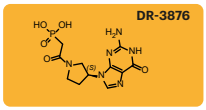
LPPO → disrupt bacterial cellular membrane

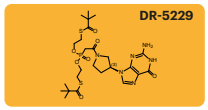


BACTERIAL STRINGENT RESPONSE



INHIBITORS OF H(X)GPRT AS POTENTIAL ANTIMALARIALS AND ANTITUBERCULOTICS





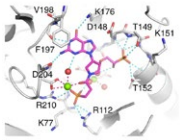
	HG(X)-PRT K_i μM			
	Human	*P. falciparum*	*P. vivax*	*E. coli*
DR-3876	73	0.4	2.6	0.23

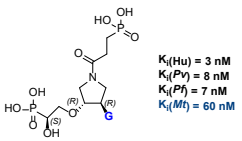
Prodrugs of this compound have very good IC_{50} values against Pf grown in cell culture:

	D6[a]		W2[b]	
	IC_{50} / μM	IC_{90} / μM	IC_{50} / μM	IC_{90} / μM
DR-3876	14.7	22.3	18.2	30.4
DR-5229	1.7	3.9	0.7	2

[a]Pf strain sensitive to most drugs
[b]chloroquine- and pyrimethamine-resistant Pf strain

- **Low cytotoxicity** (IC_{50} > 300 mM), well tolerated and **not toxic to the mice** up to 64 mg/kg
- ***Mycobacterium tuberculosis*** cell-based assay showed promising activity of DR-5229 with an **IC_{50} = 20 μM**.





Active site of the ***Pv*HGPRT.DR5930** complex; Mg^{2+} water
Keough DT, et al. *ACS Chem. Biol.* **2017**.

Research topics

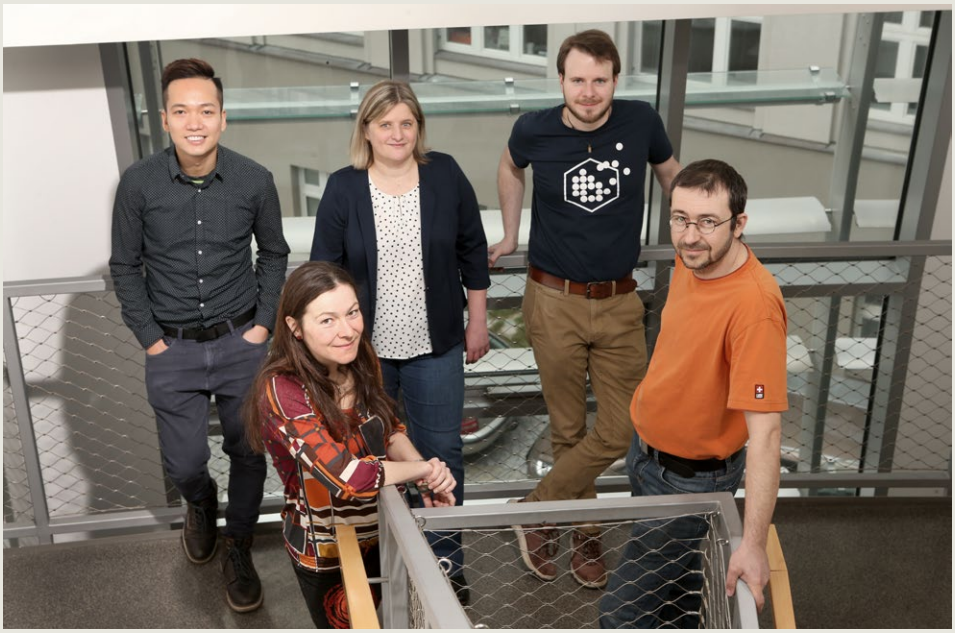
The increase in the number of bacterial strains resistant to known antibiotics combined with the decrease of new antibiotics being introduced in clinical practice is alarming. Our group is attempting to contribute to solve this serious problem. We are working on three main projects:

1. Lipophosphonoxins—novel antibacterial compounds acting by means of disrupting the bacterial cell membrane. In this project, we design and synthesize new derivatives in order to obtain compounds with good antibacterial and safety properties. We also study interactions of lipophosphonoxins with model membranes at the molecular level.

Currently, we are evaluating the use of LPPOs as local antibiotics in combination either with bone cement for orthopedics or with nanofibers for the treatment of skin infections.

2. Pyrrolidine inhibitors of hypoxanthine-guanine-xanthine phosphoribosyl transferase as potential antimalarials and/or antituberculotics. In this project, we design and synthesize various pyrrolidine phosphonate and bisphosphonate inhibitors as well as their prodrugs.

3. The study of bacterial stringent response as a potential antibiotic drug target. The idea behind this project is to focus on the regulatory pathway instead of on the metabolic one, which is a common target for current antibiotics.



Group members

Group leader Dominik Rejman
Scientist Magda Petrová
Postdocs Duy Dinh Do Pham, Gabriela Mikušová, Viktor Mojr
Ph.D. student Eva Zborníková

Selected papers

Zhang, Y.; Zborníková, E.; Rejman, D.; Gerdes, K. Novel (p)ppGpp Binding and Metabolizing Proteins of *Escherichia coli*. *mBio* **2018**, 9, e02188-17.

Eng, W.S.; Rejman, D.; Pohl, R.; West, N.P.; Woods, K.; Naesens, L.M.J.; Keough, D.T.; Guddat, L.W. Pyrrolidine nucleoside bisphosphonates as antituberculosis agents targeting hypoxanthine-guanine phosphoribosyltransferase. *Eur. J. Med. Chem.* **2018**, 159, 10–22.

Keough, D.T.; Rejman, D.; Pohl, R.; Zborníková, E.; Hocková, D.; Croll, T.; Edstein, M.D.; Birrell, G.W.; Chavchich, M.; Naesens, L.M.J.; Pierens, G.K.; Brereton, I.M.; Guddat, L.W. Design of *Plasmodium vivax* Hypoxanthine-Guanine Phosphoribosyltransferase Inhibitors as Potential Antimalarial Therapeutics. *ACS Chem. Biol.* **2018**, 13, 82–90.

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Panova, N.; Zbornikova, E.; Simak, O.; Pohl, R.; Kolar, M.; Bogdanova, K.; Vecerova, R.; Seydlova, G.; Fiser, R.; Hadravova, R.; Sanderova, H.; Vitovska, D.; Sikova, M.; Latal, T.; Lovecka, P.; Barvik, I.; Krasny, L.; Rejman, D. Insights into the Mechanism of Action of Bactericidal Lipophosphonoxins. *PLoS One* **2016**, 10, e0145918.

Gaca, A.O.; Kudrin, P.; Colomer-Winter, C.; Beljantseva, J.; Liu, K.Q.; Anderson, B.; Wang, J.D.; Rejman, D.; Potrykus, K.; Cashel, M.; Hauryliuk, V.; Lemos, J.A. From (p)ppGpp to (pp)pGpp: Characterization of Regulatory Effects of pGpp Synthesized by the Small Alarmone Synthetase of *Enterococcus faecalis*. *J. Bacteriol.* **2015**, 197, 2908.

Pohl, R.; Postova Slavetinska, L.; Soon Eng, W.; Keough, D. T.; Guddat, L.W.; Rejman, D. Synthesis, Conformational Studies, and Biological Properties of Phosphonomethoxyethyl Derivatives of Nucleobases with a Locked Conformation Via a Pyrrolidine Ring. *Org. Biomol. Chem.* **2015**, 13, 4693-4705.

Financial support

Development of novel ribosome-targeting antibiotics. JPI-EC-AMR, 2019–2021, Rejman, D. (co-PI)

Lipophosphonoxins in the prevention and treatment of musculoskeletal infections: a potential role of new antimicrobial compounds. Czech Health Research Council (AZV ČR), No. 17-29680A, 2017–2020, Rejman, D.

Development of a molecular toolkit for control and investigation of the bacterial stringent response. Czech Science Foundation (GA ČR), No. GA15-11711S, 2015–2017, Rejman, D.

Lipophosphonoxins – novel antibacterial compounds: their use in selective culture media and their potential for veterinary and human medicine. Technology Agency of the Czech Republic (TA ČR), No. TA02010035, 2012–2015, Rejman, D.

Patents

WO2017100849 (December 15, 2016)
6-Oxopurine Phosphoribosyl Transferase Inhibitor
De Jersey, J.; Guddat, L.W.; Hocková, D.; Keough, D.T.; Pohl, R.; Rejman, D.

WO2017186200A1 (CZ – April 28, 2016; EP, WO, CA, AU – April 19, 2017)
Lipophosphonoxins of second generation, and their use
Rejman, D.; Pohl, R.; Zborníková, E.; Krásný, L.; Látal, T.; Kolář, M.

Collaboration

Krásný, L. (Institute of Microbiology of the CAS, Prague, Czech Republic)

Kolář, M. (Palacký University Olomouc, Czech Republic)

Guddat, L. & Keough, D. (University of Queensland, Brisbane, Australia)

Hauliryuk, V. (Umea University, Sweden)

Wilson, D. (University of Hamburg, Germany)

Zajíček, R. (Faculty Hospital Královské Vinohrady, Prague, Czech Republic)

Barvík, I. (Charles University, Prague, Czech Republic)

Lukáš, D. (Technical University of Liberec, Czech Republic)

Gerdes, K. (University of Copenhagen, Denmark)

Ivan Rosenberg Group

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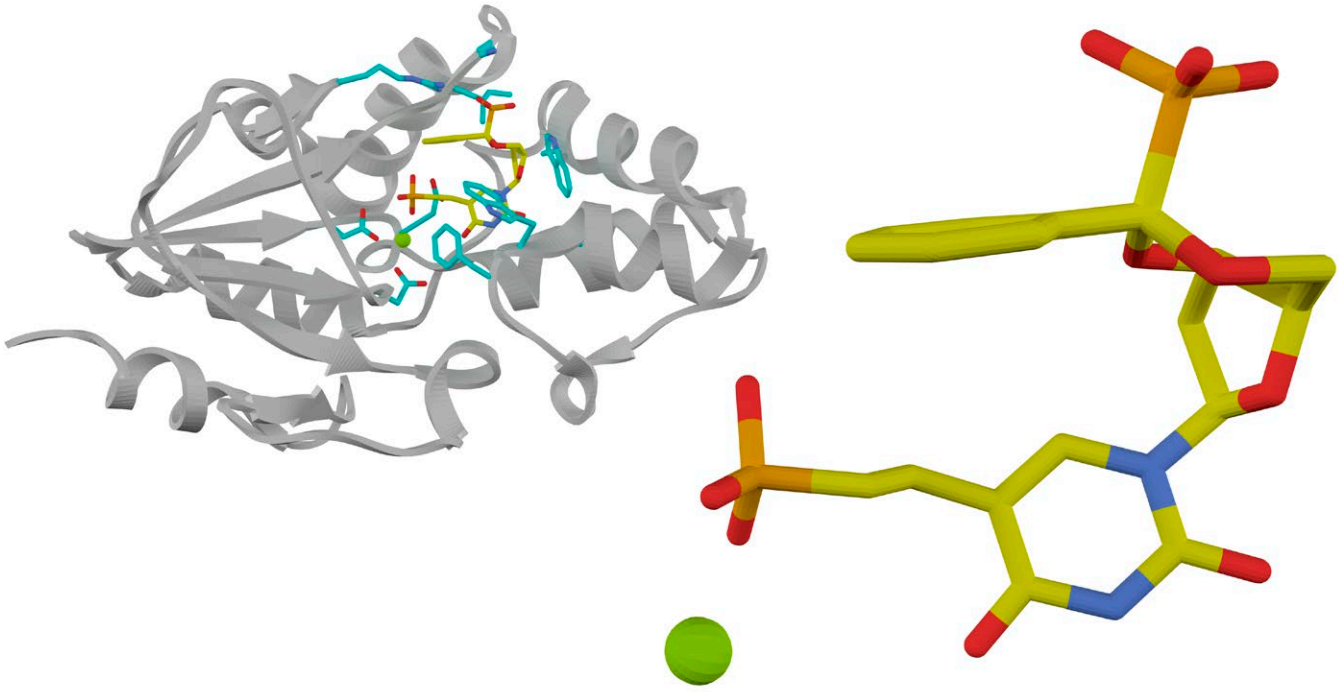
Distinguished Emeritus Scientist
nucleotide and nucleoside analogs, phosphonates, phosphinates, modified antisense oligonucleotides and siRNAs, RNase H, CpG oligonucleotides, 2′-5′-linked oligoadenylates, RNase L, solid phase synthesis

BINDING MODE OF MITOCHONDRIAL 5′(3′)-DEOXYNUCLEOTIDASE INHIBITOR

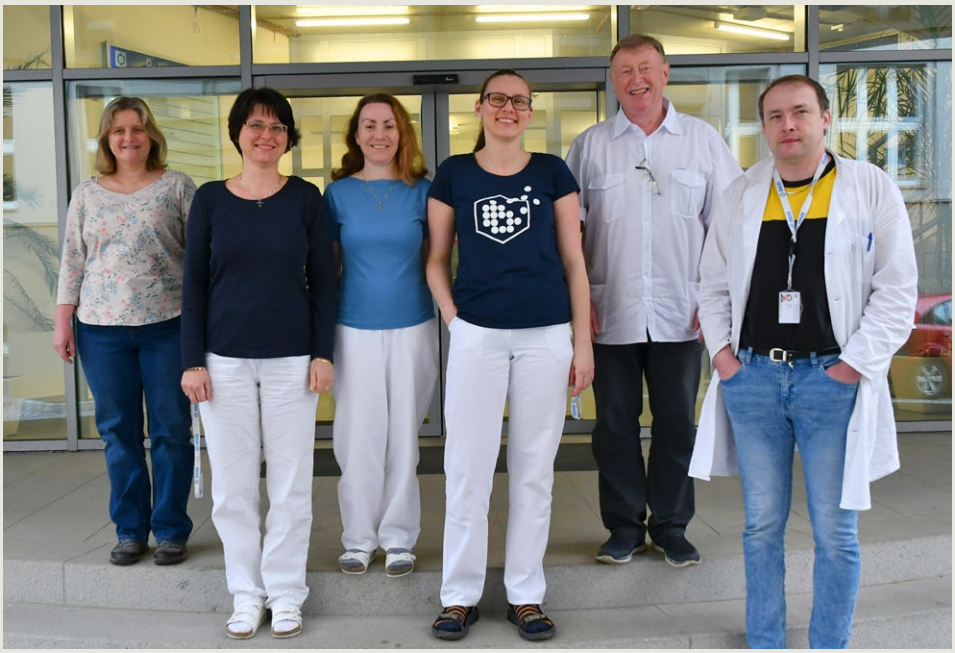


Research topics

The scientific program of the group is directed towards basic research in the area of nucleoside phosphonic acids (NPAs) as potential antimetabolites, building units for solid phase synthesis of chimeric antisense oligonucleotides as compounds capable of interfering with gene expression, and regulatory oligonucleotides (2′,5′-linked oligoadenylates and CpG oligonucleotides).

NUCLEOSIDE PHOSPHONIC ACIDS
Our investigation in the area of the chemistry of NPAs has provided an impressive number of novel structurally diverse compounds containing classical furanose and non-oxygen heterocyclic rings. Among them, potent inhibitors of several *salvage pathway* enzymes were found, e.g. selective inhibitors of human mitochondrial and cytosolic pyrimidine specific 5′(3′)-deoxynucleotidases were recognized.

OLIGONUCLEOTIDE ANALOGS
Modified oligonucleotides containing several types of nucleoside phosphonic acids exhibit significantly increased nuclease stability, enhanced hybridization, and stimulation of RNase H activity. These properties may classify phosphonate oligonucleotides for their potential use in biology as antisense compounds in regulation of gene expression. Our attention is also focused on the chemistry and biology of the modified α-D and α-L-oligodeoxynucleotides—an almost forgotten group of compounds. Of particular interest is a group of pyrrolidine nucleoside phosphonates and 4′-alkoxynucleosides that, upon their incorporation into oligonucleotides, significantly increase duplex stability and discriminate between RNA and DNA targets.



Group members

Group leader Ivan Rosenberg
Scientists Ondřej Kostov, Ivana Markusová-Kóšiová, Magdalena Petrová, Šárka Rosenbergová
Research assistants Ivana Dvořáková, Pavel Novák

Selected papers

Kaiser, M.M.; Novák, P.; Rosenbergová, Š.; Poštová-Slavětínská, L.; Rosenberg, I.; Janeba Z. Acyclic Nucleoside Phosphonates Bearing (R)- or (S)-9-[3-Hydroxy-2-(phosphonoethoxy)propyl] (HPEP) Moiety as Monomers for the Synthesis of Modified Oligonucleotides. *Eur. J. Org. Chem.* **2018**, 37, 5119–5126.

Pachl, P.; Šimák, O.; Buděšínský, M.; Brynda, J.; Rosenberg, I.; Řezáčová, P. Structure-Based Optimization of Bisphosphonate Nucleoside Inhibitors of Human 5(3)-deoxyribonucleotidases. *Eur. J. Org. Chem.* **2018**, 37, 5144–5153.

Páv, O.; Barvik, I.; Liboska, R.; Petrová, M.; Šimák, O.; Rosenbergová, Š.; Novák, P.; Buděšínský, M.; Rosenberg, I. Tuning the hybridization properties of modified oligonucleotides: from flexible to conformationally constrained phosphonate internucleotide linkages. *Org. Biomol. Chem.* **2017**, 15, 701–707.

Páv, O.; Buděšínský, M.; Rosenberg, I. Novel phosphanucleoside analogs of dideoxynucleosides. *Tetrahedron* **2017**, 73, 5220–5228.

Kostov, O.; Páv, O.; Buděšínský, M.; Liboska, R.; Šimák, O.; Petrová, M.; Novák, P.; Rosenberg, I. 4-Toluenesulfonyloxymethyl-(H)-phosphinate: A Reagent for the Introduction of O- and S-Methyl-(H)-phosphinate Moieties. *Org. Lett.* **2016**, 18, 2704–2707.

Petrová, M.; Páv, O.; Buděšínský, M.; Zborníková, E.; Novák, P.; Rosenbergová, Š.; Pačes, O.; Liboska, R.; Dvořáková, I.; Šimák, O.; Rosenberg, I. Straightforward Synthesis of Purine 4 '-Alkoxy-2 '-deoxynucleosides: First Report of Mixed Purine-Pyrimidine 4 '-Alkoxyoligodeoxynucleotides as New RNA Mimics. *Org. Lett.* **2015**, 17, 3426–3429.

Šípová, H.; Špringer, T.; Rejman, D.; Šimák, O.; Petrová, M.; Novák, P.; Rosenbergová, Š.; Páv, O.; Liboska, R.; Barvík, I.; Štěpánek, J.; Rosenberg, I.; Homola, J. 5 '-O-Methylphosphonate nucleic acids-new modified DNAs that increase the *Escherichia coli* RNase H cleavage rate of hybrid duplexes. *Nucleic Acids Res.* **2014**, 42, 5378–5389.

Košiová, I., Šimák, O.; Panova, N.; Buděšínský, M.; Petrová, M.; Rejman, D.; Liboska, R.; Páv, O.; Rosenberg, I. Inhibition of human thymidine phosphorylase by conformationally constrained pyrimidine nucleoside phosphonic acids and their "open-structure" isosteres. *Eur. J. Med. Chem.* **2014**, 74, 145–168.

Financial support

Properties of α-D- and α-L-Oligodeoxynucleotides with Isopolar Phosphonate Internucleotide Linkages. Czech Science Foundation (GA ČR), No. 17-12703S, 2017–2019, Rosenberg, I. (PI)

Targeted damage of the DNA repair mechanisms as a tool for cancer therapy. Ministry of Health (MZ), No. 15-31604A, 2015–2018, Rosenberg, I. (co-PI)

Novel DNA and RNA oligonucleotides with Phosphonothioate and Phosphonoamidate internucleotide Linkages. Czech Science Foundation (GA ČR), No. 13-26526S, 2013–2016, Rosenberg, I. (PI)

Collaboration

Oligonucleotides interfering with gene expression. Collaboration with Janssen BioPharma, Inc. (Johnson & Johnson, CA, USA)

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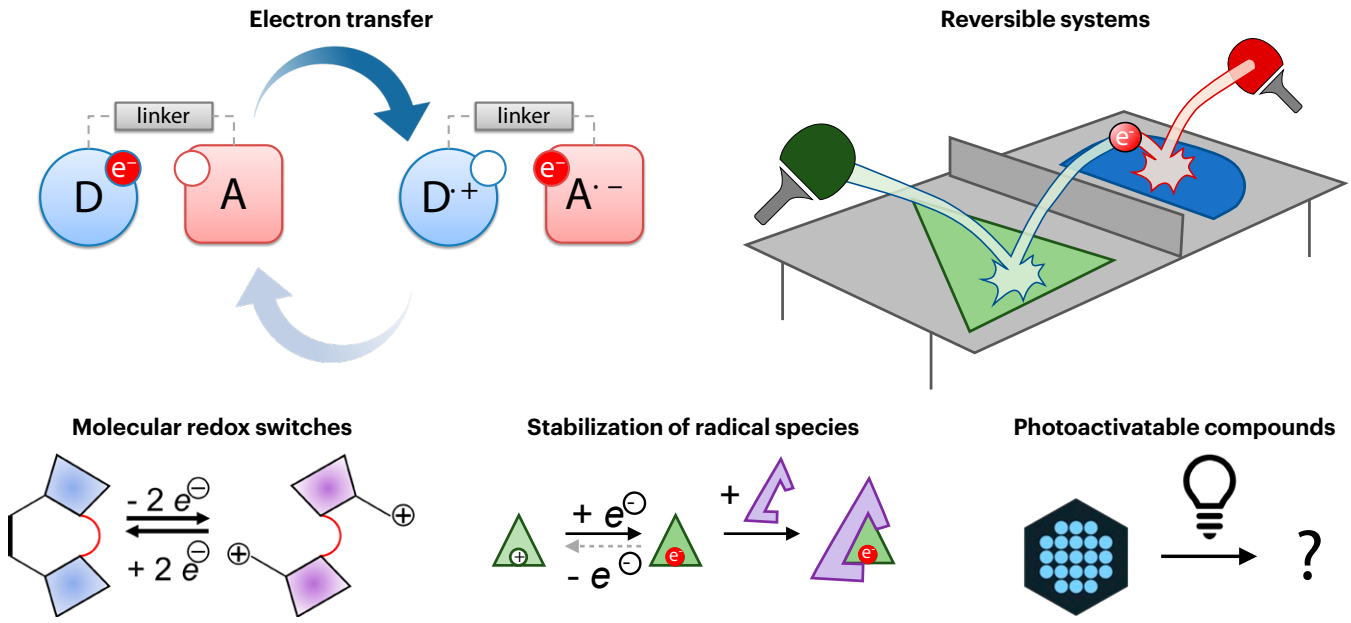
Junior Research Group

electron transfer, radical ions, redox switches, stabilization of radical species



Research topics

The general goal of our group is to govern electron transfer between suitable donor-acceptor pairs by external stimuli in order to control the position of electric charges. We develop various strategies for controlling redox reactions of organic substrates and the stabilization of charge-transfer states. This knowledge will help to prepare novel redox-active materials with unique properties, such as controlled wettability, coordination of ions, and electrostatic charging.

MOLECULAR REDOX SWITCHES

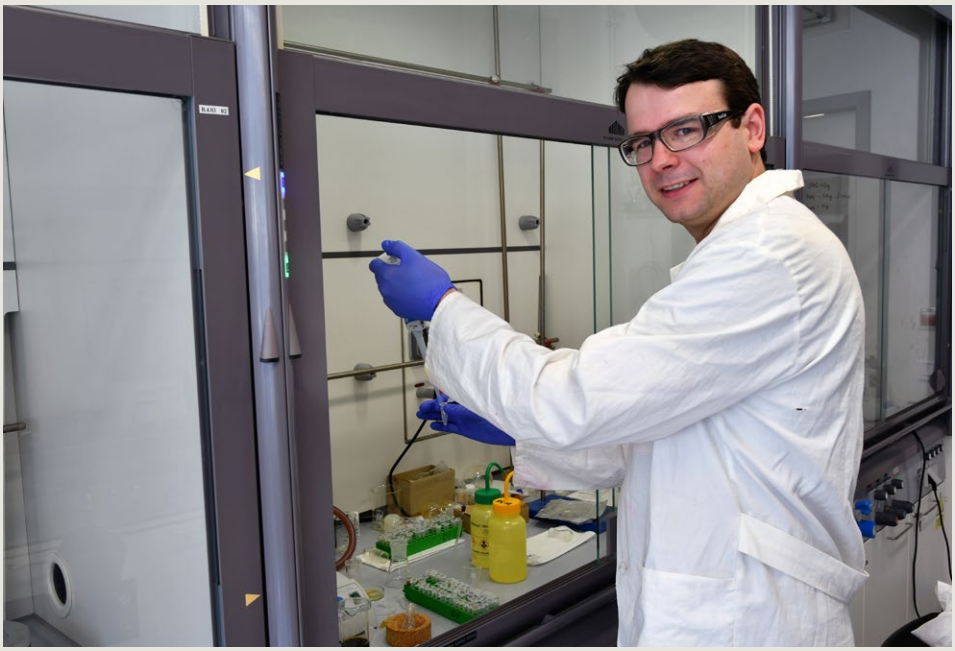
Molecular switches represent an important class of molecules which can be regulated by the action of external stimulus (light, pH, solvent change, or temperature). They exist in two chemically stable states with different geometry, chemical, and physical properties. Redox switches, a unique class of bistable molecules that change their structure through a redox process, can exist both in discharged and charged form. We develop novel molecular redox switches and characterize their switching properties. We aim to immobilize them on surfaces and into materials that will be used for charging surfaces, electrostatic bending, manipulation with counterions, and the design of molecular devices with reversible polarity.

STABILIZATION OF RADICAL SPECIES

We study stable organic radicals and radical ions and methods for their generation, stabilization, and utilization. Various strategies, such as complexation with stabilizing molecules, controlled subsequent reactivity of generated radicals, and steric isolation in a macrocyclic confined environment, are investigated. Our goal is to understand which factors can thermodynamically or kinetically hinder the back-electron transfer after a redox process.

OTHER INTERESTS

Our research group is also interested in photoactivatable compounds that undergo defined photochemical change upon excitation (bond fission, bond formation, and rearrangements). We develop systems for reversible photochemical reactions, fluorescent molecules suitable for sensing and labelling, and photo-click bioorthogonal reactions.



Group members

Group leader Tomáš Slanina
Postdoc Tej Varma Yenupuri (starts in October 2019)
Ph.D. students Virender Singh (starts in July 2019), Olena Tykhoniuk (starts in July 2019), Anna Vasilevska (starts in June 2019)
Students Jiří Doležel (starts in June 2019), Katarzyna Hanc (starts in June 2019)

Selected papers

Reinfelds, M.; Hermanns, V.; Halbritter, T.; Wachtveitl, J.; Braun, M.; Slanina, T.; Heckel, A. A Robust, Broadly-Absorbing Fulgide Derivative as a Universal Chemical Actinometer for the UV to NIR Region. *ChemPhotoChem* **2019**.

Slanina, T.; Oberschmid, T. Rhodamine 6G Radical: A Spectro (Fluoro) Electrochemical and Transient Spectroscopic Study. *ChemCatChem* **2018**, 10, 4182–4190.

Slanina, T.; Shrestha, P.; Palao, E.; Kand, D.; Peterson, J.A.; Dutton, A.S.; Rubinstein, N.; Weinstain, R.; Winter, A.H.; Klán, P. In Search of the Perfect Photocage: Structure–Reactivity Relationships in Meso-Methyl BODIPY Photoremovable Protecting Groups. *J. Am. Chem. Soc.* **2017**, 139, 15168–15175.

Fiala, T.; Ludvíková, L.; Heger, D.; Švec, J.; Slanina, T.; Vetráková, L.; Babiak, M.; Nečas, M.; Kulhánek, P.; Klán, P.; Sindelar, V. Bambusuril as a One-Electron Donor for Photoinduced Electron Transfer to Methyl Viologen in Mixed Crystals. *J. Am. Chem. Soc.* **2017**, 139, 2597–2603.

Palao, E.; Slanina, T.; Muchová, L.; Šolomek, T.; Vítek, L.; Klán, P. Transition-Metal-Free CO-Releasing BODIPY Derivatives Activatable by Visible to NIR Light as Promising Bioactive Molecules. *J. Am. Chem. Soc.* **2016**, 138, 126–133.

Madea, D.; Slanina, T.; Klán, P. A 'Photorelease, Catch and Photorelease' Strategy for Bioconjugation Utilizing a p-Hydroxyphenacyl Group. *Chem. Commun.* **2016**, 52, 12901–12904.

Ghosh, T.; Slanina, T.; König, B. Visible Light Photocatalytic Reduction of Aldehydes by Rh(Iii)–H: A Detailed Mechanistic Study. *Chem. Sci.* **2015**, 6, 2027–2034.

Financial support

IOCB institutional support for junior research groups, 2019–2024.

Light-driven Systems for Reversible Separation of Charges. Czech Science Foundation (GA ČR), No. 19-20467Y, 2019–2021.

Collaboration

Henrik Ottosson (Uppsala University, Sweden)

Alexander Heckel (Goethe University Frankfurt, Germany)

Petr Klán (Masaryk University, Brno, Czech Republic)

Awards—Tomáš Slanina

Stiftelsen Olle Engkvist Byggmästare Fellowship, 2018

Experientia Postdoctoral Fellowship, 2016

Rector's Award for the Best Ph.D. Thesis, Masaryk University, 2016

European Photochemistry Association Prize for Ph.D. Thesis in Photochemistry, 2016

1st place Jean-Marie Lehn Ph.D. Chemistry Prize, 2015

Ivo Starý Group

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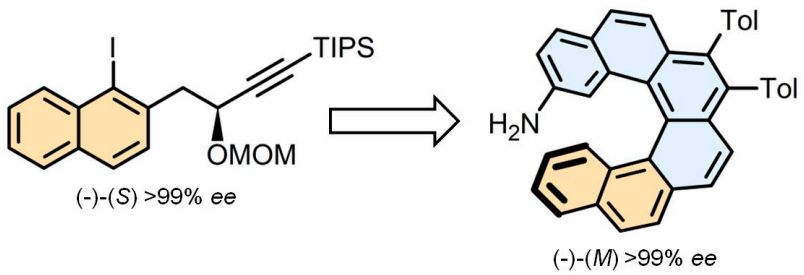
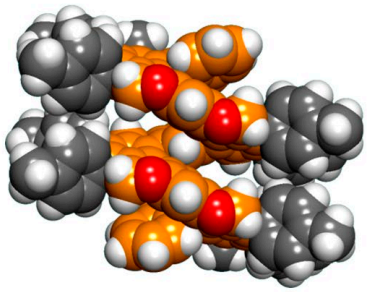
Senior Research Group

helical aromatics, functional π-electron systems, enantioselective catalysis, charge transport, 2D self-assembly, on-surface chemistry, molecular devices

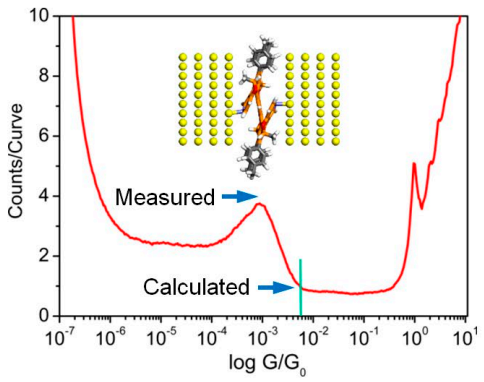
Asymmetric synthesis of helicenes



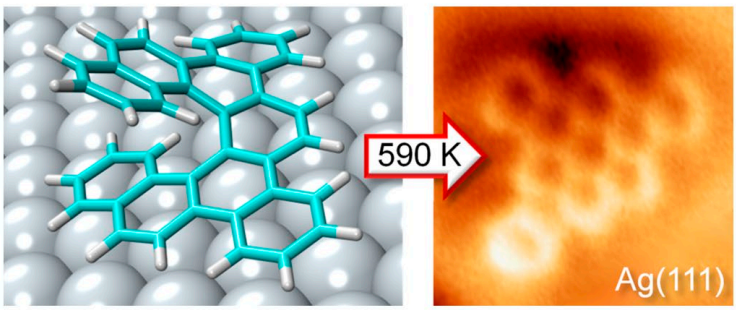
Long helical aromatics



Conductance of single helicenes



On-surface chirality transfer



Enantiomer ratio 100:0 Enantiomer ratio 92:8
(collaboration with P. Jelínek et al., Institute of Physics of the CAS)

Research topics

Our research focuses on non-trivial π-electron architectures, which are attractive for applications in chemistry, physics, and biology.

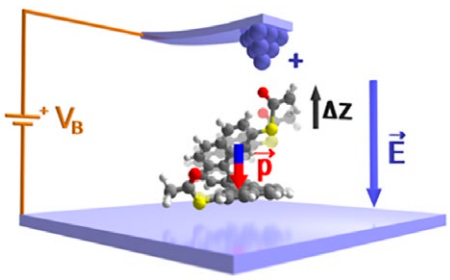
In particular, we pay attention to the synthesis of helically chiral aromatics (helicenes) that are enantiopure and properly functionalized. We systematically investigate their (chir)optical properties, self-assembly in crystals or at interfaces, charge/spin transport properties, and on-surface reactivity at the nanoscale.

We are also interested in general synthetic methodology development and enantioselective catalysis. Our ultimate goal is to develop smart molecular devices.

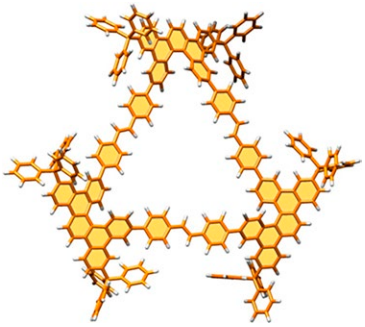
In addition, we utilize a mechanically controllable/STM break junction method to study single molecule conductivity of helical aromatics, explore properties of inorganic nanoparticles functionalized by chiral π-electron systems, and strive for fabrication and characterization of respective molecular devices.

The experimental approaches go hand in hand with computational ones in order to obtain deep insights into the reactivity and physicochemical properties of target π-electron systems in vacuum, solution, or on solid surfaces.

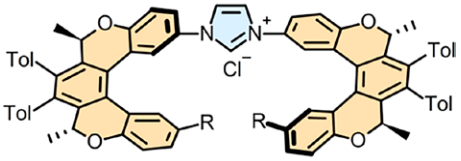
Multidisciplinary research is performed in close collaboration with experts in scanning probe microscopy techniques.



Single-molecule piezoelectricity (collaboration with P. Jelínek et al., Institute of Physics of the CAS)



Helicene-derived persistent macrocycles



Helicene ligands in enantioselective catalysis

Group members

Group leader Ivo Starý
Scientists Jiří Rybáček, Ladislav Sieger, Irena G. Stará, Michal Šámal, Jaroslav Vacek
Postdocs Shyam Mothuku Sundar, Daisuke Sakamoto
Ph.D. students Isabel Gay Sánchez, Jan Hanus, Jan Holec, Václav Houska, Jiří Janoušek, Jiří Klívar, Jindřich Nejedlý, Anna Poryvai
Students Daniel Bambas, Jan Bašus, Matúš Drexler, Magdalena Holasová, Laura Kdýrová, Daniel Mildner

Selected papers

Stetsovych, O.; Mutombo, P.; Švec, M.; Šámal, M.; Nejedlý, J.; Císařová, I.; Vázquez, H.; Moro-Lagares, M.; Berger, J.; Vacek, J.; Stará, I. G.; Starý, I.; Jelínek, P. Large Converse Piezoelectric Effect Measured on a Single Molecule on a Metallic Surface. *J. Am. Chem. Soc.* **2018**, 140, 940–946.

Stetsovych, O.; Švec, M.; Vacek, J.; Vacek Chocholoušová, J.; Jančařík, A.; Rybáček, J.; Stará, I. G.; Jelínek, P.; Starý, I. From Helical to Planar Chirality by On-Surface Chemistry. *Nat. Chem.* **2017**, 9, 213–218.

Nejedlý, J.; Šámal, M.; Rybáček, J.; Tobrmanová, M.; Szydlo, F.; Coudret, C.; Neumeier, M.; Vacek, J.; Vacek Chocholoušová, J.; Buděšínský, M.; Šaman, D.; Bednárová, L.; Sieger, L.; Stará, I. G.; Starý, I. Synthesis of Long Oxahelicenes by Polycyclization in a Flow Reactor. *Angew. Chem. Int. Ed.* **2017**, 56, 5839–5843.

Šámal, M.; Chercheja, S.; Rybáček, J.; Vacek Chocholoušová, J.; Vacek, J.; Bednárová, L.; Šaman, D.; Stará, I. G.; Starý, I. An Ultimate Stereocontrol in Asymmetric Synthesis of Optically Pure Fully Aromatic Helicenes. *J. Am. Chem. Soc.* **2015**, 137, 8469–8474.

Buchta, M.; Rybáček, J.; Jančařík, A.; Kudale, A. A.; Buděšínský, M.; Vacek Chocholoušová, J.; Vacek, J.; Bednárová, L.; Císařová, I.; Bodwell, G. J.; Starý, I.; Stará, I. G. Chimerical Pyrene-Based [7]Helicenes as Twisted Polycondensed Aromatics. *Chem. Eur. J.* **2015**, 21, 8910–8917.

Jančařík, A.; Rybáček, J.; Cocq, K.; Vacek Chocholoušová, J.; Vacek, J.; Pohl, R.; Bednárová, L.; Fiedler, P.; Císařová, I.; Stará, I. G.; Starý, I. Rapid Access to Dibenzohelicenes and their Functionalized Derivatives. *Angew. Chem. Int. Ed.* **2013**, 52, 9970-9975.

Financial support

Piezoelectric properties of molecules and related molecule materials. Czech Science Foundation (GA ČR), No. 18-20433S, 2018–2020, Starý, I.

Formation of covalent molecular complexes on surfaces driven by light induced chemical reactions. Czech Science Foundation (GA ČR), No. 18-09914S, 2018-2020, Stará, I. G. (collaboration with Jelínek, P., Institute of Physics of the CAS)

Enantioselective catalysis under the control of helical chirality. Czech Science Foundation (GA ČR), No. 19-10144S, 2019–2021, Starý, I.

Collaboration

Martin Dračínský (IOCB Prague)

Yonatan Dubi (Ben-Gurion University of the Negev, Beer-Sheva, Israel)

Pavel Jelínek (Institute of Physics of the CAS, Prague, Czech Republic)

Angelika Kühnle (University of Bielefeld, Germany)

José Ángel Martín-Gago (ICMM-CSIC, Madrid, Spain)

Bernd Schmidt (University of Potsdam, Germany)

Kenzo Soai (Tokyo University of Science, Japan)

Marek Szymoński & Bartosz Such (Jagellonian University, Krakow, Poland)

Milan Vrábel Group

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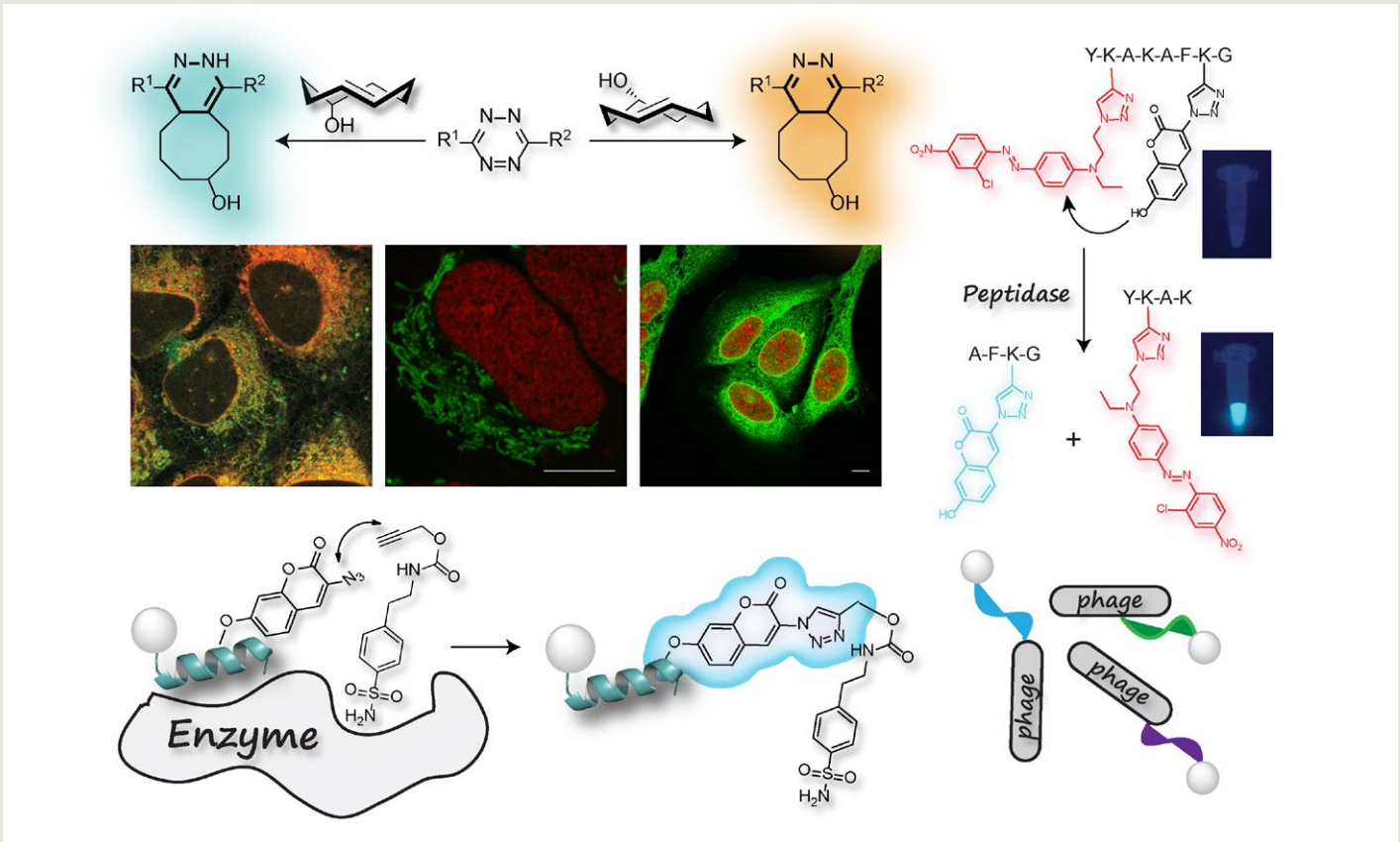
Junior Research Group
bioorthogonal reactions, click chemistry, peptide libraries, glycoconjugates, sugar-processing enzymes



Research topics

NEW BIOCONJUGATION REACTIONS
One of our goals is to develop chemical transformations that can be performed selectively and with high efficiency on various biomolecules in their native environment. We aim to improve existing bioorthogonal reactions and to discover new bioconjugations, which will enable us to study biological processes under native, physiological conditions. The use of these transformations in development of new therapeutics is also one of our intentions.

DEVELOPMENT OF ORGANELLE—SPECIFIC RELEASE REACTIONS
In this project, we aim to construct a new type of decaging systems, which will enable us to release small molecule cargoes within specific cellular compartments using bioorthogonal reactions. We believe that these systems will offer a unique possibility to activate small biologically active molecules in a particular subcellular location and, in a broader sense, to shed light on the function of individual organelles.

SELECTIVE INHIBITORS OF SUGAR PROCESSING ENZYMES
Our group aims to develop a new methodology for construction of highly selective inhibitors of various sugar processing enzymes. By combination of the biological activity of small molecules with the specificity of biologics, we want to prepare a new type of inhibitors of enzymes acting on carbohydrates. This technology will allow for understanding and study of this important class of biomolecules.

Group members

Group leader Milan Vrábel
Scientists Rastislav Dzijak, Juraj Galeta, Anna Kovalová
Research assistant Tereza Schröpferová
Ph.D. students Robert Rampmaier, Sebastian Siegl
Student Anna Beránková

Selected papers

Siegl, S.J.; Galeta, J.; Dzijak, R.; Vázquez, A.; Del-Río-Villanueva, M.; Dračínský, M.; Vrábel, M. An extended approach for the development of fluorogenic trans-cyclooctene-tetrazine cycloadditions. *ChemBioChem* **2019**, 20, 886–890.

Kovalová, A.; Pohl, R.; Vrábel, M. Stepwise triple-click functionalization of synthetic peptides. *Org. Biomol. Chem.* **2018**, 16, 5960–5964.

Siegl, S.J.; Vrábel, M. Probing the scope of the amidine-1,2,3-triazine cycloaddition as a prospective click ligation method. *Eur. J. Org. Chem.* **2018**, 5081–5085.

Siegl, S.J.; Vázquez, A.; Dzijak, R.; Dračínský, M.; Galeta, J.; Rampmaier, R.; Klepetářová, B.; Vrábel M. Design and Synthesis of aza-Bicyclononene Dienophiles for Rapid Fluorogenic Ligations. *Chem. Eur. J.* **2018**, 24, 2426–2432.

Vazquez, A.; Dzijak, R.; Dračínský, M.; Rampmaier, R.; Siegl, S.J.; Vrábel, M. Mechanism-Based Fluorogenic trans-Cyclooctene—Tetrazine Cycloaddition. *Angew. Chem. Int. Ed.* **2017**, 56, 1334–1337.

Siegl, S.; Dzijak, R.; Vazquez, A.; Pohl, R.; Vrábel, M. The Discovery of Pyridinium 1,2,4-Triazines with Enhanced Performance in Bioconjugation Reactions. *Chem. Sci.* **2017**, 8, 3593–3598.

Galeta, J.; Šála, M.; Dračínský, M.; Vrábel, M.; Havlas, Z.; Nencka, R. Single-Step Formation of Pyrimido[4,5-d]pyridazines by a Pyrimidine-Tetrazine Tandem Reaction. *Org. Lett.* **2016**, 18, 3594–3597.

Vrábel, M. and Carell T. as editors for Topics in Current Chemistry (2016), *Cycloadditions in Bioorthogonal Chemistry*, Springer, ISBN 978-3-319-29686-9.

Gattner M.J.; Ehrlich M.; Vrábel M. Sulfonyl azide-mediated norbornene aziridination for orthogonal peptide and protein labeling. *Chem. Commun.* **2014**, 50, 12568–12571.

Financial support

Smart biologics: developing new tools in glycobiology (acronym: SWEETOOLS). European Research Council (ERC Starting Grant), No. 677465, 2016–2021, Vrábel, M.

Targeting enzyme exosites by in-situ click chemistry: New strategy for anticancer drug design. Gilead Sciences & IOCB Research Center, 2017–2021, Vrábel, M.

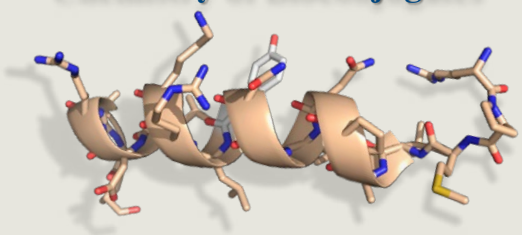
Construction of synthetic scaffolds enabling subcellular organelle-specific release chemistry. Czech Science Foundation (GA ČR), No. P207/19-13811S, 2019–2021, Vrábel, M.

Collaboration

IOCB Prague: Martin Dračínský, Pavel Majer, Michael Mareš, Pavlína Maloy Řezáčová, Kvido Stříšovský

Vrabel Group

Chemistry of Bioconjugates



Dmytro Yushchenko Group

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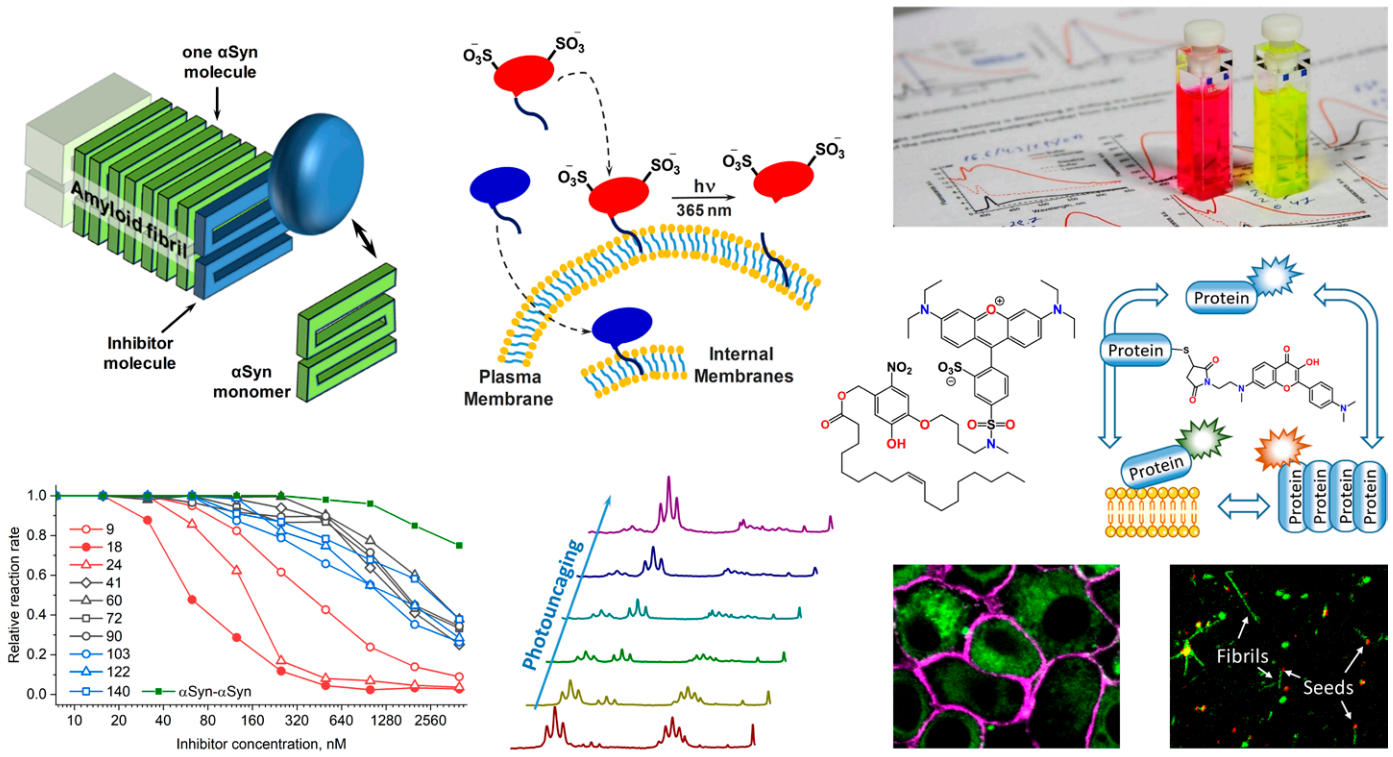
Junior Research Group
fluorescent probes, α-synuclein, inhibitors, lipid signaling, photocages, protein-lipid interaction

CHEMICAL TOOLS TO STUDY BIOLOGICAL SYSTEMS



Research topics

INVESTIGATION AND INHIBITION OF A-SYNUCLEIN AGGREGATION

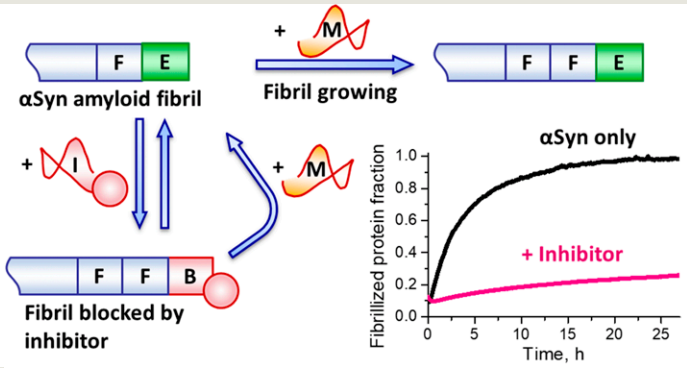
Aggregation of the neuronal protein α-synuclein into amyloid fibrils plays a central role in development of Parkinson's disease. We investigate the mechanism of α-synuclein fibrillization and cytotoxicity of aggregation intermediates using *in vitro* kinetic assays and cellular models. We develop protein-based inhibitors selectively binding to α-synuclein fibrils and blocking their growth.

CHEMICAL TOOLS FOR STUDYING LIPID SIGNALING

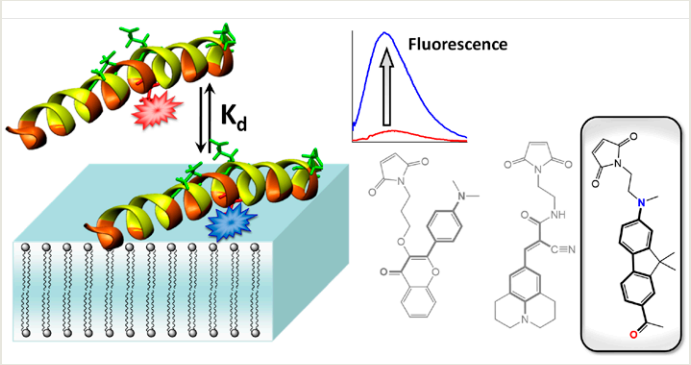
Some lipids play an essential role in cell signaling. Induced signals depend on concentration, localization, and the microenvironment of the signaling lipids in cells, which complicates their investigation. To address these challenges, we develop photocaged and photoswitchable molecules that permit delivery of signaling lipids to defined subcellular sites and their release at desirable time points.

PROBES BASED ON FLUORESCENT DYES

Fluorescent probes are widely used for biosensing, as they provide fast responses and have high sensitivity. Labelling with fluorescent dyes permits selective visualization and monitoring of biomolecules. We develop dyes able to sense the interaction of biomolecules by changing fluorescence depending on their environment as well as bright probes for microscopy applications.



Angew. Chem., Int. Ed. **2018**



Biochim. Biophys. Acta, Biomembr. **2017**

Group members

Group leader Dmytro Yushchenko
Scientist Volodymyr Shvadchak
Postdocs Pankaj Gaur, Dmytro Sysoiev
Research assistant Shubhra Sachan
Ph.D. students Kseniia Afitska, Maksym Galkin, Yevhenii Kyriukha, Andrii Kurochka, Anastasiia Priss
Fulbright student Carolyn Barnes

Selected papers

Shvadchak, V.V.; Afitska, K.; Yushchenko, D.A. Inhibition of alpha-Synuclein Amyloid Fibril Elongation by Blocking Fibril Ends. *Angew. Chem. Int. Ed.* **2018**, 57, 5690–5694.

Kucherak, O.A.; Shvadchak, V.V.; Kyriukha, Y.A.; Yushchenko, D.A. Synthesis of a Fluorescent Probe for Sensing Multiple Protein States. *Eur. J. Org. Chem.* **2018**, 5155–5162.

Kyriukha, Y.A.; Kucherak, O.A.; Yushchenko, T.I.; Shvadchak, V.V.; Yushchenko, D.A. 3-Hydroxybenzo[g]chromones: Fluorophores with red-shifted absorbance and highly sensitive to polarity emission. *Sens. Actuators, B* **2018**, 265, 691–698

Frank, J.A.; Broichhagen, J.; Yushchenko, D.A.; Trauner, D.; Schultz, C.; Hodson, D.J. Optical tools for understanding the complexity of beta-cell signalling and insulin release. *Nat. Rev. Endocrinol.* **2018**, 14, 721–737.

Afitska, K.; Fucikova, A.; Shvadchak, V.V.; Yushchenko, D.A. Modification of C Terminus Provides New Insights into the Mechanism of alpha-Synuclein Aggregation. *Biophys. J.* **2017**, 113, 2182–2191.

Shvadchak, V.V.; Kucherak, O.; Afitska, K.; Dziuba, D.; Yushchenko, D.A. Environmentally sensitive probes for monitoring protein-membrane interactions at nanomolar concentrations. *Biochim. Biophys. Acta, Biomembr.* **2017**, 1859, 852–859.

Financial support

New strategy for inhibition of amyloid fibril formation. Czech Science Foundation (GA ČR), No. 18-06255Y, 2018–2020, Shvadchak, V.

Uncovering the role of diacylglycerols in regulation of insulin secretion from β-cells. Czech Science Foundation (GA ČR), No. 19-21318S, 2019–2021, Yushchenko, D.

Uncovering Structure-Cytotoxicity Relationship of α-Synuclein Aggregates. IOCB interdisciplinary grant, 2018–2020, Yushchenko, D.

Molecular Fluorescent Probes for Selective Detection of Adenosine-5'-Triphosphate (ATP). Ministry of Education, Youth and Sports (MŠMT), No. 8J19UA048, 2019–2020, Yushchenko, D.

Collaboration

Petr Cígler (IOCB Prague), Petr Bouř (IOCB Prague), Carsten Schultz (OHSU, Portland, USA), David Hodson (IMSR, Birmingham, UK)

Drug Discovery

Pavel Majer
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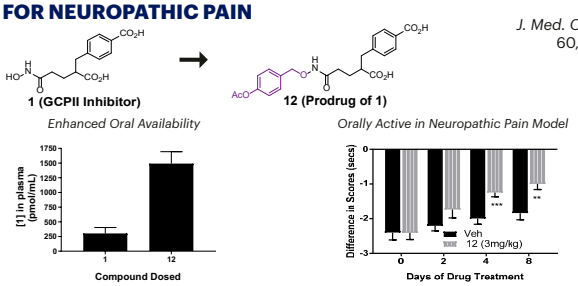
Research-Service Group

drug discovery, prodrug design and synthesis, cancer therapy, cancer cell targeting, custom synthesis of peptides and small molecules, protein sequencing, amino acid analysis, LC-MS analysis of metabolites

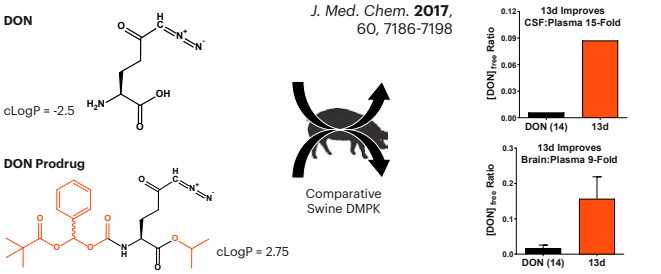
DISCOVERY OF A PARA-ACETOXY-BENZYL PRODRUG OF A HYDROXAMATE-BASED GCP II INHIBITOR AS ORAL THERAPY FOR NEUROPATHIC PAIN

J. Med. Chem. **2017**, 60, 7799-7809



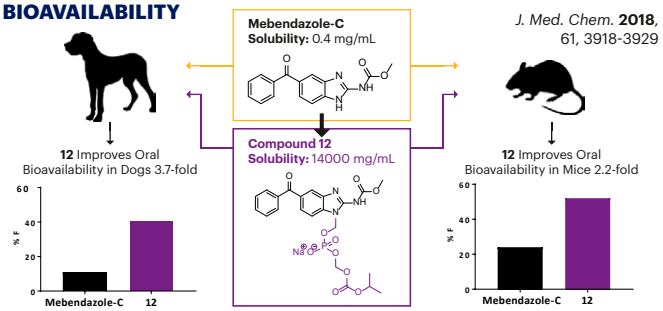
PRODRUGS OF DON AS A POTENTIAL TREATMENT FOR HIV ASSOCIATED NEUROCOGNITIVE DISORDERS

J. Med. Chem. **2017**, 60, 7186-7198



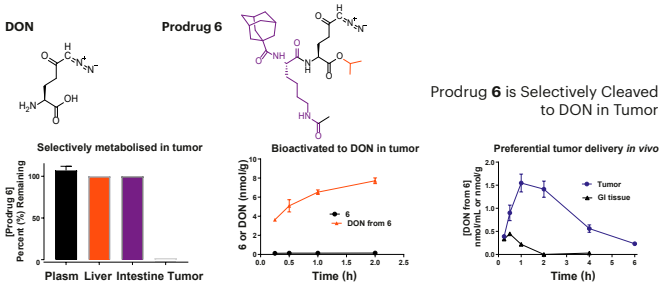
PRODRUGS OF MEBENDAZOLE IMPROVE SOLUBILITY AND ORAL BIOAVAILABILITY

J. Med. Chem. **2018**, 61, 3918-3929



TUMOR-TARGETED DELIVERY OF 6-DIAZO-5-OXO-L-NORLEUCINE (DON)

J. Med. Chem. **2019**, 62, 3524-3538



Research topics

The main mission of the Drug Discovery group is the design and synthesis of biologically active compounds. We collaborate with the Drug Discovery Group at Johns Hopkins University (JHU) in Baltimore, USA, on several projects combining our experience in chemistry with JHU expertise in biology and medicine. Together, we are developing prodrugs of glutamine antimetabolite 6-Diazo-5-oxo-L-norleucine (DON), inhibitors of Glutamate Carboxy Peptidase II (GCPII), Decitabine and Mebendazole. The prodrugs target cancer cells and selectively deliver the active drugs, thus lowering their toxicity. These compounds may find use as novel therapeutics in cancer as well as neurodegenerative and autoimmune diseases. They have been patented, and some of them are currently undergoing preclinical testing.

We collaborate with IOCB groups and provide them with biologically active small molecules and chemical probes, including projects such as iBodies: Modular synthetic antibody mimetics based on hydrophilic polymers decorated with functional moieties (J. Konvalinka); DNA-linked inhibitor antibody assay (DIANA): sensitive and selective enzyme detection and inhibitor screening (J. Konvalinka); Inhibitors of the intramembrane proteases of the rhomboid family (K. Stříšovský); Synthesis of communication substances of social insects (R. Hanus); and Controlling structure and function of biomolecules at the molecular scale (P. Hobza).

Our group also provides several services to IOCB scientists, namely solid phase synthesis of peptides, labeled peptides, substrates, etc. up to approximately 50 AA residues; synthesis of small molecules, mainly enzyme inhibitors with various warheads; qualitative and quantitative amino acid analysis of peptides and proteins; protein and peptide sequencing (standard and micro scale); and metabolic stability assays and metabolite analysis by LC-MS-TOF.

Group members

Group leader Pavel Majer
Scientist Marcela Krečmerová
Associate scientists Martin Maxmilián Kaiser, Aleš Machara, Ivan Šnajdr, Lukáš Tenora, Tomáš Tichý, Stancho Stanchev (guest)
Research assistants Jitka Bařinková, Miroslava Blechová, Martin Hradílek, Radko Souček, Zdeněk Voburka
Ph.D. students Martin Hadzima, Robert Reiberger, Václav Zima
Technician Aleksandrina Prichodko
Students Michaela Baudyšová, Kateřina Novotná

Selected papers

Tenora, L.; Alt, J.; Dash, R.P.; Gadiano, A.J.; Novotná, K.; Veeravalli, V.; Lam, J.; Kirkpatrick, Q.R.; Lemberg, K.M.; Majer, P.; Rais, R.; Slusher, B.S. Tumor-Targeted Delivery of 6-Diazo-5-oxo-l-norleucine (DON) Using Substituted Acetylated Lysine Prodrugs. *J. Med. Chem.* **2019**, 62, 3524–3538.

Zimmermann, S.C.; Tichý, T.; Vávra, J.; Dash, R.P.; Slusher, C.E.; Gadiano, A.J.; Wu, Y.; Jančařík, A.; Tenora, L.; Monincová, L.; Prchalová, E.; Riggins, G.J.; Majer, P.; Slusher, B.S.; Rais, R. N-Substituted Prodrugs of Mebendazole Provide Improved Aqueous Solubility and Oral Bioavailability in Mice and Dogs. *J. Med. Chem.* **2018**, 61, 3918–3929.

Machara, A.; Křivánek, J.; Dolejšová, K.; Havlíčková, J.; Bednárová, L.; Hanus, R.; Majer, P.; Kyjaková, P. Identification and Enantiodivergent Synthesis of (5Z,9S)-Tetradec-5-en-9-olide, a Queen-Specific Volatile of the Termite Silvestritermes minutus. *J. Nat. Prod.* **2018**, 81, 2266–2274.

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Nedelcovych, M.T.; Tenora, L.; Kim, B.-H.; Kelschenbach, J.; Chao, W.; Hadas, E.; Jančařík, A.; Prchalová, E.; Zimmermann, S.C.; Dash, R.P.; Gadiano, A.J.; Garrett, C.; Furtmüller, G.; Oh, B.; Brandacher, G.; Alt, J.; Majer, P.; Volsky, D.J.; Rais, R.; Slusher, B.S. N-(Pivaloyloxy)alkoxy-carbonyl Prodrugs of the Glutamine Antagonist 6-Diazo-5-oxo-l-norleucine (DON) as a Potential Treatment for HIV Associated Neurocognitive Disorders. *J. Med. Chem.* **2017**, 60, 7186–7198.

Rais, R.; Vávra, J.; Tichý, T.; Dash, R.P.; Gadiano, A.J.; Tenora, L.; Monincová, L.; Bařinka, C.; Alt, J.; Zimmermann, S.C.; Slusher, C.E.; Wu, Y.; Wozniak, K.; Majer, P.; Tsukamoto, T.; Slusher, B.S. Discovery of a para-Acetoxy-benzyl Ester Prodrug of a Hydroxamate-Based Glutamate Carboxypeptidase II Inhibitor as Oral Therapy for Neuropathic Pain. *J. Med. Chem.* **2017**, 60, 7799–7809.

Rais, R.; Jančařík, A.; Tenora, L.; Nedelcovych, M.; Alt, J.; Englert, J.; Rojas, C.; Le, A.; Elgogary, A.; Tan, J.; Monincová, L.; Pate, K.; Adams, R.; Ferraris, D.; Powell, J.; Majer, P.; Slusher, B.S. Discovery of 6-Diazo-5-oxo-l-norleucine (DON) Prodrugs with Enhanced CSF Delivery in Monkeys: A Potential Treatment for Glioblastoma. *J. Med. Chem.* **2016**, 59, 8621–8633.

Majer, P.; Jančařík, A.; Krečmerová, M.; Tichý, T.; Tenora, L.; Wozniak, K.; Wu, Y.; Pommier, E.; Ferraris, D.; Rais, R.; Slusher, B.S. Discovery of Orally Available Prodrugs of the Glutamate Carboxypeptidase II (GCPII) Inhibitor 2-Phosphonomethylpentanedioic Acid (2-PMPA). *J. Med. Chem.* **2016**, 59, 2810–2819.

Financial support

Development of GCPII inhibitor prodrugs for treatment of cognitive impairment in multiple sclerosis (collaboration with Johns Hopkins University, Baltimore, USA). National Multiple Sclerosis Society, 2016–2019, Majer, P. (co-PI)

Targeting enzyme exosites by in-situ click chemistry: new strategy for anticancer drug design. Gilead Sciences & IOCB Research Center, 2016–2021, Majer, P. (co-PI)

Chemical Biology Tools for Drug Discovery. Gilead Sciences & IOCB Research Center, 2016–2021, Majer, P. (co-PI)

Tumor targeted prodrugs of glutamine antagonists. Ministry of Education, Youth and Sports (MŠMT), Program INTER-EXCELLENCE, No. LTAUSA18166, 2019-2022, Majer, P.

Czech National Node to the European Infrastructure for Translational Medicine EATRIS-CZ, No. LM201564

Patents and patent applications

[1] Majer, P.; Jančařík, A.; Krečmerová, M.; Tichý, T.; Rais, R.; Slusher, B.S. Prodrugs of prostate specific membrane antigen (PSMA) inhibitor, US 9988407

[2] Majer, P.; Jančařík, A.; Tenora, L.; Rais, R.; Slusher, B.S. Prodrugs of glutamine analogs, US 10336778

[3] Majer, P.; Tenora, L.; Novotna K.; Hudlicky P.; Slusher, B.S. Prodrugs of glutamine analogs, WO 2018144718

[4] Majer, P.; Vávra, J.; Tichý, T.; Jančařík, A.; Tenora, L.; Rais, R.; Slusher, B.S. Prodrugs of hydroxamate-based GCPII inhibitors, WO 2018/094334

[5] Majer, P.; Tenora, L.; Rais, R.; Novotna, K.; Alt, J.; Slusher, B.S. Novel glutamine antagonists and uses thereof, WO 2019071110

[6] Majer, P.; Vávra, J.; Tichý, T.; Jančařík, A.; Tenora, L.; Rais, R.; Slusher, B.S.; Riggins, G. Mebendazole prodrugs with enhanced solubility and oral bioavailability, PCT/US2019/017291

Licenses

Adarga Pharmaceuticals—licensed patent 1 (May 29, 2019)

Dracen Pharmaceuticals—licensed patents and patent applications 2, 3, 5 (December 22, 2017)

Synthesis of Radiolabeled Compounds

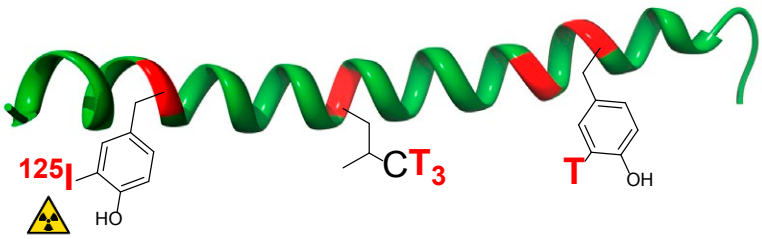
Aleš Marek
ales.marek@uochb.cas.cz
www.uochb.cz/radioisotopes

Service Group

custom synthesis of radioactive molecular tracers, γ/β⁻ label, ^{125}I, ^{3}H, ^{14}C, tritium NMR, radio-HPLC, radioactive waste management, radiation protection & safety training

Peptides labeled by 125-iodine or tritium

Obesity, diabetes and neurodegeneration
[125I]CART(61—102)
[125I]Ghrelin (+ analogs)
etc. (>20 peptides)
Dr. L. Maletínská, IOCB
[125I]Insulin (+ analogs)
[125I]IGF-1 and IGF-2
Dr. J. Jiráček, IOCB



[3H]Inotocine
Medical University of Vienna

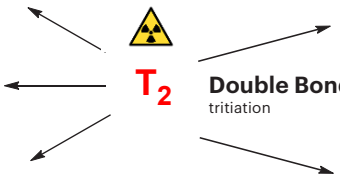
Diabetes research
[3H]Gliadines (19/33 AA)
Bartholin Institute,
Copenhagen, Denmark

Commonly used techniques for tritium labeling in our lab

Substitution / Reduction
tritium reductive dehalogenation

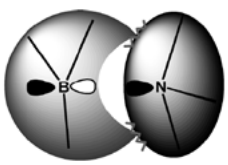
Functional Group Reduction
(metal)tritides

H / T Exchange
Iridium (Kerr-Crabtree)

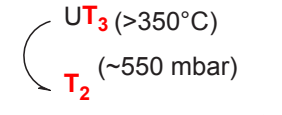


Double Bond
tritiation

Metal-Catalyst tritiation



FLP I



Frustrated Lewis Pairs
assisted activation of T_2 molecule

Research topics

RADIOACTIVE LABELS
Radioactive labels used for the tracing of studied ligands have long been a part of the biochemical laboratory repertoire. Radioactivity gives a clear, unmistakable signal, and its use is straightforward. We are devoted to the supply of radioactively labeled compounds to biochemical research teams of the institute and provide radiometric services, conduct radioactive waste management, and supervise radiation safety rules within the institute.

GAMMA RAY EMITTER—^{125}I
We use an optimized low-cost peptide labeling procedure (up 70 amino acid residues) with the IODO–GEN™–Na[^{125}I] system. Pure mono-iodinated peptides, with specific activities over 2,000 Ci/mmol, are separated from over-iodinated and starting peptides using radio-HPLC.

β⁻ PARTICLE EMITTER—^{3}H (^{14}C)
Tritium/carbon-14 labeling of complex, multifunctional drug candidates requires mild, fast, and safe preparative methods. We have expertise in the handling and introduction of tritium into biologically active molecules using well-established methods and techniques—from simple catalytic hydrogen isotope exchange, reduction of carbon-carbon multiple bonds, and catalytic reductive dehalogenations to reductions with in-house synthesized carrier-free complex metallic tritides. We have been investigating the feasibility of frustrated Lewis pairs (FLP) as mild catalysts, for various tritiations, in the quest for alternative orthogonal tritiation methods. The radiochemical purity of produced tracers is always checked by radio-HPLC, radio-TLC, and ^{3}H NMR spectra.

Group members

Group leader Aleš Marek
Scientist Břetislav Brož
Postdoc Roan Fraser

Selected papers

Al-Khawaja, A.; Haugaard, A.S.; Marek, A.; Löffler, R.; Thiesen, L.; Santiveri, M.; Damgaard, M.; Bundgaard, C.; Frølund, B.; Wellendorph, P. Pharmacological Characterization of [3H]ATPCA as a Substrate for Studying the Functional Role of the Betaine/GABA Transporter 1 and the Creatine Transporter. *ACS Chem. Neurosci.* **2018**, 9, 545–554.

Chrudinová, M.; Žáková, L.; Marek, A.; Socha, O.; Buděšínský, M.; Hubálek, M.; Pícha, J.; Macháčková, K.; Jiráček, J.; Selicharová, I. A versatile insulin analog with high potency for both insulin and insulin-like growth factor 1 receptors: Structural implications for receptor binding. *J. Biol. Chem.* **2018**, 293, 16818–16829.

Marek, A.; Nguyen, H.T.H.; Brož, B.; Tureček, F. Stereospecific control of peptide gas-phase ion chemistry with cis and trans cyclo ornithine residues. *J. Mass Spectrom.* **2018**, 53, 124–137.

Di Giglio, M.G.; Muttenthaler, M.; Harpsøe, K.; Liutkeviciute, Z.; Keov, P.; Eder, T.; Rattei, T.; Arrowsmith, S.; Wray, S.; Marek, A.; Elbert, T.; Alewood, P.F.; Gloriam, D.E.; Gruber, C.W. Development of a human vasopressin V1a-receptor antagonist from an evolutionary-related insect neuropeptide. *Sci. Rep.* **2017**, 7, 41002.

Oklestkova, J.; Tarkowská, D.; Eyer, L.; Elbert, T.; Marek, A.; Smržová, Z.; Novák, O.; Fránek, M.; Zhabinskii, V.N.; Strnad, M. Immunoaffinity chromatography combined with tandem mass spectrometry: A new tool for the selective capture and analysis of brassinosteroid plant hormones. *Talanta* **2017**, 170, 432–440.

Zemenova, J.; Sykora, D.; Adamkova, H.; Maletinska, L.; Elbert, T.; Marek, A.; Blechova, M. Novel approach to determine ghrelin analogs by liquid chromatography with mass spectrometry using a monolithic column. *J. Sep. Sci.* **2017**, 40, 1032–1039.

Collaboration

Petrine Wellendorph, Bente Froelund, Hans Bräuner-Osborne, Lennart Bunch, Daniel S. Pedersen & Darryl S. Pickering (University of Copenhagen, Department of Drug Design and Pharmacology, Denmark)

Frank Turecek (University of Washington, Seattle, USA)

Jana Oklešťková, Miroslav Strnad (Laboratory of Growth Regulators, Institute of Experimental Botany of the CAS & Palacký University Olomouc, Czech Rep.)

Marek Jindra (Laboratory of Developmental Genetics, Institute of Entomology & Biology Center of the CAS, Czech Republic)

Václav Hořejší (Institute of Molecular Genetics of the CAS, Prague, Czech Rep.)

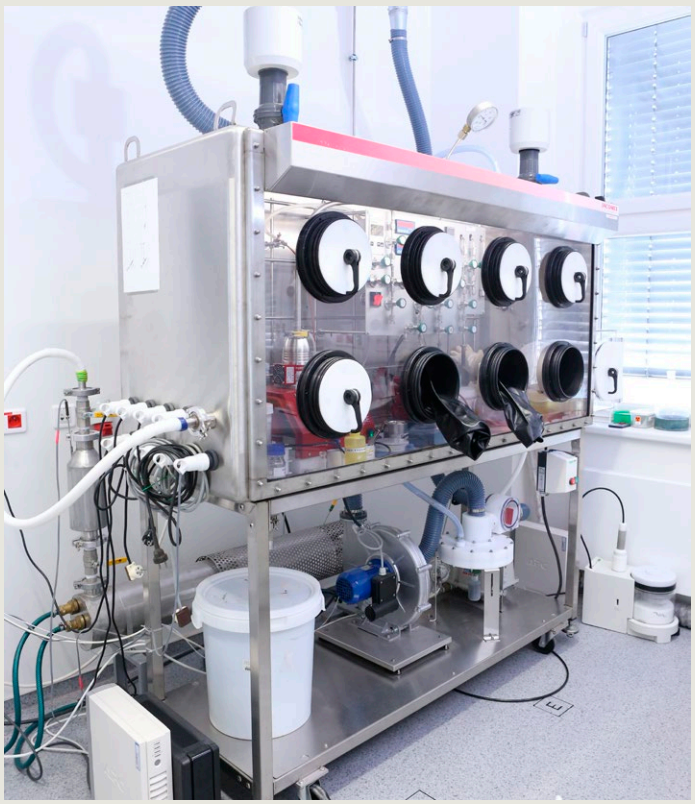
Christian W. Gruber (Center for Physiology and Pharmacology, Medical University of Vienna, Austria)

Instrumentation

The key instrument for tracer synthesis is a glove box with tritiation manifold (RC-TRITEC AG), suitable for handling 100 to 1000 Ci of carrier-free tritium gas.

Radiometric instruments: MicroBeta² Plate Counter for detection beta and gamma isotopes from 96- and 384-well plates. Liquid scintillation analyzer TriCarb 2900TR (Perkin Elmer) for activity assays of small amounts of α, β, and γ emitters. The Gamma Counter Wizard 2470 and Wizard 1470 (both Perkin Elmer). Radio-TLC scanner RITA (RAYTEST). Analytical-preparative radio-HPLC Waters Aliance e2695 and Waters 600, both with radio-detector Ramona. ^{3}H NMR BRUKER Avance II 300 MHz.

The laboratory is classified for handling of the open sources of ionizing radiation in quantities authorized for laboratories of II category according to Czech bylaw 422/2016 Sb for R&D and educational purposes. It is currently authorized to work with the main radioactive isotopes used in research, e.g. ^{3}H, ^{14}C, ^{32}P, ^{33}P, ^{35}S, ^{51}Cr, ^{54}Mn, ^{55}Fe, ^{99}Tc, and ^{125}I.



Cluster

BIO

Gabriel Birkuš Group (HBV Cure)
Evžen Bouřa Group (Structural Membrane Biology)
Hana Cahová Group (Chemical Biology of Nucleic Acids)
Edward Curtis Group (Functional Potential of Nucleic Acids)
Václav Čeřovský (Antimicrobial Peptides)
Robert Hanus Group (Chemistry of Social Insects)
Jiří Jiráček Group (Chemistry and Biology of Insulin and Insulin-Like Growth Factors)
Zuzana Kečkéšová Group (Tumor Suppressors)
Jan Konvalinka Group (Proteases of Human Pathogens)
Lenka Maletínská Group (Pathophysiological Mechanisms of Food Intake Regulation)
Pavlína Maloy Řezáčová Group (Structural Biology)
Michael Mareš Group (Cathepsin Proteases in Pathology)
Iva Pichová Group (Viral and Microbial Proteins)
Kvido Stříšovský Group (Intramembrane Proteolysis and Biological Regulation)
Norbert Weiss Group (Ion Channels and Diseases)

Biochemical Pharmacology (Helena Mertlíková-Kaiserová)
Bioinformatics (Jiří Vondrášek)
Virology (Jan Weber)

Gabriel Birkuš Group

HBV Cure
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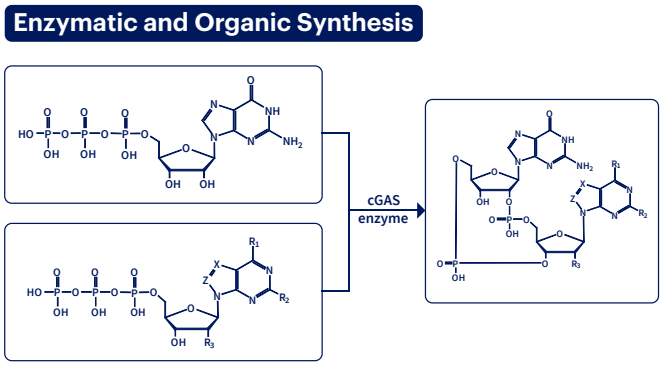
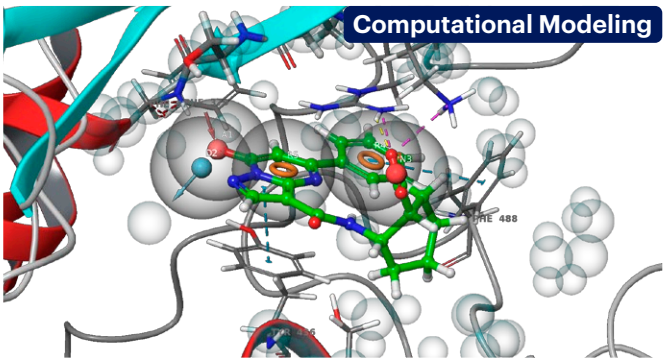
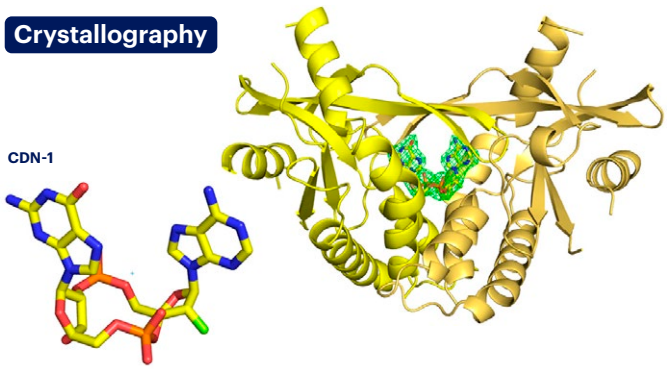
www.uochb.cz/birkus

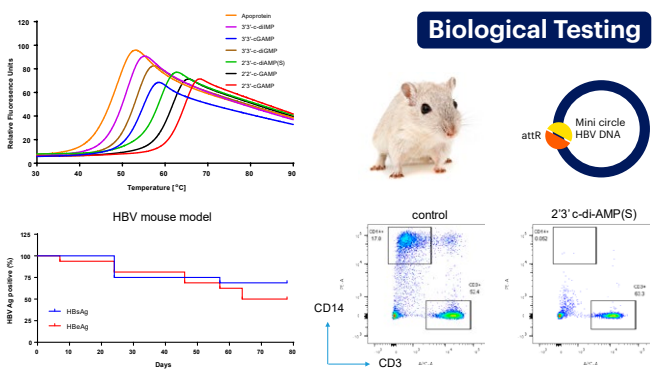
Targeted Research Group

chronic hepatitis B, STING/TMEM173, cGAS, hepatitis B virus, drug discovery, Aicardi-Goutières syndrome









Research topics

We are a cross-functional team consisting of medicinal chemists, virologists, immunologists, computational chemists, and biochemists focused on discovery of novel therapies to treat chronic hepatitis B, cancer, and inflammatory disorders.

In collaboration with our international partners, we are currently involved in the identification of novel agonists and antagonists of the cGAS-STING pathway, which plays a crucial role in the recognition of dsDNA in the cytosol. Activation of the pathway by viral, microbial, or tumor-derived dsDNA results in expression of type I IFNs and other inflammatory cytokines. This ultimately leads to induction of innate and adaptive immune responses enabling clearance of the infection or inhibition of tumor growth. Simultaneously, an abnormal overactivation of the pathway has been implicated in autoimmune disorders such as systemic lupus erythematosus and Aicardi-Goutières syndrome.

We have prepared several classes of novel cyclic dinucleotides (CDNs) with potent agonistic activity toward all STING haplotypes. Besides employing conventional chemical synthesis, we have also utilized enzymatic preparation of CDNs. For that purpose, we identified several promiscuous bacterial and vertebrate cyclic dinucleotide synthases, which have allowed for an efficient, one-step preparation of CDNs from NTP analogues. Moreover, we have developed methods for the synthesis of lipophilic prodrugs of CDNs with improved cellular activity compared to their parents. Currently, we are applying our expertise in drug discovery to identify inhibitors of the enzyme cGAS and antagonists of the STING adaptor protein.

Group members

Group leader Gabriel Birkuš
Scientists Andrea Brázdová, Florian Chevrier, Juraj Dobiaš, Radek Liboska, Jan Lukáš, Ondřej Páv, Ondřej Šimák, Ivan Štěpánek
Ph.D. students Tomáš Jandušík, Markéta Koutová, Markéta Polidarová, Lenka Vaneková, Barbora Vinšová
Technicians Hana Prouzová, Ludmila Tovchigrechko
Students Lucie Černá, Denisa Kučerová, Klára Přibyslavská, Zdeněk Vavřina

Papers & Patents

Birkus, G.; Snyder, C.; Jordan, R.; Kobayashi, T.; Dick, R.; Puscau, V.; Li, L.; Ramirez, R.; Willkom, M.; Morikawa, Y.; Delaney Iv, W. E.; Schmitz, U. Anti-HBV activity of retinoid drugs *in vitro* versus *in vivo*. *Antiviral Res.* 2019, 169, 104538.

Birkus, G.; Pav, O.; Jandusik, T.; Rosenberg, I.; Nencka, R. 2′,2′ cyclic dinucleotides with phosphonate bond activating the STING adaptor protein. (2019) US patent US20190185509.

Birkus, G.; Pav, O.; Jandusik, T.; Rosenberg, I.; Nencka, R. 2′,3′ cyclic dinucleotides with phosphonate bond activating the STING adaptor protein. (2019) US patent US20190185510.

Birkus, G.; Pav, O.; Jandusik, T.; Rosenberg, I.; Nencka, R. 3′,3′ cyclic dinucleotides with phosphonate bond activating the STING adaptor protein. (2019) US patent US20190183917.

Birkus, G.; Pav, O.; Rosenberg, I.; Simak, O. 2′2′-cyclic dinucleotides. (2018) US provisional patent application 62/654045.

Birkus, G.; Pav, O.; Rosenberg, I.; Simak, O. 2′3′-cyclic dinucleotides. (2018) US provisional patent application 62/654054.

Birkus, G.; Pav, O.; Rosenberg, I.; Simak, O. 3′3′-cyclic dinucleotides. (2018) US provisional patent application 62/654058.

Aguayo, E.; Appleby, T.; Birkus, G.; Cheng, G.; Dornan, D.; Kobayashi, T.; Mello, C.C.; Schmitz, U.; Willkom, M.; Yu, M. Methods of treating hepatitis B virus. (2016) WO2016168349A1.

Financial support

Targeting STING for Treatment of CHB and Cancer. Gilead Sciences & IOCB Research Center, 2016–2021, Birkuš, G.

Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022.

Collaboration

Gilead Sciences, Foster City, USA

Center for Innovation and Stimulation of Drug Discovery, Leuven, Belgium

Evžen Bouřa Group

Structural Membrane Biology
evzen.boura@uochb.cas.cz
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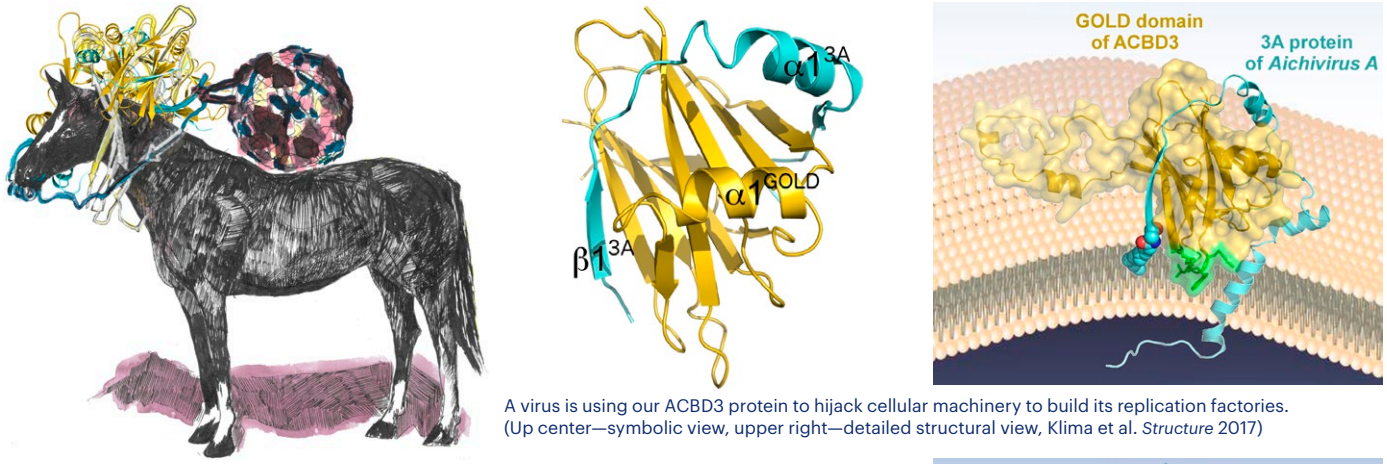
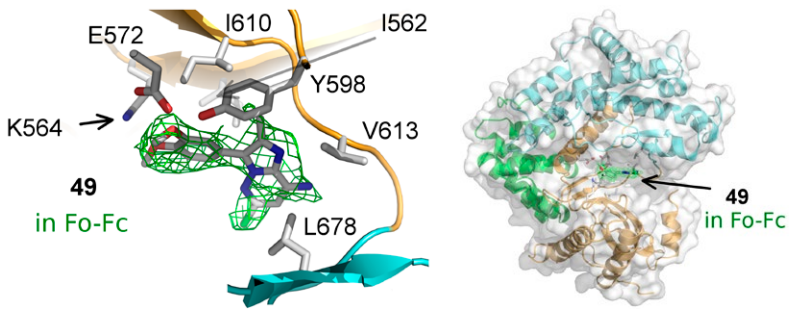
Senior Research Group

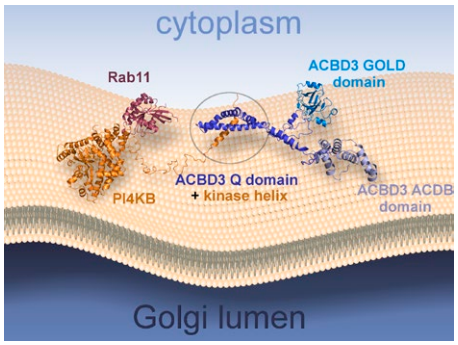
host factors for viral replication, viral polymerases, structural basis for inhibition of viral replication



A virus is using our ACBD3 protein to hijack cellular machinery to build its replication factories. (Up center—symbolic view, upper right—detailed structural view, Klima et al. *Structure* 2017)



PI4KB kinase crystallize with an inhibitor. (Mejdrova et al. *J. Med. Chem.* 2015 and 2017)



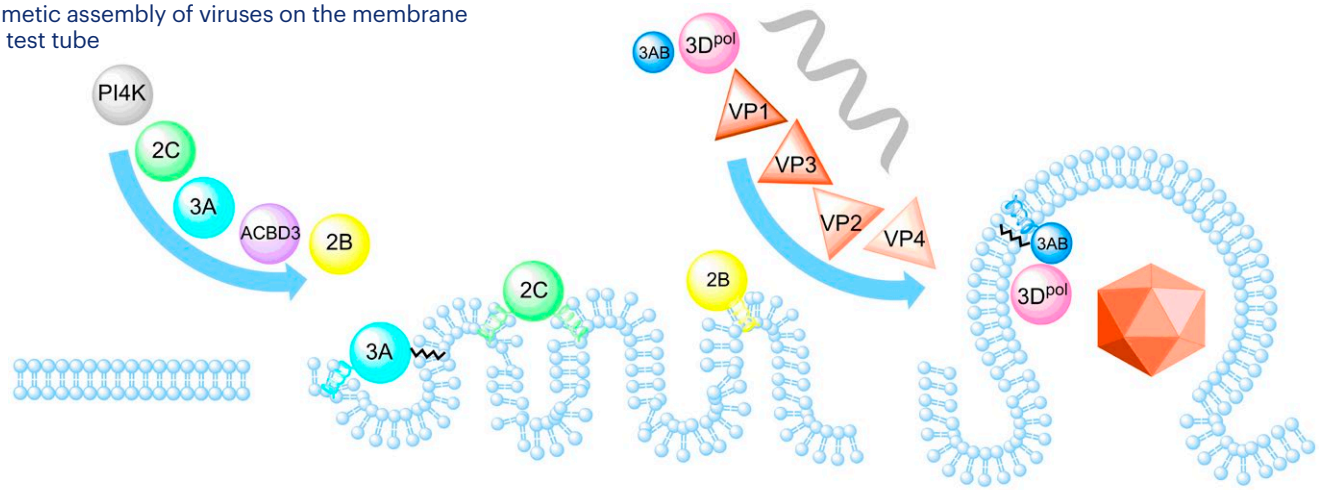
Multi-protein assembly of PI4KB. Pseudo-atomic model based on structural data. (Klima et al. *Sci Rep.* 2016)

Research topics

The way membrane binding proteins assemble into large multi protein complexes that subsequently modify the membrane chemically or physically has always puzzled me. Hijacking of host proteins (especially membrane modifying enzymes) by viruses is another key question that my laboratory aims to answer. We mainly use protein crystallography and other biophysical methods to understand the structure and function of membrane binding proteins in detail.

Recently, we have focused on the phosphatidylinositol 4-kinase B (PI4KB), which is an essential host factor for a variety of +RNA viruses such as HCV, poliovirus, Coxsackie virus, etc. The lipid it produces, phosphatidylinositol 4-phosphate (PI4P), is a hallmark of viral replication organelles (ROs) of these viruses. We have solved the crystal structures of this enzymes with small molecule inhibitors and (in collaboration with the Nencka group) we have used the structural information to develop PI4KB inhibitors that exert nanomolar inhibition activity and have a potential to be used as virostatics. Later, we became interested in a molecular mechanism of PI4KB membrane recruitment by the Golgi resident ACBD3 protein. Currently, we are focusing on the structural basis of viral hijacking of PI4Ks.

Biomimetic assembly of viruses on the membrane in the test tube



Group members

Group leader Evžen Bouřa
Scientists Jana Humpolíčková, Dominika Chalupská, Martin Klíma, Jan Šilhán
Postdocs Jitka Bartošová, Dinesh Dhurvas Chandrasekaran, Pavla Fajtová, Vladimíra Horová, Eva Konkoľová, Petra Krafčíková, Arunima Sikdar
Ph.D. students Anna Dubánková, Andrea Eisenreichová, Andrea Hušková, Kateřina Krejčová, Barbora Landová, Miroslav Smola
Technician Lenka Kloučková
Students Vojtěch Duchoslav, Lucie Pravdová

Selected papers

Klima, M.; Chalupska, D.; Różycki, B.; Humpolickova, J.; Rezabkova, L.; Silhan, J.; Baumlova, A.; Dubankova, A.; Boura, E. Kobuviral Non-structural 3A Proteins Act as Molecular Harnesses to Hijack the Host ACBD3 Protein. *Structure* **2017**, 25, 219–230.

Humpolickova, J.; Mejdrová, I.; Matousova, M.; Nencka, R.; Boura, E. Fluorescent Inhibitors as Tools To Characterize Enzymes: Case Study of the Lipid Kinase Phosphatidylinositol 4-Kinase IIIβ (PI4KB). *J. Med. Chem.* **2017**, 60, 119–127.

Mejdrová, I.; Chalupská, D.; Plačková, P.; Müller, C.; Šála, M.; Klíma, M.; Baumlová, A.; Hřebabecký, H.; Procházková, E.; Dejmek, M.; Strunin, D.; Weber, J.; Lee, G.; Matoušová, M.; Mertlíková-Kaiserová, H.; Ziebuhr, J.; Birkus, G.; Boura, E.; Nencka, R. Rational Design of Novel Highly Potent and Selective Phosphatidylinositol 4-Kinase IIIβ (PI4KB) Inhibitors as Broad-Spectrum Antiviral Agents and Tools for Chemical Biology. *J. Med. Chem.* **2017**, 60, 100–118.

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Financial support

Czech Science Foundation (GA ČR): 19-18917S, 17-21649Y, 17-07058Y, 17-05200S, 15-21030Y

Marie-Curie Actions CIG: StarPI4K #333916

Marie-Curie Actions Global Fellowship to Pavla Fajtová

Collaboration

Dr. Carlson (Umea, Sweden) is an expert in cryo-EM tomography and single particle analysis. And we collaborate, well, in cryo-EM tomography and single particle analysis.

Dr. Balla (Bethesda, USA) is the leading expert in the field of lipid transport. We collaborate on lipid transport via lipid transport proteins.

Prof. van Kuppeveld (Utrecht, Netherlands) is a leading expert in the replication of picornaviruses, in particular on how these viruses trigger membrane deformations involved in the formation of viral replication organelles. We use his expertise to confirm our structural results in vivo.

Dr. Rozycki (Warsaw, Poland) is an expert in the use of molecular dynamics simulations to interpret low resolution structural data. We especially analyze our SAXS (small-angle X-ray scattering) data together.

Hana Cahová Group

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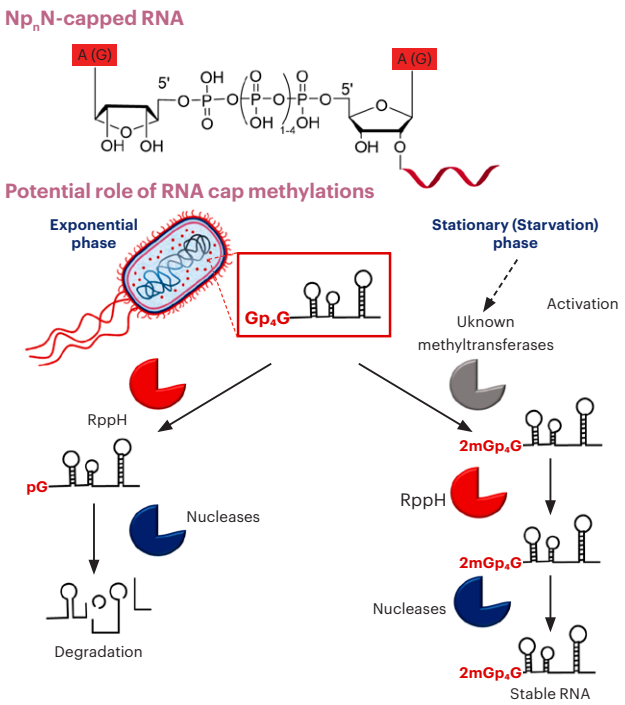
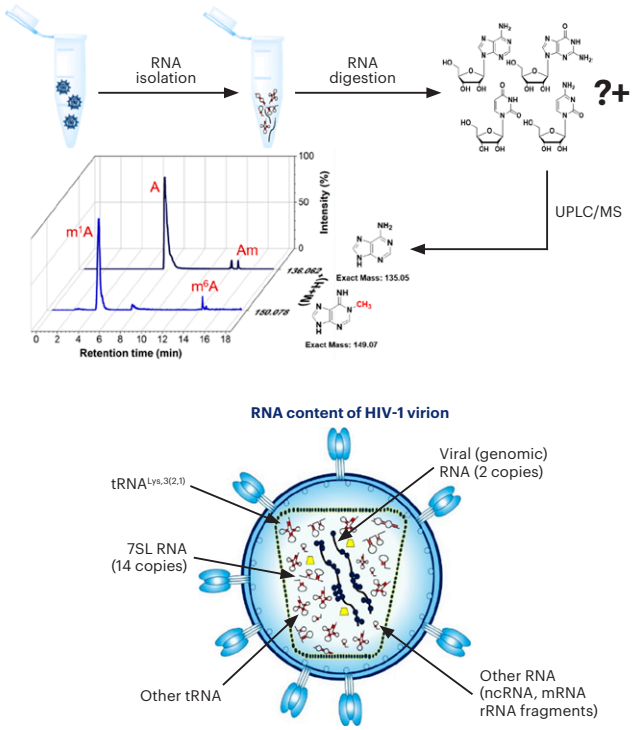
Junior Research Group

RNA cap, RNA modification, viral RNA, bacterial RNA, MS analysis of RNA

STUDIES OF BACTERIAL RNA MODIFICATIONS



STUDIES OF VIRAL RNA MODIFICATIONS



Research topics

The aim of our group is to discover new functions of noncoding mainly regulatory RNAs. We believe that chemical RNA modifications are responsible for the vast majority of various RNA functions. Only a few RNA modifications have been discovered so far in regulatory RNAs, mainly because of the lack of sensitive methods. Recently, UPLC/MS was used to discover two new RNA modifications: NAD and CoA in prokaryotes. Thanks to NAD captureSeq, it was found that NAD is covalently attached to the 5´end of some regulatory RNAs and short fragments of certain mRNAs in prokaryotes and eukaryotes. It was also found that such RNA is more stable and less prone to degradation by exonucleases.

In our recent work, we discovered a brand-new class of RNA caps—dinucleoside polyphosphates in bacteria. We found that dinucleoside polyphosphates are co-transcriptionally incorporated into RNA by RNA polymerases and cleaved by the Nudix enzyme. Further methylations stabilize cap structures and protect RNA from cleavage under stress conditions.

In addition to bacterial RNA, we also study viral RNA. We suggest that viruses are perfect model systems for searching for new eukaryotic RNA modifications, as they have a simple intrinsic organization and are amplified in infected cells. We focus on clinically relevant viral strains (e.g. HIV, picornaviruses, and vaccinia virus) and on the methylation profiling of viral RNA. We are also developing new capturing techniques for known RNA modifications of viral or bacterial RNAs.

Group members

Group leader Hana Cahová
Postdocs Roberto Benoni, Oldřich Hudeček, Mouna Ouchari, Paul Eduardo Reyes Gutierrez, Jana Trylčová
Ph.D. students Marisa Conte, Lucia Fehérová, Maria-Bianca Mititelu, Barbora Svojanovská, Anna Šimonová
Student Jiří Potužník

Selected papers

Hudecek, O.; Benoni, R.; Culka, M.; Hubalek, M.; Rulisek, L.; Cvacka, J.; Cahova, H. Dinucleoside polyphosphates act as 5′-RNA caps in *Escherichia coli*. *bioRxiv* **2019**, 563817.

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Cahová, H.; Jäschke, A. Nucleoside-Based Diarylethene Photoswitches and Their Facile Incorporation into Photoswitchable DNA. *Angew. Chem. Int. Ed.* **2013**, 52, 3186–3190.

CAHOVÁ GROUP
CHEMICAL BIOLOGY IOCB PRAGUE

Financial support

Virification. Ministry of Education, Youth and Sports (MŠMT), ERC CZ project, No. LL 1603, 2017–2021.

Collaboration

Member of COST Action EPITRAN

Pavel Plevka (CEITEC, Brno, Czech Republic)

Jan Pačes (IMG CAS, Prague, Czech Republic)

Štěpánka Vaňáčová (CEITEC, Brno, Czech Republic)

Markéta Hlaváčková (IP CAS, Prague, Czech Republic)

Libor Krásný (MBI CAS, Prague, Czech Republic)

David Staněk (MBI CAS, Prague, Czech Republic)

Awards—Hana Cahová

Neuron Award for Young Scientist in Chemistry (Neuron Foundation), 2018

Alfred Bader Prize for Young Bioorganic Chemist (Czech Chemical Society), 2016

Edward Curtis Group

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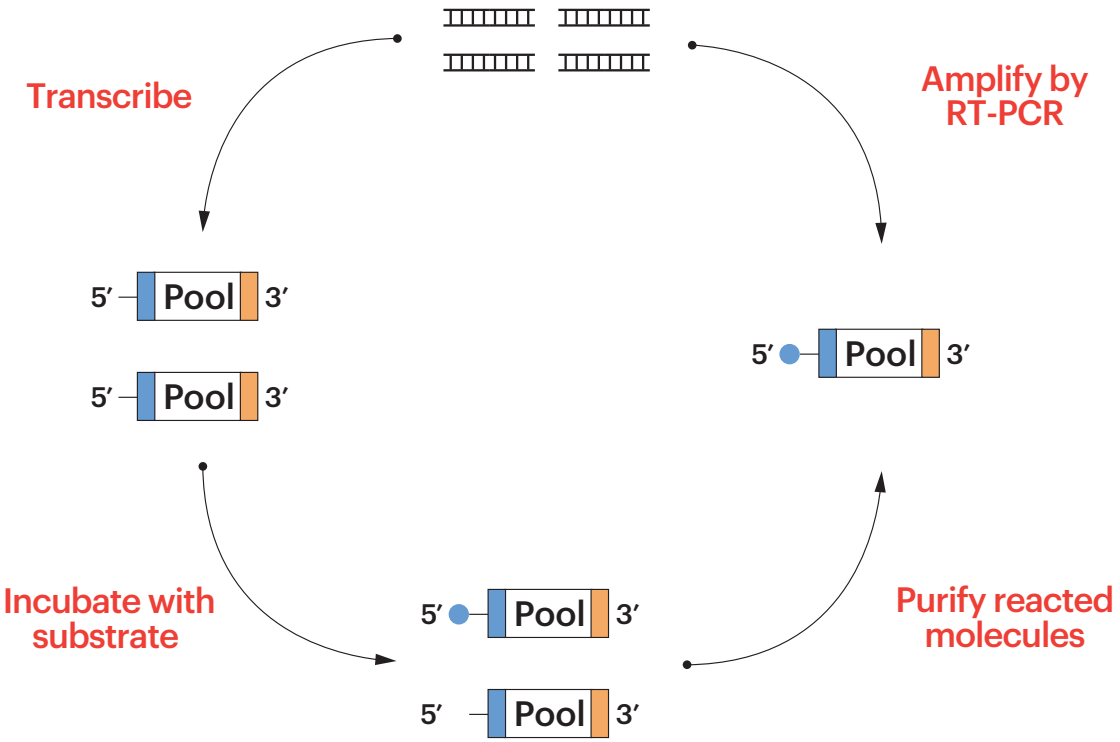
Junior Research Group
ribozyme, deoxyribozyme, *in vitro* selection, functional nucleic acid, biosensor, G-quadruplex

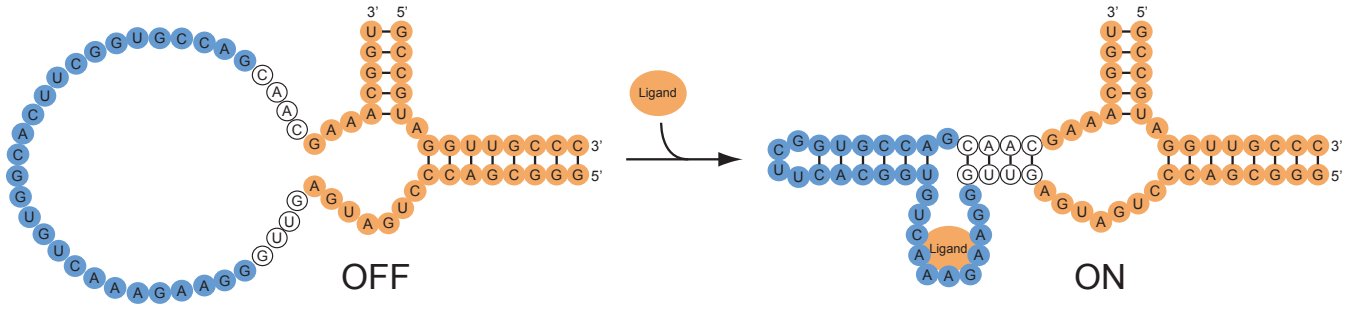
Isolation of catalytic RNA molecules using *in vitro* selection



Research topics

Once thought to function primarily as a passive carrier of genetic information, DNA and RNA molecules are now known to be capable of a wide range of functions. These include the ability to form binding sites for ligands and to catalyze chemical transformations. Nucleic acid molecules with more sophisticated functions have also been identified. Perhaps the most remarkable example is an artificial polymerase ribozyme efficient enough to synthesize smaller catalytic RNA molecules in the presence of the appropriate template. Most of these examples were identified using the technique of *in vitro* selection, in which multiple cycles of selection and amplification are performed to isolate rare molecules with unusual and interesting properties from pools containing up to 10^16 random DNA or RNA sequences. We are interested in using *in vitro* selection and related techniques to learn more about the functional capabilities of both artificial and naturally occurring DNA and RNA molecules. One focus of the group is to identify nucleic acid motifs that can be used as tools in applied and basic research. We are especially interested in generating new signaling components for nucleic acid based sensors. Another is to better understand the functional properties of an unusual type of nucleic acid structure called a G-quadruplex.

An allosterically regulated nucleic acid sensor



An allosterically regulated RNA sensor in which an ATP aptamer (blue) is fused to a self-cleaving ribozyme (orange) via a stem shared by the aptamer and ribozyme (white). In the absence of ligand (left), the aptamer is unstructured, which prevents the shared stem from forming. In the presence of ligand (right), the aptamer adopts a structure which stabilizes the shared stem and activates the self-cleaving ribozyme.

Group members

Group leader Edward Curtis
Ph.D. students Tereza Streckerová, Kateřina Švehlová, Martin Volek
Students Karolína Pšenáková, Revan Rangotis

Selected papers

Majerová, T.; Streckerová, T.; Bednárová, L.; Curtis, E.A. Sequence requirements of intrinsically fluorescent G-quadruplexes. *Biochemistry* **2018**, 57, 4052–4062.

Kolesnikova, S.; Hubálek, M.; Bednárová, L.; Cvačka, J.; Curtis, E.A. Multimerization rules for G-quadruplexes. *Nucleic Acids Res.* **2017**, 45, 8684–8696.

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Financial support

Gilead Sciences & IOCB Research Center

IOCB Interdisciplinary Grant (Structural basis of G-quadruplex biochemical specificity)

European Regional Development Fund (Chemical biology for drugging undruggable targets)

Czech Science Foundation (Making light with DNA)

Collaboration

Professor Michael Lawrence (Harvard, USA)

Dr. Václav Veverka (IOCB Prague, Czech Republic)

Dr. Iva Pichová (IOCB Prague, Czech Republic)

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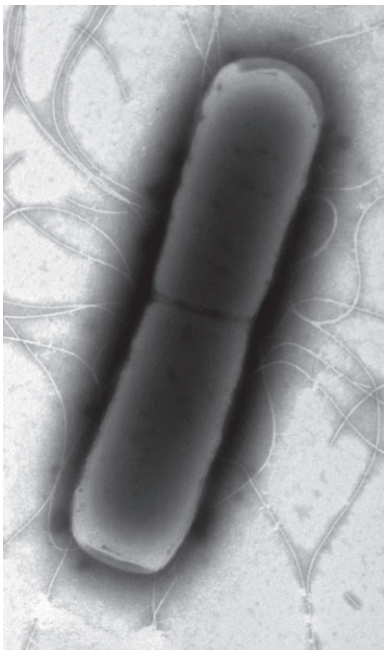
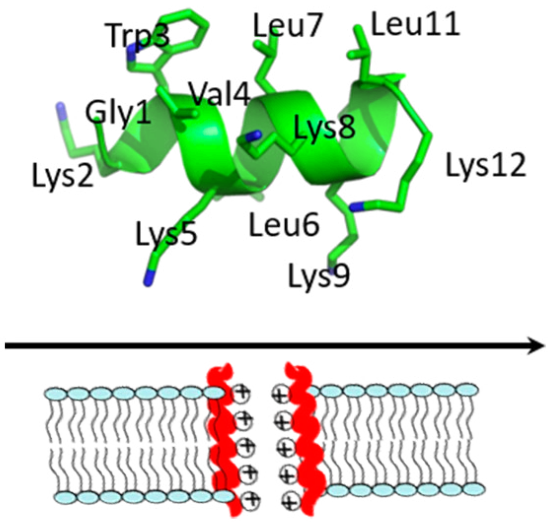
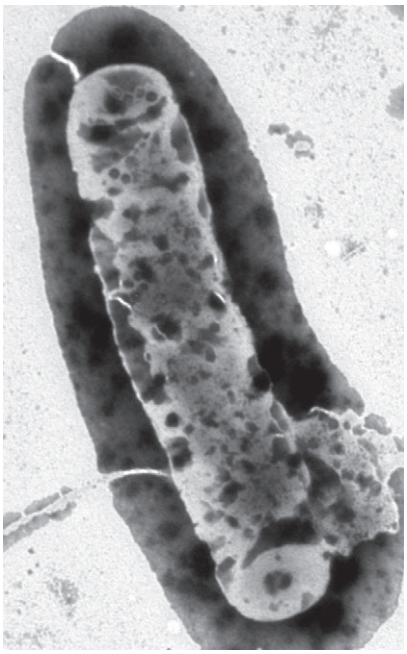
Targeted Research Group

antimicrobial peptides, osteomyelitis, bone, infection, implants, antibiotics







Research topics

Osteomyelitis (bone infection) represents serious complications in orthopedics and traumatology, which may lead to limb amputation or even death. The causative microorganisms of osteomyelitis often develop antibiotic resistance complicating healing processes. Particularly alarming is the emergence of *S. aureus* strains exhibiting resistance to vancomycin, which is frequently used as a drug of last resort. These bacteria may also colonize orthopedic implants in the form of biofilm which can lead to implant loosening and arthrodesis.

In our project, we propose to fill the cavity in an infected bone with local carriers mixed with antimicrobial peptides (AMPs). The significant advantage of AMPs resides in their mechanism of action, which is different from that of conventional antibiotics and is assumed not to develop microbial resistance. In our laboratory, we have identified numerous new AMPs composed of 12–18 amino acid residues that show significant antibacterial and antifungal activities accompanied by varying levels of toxicity to eukaryotic cells. We work with their chemically synthesized analogs which possess high efficacy against resistant pathogens including MRSA, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and the species of *Candida*, while their toxicity is low. We are testing these analogs in a model of osteomyelitis using samples of human bones obtained from the bone collection of Motol University Hospital in Prague.

Our results show that bacterial load in the focus of an infection in a bone is substantially lower after treatment with the peptides incorporated into a local carrier than in the focus treated with antibiotics such as vancomycin or gentamicin. These peptides can also be suitable for preventing infections of orthopedic implants. We proved that bacteria do not adhere to the surface of model implants prepared from bone cement containing AMP when these are implanted into an infected bone.

Group members

Group leader Václav Čeřovský
Postdoc Andrea Volejníková
Research assistant Lenka Borovičková
Ph.D. student Petra Kašparová
Students Nikola Dulíčková, Lada Brázdová

Selected papers

Kočendová, J.; Vaňková, E.; Volejníková, A.; Nešuta, O.; Buděšínský, M.; Socha, O.; Hájek, M.; Hadravová, R.; Čeřovský, V. Antifungal activity of analogues of antimicrobial peptides isolated from bee venoms against vulvovaginal *Candida* spp. *FEMS Yeast Res.* **2019**, 19, foz 013.

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Monincová, L.; Buděšínský, M.; Čujová, S.; Čeřovský, V.; Veverka, V. Structural basis for antimicrobial activity of lasiocepsin. *ChemBioChem* **2014**, 15, 301–308.

Financial support

Novel antimicrobial peptides for topical treatment of osteomyelitis and prevention of implant-related infections in orthopedics. Ministry of Health (MZ), No. 16-27726A, 2016–2019, Čeřovský, V., Melicherčík, P.

Patent

US 10,160,785 (December 25, 2018)
Antimicrobial peptides and their use for the treatment of topical infections
Čeřovský, V.; Nešuta, O.; Dudková, V.; Sychrová, H.; Kodedová, M.

Collaboration

Department of Orthopaedics, First Faculty of Medicine, Charles University in Prague and Motol University Hospital

Robert Hanus Group

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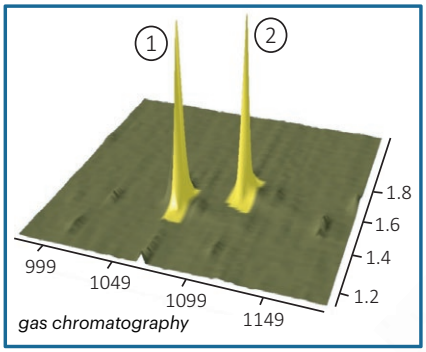
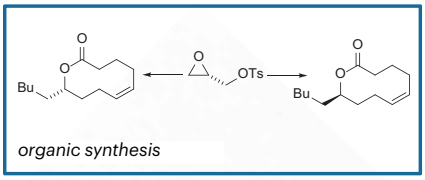
Junior Research Group

social insects, termites, insect chemical defence and communication, biosynthesis, pheromones, defensive chemicals, strategies of reproduction, endocrine signalling, ageing and longevity

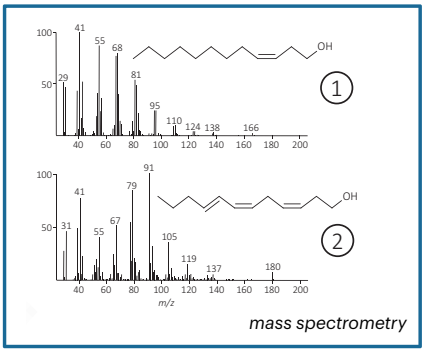


gas chromatography

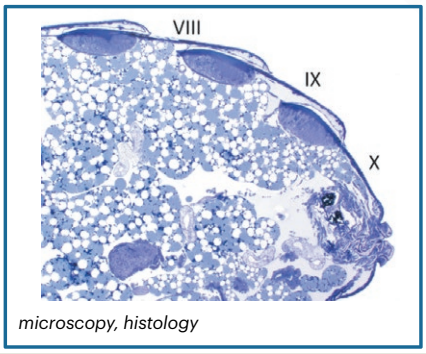


organic synthesis

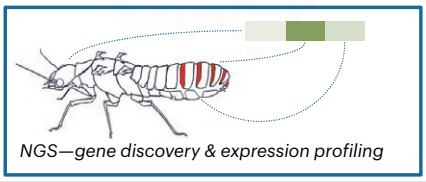

behaviour
communication
development
physiology
reproduction

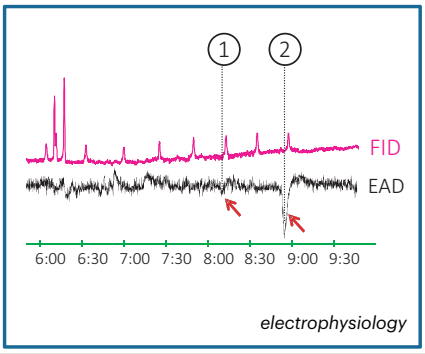


mass spectrometry



microscopy, histology


NGS—gene discovery & expression profiling



electrophysiology

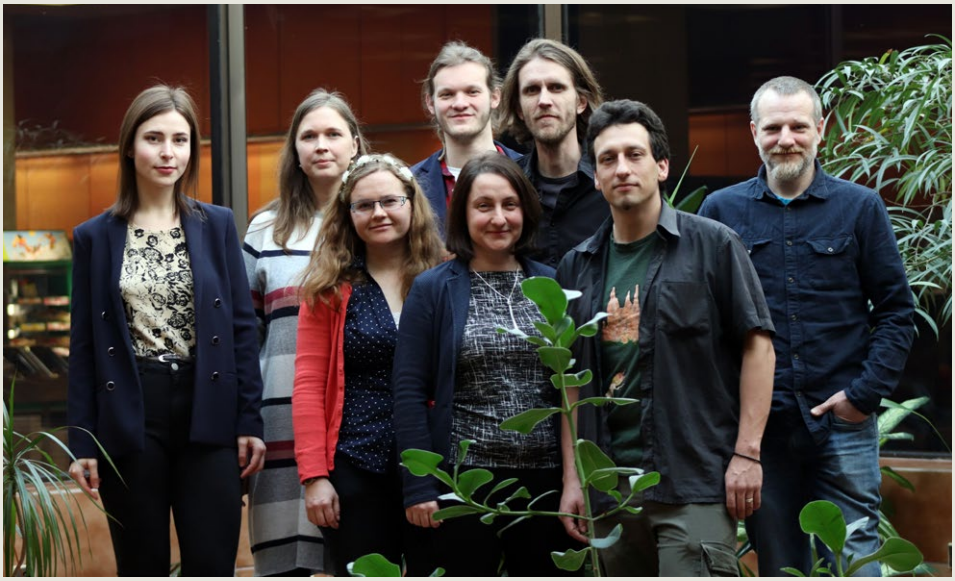
Research topics

CHEMISTRY OF SOCIAL INSECTS
We are interested in the biology, chemical ecology, physiology, and genetics of social insects, especially the termites. Our group consists of researchers and students trained in termite biology, ecology, chemistry of natural compounds, biochemistry, physiology, and molecular genetics. Our running projects can be classified into three categories.

CHEMICAL ECOLOGY
We study the chemical diversity and function of exocrine chemicals, i.e. pheromones and defensive compounds in different species of termites. In addition to descriptions of new structures, we combine our findings on termite chemistry with molecular phylogenetics for chemical taxonomy and identification of new and cryptic species. In selected cases, we search for the biosynthetic pathways that lead to termite-produced chemicals and the underlying enzymes, using a combination of biosynthetic studies and RNA-sequencing.

GENETICS OF REPRODUCTION
We study the genetic architecture of colonies and populations to unravel the mechanisms of gene flow and strategies of reproduction. Following our discovery of mixed reproductive systems in higher termites, combining the sexual reproduction with thelytokous parthenogenesis, we survey for the occurrence of this outstanding reproductive system across the phylogenetic diversity of higher termites.

MECHANISTIC ASPECTS OF LONGEVITY OF TERMITE KINGS AND QUEENS
Due to their extreme lifespan, the kings and queens of termites represent excellent models for studies on somatic maintenance and longevity regulation. We particularly focus on DNA repair and maintenance as well as on endocrine control of differential lifespan in short-lived (workers, soldiers) and long-lived (kings, queens) colony members.



Group members

Group leader Robert Hanus
Scientists Pavlína Kyjaková, Ondřej Lukšan
Postdoc Jana Brabcová
Technicians Jarmila Titzenthalerová
Students Natan Horáček, Jan Křivánek, Marie Pangrácová, Barbora Záková

Selected papers

Bittová, L.; Jedlička, P.; Dračinský, M.; Kirubakaran, P.; Vondrášek, J.; Hanus, R.; Jindra, M. Exquisite ligand stereoselectivity of a *Drosophila* juvenile hormone receptor contrasts with its broad agonist repertoire. *J. Biol. Chem.* **2019**, 294, 410–423.

Dolejšová, K.; Křivánek, J.; Kalinová, B.; Hadravová, R.; Kyjaková, P.; Hanus, R. Sex-pairing pheromones in three sympatric neotropical termite species (Termitidae: Syntermitinae). *J. Chem. Ecol.* **2018**, 44, 534–546.

Machara, A.; Křivánek, J.; Dolejšová, K.; Havlíčková, J.; Bednárová, L.; Hanus, R.; Majer, P.; Kyjaková, P. Identification and enantiodivergent synthesis of (5Z,9S)-tetradec-5-en-9-olide, a queen-specific volatile of the termite *Silvestritermes minutus*. *J. Nat. Prod.* **2018**, 81, 2266–2274.

Fougeyrollas, R.; Křivánek, J.; Roy, V.; Dolejšová, K.; Frechault, S.; Roisin, Y.; Hanus, R.; Sillam-Dussès, D. Asexual Queen Succession mediates an accelerated colony life cycle in the termite *Silvestritermes minutus*. *Mol. Ecol.* **2017**, 26, 3295–3308.

Jirošová, A.; Jančařík, A.; Menezes, R.C.; Bazalová, O.; Dolejšová, K.; Vogel, H.; Jedlička, P.; Buček, A.; Brabcová, J.; Majer, P.; Hanus, R.; Svatoš, A. Co-option of the sphingolipid metabolism for the production of nitroalkene defensive chemicals in termite soldiers. *Insect Biochem. Mol. Biol.* **2017**, 82, 52–61.

Jirošová, A.; Sillam-Dussès, D.; Kyjaková, P.; Kalinová, B.; Dolejšová, K.; Jančařík, A.; Majer, P.; Cristaldo, P.F.; Hanus, R.: Smells like home: chemically mediated co-habitation of two termite species in a single nest. *J. Chem. Ecol.* **2016**, 42, 1070–1081.

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Financial support

Evolutionary trends in chemical and mechanical defence in the termite subfamily Termitinae. Czech Science Foundation (GA ČR), 2013–2015, Kyjaková, P. (PI)

Biogenesis of (E)-1-nitropentadec-1-ene in soldiers of the termite genus *Prorhinotermes*. Czech Science Foundation (GA ČR), 2013–2015, Jirošová, A. (PI)

Regulation of reproduction in higher termites (Termitidae). Grant Agency of Charles University, 2013–2015, Dolejšová, K. (PI)

Reproductive regulation and fertility signalling in higher termites (Termitidae). Czech Science Foundation (GA ČR), 2014–2016, Hanus, R. (PI)

Facultative parthenogenesis as a part of reproductive strategies in higher termites. Grant Agency of Charles University, 2015–2016, Křivánek, J. (PI)

Phylogenetic distribution and cytogenetic mechanisms of facultative parthenogenesis in higher termites. Czech Academy of Sciences + Fonds National de la Recherche Scientifique (Belgium), Mobility Plus program, 2017–2019, Hanus, R. (PI)

Mechanistic aspects of extended longevity of termite kings and queens. Czech Science Foundation (GA ČR), 2018–2020, Hanus, R. (PI)

Collaboration

Prof. Yves Roisin et al. (Evolutionary Biology and Ecology, Université Libre de Bruxelles, Belgium)

Dr. Virginie Roy (Université Paris-Est, Créteil, France)

Dr. Aleš Svatoš (Max Planck Institute for Chemical Ecology, Jena, Germany)

Prof. Marek Jindra & Dr. David Doležel (Biology Centre of the CAS, České Budějovice, Czech Republic)

Dr. Pavel Majer et al. (IOCB Prague, Czech Republic)

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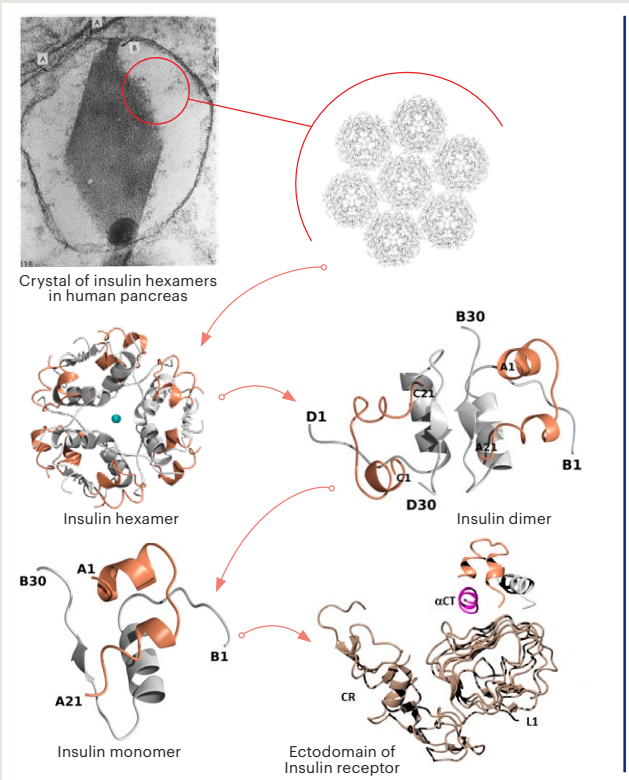
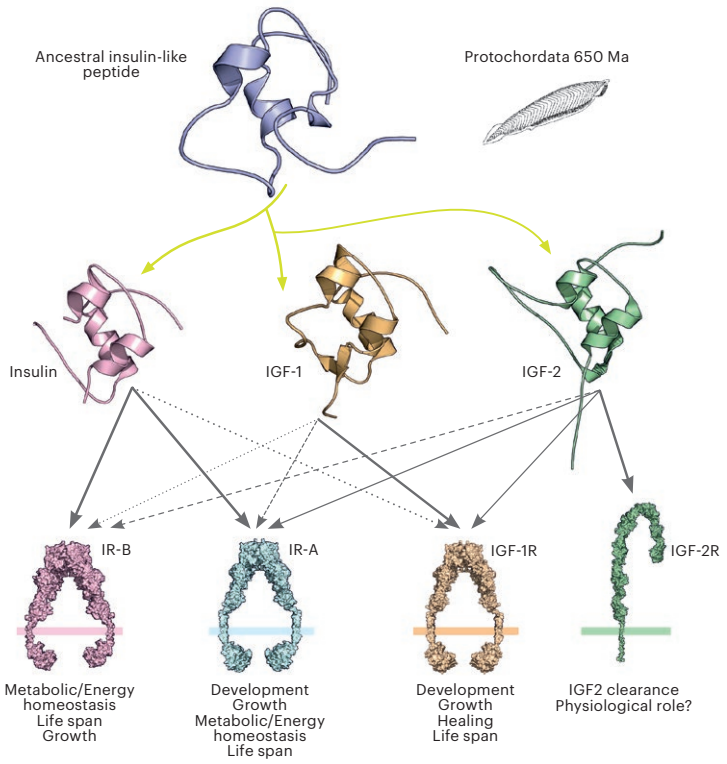
Senior Research Group

insulin, IGF-1/2, analog, peptidomimetics, tyrosine kinase receptor, drug discovery, medicinal chemistry, structure-activity relationship, diabetes, growth, insulin secretory granules





Research topics

Our research group is interested in all aspects of insulin and insulin-like growth factors 1 and 2 (IGF-1/2) physiology.

These important hormones share similar 3D structures and cell membrane receptors; two isoforms of an insulin receptor (IR-A and IR-B) and receptors for IGF-1 (IGF-1R) and IGF-2 (IGF-2R). Insulin and IGFs cross-bind to these receptors with different affinities and trigger distinct but overlapping physiological effects; predominantly metabolic for insulin and predominantly mitogenic for IGFs. Hence, insulin, IGFs and their receptors form a complex system that plays a major role in the regulation of metabolism, growth, development, healing, and lifespan. In addition, it has a role in the development of cancer, diabetes, and growth-related and neurological diseases.

Our general goal in insulin and IGF research is understanding the structural basis for the different cellular responses, metabolic and mitogenic, generated by insulin and IGFs. We synthesize analogs of insulin and IGFs to study their interactions with cognate receptors and to develop new drugs for the treatment of diabetes, cancers, and neurological disorders. We are also involved in the development of insulin/IGF mimetics and in the study of structural forms of insulin in pancreatic secretory granules.

Our group comprises biochemists and organic chemists and combines chemical synthesis with biochemical approaches. We collaborate closely with structural biologists at the University of York in the UK.

Group members

Group leader Jiří Jiráček
Scientists Jan Hajduch, Jan Pícha, Irena Selicharová, Lenka Žáková
Postdoc Benjamin Fabre
Research assistants Jingjing Lin, Katarína Mitrová
Ph.D. students Seiya Asai, Martina Chrudinová, Květoslava Křížková, Terezie Páníková, Pavlo Potalitsyn
Technician Jitka Viková
Students Michaela Křivská, Denisa Zrubecká

Selected papers

Chrudinová, M.; Žáková, L.; Marek, A.; Socha, O.; Buděšínský, M.; Hubálek, M.; Pícha, J.; Macháčková, K.; Jiráček, J.; Selicharová, I. A versatile insulin analog with high potency for both insulin and insulin-like growth factor 1 receptors: Structural implications for receptor binding. *J. Biol. Chem.* **2018**, 293, 16818–16829.

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Financial support

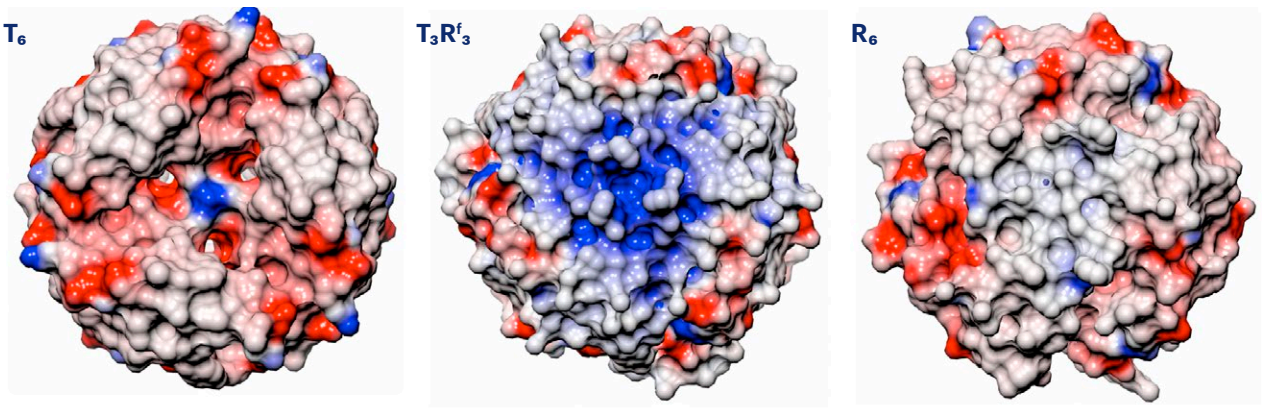
A molecular dissection of the interplay between diabetes and cancer: an integrated, multidisciplinary approach II. Medical Research Council (MRC, UK), No. MR/R009066/1, 2018–2020, Jiráček, J. (co-PI) and Brzozowski, A.M. (PI).

Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022.

The structure-activity study of peptides derived from pro-IGF2 playing a role in the pathogenesis of cancer, type 2 diabetes and osteoporosis. Czech Science Foundation (GA ČR), No. 19-14069S, 2019–2021, Žáková, L. (PI)

Collaboration

York Structural Biology Laboratory, Department of Chemistry, University of York, Heslington, York, UK



Different structural forms of insulin hexamers. From Palivec et al. *J. Biol. Chem.* **2017**, 292, 8342–8355.

Zuzana Kečkéšová Group

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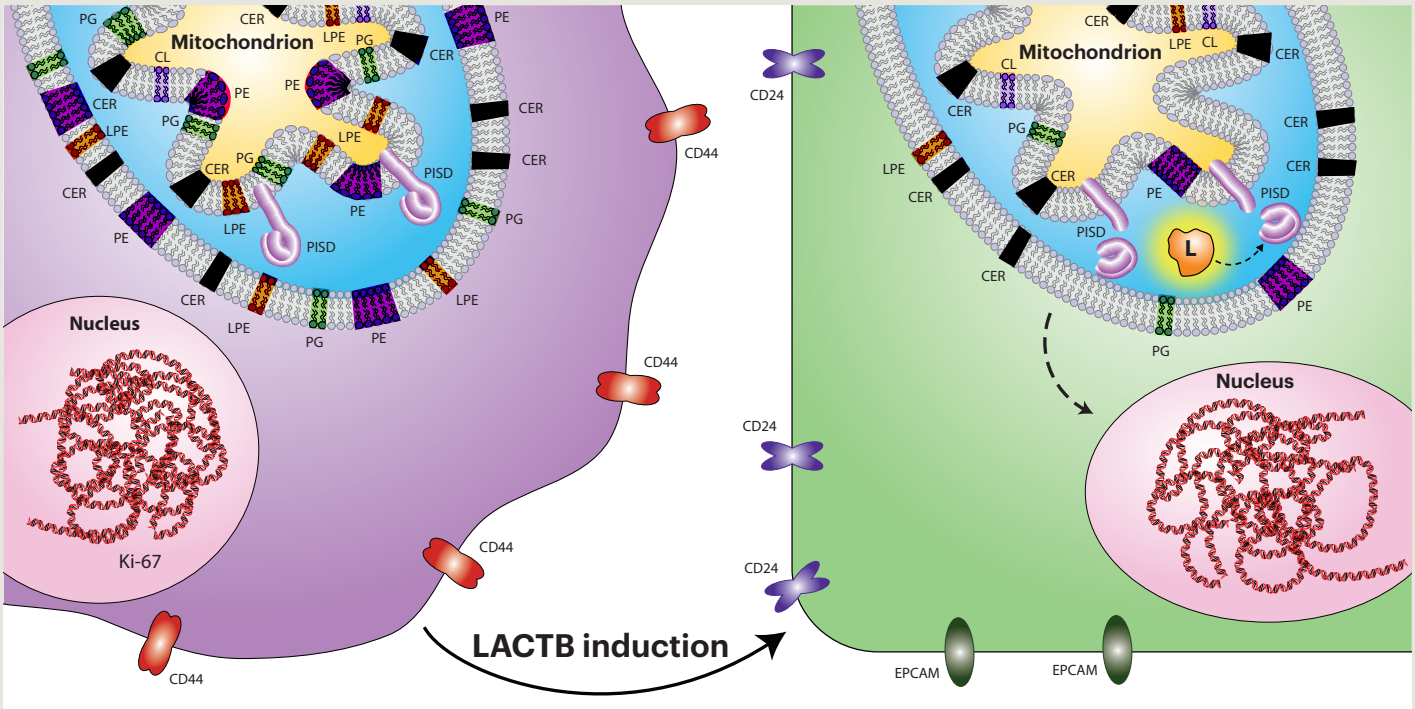
Junior Research Group
cancer research, tumor suppressors, differentiation, cancer stem cells, postmitotic tissues, mitochondria, lipids, cell signaling, breast cancer

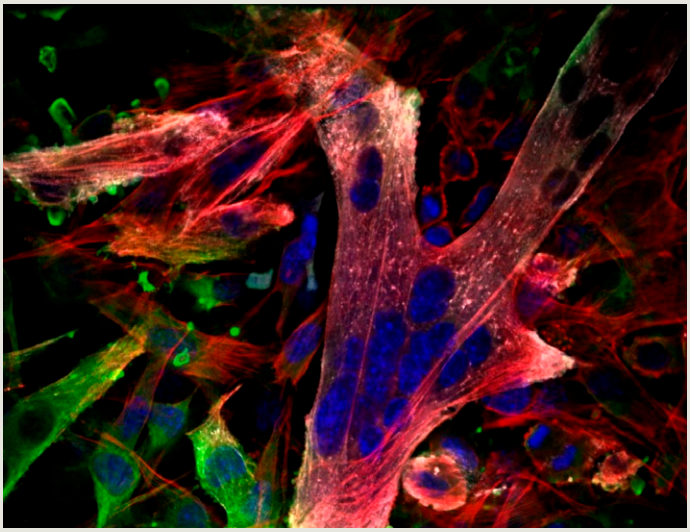


Research topics

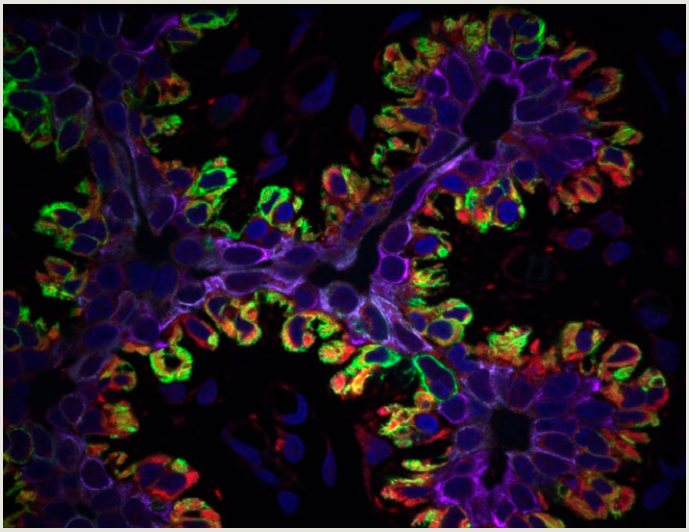
The aim of Dr. Zuzana Keckesova's lab (Zuzu Lab) is to identify and characterize new tumor suppressor pathways and circuitries in human cells with the ultimate goal of translating this new knowledge into therapeutic use. Dr. Keckesova's lab is researching tissues/cell types that rarely undergo tumorigenesis. These are the cellular models that have already found a way to battle cancer and can provide us with important knowledge on how to fight cancer in tissues that are susceptible to it.

Based on studies in these cell types, we have recently determined that lactamase B (LACTB) is a novel mitochondrial tumor suppressor that acts through reprogramming of cancer metabolism. We demonstrated that LACTB is an enzyme with the ability to perturb mitochondrial lipid metabolism and, through such reprogramming, to modulate the differentiation state of cancer cells. This is achieved through the downregulation of the lipid-synthesizing mitochondrial phosphatidylserine decarboxylase (PISD) enzyme, which leads to subsequent changes in the levels of mitochondrial lyso-phosphatidylethanolamine (LPE) and phosphatidylethanolamine (PE) (1). While our work has shown important aspects of the LACTB mechanism, it has yet to provide a deeper mechanistic insight into the regulation of LACTB, identity of the LACTB substrate, and the role of glucose and lipid metabolism in the differentiation program of cancer cells. This will allow us to uncover additional factors and circuitries involved in the differentiation of cancer cells, the knowledge of which can help us design new approaches for therapeutic differentiation and the subsequent elimination of cancer stem cells.

In parallel with examining the LACTB mechanism, we are also trying to characterize several new tumor suppressors, which we discovered in tumor-resistant tissues, and their mechanisms.



Human muscle cell differentiation



Human mammary gland

Group members

Group leader Zuzana Kečkésová
Scientist Beata Malčeková
Postdocs Pavel Marášek, Juan Morena, Valentina Cutano
Student Alžběta Baudyšová

Selected papers

Kečkésová, Z.; Donaher, J.L.; De Cock, J.; Freinkman, E.; Lingrell, S.; Bachovchin, D.A.; Bierie, B.; Tischler, V.; Noske, A.; Reinhardt, F.; Thiru, P.; Golub, T.R.; Vance, J.E.; Weinberg, R.A. LACTB is a tumor suppressor that modulates lipid metabolism and cell state. *Nature* **2017**, 543, 681–686.

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Financial support

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EMBO Installation Grant, 2018–2020/2022.

BPD private funding, 2018–2022.

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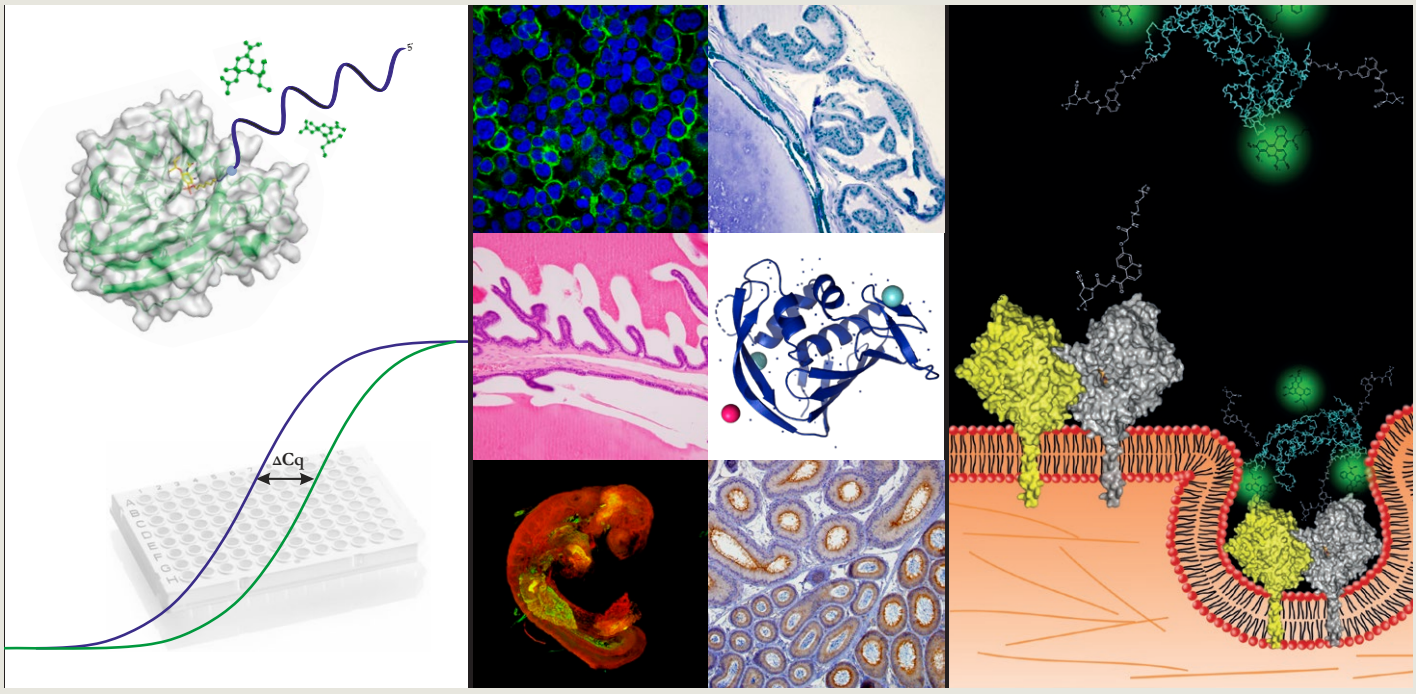
Senior Research Group

therapeutic targets, HIV maturation, glutamate carboxypeptidase II, DNA damage-inducible protein, influenza neuraminidase and polymerase, molecular tools



Research topics

The main mission of the group is to identify, characterize, and exploit enzymes, predominantly proteases, as targets for therapeutic intervention. Along the way, we also develop novel chemical tools for molecular characterization of complex biological processes.

The proteins we work on involve well-established and proven therapeutic targets, such as HIV protease and the complex process of HIV processing and maturation, or glutamate carboxypeptidase II, a cancer marker and a neuropeptidase. We also pursue novel pathways to combat viral replication, such as protein-protein interaction of the subunits of influenza polymerase. Finally, we also evaluate the potential of novel, poorly characterized proteins with potential proteolytic activity, such as DNA damage-inducible protein 1 or 2, as therapeutic targets. For their structural and functional characterization, we use a vast array of methods, from X-ray and NMR structure determination and ITC to recombinant DNA technology, mammalian cell cultures, and mouse models.

In order to visualize and quantify our target proteins, we recently developed synthetic antibody-like polymer scaffolds containing a specific ligand of the particular protein ("molecular address"), affinity anchor (typically biotin moiety), and an imaging marker (fluorescent probe) attached to a hydrophilic copolymer. This versatile, easy to assemble scaffold called iBody is able to replace a monoclonal antibody in a number of *in vitro* and *in vivo* applications. Furthermore, we developed a novel assay for detecting enzymes as diagnostic markers and identifying enzyme inhibitors in drug development. The system called DIANA enables quantification of zeptomolar amounts of enzymes and high-throughput screening of potential inhibitors.

The group enjoys a number of national and international collaborations, most notably with the groups of Hans-Georg Kräusslich at the University of Heidelberg and Barbara Slusher at Johns Hopkins University in Baltimore.

Group members

Group leader Jan Konvalinka
Scientists Klára Hlouchová, Milan Kožíšek, Taťána Majerová, Pavel Šácha, Klára Grantz Šašková, Tereza Ormsby, Jana Pokorná
Postdocs Adriana Bäumlová, Irina Kontsevaya, Lenka Šlachtová
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Technicians & Research assistants Jitka Krčmářová, Jana Starková, Karolína Šrámková
Students Michael Adámek, Tereza Gistrová, Karolína Janoušková, Ivana Klikarová, Anežka Kramná, Vojtěch Kramný, Eliška Krýsová, Robin Kryštůfek, Jaroslav Kurfürst, Pavel Novotný, Martin Pehr, Magdalena Poukarová, Natan Sidej, Jakub Staníček, Lenka Šimonová, Kristýna Šmilauerová, Filip Trajhan, Vyacheslav Tretyachenko

Selected papers

Šimon, P.; Knedlík, T.; Blažková, K.; Dvořáková, P.; Březinová, A.; Kostka, L.; Šubr, V.; Konvalinka, J.; Šácha, P. Identification of Protein Targets of Bioactive Small Molecules Using Randomly Photomodified Probes. *ACS Chem. Biol.* **2018**, 13, 3333–3342.

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Navrátil, V.; Schimer, J.; Tykvart, J.; Knedlík, T.; Vik, V.; Majer, P.; Konvalinka, J.; Šácha, P. DNA-linked Inhibitor Antibody Assay (DIANA) for sensitive and selective enzyme detection and inhibitor screening. *Nucleic Acids Res.* **2017**, 45, e10.

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Financial support

Macromolecular conjugates for targeted drug delivery, imaging, and isolation of proteins based on hydrophilic polymers decorated by functional moieties. Czech Science Foundation (GA ČR), No. 16-02938S, 2016–2018, Konvalinka, J. (PI)

Novel concepts for the therapeutic targeting of tumor microenvironment in human glioblastomas. Ministry of Health (MZ), No. 15-31379A, 2015–2019, Konvalinka, J. (co-PI)

InterBioMed, National Programme for Sustainability I (NPU I). Ministry of Education, Youth and Sports (MŠMT), No. LO1302, 2014–2019, Konvalinka, J.

Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022, Konvalinka, J.

Molecules for Life. Gilead Sciences & IOCB Research Center, 2017–2021, Konvalinka, J.

DIANA—the analytical method for the determination of enzyme inhibition. Czech Science Foundation (GA ČR), No. 19-10280S, 2019–2021, Šácha, P. (PI)

Awards

Jan Konvalinka: Datta Medal awarded for outstanding achievement in the field of biochemistry and molecular biology or a related area (43rd FEBS Congress in Prague, 2018, Czech Republic)

Václav Navrátil, Pavel Šácha, Jiří Schimer, Jitka Zemanová: Werner von Siemens Award for the most significant result in the field of development and innovation 2017—Development of technology for ultrasensitive quantification of enzymes and identification of their inhibitors (Siemens Česká republika)

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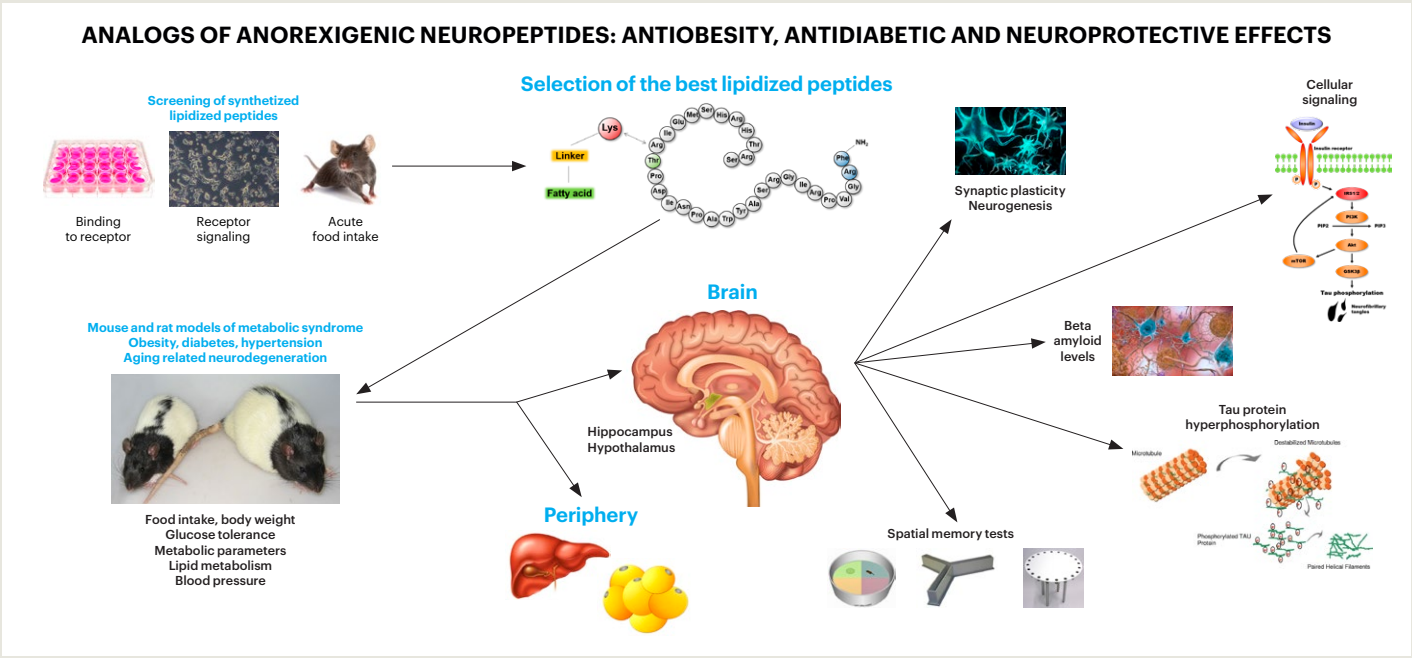
Senior Research Group

anorexigenic neuropeptides, obesity, metabolic syndrome, diabetes, neurodegeneration, prolactin-releasing peptide, lipopeptide, CART peptide, ghrelin analogs



Research topics

Our multidisciplinary research involving peptide chemistry, biochemistry, physiology, and pharmacology is focused on food intake regulation with the aim of developing new pharmacological interventions for obesity and related conditions.

Recently discovered anorexigenic neuropeptides, such as prolactin-releasing peptide (PrRP) and cocaine and amphetamine-regulated transcript (CART) peptide, represent new trends in the development of anti-obesity agents. They directly target the brain areas regulating food intake and are non-toxic but generally do not cross the blood-brain barrier if administered peripherally. We designed stable lipidized analogs of PrRP with an agonistic effect capable of crossing the blood-brain barrier. These analogs have prolonged half-lives in blood and exert anti-obesity and antidiabetic effects after peripheral administration in mice and rats with diet-induced obesity and insulin resistance. For CART peptide, its receptor has not been discovered; however, we identified its possible signaling pathway JNK-c-Jun in PC12 cells, where we previously found CART peptide specific binding sites, potential receptors.

Type 2 diabetes and obesity were shown to be risk factors for Alzheimer's disease (AD), thus compounds with glucose-lowering and/or anorexigenic properties were proposed to have neuroprotective properties. We demonstrated that PrRP is a potential neuroprotective tool improving spatial memory and attenuated Tau hyper-phosphorylation in THY-Tau22 mice and reducing β-amyloid (Aβ) plaques in APP/PS1 mice. Aβ plaques and Tau hyper-phosphorylation are hallmarks of AD.

Ghrelin is the only orexigenic peptide of gut origin. Its agonists represent a possible method for treating muscle wasting syndrome and cachexia. We designed several potent stable orexigenic analogs of ghrelin and tested them in mice with LPS-induced cachexia, where they significantly increased food intake and normalized blood levels of proinflammatory cytokines, showing the anti-cachectic potential of the analogs.

Group members

Group leader Lenka Maletínská
Scientists Jaroslav Kuneš, Zdenko Pirník, Blanka Železná
Postdocs Michal Bencze, Martina Holubová, Miroslava Kacířová, Barbora Neprašová, Andrea Popelová, Veronika Pražienková
Research assistants Lucie Hrubá, Martina Kojecká
Ph.D. students Lucia Kořínková, Anna Zmeškalová
Technician Hedvika Vysušilová
Students Aneta Exnerová, Anna Freislebenová, Alena Karnošová, Veronika Miklasová, Anna Neužilová

Selected papers

Čermáková, M.; Pelantová, H.; Neprašová, B.; Šedivá, B.; Maletínská, L.; Kuneš, J.; Tomášová, P.; Železná, B.; Kuzma, M. Metabolomic Study of Obesity and Its Treatment with Palmitoylated Prolactin-Releasing Peptide Analog in Spontaneously Hypertensive and Normotensive Rats. *J. Proteome Res.* **2019**, 18, 1735–1750.

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Pražienková, V.; Holubová, M.; Pelantová, H.; Bugáňová, M.; Pirník, Z.; Mikulášková, B.; Popelová, A.; Blechová, M.; Haluzík, M.; Železná, B.; Kuzma, M.; Kuneš, J.; Maletínská, L. Impact of novel palmitoylated prolactin-releasing peptide analogs on metabolic changes in mice with diet-induced obesity. *PLOS ONE* **2017**, 12, e0183449.

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Holubová, M.; Zemenová, J.; Mikulášková, B.; Panajotova, V.; Stöhr, J.; Haluzík, M.; Kuneš, J.; Železná, B.; Maletínská, L. Palmitoylated PrRP analog decreases body weight in DIO rats but not in ZDF rats. *J. Endocrinol.* **2016**, 229, 85–96.

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Financial support

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Neuroprotective effects of novel analogs of anorexigenic prolactin-releasing peptide (PrRP) in mouse models of neurodegeneration and obesity. Czech Science Foundation (GA ČR), No. 16-00918S, 2016–2018, Maletínská, L.

Center for development of original drugs. Technology Agency of the Czech Republic (TA ČR), No. TE01020028, 2012–2019, Havlas, Z.

The role of prolactin-releasing peptide in obesity and neurodegeneration. Research collaborative project with Novo Nordisk, 2017-2020, Maletínská, L.

Collaboration

Marie-Christine Galas (INSERM, Lille, France)

Christian Holscher (University of Lancaster, UK)

Jean Martinez, Jean-Alain Fehrentz (CNRS, Montpellier, France)

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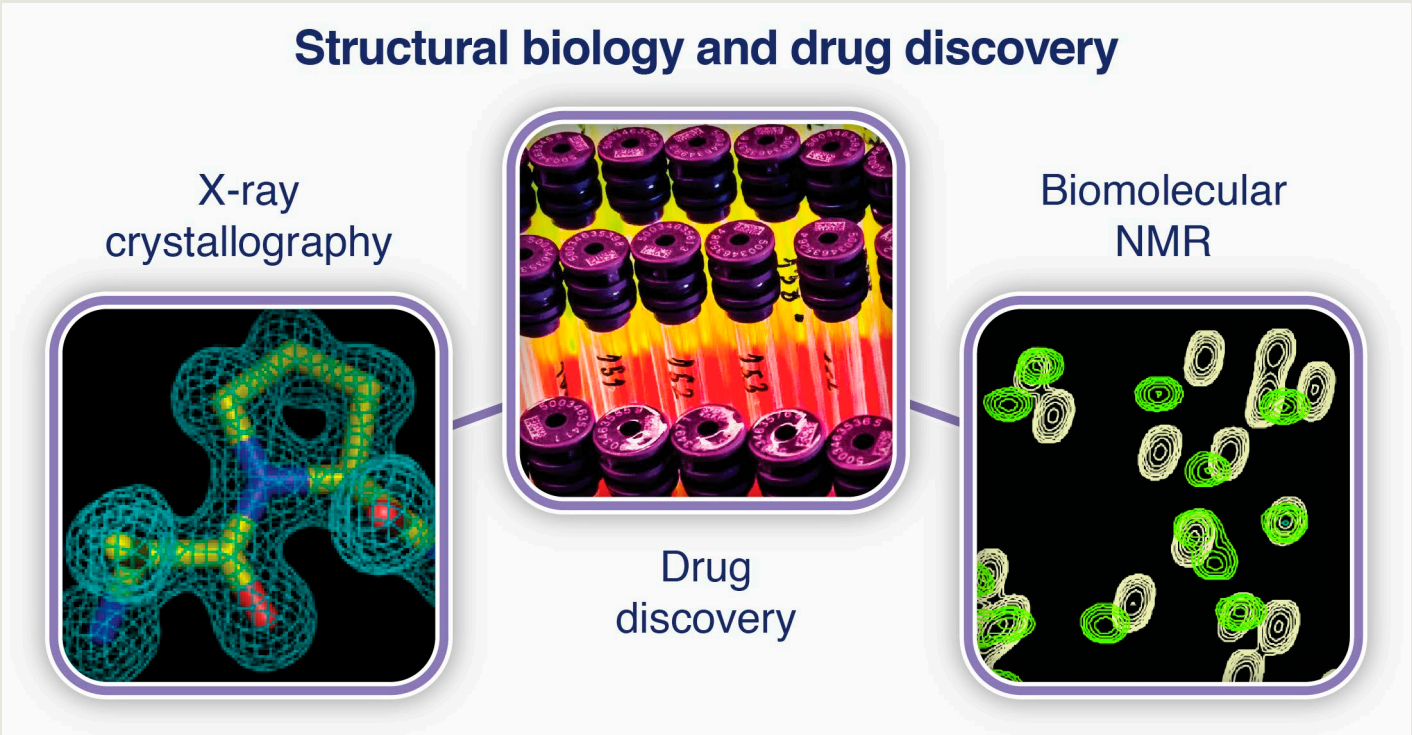
Senior Research Group
X-ray crystallography, biomolecular NMR spectroscopy, rational drug design, fragment-based drug discovery, transcription regulation, medicinal targets



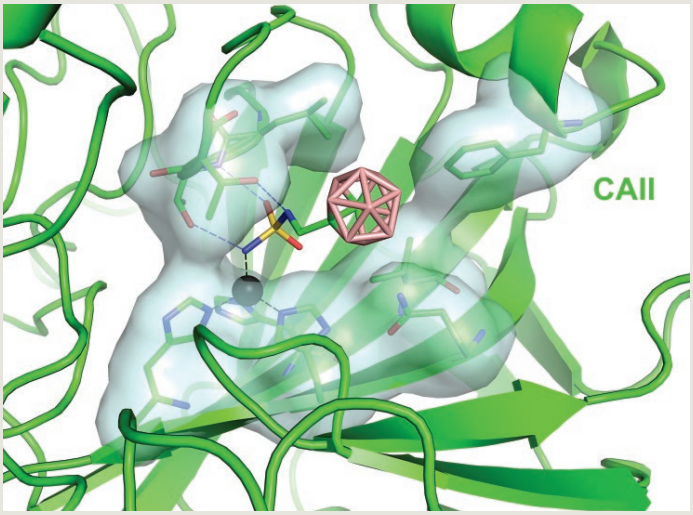
Research topics

Structural characterization of proteins and protein-protein complexes helps us address fundamental biological questions. We use structural knowledge obtained by X-ray crystallography or NMR spectroscopy and other techniques for understanding and modulation of biological roles and functions of proteins and protein-protein complexes with emphasis on medicinally relevant systems.

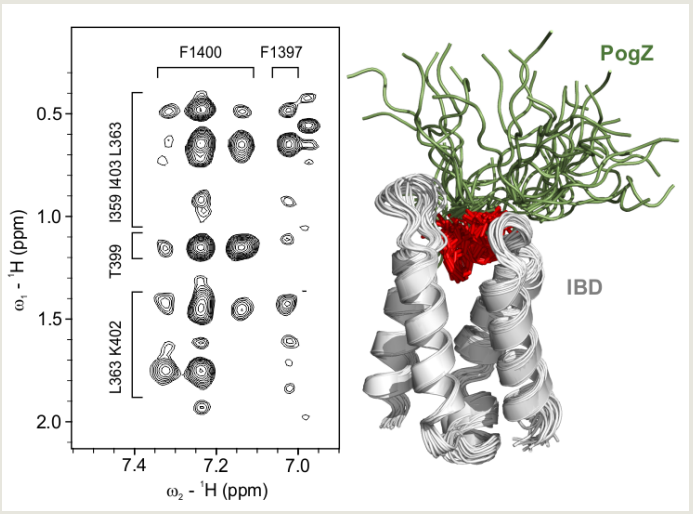
We are interested in the structure-function relationship of prokaryotic and eukaryotic transcription factors. To understand the mechanism of regulation of bacterial transcription, we structurally characterize selected transcription regulators from *Bacillus subtilis*. Our goal is to understand how repressors belonging to various protein families perform their function as molecular switches. Structural studies of human transcription factors are focused on proteins interacting with an epigenetic reader LEDGF/p75, a prominent cellular cofactor for HIV integration.

In our structure-based drug discovery projects, we target enzymes from pathogenic organisms as well as human enzymes involved in pathologies (e.g. carbonic anhydrases, cyclin-dependent kinases, purine nucleoside phosphorylases or purine nucleotidases). The knowledge of protein structures provides a platform for the rational design of specific inhibitors. We also use fragment-based drug discovery techniques to identify small molecules targeting protein-protein interactions important for development of hematological malignancies.

We also use the means of integrative structural biology for detailed characterization of non-canonical DNA molecules and membrane proteins.



We have identified carborane-based compounds as promising lead structures for development of inhibitors of human carbonic anhydrases. The crystal structure provided information that can be applied to the structure-based design of inhibitors specific for the cancer-specific isoform CAIX.



We have identified the LEDGF/p75 binding motive present in all known cellular interaction partners that are modular proteins with intrinsically disordered elements. The structure of the binding motive in complex with the LEDGF/p75 domain was determined by means of NMR.

Group members

Group leader Pavlína Maloy Řezáčová
Scientists Jiří Brynda, Václav Veverka
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Students Vítězslav Brinsa, Karolína Naušová

Selected papers

Sharma, S.; Cermakova, K.; De Rijck, J.; Demeulemeester, J.; Fabry, M.; El Ashkar, S.; Van Belle, S.; Lepsik, M.; Tesina, P.; Duchoslav, V.; Novak, P.; Hubalek, M.; Srb, P.; Christ, F.; Rezacova, P.; Hodges, H.C.; Debyser, Z.; Veverka, V. Affinity switching of the LEDGF/p75 IBD interactome is governed by kinase-dependent phosphorylation. *PNAS* **2018**, 115, E7053–E7062.

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Tesina, P.; Čermáková, K.; Hořejší, M.; Procházková, K.; Fábry, M.; Sharma, S.; Christ, F.; Demeulemeester, J.; Debyser, Z.; De Rijck, J.; Veverka, V.; Řezáčová, P. Multiple cellular proteins interact with LEDGF/p75 through a conserved unstructured consensus motif. *Nat. Commun.* **2015**, 6, 14.

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Financial support

Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022, Maloy Řezáčova, P.

Center for Development of Original Drugs. Technology Agency of the Czech Republic (TA ČR), No. TE01020028, 2012–2019, Maloy Řezáčová, P.

Support of sustainability of the Institute of Molecular and Translational Medicine. Ministry of Education, Youth and Sports (MŠMT), No. LO1304, 2014–2019, Maloy Řezáčová, P.

The evolutionary and functional relationship between LEDGF/p75 and Pdp3. Czech Science Foundation (GA ČR), No. 19-14360S, 2019–2021, Veverka, V.

Gilead Sciences & IOCB Research Center, 2016–2021, PI: Maloy Řezáčová, P., co-PIs: Veverka, V., Brynda, J., Pachl, P.

Structural basis for the biological function of LEDGF/p75 and HRP-2. Czech Science Foundation (GA ČR), No. 16-06357S, 2016–2018, Veverka, V.

Development of methods to the study structures of pharmacologically active enzymes, Multilateral Scientific and Technological Cooperation Projects in the Danube Region. Ministry of Education, Youth and Sports (MŠMT), No. 8X17050, 2017–2018, Maloy Řezáčová, P.

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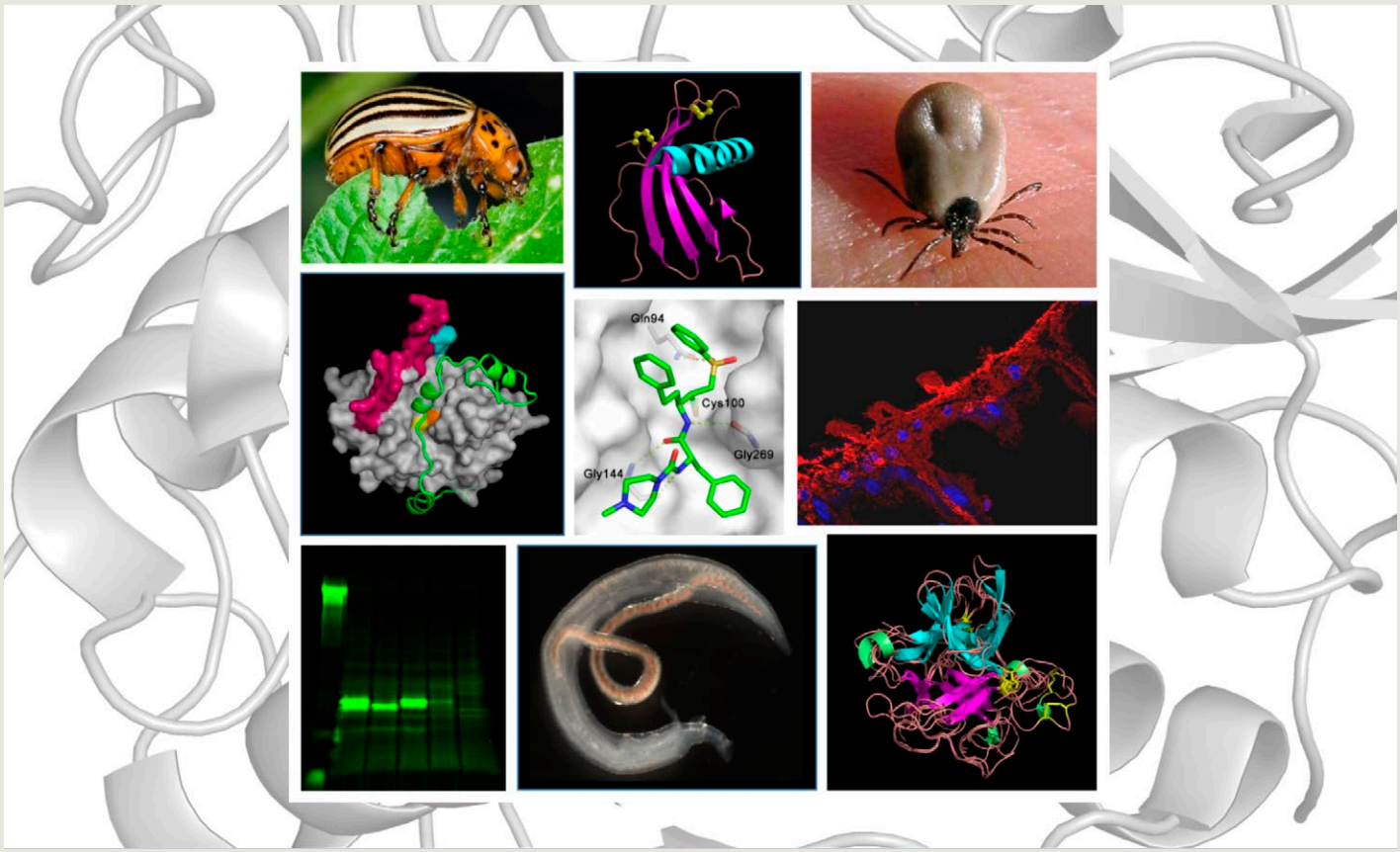
Senior Research Group
cathepsins, proteolytic systems, proteases as therapeutic targets, protease inhibitors, rational drug design, protein structures, blood-feeding parasites

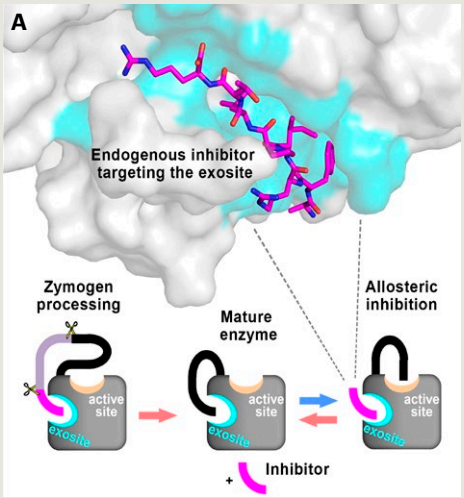


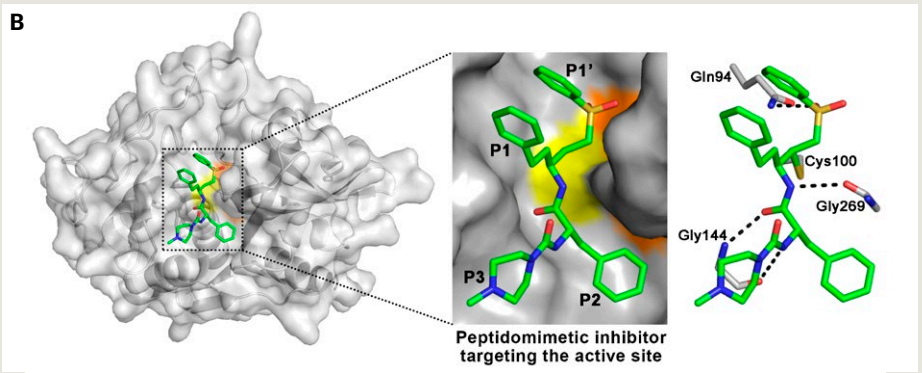
Research topics

Our research focuses on cathepsin proteases and cathepsin-driven proteolytic systems involved in parasitic diseases, cancer, and degenerative diseases. We develop novel molecular tools and strategies to regulate cathepsins and associated pathologies.

In blood-feeding parasites, cathepsins function as digestive enzymes responsible for the breakdown of host blood proteins and represent therapeutic targets. The blood flukes that cause schistosomiasis infect more than 250 million people worldwide. We investigate structure-function relationships in schistosome proteases for the rational design of inhibitory drugs. Ixodes ticks are vectors of encephalitis and borreliosis in Europe and the US. We study proteolytic systems in the gut and saliva of ticks as molecular vaccines against ticks and tick-borne diseases.

For human cathepsins associated with cancer and degenerative diseases, we focus on novel biochemical mechanisms of functional regulation and their exploitation for the development of therapeutic molecules. In particular, we are interested in biomimetic inhibitors inspired by natural molecules of plant, microbial, and invertebrate origin.





(a) We discovered a novel regulatory mechanism in cathepsin D and other medically important aspartic proteases. It is executed by an allosteric peptide inhibitor that is generated by autoproteolysis. (b) We identified peptidomimetic vinyl sulfones as the most potent inhibitors of cathepsin B1 drug target from the parasitic blood fluke *Schistosoma*.

Group members

Group leader Michael Mareš
Scientists Martin Horn, Jan Dvořák, Lucie Marešová, Jana Pytelková
Postdocs Adéla Jílková, Jaroslav Srp
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Technician Milana Štajfová
Students Květoslava Klajblová, Lukáš Pinc

Selected papers

Hánová, I.; Brynda, J.; Hobizalová, R.; Alam, N.; Sojka, D.; Kopáček, P.; Marešová, L.; Vondrášek, J.; Horn, M.; Schueler-Furman, O.; Mareš, M. Novel structural mechanism of allosteric regulation of aspartic peptidases via an evolutionarily conserved exosite. *Cell Chem. Biol.* **2018**, 25, 318–329.

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Srp, J.; Nussbaumerová, M.; Horn, M.; Mareš, M. Digestive proteolysis in the colorado potato beetle, *Leptinotarsa decemlineata*: activity-based profiling and imaging of a multipeptidase network. *Insect Biochem. Mol. Biol.* **2016**, 78, 1–11.

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Financial support

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Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022, Mareš, M. (co-PI)

Targeting enzyme exosites by in situ click chemistry: new strategy for anticancer drug design. Gilead Sciences & IOCB Research Center, 2017–2019, Mareš, M. (co-PI)

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Center of molecular interactions in biomedicine (InterBioMed). Ministry of Education, Youth and Sports (MŠMT), No. LO1302, 2014–2019, Mareš, M. (co-PI)

The role of hemoglobin in tick metabolism and transmission of tick-borne pathogens, Project no. 13-11043S, Czech Science Foundation, 2013–2017, Mareš, M.

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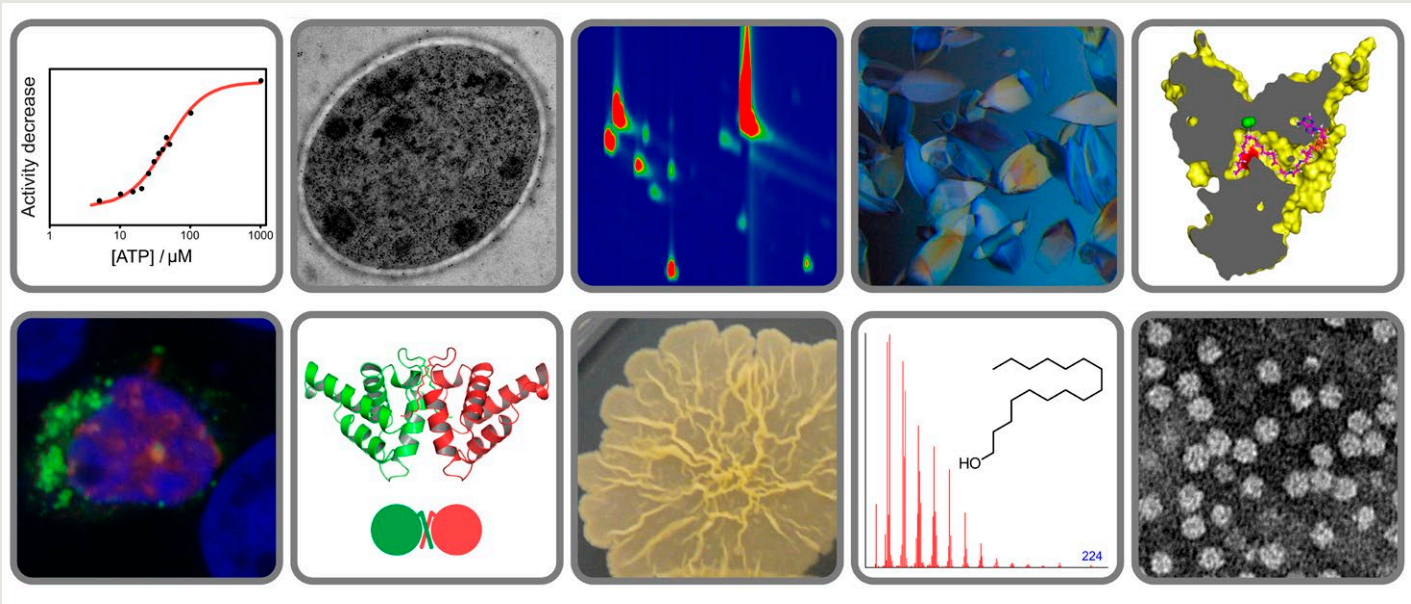
hepatitis B virus, HBx protein, Hbe processing, *Mycobacterium tuberculosis*, metabolism, latent infection, pathogenic *Candida* yeasts, anhydrases, evolution of insect enzymes

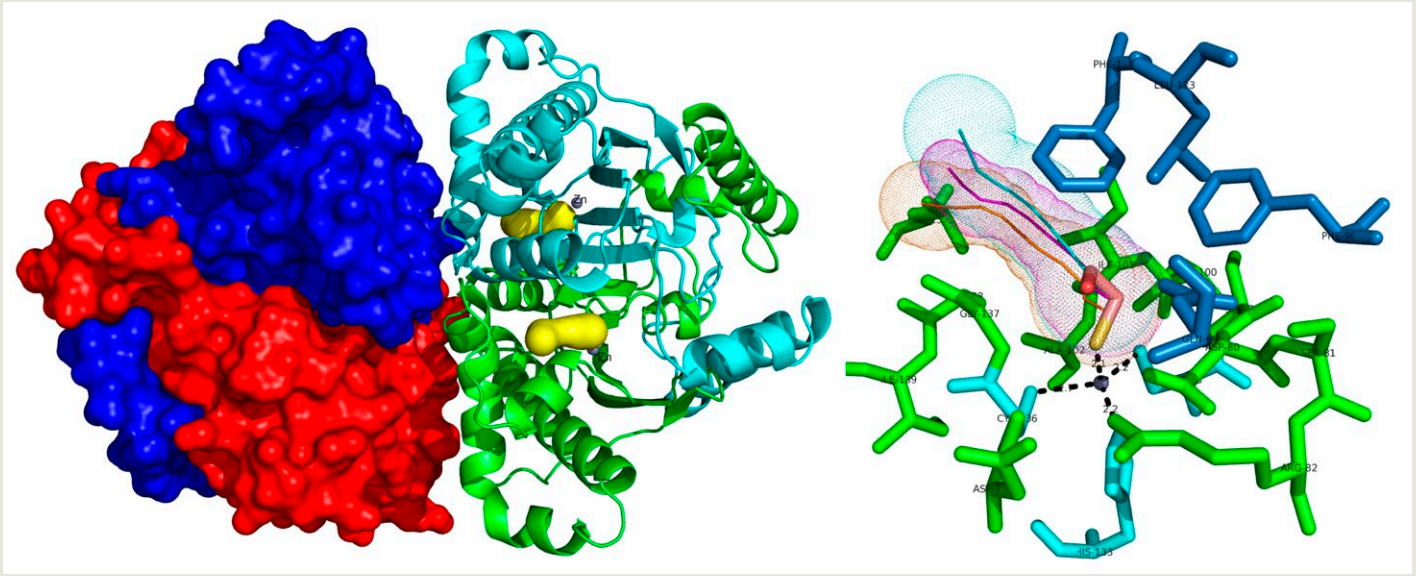


Research topics

The interdisciplinary research of our group is oriented on two main topics: i) investigation of different aspects of the life cycles of selected human pathogens: hepatitis B virus, *Mycobacterium tuberculosis*, *Candida spp.* and their interaction with host cells, ii) regulation and evolution of enzymes involved in pheromone biosynthesis.

In the HBV project, we investigated interactions of hepatitis B virus X protein with cellular factors Smc5/Smc6 and DDB1 and studied maturation of precore protein HBe during the HBV life cycle. Another target of our group is *Mycobacterium tuberculosis* (Mtb). We have explored enzymes from central carbon metabolism and investigated the role of metabolic allosteric regulators (activators or inhibitors) on the function of Mtb pyruvate kinase and phosphofructokinase A and B. We also studied purine biosynthesis in mycobacteria and performed characterization of guanosine 5´-monophosphate reductases that regulate the level of GMP and IMP in Mtb. In our research of *Candida* pathogenic yeasts, we characterized carbonic anhydrases (CA) representing a potential target for development of antifungal disinfectants or ointments. We solved the structure of CA from *C. albicans*, which has provided an opportunity to develop specific inhibitors of this enzyme.

In the project focused on regulation of pheromone biosynthesis and the evolution of enzymes involved in the synthesis of pheromone components, we used representatives of the genus *Bombus* as a model. We showed that the bumble bees and their close relatives, stingless bees, often have extra copies of genes for certain fatty acyl reductases (FAR) that contribute to biosynthesis of fatty alcohols, the components of the pheromone blend. We uncovered the important role of transposable elements that led to a dramatic increase in the number of genes for FAR enzymes in a common ancestor of bumble bees and stingless bees, ultimately allowing a new pheromone "language" to evolve in these insects. These results add to our understanding of the chemical and genetic events that influence what chemicals insects use to communicate with each other.



Group members

Group leader Iva Pichová
Scientists Jiří Dostál, Olga Heidingsfeld, Zdeněk Knejzlík, Jan Snášel, Helena Zábranská, Aleš Zábranský
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Research assistants Mária Čechová, Romana Hadravová
Technicians Romana Cubínková, Elena Dolejší, Dagmar Grundová
Students Ondřej Bulvas, Dajána Kolářová, Stanislav Macháček, Karolína Pokorná, Michal Tupec

Selected papers

Tupec, M.; Bucek, A.; Janoušek, V.; Vogel, H.; Prchalová, D.; Kindl, J.; Pavlíčková, T.; Wenzelová, P.; Jahn,U.; Valterová, I.; Pichová, I. Expansion of the fatty acyl reductase gene family shaped pheromone communication in Hymenoptera. *eLife* **2019**, e39231.

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Buček, A.; Brabcová, J.; Vogel, H.; Prchalová, D.; Kindl, J.; Valterová, I., Pichová, I. Exploring complex pheromone biosynthetic processes in the bumblebee male labial gland by RNA sequencing. *Insect Mol. Biol.* **2016**, 25, 3, 295–314.

Financial support

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Study of Structures of carbonic anhydrases from pathogenic Candida spp. as a tool for design of potential antimycotics. Czech Science Foundation (GA ČR), No. 17-08343S, 2017–2019, Pichová, I.

Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022, Pichová, I. (co-PI)

Gilead Sciences & IOCB Research Center, Z2017–2021, Pichová, I.

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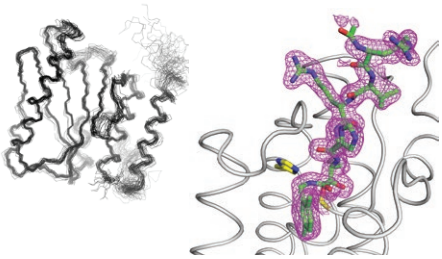
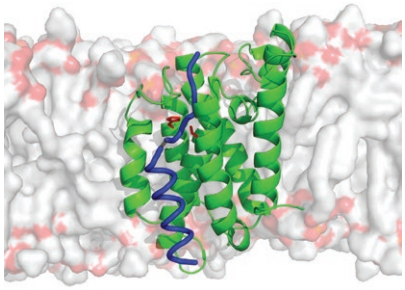
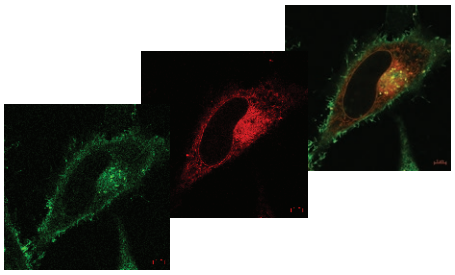
Junior Research Group
lipid membrane, membrane protein, signaling, intramembrane proteolysis, protein structure

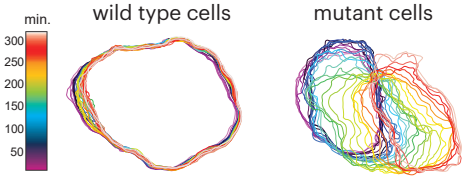
Structural biology



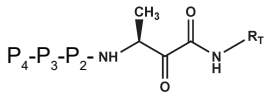


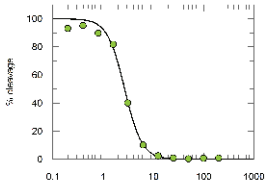
Cell biology

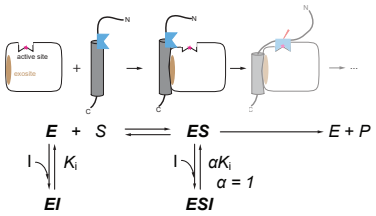




Chemical biology







Research topics

The complexity of biological membranes and chemical processes occurring in their context are fascinating and essential for life. Most of the functions of biological membranes are performed or catalyzed by proteins integrated in or associated with membranes, and as much as 25 to 30 percent of all protein coding genes in a genome encode transmembrane proteins. Regulated proteolysis of many of them controls biological processes as diverse as developmental and stress signaling, membrane homeostasis, and the pathogenicity of microbes. We study the mechanisms that regulate the biogenesis and quality control of transmembrane proteins and devise ways to manipulate them with a perspective of therapeutic use in disease contexts. In particular, we study the intramembrane proteases, which recognize and cleave transmembrane domains of other membrane proteins within the hydrophobic, lipid environment. They have been implicated in human diseases, including Alzheimer's, Parkinson's, immune disorders, cancer, and some infectious diseases. Understanding the mechanisms, structures, and regulation of these enzymes can open new ways to fight multiple pathological conditions. We focus on intramembrane proteases of the rhomboid family, which control growth factor signaling in flies, mitochondrial dynamics in yeast, and the pathogenicity of the malaria parasite as well as on their proteolytically inactive cousins, iRhoms, regulating membrane protein trafficking and inflammatory signaling.

In our integrative approach, we combine membrane biochemistry, enzymology, and structural biology to understand how rhomboid proteases and iRhoms recognize and select substrates, and we employ methods of quantitative proteomics, cell biology, and genetics to uncover rhomboid functions in selected organisms. We are interested in the basic aspects of intramembrane proteolysis relevant to biological signaling and membrane protein biogenesis and homeostasis, but we also exploit the acquired mechanistic insight in the development of specific inhibitors with therapeutic potential.

Group members

Group leader Kvido Stříšovský
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Research assistant Petra Rampírová
Ph.D. students Jakub Began, Jana Březinová, Edita Poláchová, Jan Škerle
Students Markéta Bařinková, Šárka Boháčová, Jano Kuzmík, Jan Šugar, Květa Trávníčková
Sabbatical visitor Prof. Bil Clemons (Caltech, USA)

Selected papers

Tichá, A.; Collis, B.; Strisovsky, K. The Rhomboid Superfamily: Structural Mechanisms and Chemical Biology Opportunities. *Trends Biochem. Sci.* **2018**, 43, 726–739.

Oikonomidi, I.; Burbridge, E.; Cavadas, M.; Sullivan, G.; Collis, B.; Naegele, H.; Clancy, D.; Brezinova, J.; Hu, T.; Bileck, A.; Gerner, C.; Bolado, A.; von Kriegsheim, A.; Martin, S.J.; Steinberg, F.; Strisovsky, K.; Adrain, C. iTAP, a novel iRhom interactor, controls TNF secretion by policing the stability of iRhom/TACE. *eLife* **2018**, 7, e35032.

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Johnson, N.; Březinová, J.; Stephens, E.; Burbridge, E.; Freeman, M.; Adrain, C.; Strisovsky, K. Quantitative proteomics screen identifies a substrate repertoire of rhomboid protease RHBDL2 in human cells and implicates it in epithelial homeostasis. *Sci. Rep.* **2017**, 7, 7283.

Tichá, A.; Stanchev, S.; Škerle, J.; Began, J.; Ingr, M.; Švehlová, K.; Polovinkin, L.; Růžička, M.; Bednárová, L.; Hadravová, R.; Poláchová, E.; Rampírová, P.; Březinová, J.; Kašička, V.; Majer, P.; Strisovsky, K. Sensitive Versatile Fluorogenic Transmembrane Peptide Substrates for Rhomboid Intramembrane Proteases. *J. Biol. Chem.* **2017**, 292, 2703–2713.

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Zettl, M.; Adrain, C.; Strisovsky, K.; Lastun, V.; Freeman, M. Rhomboid Family Pseudoproteases Use the ER Quality Control Machinery to Regulate Intercellular Signaling. *Cell* **2011**, 145, 79–91.

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Financial support

Organismal role of the ER membrane complex: a conserved machinery required for membrane protein biogenesis. "la Caixa" Banking Foundation, No. HR17-00595, 2019–2021, PI: Adrain, C. (IGC Lisbon, PT)

Structural and biophysical basis of the reaction mechanism of intramembrane proteolysis. Czech Science Foundation (GA ČR), No. 18-09556S, 2018–2020, PI: Stříšovský, K.

Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022, PI: Hocek, M.

Targeting enzyme exosites by in-situ click chemistry: new strategy for anticancer drug design (Exoclick). Gilead Sciences & IOCB Research Center, 2017–2021, PI: Maloy-Řezáčová, P.

InterBioMed. Ministry of Education, Youth and Sports (MŠMT), Sustainability grant to research centers of excellence (NPU I), No. LO1302, 2015–2019, PI: Pichová, I.

Collaboration

Dr. Colin Adrain (Instituto Gulbenkian de Ciência, Lisbon, Portugal)

Prof. Rasmus Linser (LMU Munich, Germany)

Prof. Sinisa Urban (Johns Hopkins University, Baltimore, USA)

Prof. Dan Bachovchin (Cornell University, Ithaca, USA)

Dr. Pavel Majer (IOCB Prague, Czech Republic)

Awards—Kvido Stříšovský

Member of the Council of International Proteolysis Society, 2017–2019

Member of the EMBO Young Investigator Programme, EMBO, 2011

J. E. Purkyně Fellowship, Czech Academy of Sciences, 2010

MRC Career Development Fellowship, 2009–2012 (resigned 2011)

EMBO Long-Term Fellowship, 2007–2009

Marie-Curie Intra-European Fellowship, 2005–2007

Norbert Weiss Group

Ion Channels and Diseases
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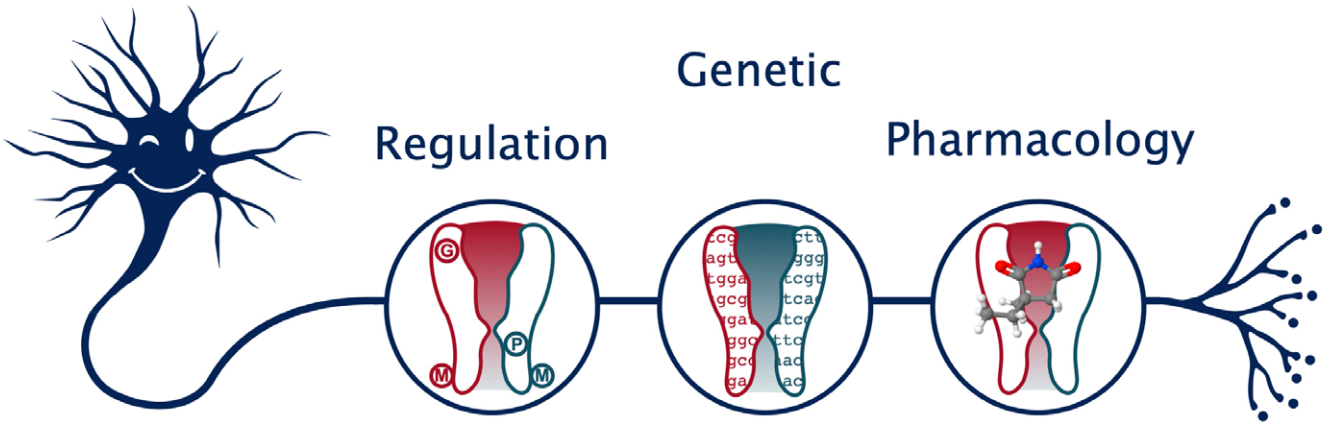
Junior Research Group
ion channels, calcium channels, channelopathies, neuron, neuroscience, pain, epilepsy, ALS



Research topics

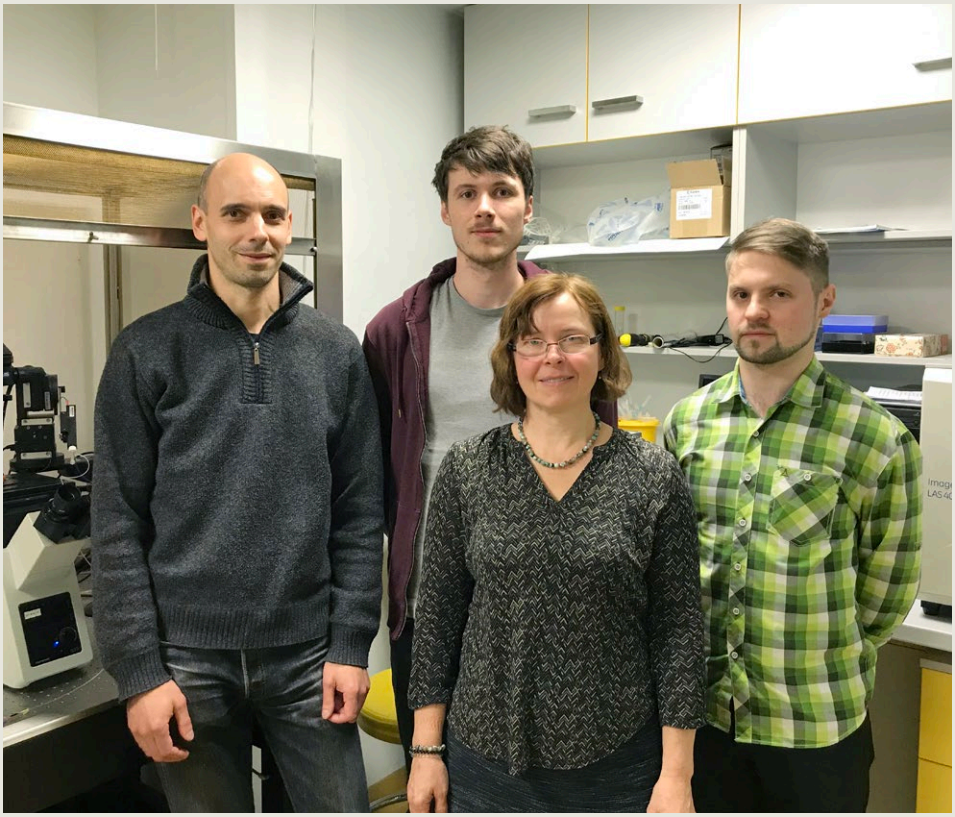
Voltage-gated-calcium channels are the primary mediators of the depolarization-induced calcium entry into neurons that initiates many cellular events. While calcium channels are of critical importance for neuronal function, it is also apparent that inappropriate expression or dysfunction gives rise to a variety of neurological disorders.

We investigate the intrinsic gating processes, as well as cell signaling pathways that control channel activity and trafficking to and from the plasma membrane, and how these regulations are compromised in disease states or by genetic mutations. Specifically, we focus on the subfamily of T-type calcium channels that are implicated in several neurological conditions, including neuropathic pain and epilepsy.

Using a multidisciplinary approach, including patch clamp electrophysiology, molecular biology, biochemistry, confocal imaging microscopy, and rodent models, we investigate:

POST-TRANSLATIONAL REGULATION OF T-TYPE CHANNELS
We analyze the importance of post-translational modifications, especially glycosylation and phosphorylation, on the trafficking and function of the channel, and how these regulations are compromised by metabolic conditions (diabetes and homocysteinemia) leading to secondary neuronal disorders such as peripheral neuropathic pain.

GENETIC CHANNELOPATHIES OF T-TYPE CHANNELS
In collaboration with geneticists and physicians, we investigate the consequence and underlying mechanisms by which genetic mutations in the genes encoding for T-type channels alter channel function to provide structure/function/phenotype information to inherited T-type channelopathies.



Group members

Group leader Norbert Weiss
Postdoc Andriy Tomin
Student Leoš Cmarko
Assistant Alena Habartová

Selected papers

Jurkovicova-Tarabova, B.; Cmarko, L.; Rehak, R.; Zamponi, G.W.; Lacinova, L.; Weiss, N. Identification of a molecular gating determinant within the carboxy terminal region of $Ca_v3.3$ T-type channels. *Mol. Brain* **2019**, 12, 34.

Weiss, N.; Zamponi, G.W. T-type calcium channels: From molecule to therapeutic opportunities. *Int. J. Biochem. Cell Biol.* **2019**, 108, 34–39.

Proft, J.; Rzhepetskyy, Y.; Lazniewska, J.; Zhang, F.-X.; Cain, S.M.; Snutch, T.P.; Zamponi, G.W.; Weiss, N. The Cacna1h mutation in the GAERS model of absence epilepsy enhances T-type Ca^{2+} currents by altering calnexin-dependent trafficking of $Ca_v3.2$ channels. *Sci. Rep.* **2017**, 7, 11513.

Rivas-Ramirez, P.; Gadotti, V.M.; Zamponi, G.W.; Weiss, N. Surfen is a broad-spectrum calcium channel inhibitor with analgesic properties in mouse models of acute and chronic inflammatory pain. *Pflugers Arch. – Eur. J. Physiol.* **2017**, 469, 1325–1334.

Lazniewska, J.; Weiss, N. Glycosylation of voltage-gated calcium channels in health and disease. *Biochim. Biophys. Acta, Biomembr.* **2017**, 1859, 662–668.

Lazniewska, J.; Rzhepetskyy, Y.; Zhang, F.-X.; Zamponi, G.W.; Weiss, N. Cooperative roles of glucose and asparagine-linked glycosylation in T-type calcium channel expression. *Pflugers Arch. – Eur. J. Physiol.* **2016**, 468, 1837–1851.

Rzhepetskyy, Y.; Lazniewska, J.; Blesneac, I.; Pamphlett, R.; Weiss, N. CACNA1H missense mutations associated with amyotrophic lateral sclerosis alter $Ca_v3.2$ T-type calcium channel activity and reticular thalamic neuron firing. *Channels* **2016**, 10, 466–477.

Rzhepetskyy, Y.; Lazniewska, J.; Proft, J.; Campiglio, M.; Flucher, B.E.; Weiss, N. A $Ca_v3.2$/Stac1 molecular complex controls T-type channel expression at the plasma membrane. *Channels* **2016**, 10, 346–354.

Financial support

Exploring the molecular determinants and functional role of T-type channel dimerization. Czech Academy of Sciences, No. SAV-18-22, 2018–2020, Weiss, N.

Collaboration

Dr. Ľubica Lacinová (Slovak Academy of Sciences, Slovakia)

Dr. Gerald W. Zamponi (University of Calgary, Canada)

Dr. Roger Pamphlett (University of Sydney, Australia)

Dr. Guzel Sitdikova (Kazan Federal University, Russia)

Biochemical Pharmacology

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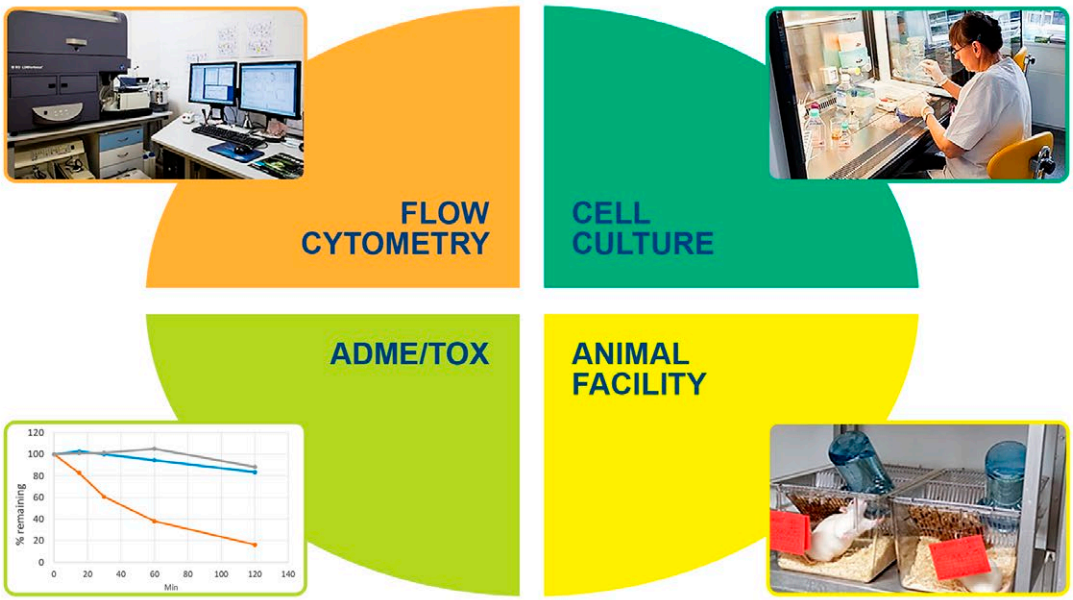
Research-Service Group

drug discovery, cell culture, screening, biotransformation, cancer, inflammation, assay development



Research topics

Biochemical Pharmacology is a research-service group aiming to promote drug discovery programs for the original compounds synthesized at IOCB. The team engages in close cooperation with medicinal chemistry as well as with biology-oriented research groups (e.g. structural biology). We rely heavily on cellular models, sometimes modified by means of molecular biology methods, but we also employ conventional in vitro assays commonly used in biochemistry and pharmacology (e.g. enzyme inhibition or receptor-binding assays). We follow modern trends and implement them in the portfolio of our methods (iPSC-derived cells, 3D cultures etc.). We also provide short, comprehensive courses for our colleagues at IOCB in the areas of our expertise.

We provide services and user support in these areas:
—Flow cytometry
—Cell/tissue culture
—ADME/Tox characterization of compounds
—Experimental animal facility

Within our research projects, we typically investigate drug mechanisms of action, target identification, and multilevel validation of the data harvested in basic biological screens. We largely focus on projects in the field of oncology, but also immunology and virology and their overlaps.

Currently we are engaged in the following projects:
—Anti-inflammatory effects of substituted pyrimidine analogs
—Inhibitors of purine nucleoside phosphorylase for the treatment of T-cell leukemias
—Galectin-1/3 inhibitors for cancer treatment
—Novel amide-based steroidal inhibitors of NMDA receptors
—Nuclear hormone receptors as pharmacological targets

Group members

Group leader Helena Mertlíková-Kaiserová
Scientists Karel Chalupský, Miroslav Hájek, Marika Matoušová, Markéta Šmídková, Martin Zavřel
Postdocs Jaroslav Kozák, Erika Kužmová
Research assistants Alexandra Dvořáková, Jana Günterová, Ludmila Jandová, Alžbeta Magdolenová, Eva Tloušťová
Ph.D. students Lenka Barchánková, Jan Voldřich
Technicians Pavlína Hovorková, Karolína Müllerová, Lucie Pospíšilová
Students Tadeáš Bílek, Andrea Schovánková

Selected papers

Matoušová, M.; Souček, R.; Tloušťová, E.; Slavíková, B.; Chodounská, H.; Mertlíková-Kaiserová, H.; Kudová, E. Pregn-5-en-3β-ol and androst-5-en-3β-ol dicarboxylic acid esters as potential therapeutics for NMDA hypofunction: In vitro safety assessment and plasma stability. *Steroids* **2018**.

Česnek, M.; Skácel, J.; Jansa, P.; Dračínský, M.; Šmídková, M.; Mertlíková-Kaiserová, H.; Soto-Velasquez, M.P.; Watts, V.J.; Janeba, Z. Nucleobase Modified Adefovir (PMEA) Analogues as Potent and Selective Inhibitors of Adenylate Cyclases from Bordetella pertussis and Bacillus anthracis. *ChemMedChem* **2018**, 13, 1779–1796.

Mejdrová, I.; Chalupská, D.; Plačková, P.; Müller, C.; Šála, M.; Klíma, M.; Baumlová, A.; Hřebabecký, H.; Procházková, E.; Dejmek, M.; Strunin, D.; Weber, J.; Lee, G.; Matoušová, M.; Mertlíková-Kaiserová, H.; Ziebuhr, J.; Birkuš, G.; Bouřa, E.; Nencka, R. Rational Design of Novel Highly Potent and Selective Phosphatidylinositol 4-Kinase IIIβ (PI4KB) Inhibitors as Broad-Spectrum Antiviral Agents and Tools for Chemical Biology. *J. Med. Chem.* **2017**, 60, 100–118.

Plačková, P.; Šála, M.; Šmídková, M.; Dejmek, M.; Hřebabecký, H.; Nencka, R.; Thibaut, H.J.; Neyts, J.; Mertlíková-Kaiserová, H. 9-Norbornyl-6-chloropurine (NCP) induces cell death through GSH depletion-associated ER stress and mitochondrial dysfunction. *Free Radical Biol. Med.* **2016**, 97, 223–235.

Šlégerová, J.; Hájek, M.; Řehoř, I.; Sedlák, F.; Štursa, J.; Hrubý, M.; Cígler, P. Designing the nanobiointerface of fluorescent nanodiamonds: highly selective targeting of glioma cancer cells. *Nanoscale* **2015**, 7, 415–420.

Financial support

Center for Development of Original Drugs. Technology Agency of the Czech Republic (TA ČR), No. TE01020028, 2012–2019, Havlas, Z.

InterBioMed. Ministry of Education, Youth and Sports (MŠMT), NPU I, No. LO1302, 2014–2019, Pichová, I.

Personalized Medicine—Diagnostics and Therapy. National Center of Competence 1, NCK1, No. TN01000013, 2019–2020, Fusek, M.

Development of DIANA-based *in vitro* ADME methods for new drug discovery. Technology Agency of the Czech Republic (TA ČR), No. TJ02000276, 2019–2021, DIANA Biotechnologies—IOCB Prague.

Bioinformatics

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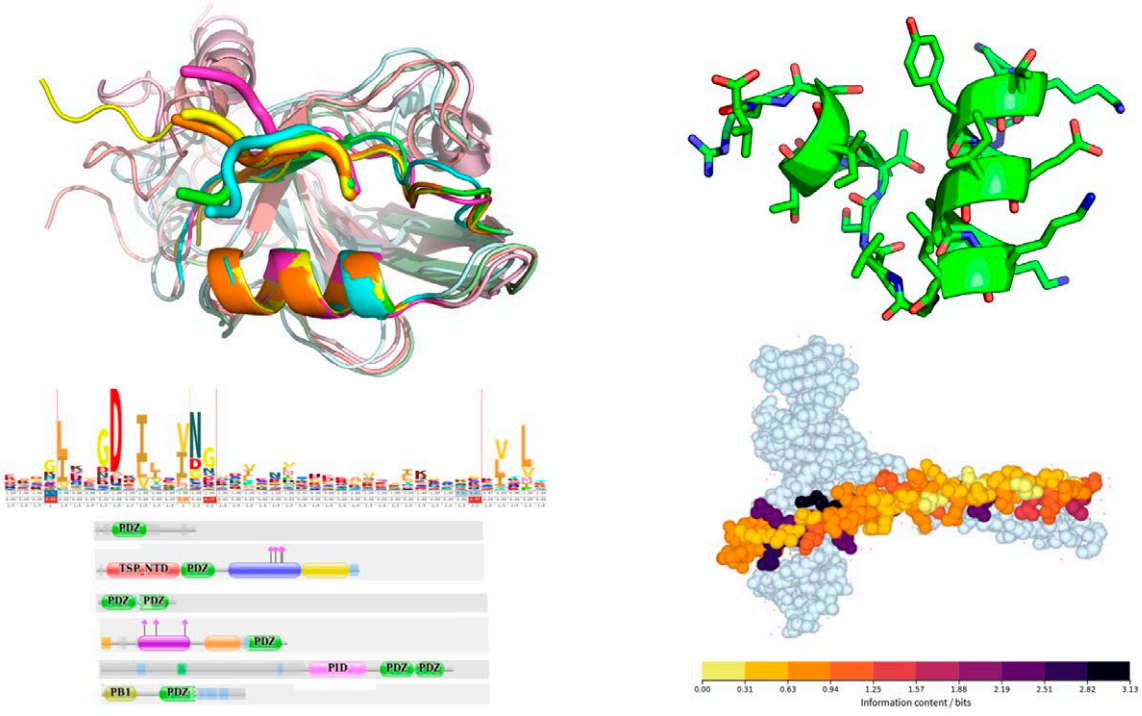
Research-Service Group
bioinformatics, proteomics, computational methods, protein/DNA interactions, molecular modeling, structure-function predictions, cheminformatics

Complexity of molecular Information—from sequence to structure and farther



Research topics

The primary subjects of research in our group are biomolecules, their sequences, evolution, structures, architectures, interactions, and complexes. We specifically focus on the problems relating to the sequence-structure-function paradigm and study the evolutionary pathways in which functions emerged and were further optimized. Our expertise in various fields of molecular biology and informatics allows us to design biomolecules with specific functions. Currently, the main biological systems of interest include multidomain proteins and DNA-binding proteins.

Our research methods combine molecular modeling, molecular simulations, and computational chemistry with bioinformatic analysis and mathematical statistics. Additionally, we run a dedicated experimental laboratory where the designed proteins are produced and analyzed. Our aim is to establish a robust methodological background suitable for providing a foundation for answering various questions of structural biology and life sciences.

We also offer professional computational support for institutional users in analysis of protein sequences, modeling of protein structures, prediction of protein-protein interactions, and state-of-the-art bioinformatic analysis and tools. Our recent efforts include the Integrated Database of Small Molecules, which aims to provide a solid connection between existing chemical and biological data spaces. The database is a national contribution to the pan-European ESFRI project "ELIXIR—the infrastructure for biological data"; we are responsible for maintaining this infrastructure. Our lab also serves as the central communication and management node of the ELIXIR CZ infrastructure.

Group members

Group leader Jiří Vondrášek
Scientists Robert Pergl, Jan Pačes
Postdocs Kristýna Boušová, Jakub Galgonek, Jiří Vymětal
Ph.D. students Dávid Jakubec, Kateřina Mertová, Klára Poštulková, Veronika Vetýšková, Monika Zouharová
Project manager Anna Strachotová
IT specialist Pavel Dvořák
Students Kateřina Faltejsková, Miroslav Kratochvíl
Assistant Kateřina Bayerová

Selected papers

Jakubec, D.; Vondrášek, J.; Finn, R.D. 3DPatch: fast 3D structure visualization with residue conservation. *Bioinformatics* **2019**, 35, 332–334.

Kratochvíl, M.; Vondrášek, J.; Galgonek, J. Sachem: a chemical cartridge for high-performance substructure search. *J. Cheminf.* **2018**, 10, 27–27.

Jakubec, D.; Kratochvíl, M.; Vymětal, J.; Vondrášek, J. Widespread evolutionary crosstalk among protein domains in the context of multi-domain proteins. *PLoS One* **2018**, 13, e0203085.

Bousova, K.; Herman, P.; Vecer, J.; Bednarova, L.; Monincova, L.; Majer, P.; Vyklicky, L.; Vondrasek, J.; Teisinger, J. Shared CaM- and S100A1-binding epitopes in the distal TRPM4 N terminus. *FEBS J.* **2018**, 285, 599–613.

Zemanová, L.; Kirubakaran, P.; Pato, I.H.; Štambergová, H.; Vondrášek, J. The identification of new substrates of human DHRS7 by molecular modeling and in vitro testing. *Int. J. Biol. Macromol.* **2017**, 105, 171–182.

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Vymetal, J.; Bednarova, L.; Vondrasek, J. Effect of TFE on the Helical Content of AK17 and HAL-1 Peptides: Theoretical Insights into the Mechanism of Helix Stabilization. *J. Phys. Chem. B* **2016**, 120, 1048–1059.

Towse, C.L.; Vymetal, J.; Vondrasek, J.; Daggett, V. Insights into Unfolded Proteins from the Intrinsic phi/psi Propensities of the AAXAA Host-Guest Series. *Biophys. J.* **2016**, 110, 348–361.

Kirubakaran, P.; Pfeiferová, L.; Boušová, K.; Bednarova, L.; Obšilová, V.; Vondrášek, J. Artificial proteins as allosteric modulators of PDZ3 and SH3 in two-domain constructs: A computational characterization of novel chimeric proteins. *Proteins: Struct., Funct., Bioinf.* **2016**, 84, 1358–1374.

Jakubec, D.; Hostas, J.; Laskowski, R.A.; Hobza, P.; Vondrasek, J. Large-Scale Quantitative Assessment of Binding Preferences in Protein-Nucleic Acid Complexes. *J. Chem. Theory Comput.* **2015**, 11, 1939–1948.

Financial support

Working from a distance: engineering allosteric control on PDZ3 domain selectivity from ZO-1 protein through chimera domain fusion. Czech Science Foundation (GA ČR), No. 19-03488S, 2019–2021, Vondrášek, J.

Czech national Infrastructure for biological data. Ministry of Education, Youth and Sports (MŠMT), No. LM2015047, 2016–2019, Vondrášek, J.

ELIXIR-EXCELERATE: Fast-track ELIXIR implementation and drive early user exploitation across the life-sciences. European Commission (H2020-INFRADEV-1-2015-1), No. 676559, 2015–2019, Vondrášek, J.

ELIXIR CZ

The lab is responsible for running and managing ELIXIR, the pan-European infrastructure for biological data, and it is also the central node of the ELIXIR CZ infrastructure.

The mission of ELIXIR CZ is to create a sustainable infrastructure for storing, processing, and analyzing life science data in the Czech Republic and to provide access to tools and training to facilitate these activities. The uniqueness of ELIXIR CZ lies in the expertise provided by specialized groups at significant Czech life research organizations—members of the ELIXIR CZ consortium. Jointly, they create a bioinformatics platform offering services for the greater research community in the open access regime. ELIXIR CZ participates in the ELIXIR pan-European research infrastructure.

elixir CZECH REPUBLIC

Virology

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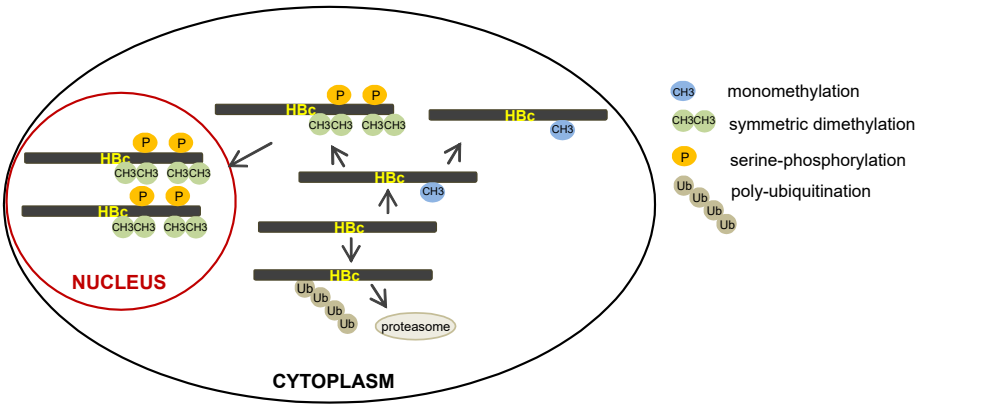
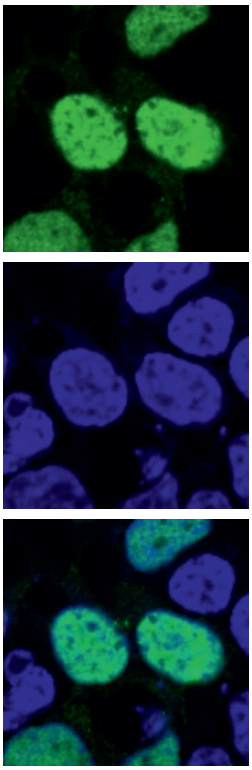
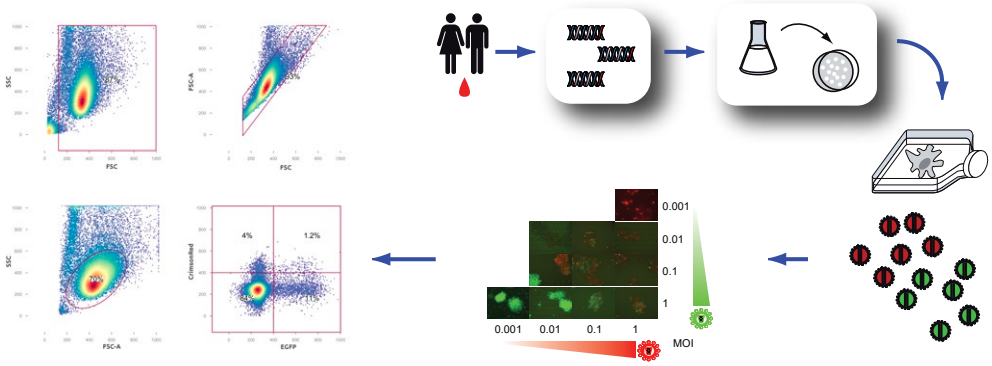
Research-Service Group

antiviral screening, drug discovery, human immunodeficiency virus, hepatitis B virus, replication, latency, reactivation, HIV fitness





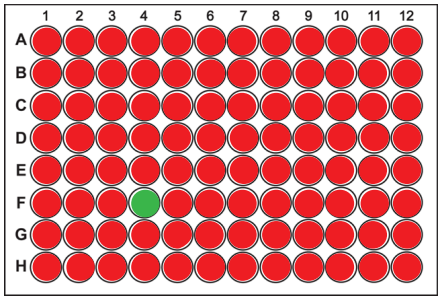


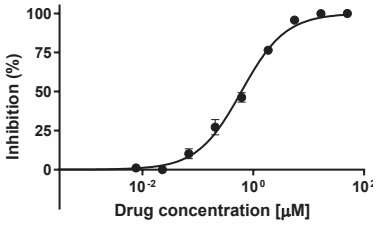
Research topics

The virology research-service team assists in the IOCB drug discovery program by providing an in-house BSL3 facility for the screening of antiviral compounds against a variety of viruses and collaborates with other IOCB groups in projects involving viruses. Antiviral screening is currently performed against the human immunodeficiency virus, influenza virus, dengue virus, herpes simplex virus, and coxsackievirus. Furthermore, we collaborate with other groups to improve entry of active compounds into cells using liposomal and macrocyclic delivery systems. In addition, we are involved in the search for nanoparticles and nanomaterials with antiviral and virucidal activity.

In our research, we are particularly interested in new strategies for HIV inhibition, HIV drug resistance, HIV reactivation and latency, viral fitness and its implication for HIV pathogenesis, and disease progression. Disease progression varies significantly in HIV-infected patients and is dependent on a number of host genetic, immune, and virological factors. We investigate the role of HIV fitness in disease progression in the absence of antiretroviral treatment.

Recently, we have focused our research on interactions of the hepatitis B virus core protein with host cell proteins. In particular, we are interested in the characterization of proteins and cellular pathways involved in (i) epigenetic regulation of transcription, (ii) ubiquitin-proteasome degradation, and (iii) post-translational modifications.





Group members

Group leader Jan Weber
Scientist Barbora Lubyová
Postdocs Ludovic Aillot, Jan Hodek, Marcela Pávová, Dmytro Strunin
Research assistants Václav Janovec, Hana Langerová, Barbora Lapuníková, Michala Zgarbová
Ph.D. students Kristýna Glendová, Lenka Sácká
Technician Jitka Weberová
Student Anežka Rajmonová

Selected papers

Humpolíčková, J.; Weber, J.; Starková, J.; Mašínová, E.; Günterová, J.; Flaisigová, I.; Konvalinka, J.; Majerová, T. Inhibition of the precursor and mature forms of HIV-1 protease as a tool for drug evaluation. *Sci. Rep.* **2018**, 8, 10438.

Janovec, V.; Aouar, B.; Font-Haro, A.; Hofman, T.; Trejbalova, K.; Weber, J.; Chaperot, L.; Plumas, J.; Olive, D.; Dubreuil, P.; Nunès, J. A.; Stranska, R.; Hirsch, I. The MEK1/2-ERK Pathway Inhibits Type I IFN Production in Plasmacytoid Dendritic Cells. *Front. Immunol.* **2018**, 9, 364.

Cagno, V.; Andreozzi, P.; D'Alicarnasso, M.; Jacob Silva, P.; Mueller, M.; Galloux, M.; Le Goffic, R.; Jones, S.T.; Vallino, M.; Hodek, J.; Weber, J.; Sen, S.; Janeček, E.-R.; Bekdemir, A.; Sanavio, B.; Martinelli, C.; Donalisio, M.; Rameix Welti, M.-A.; Eleouet, J.-F.; Han, Y.; Kaiser, L.; Vukovic, L.; Tapparel, C.; Král, P.; Krol, S.; Lembo, D.; Stellacci, F. Broad-spectrum non-toxic antiviral nanoparticles with a virucidal inhibition mechanism. *Nat. Mater.* **2017**, 17, 195.

Lubyova, B.; Hodek, J.; Zabransky, A.; Prouzova, H.; Hubalek, M.; Hirsch, I.; Weber, J. PRMT5: A novel regulator of Hepatitis B virus replication and an arginine methylase of HBV core. *PLOS ONE* **2017**, 12, e0186982.

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Hodek, J.; Zajícová, V.; Lovětinská-Šlamborová, I.; Stibor, I.; Müllerová, J.; Weber, J. Protective hybrid coating containing silver, copper and zinc cations effective against human immunodeficiency virus and other enveloped viruses. *BMC Microbiol.* **2016**, 16, 56.

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Financial support

Sensing of hepatitis B virus-infected hepatocytes by plasmacytoid dendritic cells. Czech Science Foundation (GA ČR), No. 17-15422S, 2017–2019, PI: Hirsch I., co-PI: Weber, J.

Gilead Sciences & IOCB Research Center, 2017–2021, PI: Iva Pichová, co-PIs: Weber, J., Grantz Šašková, K., Curtis, E., Hirsch, I.

Chemical biology for drugging undruggable targets (ChemBioDrug). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022, co-PI: Weber, J.

Cluster

PHYS

Petr Bouř Group (Biomolecular Spectroscopy)
Zdeněk Havlas Group (Computational Chemistry)
Pavel Hobza Group (Non-Covalent Interactions)
Pavel Jungwirth Group (Molecular Modeling)
Josef Lazar Group (Advanced Optical Microscopy)
Lubomír Rulíšek Group (Theoretical Bioinorganic Chemistry)

Analytical Laboratory (Stanislava Matějková)
Electromigration Methods (Václav Kašička)
Mass Spectrometry (Josef Cvačka)
NMR and Molecular Spectroscopy (David Šaman)

Petr Bouř Group

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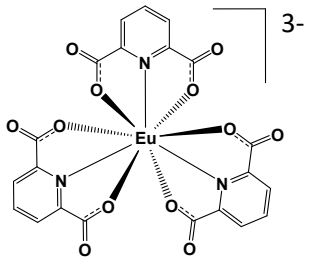
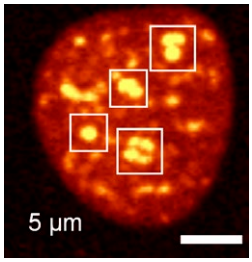
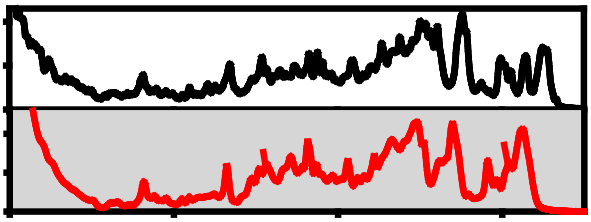
Senior Research Group
optical spectroscopy, molecular modeling, organic synthesis, optical activity, method development

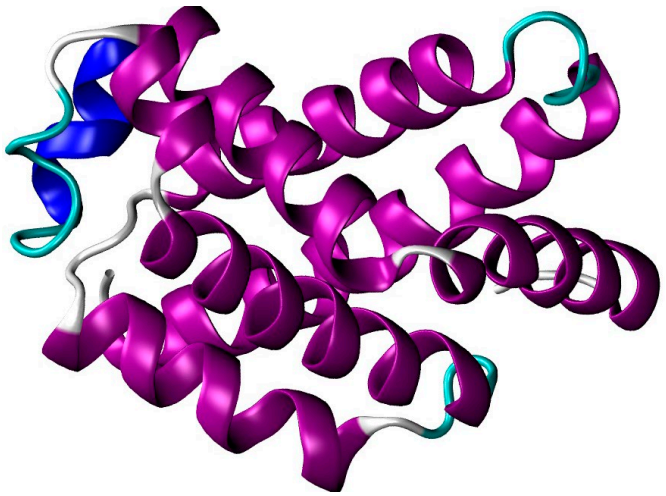
Spectroscopy / Imaging







Applications



Theory

$$B_{LORG} = \frac{1}{2}\{\sum_{k\neq n}[\frac{\langle k|\sum_{i=1}^{N_e}\mathbf{r}_i\times\nabla_i|n\rangle}{E_{kn}} + \frac{1}{2N_e}(\sum_{l\neq n}\frac{\boldsymbol{\mu}_{kl}\times\nabla_{l\,n}}{E_{l\,n}} + \sum_{l\neq k}\frac{\boldsymbol{\mu}_{l\,n}\times\nabla_{kl}}{E_{kl}})]\cdot\boldsymbol{\mu}_{nj}\times\boldsymbol{\mu}_{jk}$$

Research topics

Biomolecules may be conveniently studied by optical spectroscopy to unravel their structure, interactions, and functions in living cells. Our group is devoted to development of theoretical and experimental spectroscopy methods contributing to our understanding of biomolecular properties. This may be useful in exploring new functional compounds, or, in the long term, computational modeling could also reduce drug testing on animals.

For example, we develop chiral spectroscopic methods. Such techniques use circularly-polarized light and are very sensitive to variations in molecular structure. Among them, vibrational optical activity reveals especially valuable information about the studied systems. To interpret the spectra, we upgraded and extended the combined computational and spectroscopic approach to handle large proteins bearing thousands of atoms. Lately, we have developed a sensitive method for detecting circularly polarized luminescence useful for chemical imaging techniques.

Our group also employs advanced organic synthesis to prepare model systems relevant to studying biological activity, such as functionalized proteins with modified folding properties implicated in Alzheimer's and other neurodegenerative diseases.

Group members

Group leader Petr Bouř
Scientists Valery Andrushchenko, Jana Hudecová, Jakub Kaminský, Jiří Kessler, Radek Pelc, Vladimír Sychrovský, Jaroslav Šebestík
Postdocs Jashobanta Sahoo, Jakub Šebera, Tao Wu
Ph.D. students Jiří Fukal, Mohamed Hamissa, Monika Krupová, Petr Niederhafner, Jiří Průša
Technician Martin Šafařík
Students Adam Bouz, Luboš Plamitzer

Selected papers

Keiderling, T.A.; Bouř, P. Theory of Molecular Vibrational Zeeman Effects as Measured with Circular Dichroism. *Phys. Rev. Lett.* **2018**, 121, 073201.

Pramanik, G.; Humpolíčková, J.; Valenta, J.; Kundu, P.; Bals, S.; Bouř, P.; Dračínský, M.; Cígler, P. Gold Nanoclusters with Bright Near-Infrared Photoluminescence. *Nanoscale* **2018**, 10, 3792.

Jungwirth, J.; Šebestík, J.; Šafařík, M.; Kapitán, J.; Bouř, P. Quantitative Determination of Ala-Ala Conformer Ratios in Solution by Decomposition of Raman Optical Activity Spectra. *J. Phys. Chem. B* **2017**, 121, 8956–8964.

Šugar, J.; Bouř, P. Quantitative analysis of sugar composition in honey using 532-nm excitation Raman and Raman optical activity spectra. *J. Raman Spectrosc.* **2016**, 47, 1298–1303.

Šebestík, J.; Kapitán, J.; Pačes, O.; Bouř, P. Diamagnetic Raman Optical Activity of Chlorine, Bromine, and Iodine Gases. *Angew. Chem. Int. Ed.* **2016**, 55, 3504–3508.

Kessler, J.; Kapitán, J.; Bouř, P. First-Principles Predictions of Vibrational Raman Optical Activity of Globular Proteins. *J. Phys. Chem. Lett.* **2015**, 6, 3314–3319.

Pour, S.O.; Rocks, L.; Faulds, K.; Graham, D.; Parchaňský, V.; Bouř, P.; Blanch, E.W. Through-space transfer of chiral information mediated by a plasmonic nanomaterial. *Nat. Chem.* **2015**, 7, 591–596.

Financial support

Exploring Resonance and Anharmonic Phenomena in Biomolecular Spectroscopy. Czech Science Foundation (GA ČR), No. 18-05770S, Bouř, P.

An integrative action for multidisciplinary studies on cellular structural networks (EuroCellNet). EU COST Action CA 15214, Ministry of Education, Youth and Sports (MŠMT), No. LTC17012 , Bouř, P.

Novel applications of vibrational optical activity to biomolecules. Czech Science Foundation (GA ČR), No. P208/11/0105, 2011–2015, Bouř, P.

Magnetic circular dichroism as an analytical tool for fullerenes and carbon nanostructures. Czech Science Foundation (GA ČR), No. 13-03978S, 2013–2016, Bouř, P.

Development of theoretical and spectroscopic tools for studies of amyloid fibrils. Czech Science Foundation (GA ČR), No. 15-09072S, 2015–2017, Bouř, P.

Combination of classical and quantum-mechanical computational techniques for vibrational optical activity. Czech Science Foundation (GA ČR), No. 16-05935S, 2016–2018, Bouř, P.

Zdeněk Havlas Group

Computational Chemistry
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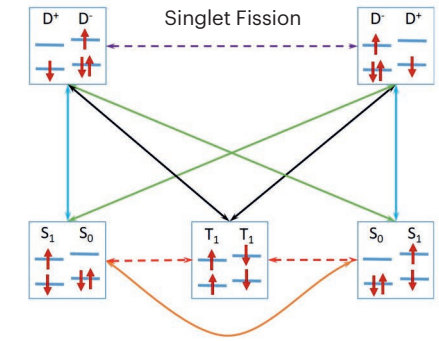
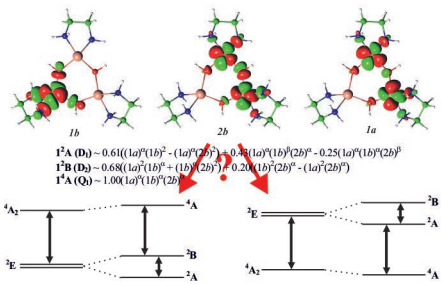
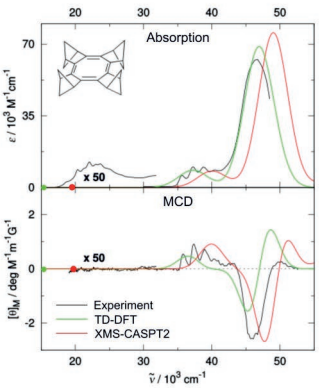
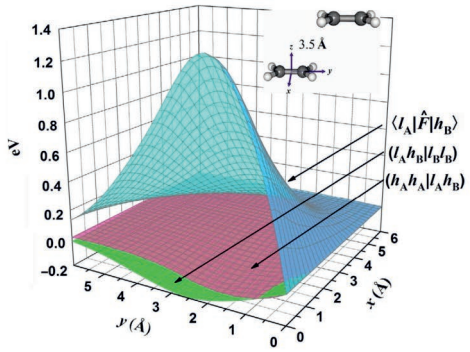
Honorary Chair

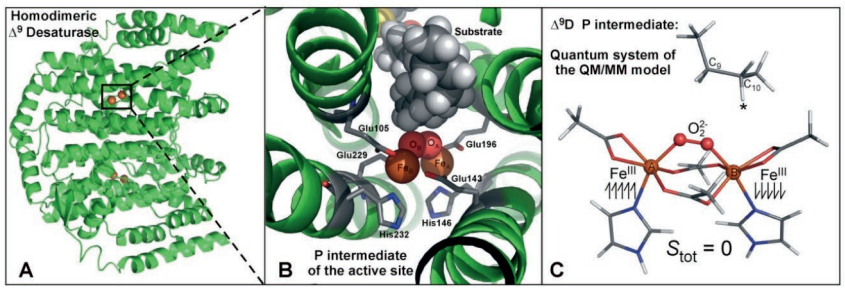
theoretical chemistry, excited states, molecular properties, spectroscopy, relativistic effects, parity violation, solar energy, software development











Research topics

The group is mainly focused on theoretical studies of the properties and chemistry of organic and bioinorganic compounds with complex electronic structures, such as biradicals and transition metal containing systems.

These species typically possess chemical and physical properties significantly different from simple closed-shell molecules. As such, they might, for example, represent suitable candidates for a singlet fission process, a promising alternative for improving the efficiency of organic solar cells. We search for new chromophores (organic dyes) and mutual disposition of chromophores for singlet fission. Among other special properties, the studied systems also exhibit strong relativistic effects, especially spin-orbit and spin-spin coupling.

For this reason, the systems are well suited for studying normal and inverse heavy-atom effects, which play an important role in spin-forbidden chemistry, as well as for searching for a molecule with a measurable electronic excitation frequency shift due to parity-violation effects. These are responsible for different properties of enantiomers due to the weak forces. In the realm of transition metal chemistry, we focus on spectroscopic properties and reactivity of metalloenzymatic active sites and structurally related transition metal complexes.

Thanks to the group's interests, our results are mostly based on modern multi-reference electronic structure methods, and the group is engaged not only in performing the calculations but also in methodology development and scientific programming. Strong interaction with synthetic groups and groups measuring physical properties is typical.

Group members

Group leader Zdeněk Havlas
Scientist Mojmír Kývala
Postdocs Jakub Chalupský, Jin Wen
Student Alexandr Zaykov
Secretary Anna Kozáková

Selected papers

Wen, J.; Han, B.W.; Havlas, Z.; Michl, J. An MS-CASPT2 Calculation of the Excited Electronic States of an Axial Difluoroborondipyrromethene (BODIPY) Dimer. *J. Chem. Theory Comput.* **2018**, 14, 4291–4297.

Buchanan, E.A.; Havlas, Z.; Michl, J. Singlet Fission: Optimization of Chromophore Dimer Geometry. *Adv. Quantum Chem.* **2017**, 75, 175–227.

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Havlas, Z.; Michl, J. Guidance for Mutual Disposition of Chromophores for Singlet Fission. *Isr. J. Chem.* **2016**, 56, 96–106.

Wen, J.; Havlas, Z.; Michl, J. Captodatively Stabilized Biradicaloids as Chromophores for Singlet Fission. *J. Am. Chem. Soc.* **2015**, 137, 165–172.

Kottas, G.S.; Brotin, T.; Schwab, P.F.H.; Gala, K.; Havlas, Z.; Kirby, J.P.; Miller, J.R.; Michl, J. Tetraarylcyclobutadienecyclopentadienylcobalt Complexes: Synthesis, Electronic Spectra, Magnetic Circular Dichroism, Linear Dichroism, and TD DFT Calculations. *Organometallics* **2014**, 33, 3251–3264.

Chalupský, J.; Rokob, T.A.; Kurashige, Y.; Yanai, T.; Soomon, E. I.; Rulíšek, L.; Srnec, M. Reactivity of the Binuclear Non-Heme Iron Active Site of Δ^9 Desaturase Studied by Large-Scale Multireference Ab Initio Calculations. *J. Am. Chem. Soc.* **2014**, 136, 15977–15991.

Financial support

Center for Development of Original Drugs. Technology Agency of the Czech Republic (TA ČR), No. TE01020028, 2012–2019.

Gilead Sciences & IOCB Research Center, 2006–2021.

Awards—Zdeněk Havlas

Czech Senate Silver medal, 2015

De scientia et humanitate optime meritis, CAS, 2013

Medal of the Czech Chemical Society for significant contribution to natural sciences, 2011

Jan Hellich medal for successful implementation in the field and solidarity with the city, Poděbrady, 2007

Member of the Learned Society of the Czech Republic, 2002

Award of the Learned Society of the Czech Republic, 2001

Pavel Hobza Group

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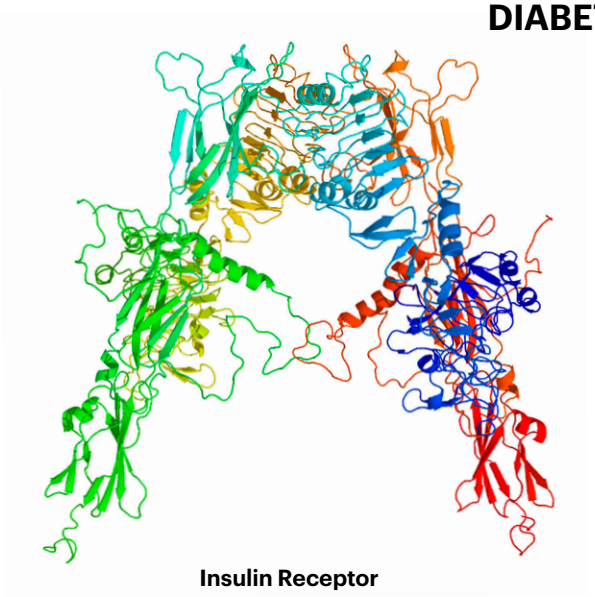
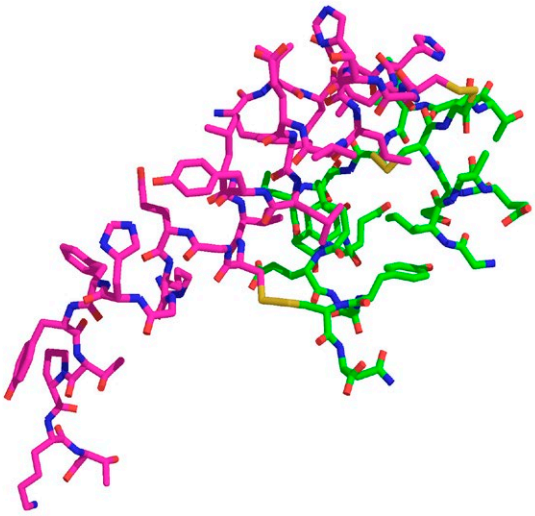
Distinguished Chair
noncovalent interaction, quantum chemistry, drug design, protein-ligand binding, molecular dynamics

DIABETES TREATMENT



Insulin Receptor



Insulin Analog

Research topics

Our ultimate goal is to find new drugs against devastating or chronic diseases, such as cancer or diabetes. To this aim, we develop our own quantum mechanics-based scoring function and apply it in docking and virtual screening. We build on our decade-long experience in the computational description of noncovalent interactions in biomacromolecules using quantum chemical and molecular dynamics methods. We have applied our methodology to discover and optimize new ligands of cyclin-dependent kinases and understand the binding of HIV-1, aldose reductase, and parasitic cysteine peptidase inhibitors. Currently, we focus on insulin analogs and mimetics using the structures of the insulin receptor. The generality of the newly developed quantum mechanics-based scoring functions has been tested on an extended dataset of diverse protein-ligand complexes, and their performance was compared to that of widely used scoring functions from academia and industry. We found that our scoring functions clearly outperform the standard functions. We propose this method for general use in computer-aided drug design.

Our new project concerns the application of noncovalent interactions in material sciences. Electronic and spin states of metal-containing organic molecules can be tuned by their noncovalent interactions with metallic and carbon-containing surfaces. Doping of the latter surfaces with nitrogen or boron significantly affects these molecules. The project extends to the investigation of the excited-state behavior of graphene-derived quantum dots modified by covalent and noncovalent interactions. Molecular sieves prepared by a recently discovered synthetic pathway using 2D layers as nanoscale building blocks do not obey criteria for traditional solvothermal synthesis. We are focusing on unique properties of these molecular frameworks leading to novel functions and new applications. Our main goal is (i) to develop a precise and reliable methodology for evaluating the properties of these materials and (ii) to determine how they can be utilized in technologically important processes such as adsorption, gas separation, and catalysis.

Group members

Group leader Pavel Hobza
Scientists Ota Bludský, Jindřich Fanfrlík, Martin Lepšík, Dana Nachtigallová, Jan Řezáč, Radek Zbořil
Postdocs Thomas Evangelidis, Rabindranath Lo, Debashree Manna, Vijay Madhav Miriyala, Anja Muždalo, Miroslav Rubeš, Amrit Sarmah, Yevgen Yurenko
Ph.D. students Saltuk Mustafa Eyrilmez, Cemal Köprülüoğlu, Kristián Kříž, Radek Majdloch, Michal Trachta
Student Michaela Černeková
Secretary Helena Černá

Selected papers

Nachtigallova, D.; Antalik, A.; Lo, R.; Sedlak, R.; Manna, D.; Tucek, J.; Ugolotti, J.; Veis, L.; Legeza, O.; Pittner, J.; Zboril, R.; Hobza, P. An Isolated Molecule of Iron(II) Phthalocyanin Exhibits Quintet Ground-State: A Nexus between Theory and Experiment. *Chem. – Eur. J.* **2018**, 24, 13413–13417.

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Jia, C.D.; Zuo, W.; Yang, D.; Chen, Y.M.; Cao, L.P.; Custelcean, R.; Hostaš, J.; Hobza, P.; Glaser, R.; Wang, Y.Y.; Yang, X.J.; Wu, B. Selective binding of choline by a phosphate-coordination-based triple helicate featuring an aromatic box. *Nat. Commun.* **2017**, 8, 938.

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Řezáč, J.; Hobza, P. Benchmark Calculations of Interaction Energies in Noncovalent Complexes and Their Applications. *Chem.Rev.* **2016**, 116, 5038–5071.

Kolář, M.H.; Hobza, P. Computer Modeling of Halogen Bonds and Other σ-Hole Interactions. *Chem. Rev.* **2016**, 116, 5155–5187.

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Trachta, M.; Nachtigall, P.; Bludský, O. The ADOR synthesis of new zeolites: In silico investigation. *Catal. Today* **2015**, 243, 32–38.

Financial support

Control of electronic properties of metal-containing molecules through their noncovalent interactions with solvents, ligands and 2D nanosystems. Czech Science Foundation (GA ČR), No. 19-27454X, 2019–2023, Hobza, P.

Building a database of benchmark data for parametrization of next-generation semiempirical quantum-mechanical methods. Czech Science Foundation (GA ČR), No. 19-13905S, 2019–2021, Řezáč, J.

A Structure-Based Predictive Model for Brønsted Acid Catalyzed Reactions. Czech Science Foundation (GA ČR), No. 19-19542S, 2019–2021, Bludský, O.

Unfeasible molecular frameworks: properties and applications. Czech Science Foundation (GA ČR), No. 17-07642S, 2018–2020, Bludský, O.

Formation of covalent molecular complexes on surfaces driven by light induced chemical reactions. Czech Science Foundation (GA ČR), No. 18-09914S, 2018–2020, Nachtigallová, D.

Getting stronger together: exo-substituted heteroboranes and their adducts as suitable motifs for exploration of non-covalent interactions. Czech Science Foundation (GA ČR), No. 17-08045S, 2017–2019, Fanfrlík, J.

Awards—Pavel Hobza

Pavel Jungwirth Group

Molecular Modeling
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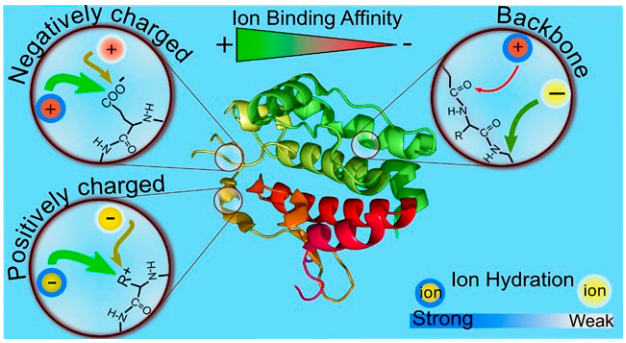
Distinguished Chair

molecular simulations, water, ions, proteins, membranes, solvated electrons, Hofmeister series

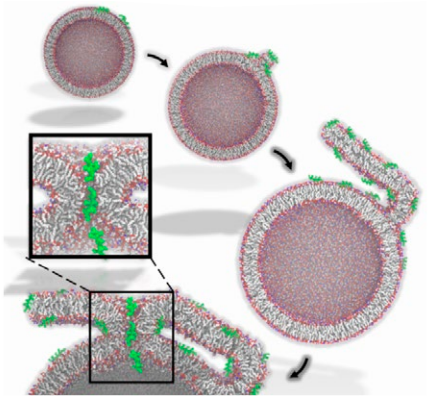
Ion Protein Interactions in Solution

J. Phys. Chem. B 121, 1997-2014 (2017)



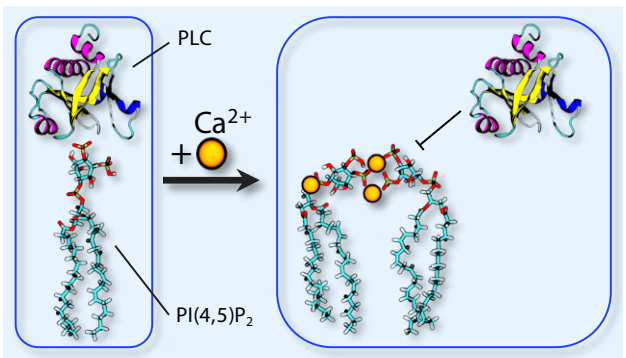
Cell Penetrating peptides and Membrane Fusion

PNAS 115, 11923-11928 (2018)



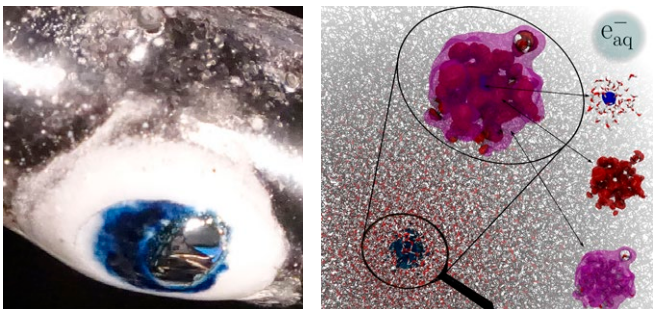
Calcium Signaling at Cell Membranes

J. Am. Chem. Soc. 139, 4019-4024 (2017)



Structure, Dynamics, and Reactivity of Solvated Electrons

Angew. Chem. Int. Ed. 55, 13019-13022 (2016), Nature Chemistry 7, 250-254 (2015)



Research topics

We aim at gaining a molecular-level understanding of biological processes involving ions using computer simulations in close contact with spectroscopic experiments. Using molecular dynamics simulations and quantum chemical methods, we are attempting to establish the mechanisms of ion-protein interactions responsible for the salting-out (Hofmeister) series and beyond. Applications of our research range from influencing protein aggregation, precipitation or denaturation, and controlling enzymatic activity to establishing properties of phospholipid bilayers in the presence of ions. One of the key aims within the latter subject is to establish molecular principles governing the action of calcium ions involved in membrane fusion and cationic cell penetrating peptides (important, e.g., for novel ways of drug delivery to cells).

Our related research activities concern electron solvation pertinent to radiation chemistry and DNA damage. Additionally, in our free time, we entertain ourselves with “balcony experiments” involving, for example, explosions of alkali metals in water, which also allows us to connect to the general public and popularize science.

Group members

Group leader Pavel Jungwirth
Scientists Hector Martinez-Seara Monne, Phil Mason, Lukasz Cwiklik
Postdocs Matti Javanainen, Balázs Fábián, Pauline Delcroix
Research assistant Barbara Jagoda-Cwiklik
Ph.D. students Tomáš Martinek, Vladimír Palivec, Ondřej Ticháček, Daniel Holý, Nguyen Man, Katarína Baxová
Students Kryštof Březina, Martin Crhán

Selected papers

Allolio, C.; Magarkar, A.; Jurkiewicz, P.; Baxová, K.; Javanainen, M.; Mason, P.E.; Šachl, R.; Cebecauer, M.; Hof, M.; Horinek, D.; Heinz, V.; Rachel, R.; Ziegler, C.M.; Schröfel, A.; Jungwirth, P. Arginine-rich cell-penetrating peptides induce membrane multilamellarity and subsequently enter via formation of a fusion pore. *PNAS* **2018**, 115, 11923.

Timr, Š.; Pleskot, R.; Kadlec, J.; Kohagen, M.; Magarkar, A.; Jungwirth, P. Membrane Binding of Recoverin: From Mechanistic Understanding to Biological Functionality. *ACS Cent. Sci.* **2017**, 3, 868–874.

Bilkova, E.; Pleskot, R.; Rissanen, S.; Sun, S.; Czogalla, A.; Cwiklik, L.; Róg, T.; Vattulainen, I.; Cremer, P.S.; Jungwirth, P.; Coskun, Ü. Calcium Directly Regulates Phosphatidylinositol 4,5-Bisphosphate Headgroup Conformation and Recognition. *J. Am. Chem. Soc.* **2017**, 139, 4019–4024.

Mason, P.E.; Buttersack, T.; Bauerecker, S.; Jungwirth, P. A Non-Exploding Alkali Metal Drop on Water: From Blue Solvated Electrons to Bursting Molten Hydroxide. *Angew. Chem. Int. Ed.* **2016**, 55, 13019–13022.

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Mason, P.E.; Uhlig, F.; Vaněk, V.; Buttersack, T.; Bauerecker, S.; Jungwirth, P. Coulomb explosion during the early stages of the reaction of alkali metals with water. *Nat. Chem.* **2015**, 7, 250.

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Savolainen, J.; Uhlig, F.; Ahmed, S.; Hamm, P.; Jungwirth, P. Direct observation of the collapse of the delocalized excess electron in water. *Nat. Chem.* **2014**, 6, 697.

Paterová, J.; Rembert, K.B.; Heyda, J.; Kurra, Y.; Okur, H.I.; Liu, W.R.; Hilty, C.; Cremer, P.S.; Jungwirth, P. Reversal of the Hofmeister Series: Specific Ion Effects on Peptides. *J. Phys. Chem. B* **2013**, 117, 8150–8158.

Financial support

Concert of lipids, ions, and proteins in cell membrane dynamics and function. Czech Science Foundation (GA ČR), EXPRO, No. 19-26854X, 2018–2022.

Chemical biology for development of new therapies. European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022.

Beyond the Hofmeister series: from molecular understanding of specific ion effects to their biological function. Czech Science Foundation (GA ČR), No. 16-01074S, 2016–2018.

Translocation of molecules across cell membranes. Finland Distinguished Professor of the Academy of Finland, 2013–2017.

Interaction of ions with biomolecules in solutions: computer simulations and experiments. Czech Academy of Sciences, Praemium Academiae, 2010–2016.

Awards—Pavel Jungwirth

Spiers Memorial Prize of the Royal Society for Chemistry (2008)

Elected member of the Learned Society of the Czech Republic (2009)

Praemium Academie Prize of the Czech Academy of Sciences (2010)

Jaroslav Heyrovsky Medal of the Czech Academy of Sciences (2016)

Service to the scientific community

Senior Editor of Journal of Physical Chemistry of the American Chemical Society

Popularization of science—regular articles in Czech newspapers and magazines on science and society. Numerous radio and TV shows on popular science.

Josef Lazar Group

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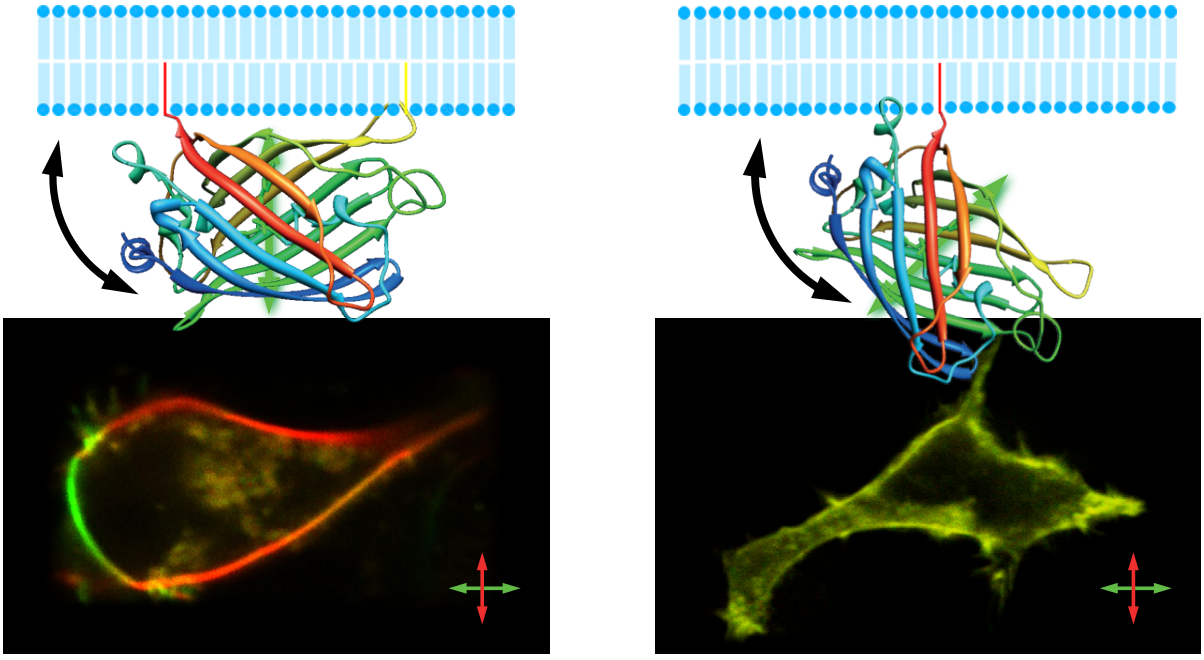
Junior Research Group
Advanced optical microscopy, two-photon polarization microscopy, fluorescent proteins, image processing, linear dichroism, molecular probes, G-proteins, voltage sensors

OBSERVING MOLECULAR ORIENTATIONS USING TWO-PHOTON POLARIZATION MICROSCOPY

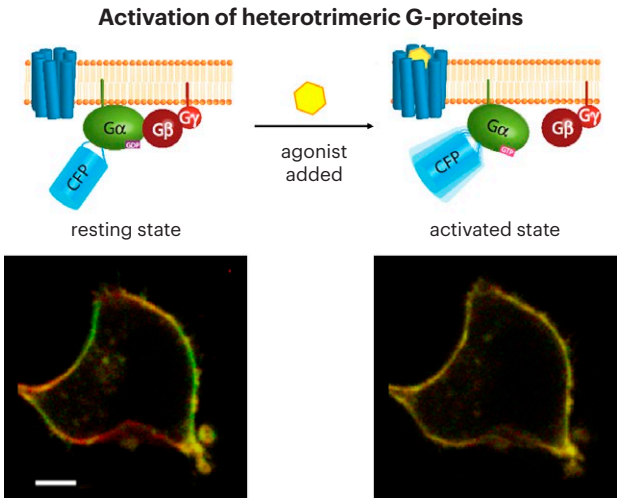


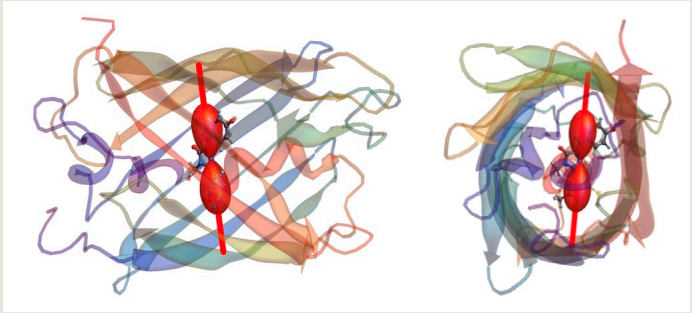
Research topics

The Laboratory of Advanced Optical Microscopy develops advanced techniques of optical microscopy and uses them to gain information about mechanisms of molecular processes taking place in living cells and organisms. The laboratory has developed the technique of two-photon polarization microscopy (2PPM), which allows sensitive observations of changes in conformation of membrane proteins. Such conformational changes can occur, for example, in response to a therapeutic drug or to changes in cell membrane voltage. We are particularly interested in observing various molecular processes involved in GPCR/G-protein signaling, as well as in signaling by tyrosine kinases, such as the insulin receptor. Apart from allowing detection of molecular processes in living cells, the 2PP technique should also allow for detailed insights into the molecular structure of the participating proteins. In order to take full advantage of these capabilities, we have been investigating linear and nonlinear optical properties of fluorescent proteins, particularly through optical measurements of crystals of fluorescent proteins.

The laboratory is equipped with a laser scanning confocal/two-photon microscope (Olympus FluoView 1200MPE-IX83) adapted for single- and two-photon polarization microscopy. The microscope's versatile design accommodates a wide range of microscopy techniques and custom solutions.

The laboratory's extensive multidisciplinary expertise spans physiology, biochemistry, molecular and cell biology, protein crystallography, biophysics, optics, electronic engineering, computer programming, and mathematical modeling. This broad range of skills makes it possible to tackle a range of difficult scientific questions.





Above: The laboratory is investigating directional optical properties of fluorescent proteins, which allow gaining insights into the structure of fluorescently labeled membrane proteins. Left: Two-photon polarization microscopy allows sensitive imaging of activation of G protein signaling, by detecting changes in orientation of a fluorescent label accompanying activation of G proteins.

Group members

Group leader Josef Lazar
Postdocs Alexey Bondar, Petro Khoroshyy, Paul Sebastian Miclea, Jitka Myšková
Research assistant Gabriela Kocurová
Students Veronika Bělíková, Jan Dohnálek, Olga Rybakova, Alina Sakhi

Selected papers

Bondar, A.; Lazar, J. The G protein G(i1) exhibits basal coupling but not preassembly with G protein-coupled receptors. *J. Biol. Chem.* **2017**, 292, 9690–9698.

Bondar, A.; Lazar, J. Dissociated GαGTP and Gβγ Protein Subunits Are the Major Activated Form of Heterotrimeric Gi/o Proteins. *J. Biol. Chem.* **2014**, 289, 1271–1281.

Timr, Š.; Bondar, A.; Cwiklik, L.; Štefl, M.; Hof, M.; Vazdar, M.; Lazar, J.; Jungwirth, P. Accurate Determination of the Orientational Distribution of a Fluorescent Molecule in a Phospholipid Membrane. *J. Phys. Chem. B* **2014**, 118, 855–863.

Han, Z.; Jin, L.; Chen, F.; Loturco, J.J.; Cohen, L.B.; Bondar, A.; Lazar, J.; Pieribone, V.A. Mechanistic Studies of the Genetically Encoded Fluorescent Protein Voltage Probe ArcLight. *PLoS One* **2014**, 9, e113873.

Lazar, J.; Bondar, A.; Timr, S.; Firestein, S.J. Two-photon polarization microscopy reveals protein structure and function. *Nat. Methods* **2011**, 8, 684.

Financial support

Chemical biology for development of new therapies. European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022.

Systems biology center (C4Sys), Ministry of Education, Youth and Sports (MŠMT), Center of excellence, No. LM2015055, 2016–2019, Lazar, J.

Lubomír Rulíšek Group

Theoretical Bioinorganic Chemistry
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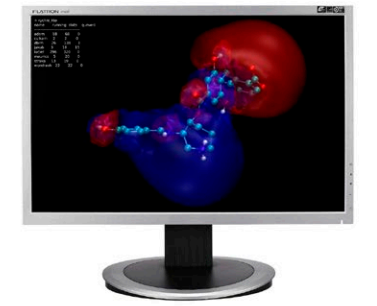
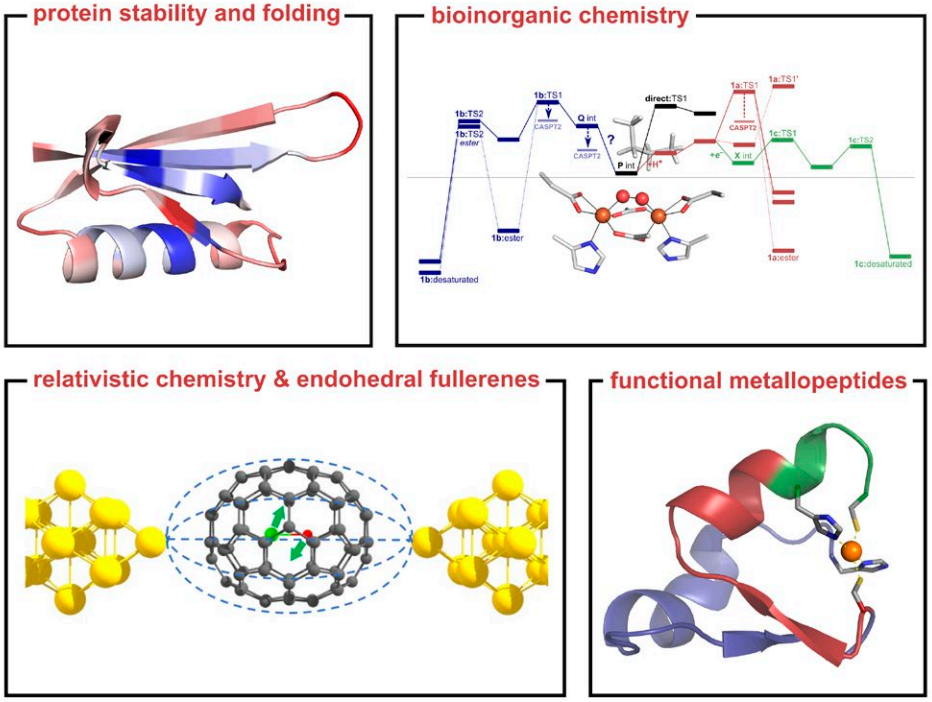
Senior Research Group
metalloenzymes, catalysis, molecular design, structure-function correlations, molecular switches, principles of protein folding, ligand binding, relativistic effects, theoretical spectroscopy



> COMPUTATIONAL CHEMISTRY_



Research topics

Computational (bio)chemistry has become an integral part of our understanding of chemical and biological systems and processes. Specifically, it has greatly assisted in shedding light on the catalytic action of metalloproteins, mostly by elucidating their reaction mechanisms. The accumulated expertise, applicability of modern quantum mechanical methods for realistic systems, availability of reasonably accurate solvation models and QM/MM-like coupling schemes along with bioinformatics, or structural search engines may ultimately unleash its predictive power and lead to delivery of a material output in the near future.

The major efforts of the group aim at an *ab initio* design of both small catalytic metallopeptides and highly specific metal chelators. Our approach involves development of a unique set of computer programs operating on top of a database of peptidic fragments obtained from the Protein Data Bank or resulting from large-scale conformational searches of short peptides and merging them into a predefined single-chain scaffold, either mimicking a protein active site or a chelator. A sophisticated coupling to external QM or QM/MM(MD) programs is implemented to verify inherent stability and catalytic properties of the designed systems.

Other research topics in the group include development of quantum and molecular mechanical (QM/MM) methods, organic reactivity, computational homogeneous catalysis, protein-ligand interactions, computational electrochemistry, theoretical spectroscopy, relativistic quantum chemistry, and the design of novel fullerenes that can act as molecular switches, transistors, and memristors. Our recent contributions to general chemical knowledge include theoretical and experimental proof of hydrogen bonding to gold and understanding of heavy-atom effects on NMR chemical shifts across the periodic table.

Group members

Group leader Lubomír Rulíšek
Scientists Michal Straka, Martin Srnec (J. Heyrovský Inst. Phys. Chem. CAS, part-time commitment at IOCB)
Postdocs Daniel Bím, Martin Culka, Ondrej Gutten
Ph.D. student Adam Jaroš
Students Daniel Herman, Tadeáš Kalvoda, Lucie Tučková

Selected papers

Vícha, J.; Foroutan-Nejad, C.; Straka, M. ^{1}H NMR is not a proof of hydrogen bonds in transition metal complexes *Nat. Commun.* **2019**, 10, 1643.

Culka, M.; Galgonek, J.; Vymětal, J.; Vondrášek, J.; Rulíšek, L. Toward Ab Initio Protein Folding: Inherent Secondary Structure Propensity of Short Peptides from the Bioinformatics and Quantum-Chemical Perspective. *J. Phys. Chem.* B **2019**, 123, 1215–1227.

Straka, M.; Andris, E.; Vícha, J.; Růžička, A.; Roithová, J.; Rulíšek, L. Spectroscopic and Computational Evidence of Intramolecular Au···H^{+}–N Hydrogen Bonding. *Angew. Chem. Int. Ed.* **2019**, 58, 2011–2016.

Foroutan-Nejad, C.; Straka, M.; Fernandez, I.; Frenking, G. Buckyball Difluoride F_2(-) @C_{60}(+) -A Single-Molecule Crystal *Angew. Chem. Int. Ed.* **2018**, 57, 13931.

Bím, D.; Maldonado-Domínguez, M.; Rulíšek, L.; Srnec, M. Beyond the Classsical Thermodynamic Contributions to Hydrogen Atom Abstraction Reactivity. *PNAS* **2018**, 115, E10287–E10294.

Andris, E.; Andrikopoulos, P.C.; Schulz, J.; Turek, J.; Růžička, A.; Roithová, J.; Rulíšek, L. Aurophilic Interactions in [(L)AuCl]...[(L')AuCl] Dimers: Calibration by Experiment and Theory. *J. Am. Chem. Soc.* **2018**, 140, 2316–2325.

Gutten, O.; Bím, D.; Řezáč, J.; Rulíšek, L. Macrocycle Conformational Sampling by DFT-D3/COSMO-RS Methodology. *J. Chem. Inf. Model* **2018**, 58, 48–60.

Rokob, T.A.; Chalupský, J.; Bím, D.; Andrikopoulos, P.C.; Srnec, M.; Rulíšek, L. Mono- and binuclear non-heme iron chemistry from a theoretical perspective. *J. Biol. Inorg. Chem.* **2016**, 21, 619–644. Invited Perspective.

Bím, D.; Rulíšek, L.; Srnec, M. Accurate Prediction of One-Electron Reduction Potentials in Aqueous Solution by Variable-Temperature H-Atom Addition/ Abstraction Methodology. *J. Phys. Chem. Lett.* **2016**, 7, 7–13.

Chalupský, J.; Rokob, T.A.; Kurashige, Y.; Yanai, T.; Solomon, E.I.; Rulíšek, L.; Srnec, M. Reactivity of the Binuclear Non-Heme Iron Active Site of D9 Desaturase Studied by Large-Scale Multireference Ab Initio Calculations. *J. Am. Chem. Soc.* **2014**, 136, 15977–15991.

Financial support

Exploring Conformational Space of Short Peptides by Advanced Quantum Chemical and Solvation Methods: A Key to Understand Protein Structures? Czech Science Foundation (GA ČR), No. 17-24155S, 2017–2019, Rulíšek, L.

Novel Single-Molecule Switches Based on Endohedral Fullerenes. Czech Science Foundation (GA ČR), No. 17-07091S, 2017–2019, Straka, M.

Gilead Sciences & IOCB Research Center, 2016-2021, Rulíšek, L.

Collaboration

IOCB Prague: Petr Beier, Michal Hocek, Pavel Hobza, Ullrich Jahn, Jan Konvalinka, Josef Michl, Jan Řezáč, Ivo Starý, Miloslav Polášek

Domestic: Radek Marek (*Masaryk Univ., CEITEC, Brno*), Pavel Kočovský, Petr Hermann (*Charles University, Prague*), Aleš Růžička (*Univ. Pardubice*), Jan Vícha (*Univ. TB, Zlín*)

International: Edward I. Solomon (*Stanford Univ., USA*), Ulf Ryde (*Lund Univ., Sweden*), Jana Roithová (*Radboud University, Nijmegen, Netherlands*), Aleš Svatoš (*MPI Chemical Ecology, Jena, Germany*), Takeshi Yanai (*Institute for Molecular Science, Okazaki, Japan*), Tibor András Rokob (*Hungary*), František Tureček (*Univ. Washington, Seattle, USA*), Juha Vaara (*Univ. Oulu, Finland*), Martin Kaupp (*TU Berlin, Germany*), Gernot Frenking (*Philipps-Universität Marburg, Germany*)

Awards—Lubomír Rulíšek

Hlavka Foundation Prize (2001)—an annual award for outstanding Ph.D. students in the Czech Republic

Wichterle Prize of the ASCR (2006)—an award of the Czech Academy of Sciences for an outstanding young researcher

Fulbright Fellowship (2014)—Stanford University

Analytical Laboratory

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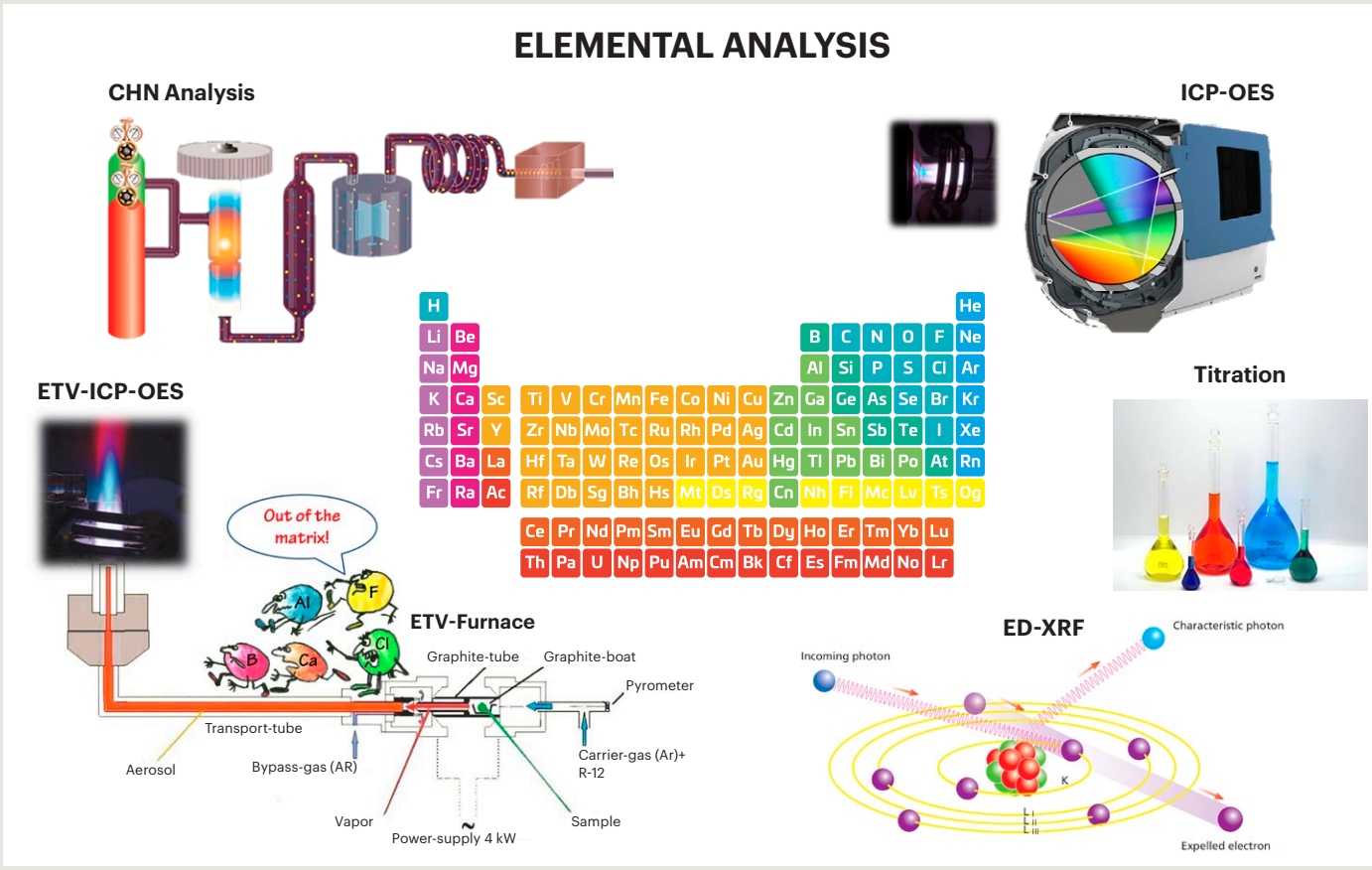
www.uochb.cz/analysis

Service Group

elemental analysis, optical emission spectrometry, energy-dispersive X-ray fluorescence, inductively coupled plasma, electrothermal vaporisation, optical activity, IOCB Library



Research topics

Elemental composition is one of the important basic characteristics of materials. Knowledge of it along with knowledge of the structure makes it possible to explain or even predict many properties of substances. For chemical individuals, precise elemental composition is a criterion of their purity.

The Analytical Laboratory has undergone a gradual development of methodologies and instrumentation to allow a complete elemental analysis of a minimal amount (units of mg) of various sample types. At the moment, we routinely perform C, H, and N determination and identification or quantitative determination of virtually all the other elements of the periodic table (except for radioactive elements and rare gases) by means of X-ray fluorescence spectroscopy (XRF) and inductively coupled plasma optical emission spectrometry (ICP-OES), possibly coupled to electrothermal evaporation of the sample (ETV-ICP-OES). The F content is determined using an ion-selective electrode.

In special cases, we perform S, P, Cl, Br, and I determination using classical titration methods. We also perform precise weighing of small quantities of substances, measurement of optical rotation of substances, and determination of water in organic solvents.

Group members

Group leader Stanislava Matějková
Research assistants Věra Bártová, Jaroslava Hniličková, Lucie Holasová, Martin Loula
Technicians Magdalena Hošková, Petr Šálek, Luisa Šerá, Štefan Štanga

Selected papers

Mazánek, V.; Luxa, J.; Matějková, S.; Kučera, J.; Sedmidubský, D.; Pumera, M.; Sofer, Z. Ultrapure Graphene Is a Poor Electrocatalyst: Definitive Proof of the Key Role of Metallic Impurities in Graphene-Based Electrocatalysis. *ACS Nano* **2019**, 13, 1574–1582.

Villa, K.; Manzanares Palenzuela, C.L.; Sofer, Z.; Matějková, S.; Pumera, M. Metal-Free Visible-Light Photoactivated C3N4 Bubble-Propelled Tubular Micromotors with Inherent Fluorescence and On/Off Capabilities. *ACS Nano* **2018**, 12, 12482–12491.

Lojka, M.; Jankovský, O.; Sedmidubský, D.; Mazánek, V.; Bouša, D.; Pumera, M.; Matějková, S.; Sofer, Z. Synthesis and properties of phosphorus and sulfur co-doped graphene. *New J. Chem.* **2018**, 42, 16093–16102.

Mazánek, V.; Matějková, S.; Sedmidubský, D.; Pumera, M.; Sofer, Z. One-Step Synthesis of B/N Co-doped Graphene as Highly Efficient Electrocatalyst for the Oxygen Reduction Reaction: Synergistic Effect of Impurities. *Chem. – Eur. J.* **2018**, 24, 928–936.

Blahut, J.; Bernášek, K.; Gálisová, A.; Herynek, V.; Císařová, I.; Kotek, J.; Lang, J.; Matějková, S.; Hermann, P. Paramagnetic 19F Relaxation Enhancement in Nickel(II) Complexes of N-Trifluoroethyl Cyclam Derivatives and Cell Labeling for 19F MRI. *Inorg. Chem.* **2017**, 56, 13337–13348.

Řehoř, I.; Macháčková, L.; Bučánková, A.; Matějková, S.; Černá, K.; Straka, J. Measuring the sugar consumption of larvae in bumblebee micro-colonies: a promising new method for tracking food economics in bees. *Apidologie* **2014**, 45, 116–128.

Collaboration

Department of Inorganic Chemistry, Faculty of Sciences, Charles University, Prague, Czech Republic

Department of Inorganic Chemistry, University of Chemistry & Technology, Prague, Czech Republic

Department of Zoology, Faculty of Sciences, Charles University, Prague, Czech Republic

Instrumentation

Organic elemental analysis
PE 2400 Series II CHNS/O Analyzer

Atomic emission spectroscopy
X-ray Fluorescence Spectrometer SPECTRO Xepos P
ICP-OES spectrometer SPECTRO Arcos SOP coupled with electrothermal vaporisation unit ETV 4000c Spectral Systems P. Perzl
ICP-OES spectrometer SPECTRO Arcos MultiView

Microbalances
MX Mettler-Toledo
MSA6.6S-OCE-DM Sartorius
MYA 5.3Y Radwag

Other instruments
Autopol IV Polarimeter Rudolph Research
Coulometer WTD Diram—Karl Fischer moisture determination

Electromigration Methods

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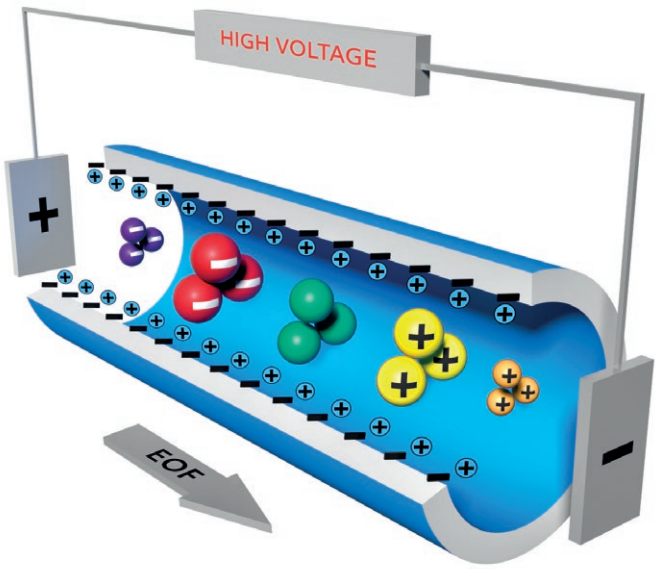
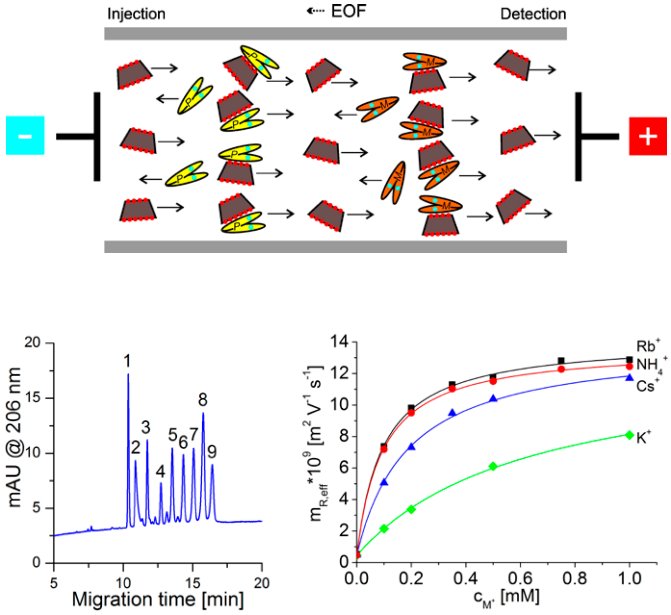
Research-Service Group

electroseparation methods, capillary electrophoresis, affinity electrophoresis, isotachophoresis, isoelectric focusing, electrokinetic chromatography, electrochromatography, analytical chemistry





Research topics

The group is engaged in research and development of theory, methodology, and instrumentation of capillary electromigration (CE) methods and their application for the separation, analysis, micropreparation, and characterization of (bio) molecules.

METHODOLOGY

Methodology developments include all major CE techniques: zone electrophoresis, affinity electrophoresis, isotachophoresis, isoelectric focusing, electrokinetic chromatography, and electrochromatography. New background electrolytes and (pseudo)stationary phases are being developed with the aim of increasing the separation efficiency and selectivity of CE methods. Special procedures are being elaborated for physico-chemical and biochemical characterization of (bio) molecules and for investigation of their interactions. New coatings of fused silica capillaries are being prepared to suppress adsorption of analytes to the inner capillary wall and to control the electroosmotic flow.

INSTRUMENTATION

New devices for one- and two-dimensional CE methods with a multidimensional detection system are under development. Two-dimensional separations are implemented by on-line combination of orthogonal CE methods in two in-series connected capillaries. The detection system is composed of contactless conductivity, UV spectrophotometric, laser induced fluorescence, and mass spectrometric detectors.

APPLICATIONS

The developed methods are employed for fast, high-efficient separation, highly sensitive qualitative and quantitative ultramicroanalysis, microscale isolation, and physico-chemical and biochemical characterization of amino acids, peptides, proteins, nucleosides, nucleotides, steroids, and other (bio)molecules.

Group members

Group leader Václav Kašička
Scientists Jana Jaklová Dytrtová, Dušan Koval, Petra Sázelová, Veronika Šolínová, Sille Štěpánová
Postdoc Renáta Konášová
Research assistant Michal Jakl
Ph.D. students Jan Hošek, Ishak Kovač, Sachinkumar Pangavhane

Selected papers

Šolínová, V.; Žáková, L.; Jiráček, J.; Kašička, V. Pressure assisted partial filling affinity capillary electrophoresis employed for determination of binding constants of human insulin complexes with serotonin, dopamine, arginine, and phenol. *Anal. Chim. Acta* **2019**, 1052, 170–178.

Štěpánová, S.; Procházková, E.; Čechová, L.; Žurek, J.; Janeba, Z.; Dračínský, M.; Kašička, V. Separation of rotamers of 5-nitrosopyrimidines and estimation of binding constants of their complexes with β-cyclodextrin by capillary electrophoresis. *J. Chromatogr. A* **2018**, 1570, 164–171.

Konášová, R.; Koval, D.; Jaklová Dytrtová, J.; Kašička, V. A comparative study of two CE-ESI/MS interfaces for the determination of the stability constants of complexes by affinity capillary electrophoresis with ESI/MS detection, *J. Chromatogr. A* **2018**, 1568, 197–204.

Talele, H.R.; Koval, D.; Severa, L.; Reyes-Gutiérrez, P.E.; Císařová, I.; Sázelová, P.; Šaman, D.; Bednárová, L.; Kašička, V.; Teplý, F. Diquats with robust chirality: Facile resolution, synthesis of chiral dyes and application as selectors in chiral analysis, *Chem. – Eur. J.* **2018**, 24/30, 7601–7604.

Štěpánová, S.; Kašička, V. Application of capillary electromigration methods for physicochemical measurements, chapter in the book, Colin Poole (Ed.): *Capillary Electromigration Separation Methods*, Elsevier, Amsterdam, **2018**, pp. 547–591.

Kašička V. Recent developments in capillary and microchip electroseparations of peptides (2015–mid 2017), *Electrophoresis* **2018**, 39, 209–234.

Pangavhane, S.; Böhm, S.; Makrlík, E.; Ruzza, P.; Kašička, V. Affinity capillary electrophoresis and density functional theory study of noncovalent interactions of cyclic peptide [Gly6]-antamanide with small cations, *Electrophoresis* **2017**, 38, 2025–2033.

Tůmová, T.; Monincová, L.; Nešuta, O.; Čeřovský, V.; Kašička, V. Determination of effective charges and ionic mobilities of polycationic antimicrobial peptides by capillary isotachophoresis and capillary zone electrophoresis. *Electrophoresis* **2017**, 38, 2018–2024.

Sázelová, P.; Koval, D.; Severa, L.; Teplý, F.; Kašička, V. Chiral analysis of alpha-diimine Ru(II) and Fe(II) complexes by capillary electrophoresis using sulfated cyclodextrins as stereoselectors, *Electrophoresis* **2017**, 38, 1913–1921.

Štěpánová, S.; Kašička, V. Analysis of proteins and peptides by electromigration methods in microchips, *J. Sep. Sci.* **2017**, 40, 228–250.

Geffertová, G.; Ali, S.T.; Šolínová, V.; Krečmerová, M.; Holý, A.; Havlas, Z.; Kašička, V. Investigation of the acid-base and electromigration properties of 5-azacytosine derivatives using capillary electrophoresis and density functional theory calculations, *J. Chromatogr. A* **2017**, 1479, 185–193.

Financial support

Capillary electromigration techniques using affinity selectors and smart polymers for analysis and properties and interactions studies of biomolecules. Czech Science Foundation (GA ČR), No. 15-01948S, 2015–2017, Kašička, V.

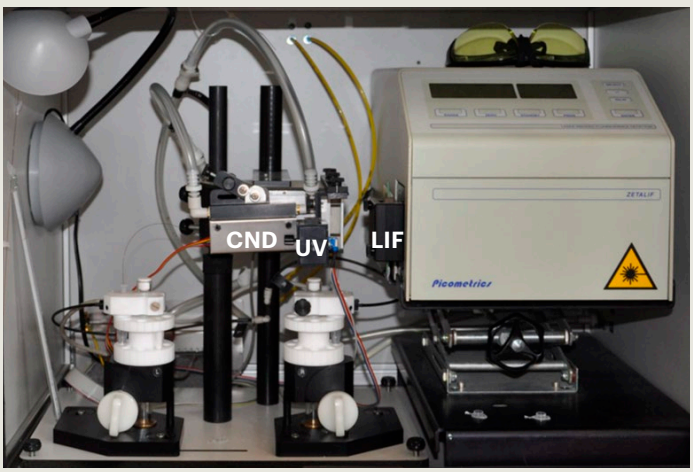
Novel stationary phases for chromatographic separation of chiral compounds. Ministry of Industry and Trade (MPO), Program Trio, 2016–2019, Koval, D.

Advanced instrumentation and methodology for separation, analysis and characterization of (bio)moleclues by capillary electromigration methods. Czech Science Foundation (GA ČR), No. 17-10832S, 2017–2019, Kašička, V.

Tools for separation optimization in capillary electrophoresis. Czech Science Foundation (GA ČR), No. 17-12648S, 2017–2019, Koval, D.

Group interactions of azol pesticides and their effects on essential enzymes. Czech Science Foundation (GA ČR), No. 18-01710S, 2018–2020, Jaklová Dytrtová, J.

New multibinding (pseudo)stationary phases for chromatographic and electromigration separations of (bio)molecules. Czech Science Foundation (GA ČR), No. 18-02597S, 2018–2020, Kašička, V.



Capillary electrophoretic analyzer with multidimensional detection system consisting of conductivity (CND), UV-absorption (UV), and laser-induced fluorescence (LIF) detectors.

Mass Spectrometry

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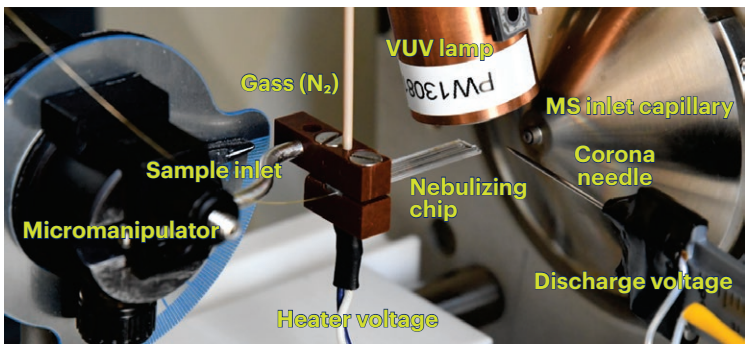
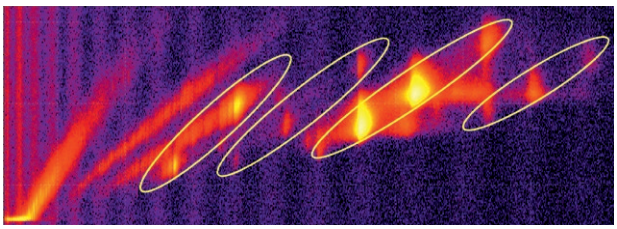
Research-Service Group

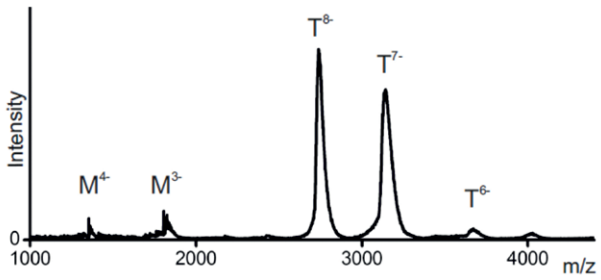
mass spectrometry, organic compounds, structure elucidation, development of methods and instrumentation

Development of ion sources

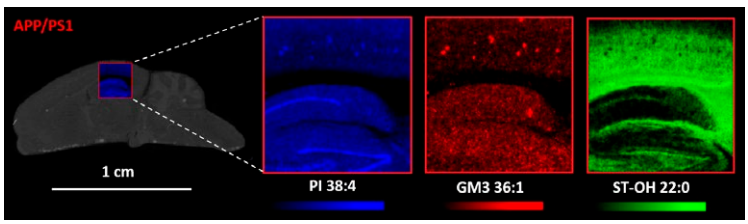


Ion mobility of oligonucleotides





MALDI imaging of lipids



Research topics

Our group uses mass spectrometry to answer diverse scientific questions. Mass spectrometry (MS) is utilized for structure elucidation, identification, and quantification of organic compounds ranging from small molecules to large biomacromolecules. As the current approaches are sometimes inappropriate for particular tasks, new methods, applications, and devices are being developed. In addition to our own research program, the group members perform routine analyses for the IOCB scientific community, maintain open-access instruments, and provide collaborative support.

The group's projects are largely focused on lipids. These compounds are characterized using chromatography and MS with the aim of understanding their biologic roles. Our workflows encompass extraction of the biological material, fractionation, isolation of a lipid class of interest, and comprehensive characterization of lipid species. Ingenious MS approaches are used to elucidate lipid structures, including, for example, establishing double bond position(s). The current projects are mostly concerned with rather non-polar lipids having long aliphatic chains. Such lipids are found on human skin and in the vernix caseosa, which covers the developing fetus. Our long-term involvement in vernix caseosa research has led to the discovery of several new lipid classes. MS imaging is used for visualizing the spatial distribution of various lipids on the surfaces of insect and plant samples, or in tissue sections. For instance, MALDI imaging is used to study lipids in the brains of mouse models of neurodegeneration. We are also involved in numerous projects requiring identification, characterization, and quantification of other biomolecules such as proteins or nucleic acids. In addition to routinely used classical workflows, methods relevant for structural biology, including native, crosslinking, and hydrogen exchange MS, are being implemented to study noncovalent protein complexes. As regards instrumentation, we try to develop new types of ion sources for sensitive detection of various analytes.

Group members

Group leader Josef Cvačka
Scientists Martin Hubálek, Vladimír Vrkoslav
Postdocs Eva Harazim, Petra Junková
Research assistants Ondřej Hodek, Kvetoslava Kertisová, Alena Křenková, Martina Mušutová, Kateřina Nováková, Eva Slabá, Martin Svoboda
Ph.D. students Jana Březinová, Petra Horká, Aneta Kalužíková, Barbora Rumlová, Timotej Strmeň, Štěpán Strnad
Technician Michal Korecký
Students Adéla Pravdová, Sabina Tomášková

Selected papers

Strnad, Š.; Pražienková, V.; Sýkora, D.; Cvačka, J.; Maletínská, L.; Popelová, A.; Vrkoslav, V. The use of 1,5-diaminonaphthalene for matrix-assisted laser desorption/ionization mass spectrometry imaging of brain in neurodegenerative disorders. *Talanta* **2019**, 201, 364–372.

Tok, O.L.; Lang, K.; Růžička, A.; Cvačka, J. Helicenes Built from Silacyclopentadienes via Ring-by-Ring Knitting of the Helical Framework. *Angew. Chem. Int. Ed.* **2019**, 58, 1654–1658.

Harazim, E.; Vrkoslav, V.; Buděšínský, M.; Harazim, P.; Svoboda, M.; Plavka, R.; Bosáková, Z.; Cvačka, J. Nonhydroxylated 1-O-acylceramides in vernix caseosa. *J. Lipid Res.* **2018**, 59, 2164–2173.

Strnad, Š.; Vrkoslav, V.; Klimšová, Z.; Zemenová, J.; Cvačka, J.; Maletínská, L.; Sýkora, D. Application of matrix-assisted laser desorption/ionization mass spectrometry imaging in combination with LC-MS in pharmacokinetic study of metformin. *Bioanalysis* **2018**, 10, 71–81.

Vrkoslav, V.; Rumlová, B.; Strmeň, T.; Nekvasilová, P.; Šulc, M.; Cvačka, J. Applicability of low-flow atmospheric pressure chemical ionization and photoionization mass spectrometry with a microfabricated nebulizer for neutral lipids. *Rapid Commun. Mass Spectrom.* **2018**, 32, 639–648.

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Equipment

Orbitrap Fusion Lumos hybrid MS with 1M option, ETD, UVPD and with ESI, nano-ESI, APPI and APCI sources (Thermo Fisher Scientific)

LTQ Orbitrap XL hybrid MS with ESI, nano-ESI and APCI sources (Thermo Fisher Scientific)

LCQ Fleet quadrupole ion trap MS with ESI, nano-ESI and APCI sources (Thermo Fisher Scientific)

SYNAPT G2 quadrupole-ion mobility-TOF hybrid MS with ESI, nano-ESI, APCI and MALDI sources (Waters)

Q-Tof micro hybrid quadrupole TOF MS with ESI, nano-ESI and APCI sources (Waters)

TripleTOF 5600 hybrid quadrupole TOF MS with nanoESI source (AB SCIEX)

QTRAP 6500+ triple quadrupole with SelexION+ MS and with ESI, nano-ESI and APCI sources (Sciex)

UltrafleXtreme MALDI-TOF/TOF MS (Bruker)

MSD 5975 quadrupole EI-MS coupled to GC (Agilent)

NMR and Molecular Spectroscopy

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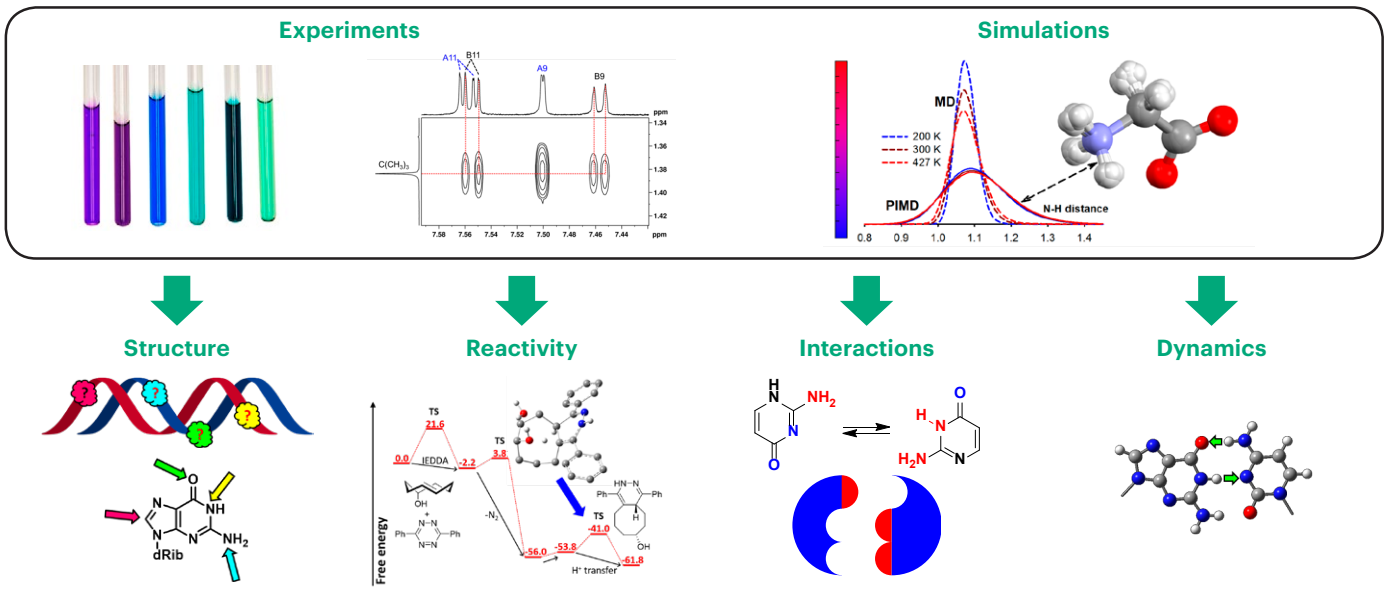
Research-Service Group

NMR, EPR, IR, Raman, circular dichroism, structural analysis, theoretical calculation



Research topics

Our research is focused on structural studies of both synthetic compounds originating in the IOCB laboratories and compounds isolated from natural sources. We utilize modern one- and multidimensional NMR techniques for structure elucidation of nucleosides, nucleotides, peptides, steroids, saccharides, pheromones, helicenes, and other classes of compounds. We develop new methods for determination of configuration on chiral centers. Our research is also focused on intra- and intermolecular hydrogen bonds and other non-covalent interactions, the mechanism and kinetics of chemical reactions, and determination of conformational dynamics in flexible five-membered rings.

Quantum-chemical calculations of NMR parameters are another important research area of our group. The computational data are useful for prediction and interpretation of experimental NMR spectra. We develop new methods for accurate theoretical predictions that include nuclear quantum effects, vibrational and solvation effects, and molecular dynamics.

The presence and structure of paramagnetic species can be determined by EPR spectrometry. Together with quantum chemical calculations, the method is applied in order to solve structures of paramagnetic molecules/intermediates in chemistry and biochemistry. We have studied redox reactions, such as reduction of viologenlike structures, nitroimidazole derivatives or phthalocyanines on graphite, and oxidation of flavonoid compounds and cobalt complexes used as mediators in synthetic chemistry.

Molecular spectroscopy, namely UV-vis and IR absorption spectroscopy, their chiral variants, and fluorescence spectroscopy are used for structural characterization of many molecular systems and/or studies of their dynamics. Particular attention is given to the study of the secondary and tertiary structure of peptides and proteins and structural studies of other biopolymers (DNA, RNA, etc.). Our research is oriented towards studies of molecular conformation and investigation of molecular dynamics of biopolymers and on assignment of absolute configuration of peptides or their analogs (combining chiral spectroscopy and quantum chemical calculations).

Group members

Group leader David Šaman
Scientists Lucie Bednárová, Miloš Buděšínský, Martin Dračínský, Radek Pohl, Lenka Poštová Slavětínská, Ján Tarábek
Postdoc Eliška Procházková
Research assistants Pavel Fiedler, Markéta Pazderková
Ph.D. students Kateřina Bártová, Ondřej Socha
Students Zuzana Osifová, Jakub Štoček

Selected papers

Pohl, R.; Socha, O.; Slavíček, P.; Šála, M.; Hodgkinson, P.; Dračínský, M. Proton transfer in guanine–cytosine base pair analogues studied by NMR spectroscopy and PIMD simulations. *Faraday Discuss.* **2018**, 212, 331–344.

Dračínský, M.; Buchta, M.; Buděšínský, M.; Vacek-Chocholoušová, J.; Stará, I.G.; Starý, I.; Malkina, O.L. Dihydrogen contacts observed by through-space indirect NMR coupling. *Chem. Sci.* **2018**, 9, 7437–7446.

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Karras, M.; Dąbrowski, M.; Pohl, R.; Rybáček, J.; Vacek, J.; Bednárová, L.; Grela, K.; Starý, I.; Stará, I.G.; Schmidt, B. Helicenes as Chirality-Inducing Groups in Transition-Metal Catalysis: The First Helically Chiral Olefin Metathesis Catalyst. *Chem. – Eur. J.* **2018**, 24, 10994–10998.

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Financial support

Intermolecular interactions studied by NMR spectroscopy and advanced quantum-chemical calculations. Czech Science Foundation (GA ČR), No. 18-11851S, 2018–2020.

Role of white adipose tissue in the thermogenic response. Czech Science Foundation (GA ČR), No. 18-04483S, 2019–2021.

Gilead Sciences & IOCB Research Center, 2017–2021.

Instrumentation

Molecular spectroscopy
- FT-IR spectrometer Nicolet 6700 with GC Agilent GC 6850
- CD Spectrometer Jasco 815
- Spectrometer for Raman spectroscopy—ChiralRMAN-2X

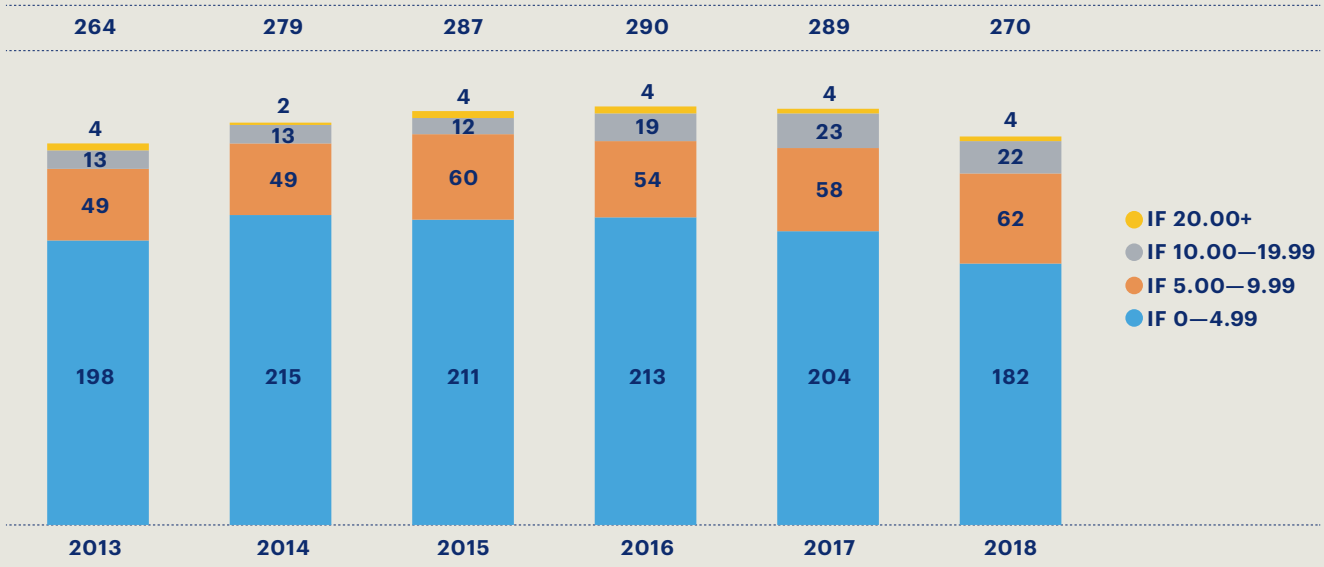
EPR spectroscopy
- Bruker EMX Plus

NMR spectroscopy
- Bruker Avance III HD 850 MHz—with 5 mm TCI cryoprobe
- Bruker Avance III HD 600 MHz—with 1.7 mm TXI and 5 mm TCI cryoprobes
- Bruker Avance III HD 500 MHz—with 5 mm CPBBO cryoprobe
- Bruker Avance II 500 MHz—for SS NMR experiments
- Bruker Avance III HD 400 MHz with PRODIGY cryoprobe
- Bruker Avance III HD 400 MHz
- JEOL ECZ600R/M1 600 MHz—for SS NMR experiments
- JEOL ECZ500R/S3 500 MHz

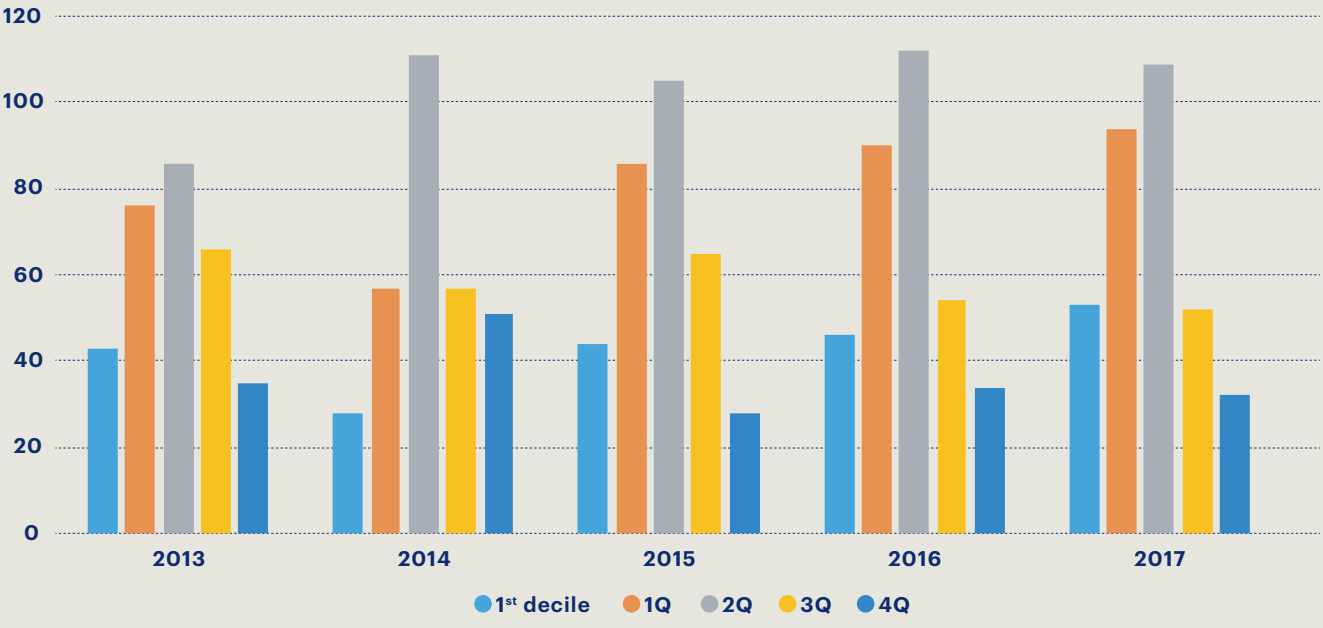
Publications

When it comes to publications, we focus on quality rather than quantity. Today, IOCB scientists publish approximately 300 papers per year, often in top-tier journals in the upper quartile. These articles are often highly cited – some of them more than 1, 000 times.

Publications by Impact Factor



Publications by Decile/Quartile Ranking

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Most significant papers

The most significant publications in three to four categories are selected each year by both external (international) and internal panels of reviewers. Winning papers are awarded prizes.

2018

Zawada, Z. et al. Transport of Nucleoside Triphosphates into Cells by Artificial Molecular Transporters. *Angew. Chem. Int. Ed.* **2018**, 57, 9891–9895.

Shvadchak, V.V. et al. Inhibition of alpha-Synuclein Amyloid Fibril Elongation by Blocking Fibril Ends. *Angew. Chem. Int. Ed.* **2018**, 57, 5690–5694.

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Stetsovych, O. et al. Large Converse Piezoelectric Effect Measured on a Single Molecule on a Metallic Surface. *J. Am. Chem. Soc.* **2018**, 140, 940–946.

Havlik, J. et al. Extremely rapid isotropic irradiation of nanoparticles with ions generated in situ by a nuclear reaction. *Nat. Commun.* **2018**, 9, 4467.

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Keiderling, T.A. and Bouř, P. Theory of Molecular Vibrational Zeeman Effects as Measured with Circular Dichroism. *Phys. Rev. Lett.* **2018**, 121, 073201.

2017

Rendler, T. et al. Optical imaging of localized chemical events using programmable diamond quantum nanosensors. Nat. Commun. **2017**, 8, 1–8.

Stetsovych, O. et al. From helical to planar chirality by on-surface chemistry. *Nat. Chem. 9,* 213–218.

Tesei, G. et al. Self-association of a highly charged arginine-rich cell-penetrating peptide. *PNAS* **2017**, 114, 11428–11433.

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Tichá, A. et al. General and Modular Strategy for Designing Potent, Selective, and Pharmacologically Compliant Inhibitors of Rhomboid Proteases. *Cell Chem. Biol.* **2017**, 24, 1–24.

Vázquez, A. et al. Mechanism-Based Fluorogenic trans-Cyclooctene- Tetrazine Cycloaddition. *Angew. Chem. Int. Ed.* **2017**, 56, 1334–1337.

Mejdrová, I. et al. Rational Design of Novel Highly Potent and Selective Phosphatidylinositol 4-Kinase IIIb (PI4KB) Inhibitors as Broad-Spectrum Antiviral Agents and Tools for Chemical Biology. *J. Med. Chem.* **2017**, 60, 100–118.

Špaček, P. et al. Synthesis and Evaluation of Asymmetric Acyclic Nucleoside Bisphosphonates as Oinhibitors of Plasmodium falciparum and Human Hypoxanthine- Guanine-(Xanthine) Phosphoribosyltransferase. *J. Med. Chem.* **2017**, 60, 7539–7554.

Johnson, N. et al. Quantitative proteomics screen identifies a substrate repertoire of rhomboid protease RHBDL2 in human cells and implicates it in epithelial homeostasis. *Sci. Rep.* **2017**, 7, 1–13.

Klima, M. et al. Kobuviral Non-structural 3A Proteins Act as Molecular Harnesses to Hijack the Host ACBD3 Protein. *Structure* **2017**, 25, 1–12.

Navrátil, V. et al. DNA-linked Inhibitor Antibody Assay (DIANA) for sensitive and selective enzyme detection and inhibitor screening. *Nucleic Acids Res.* **2017**, 45, 1–13.

Lubyova, B. et al. PRMT5: A novel regulator of Hepatitis B virus replication and an arginine methylase of HBV core. *PLoS One* **2017**, 12, 1–28.

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Havlík, J. et al. Benchtop Fluorination of Fluorescent Nanodiamonds on a Preparative Scale: Toward Unusually Hydrophilic Bright Particles. *Adv. Funct. Mater.* **2016**, 26, 4134–4142.

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Rais, R. et al. Discovery of 6-Diazo-5-oxo-L-norleucine (DON) Prodrugs with Enhanced CSF Delivery in Monkeys: A Potential Treatment for Glioblastoma. *J. Med. Chem. Soc* **2016**, 59, 8621–8633.

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Boards

Board of the Institute

The board serves as an advisory authority to the Director and decides on essential scientific and organizational issues.

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Vice-chairman:
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International Advisory Board

The main task of the IAB is to evaluate the research groups at IOCB, provide constructive feedback and suggest future goals and strategies.

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The board monitors the financial and legal matters related to the institute administration.

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Members:
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Research at IOCB Prague 2019

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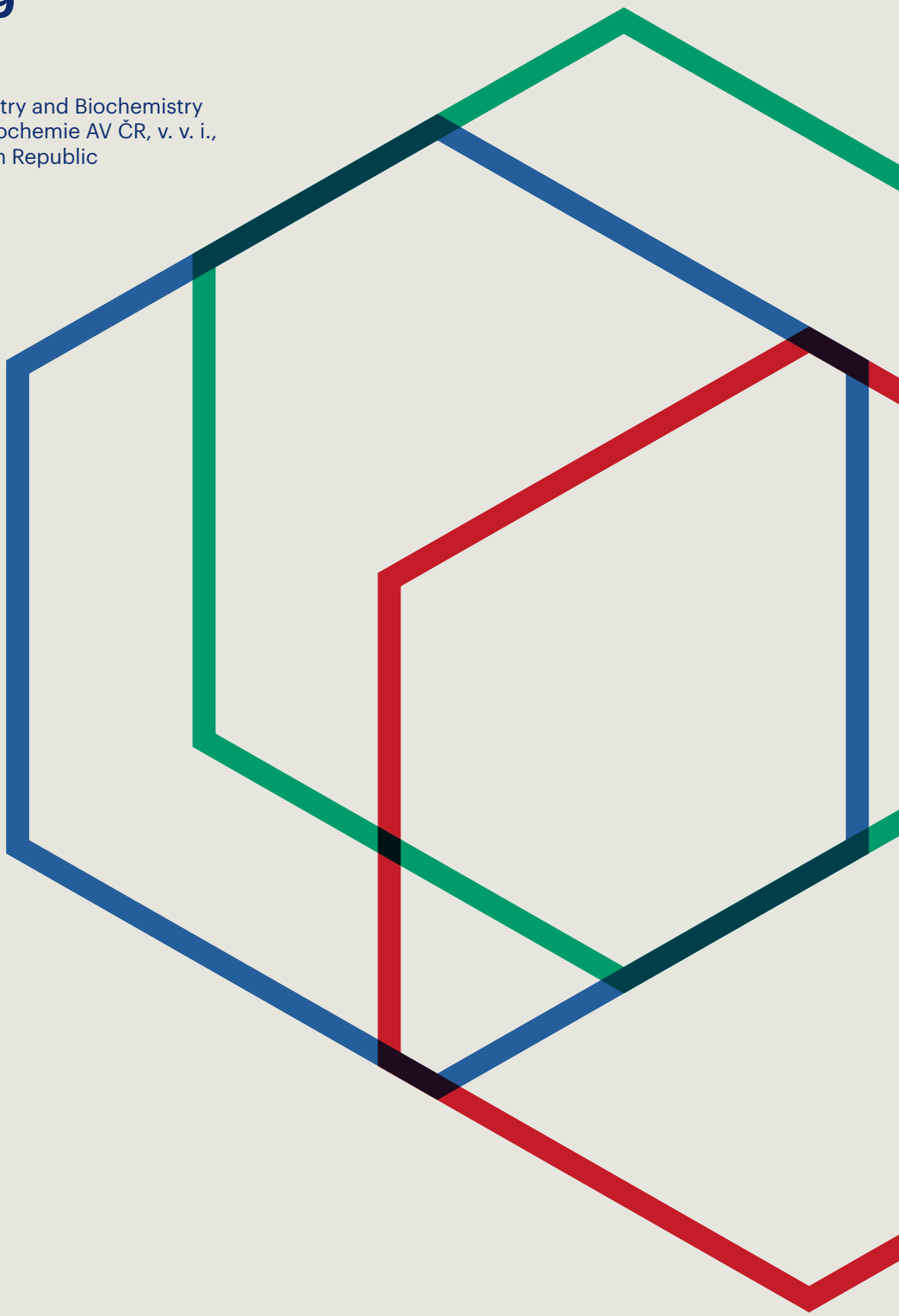

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