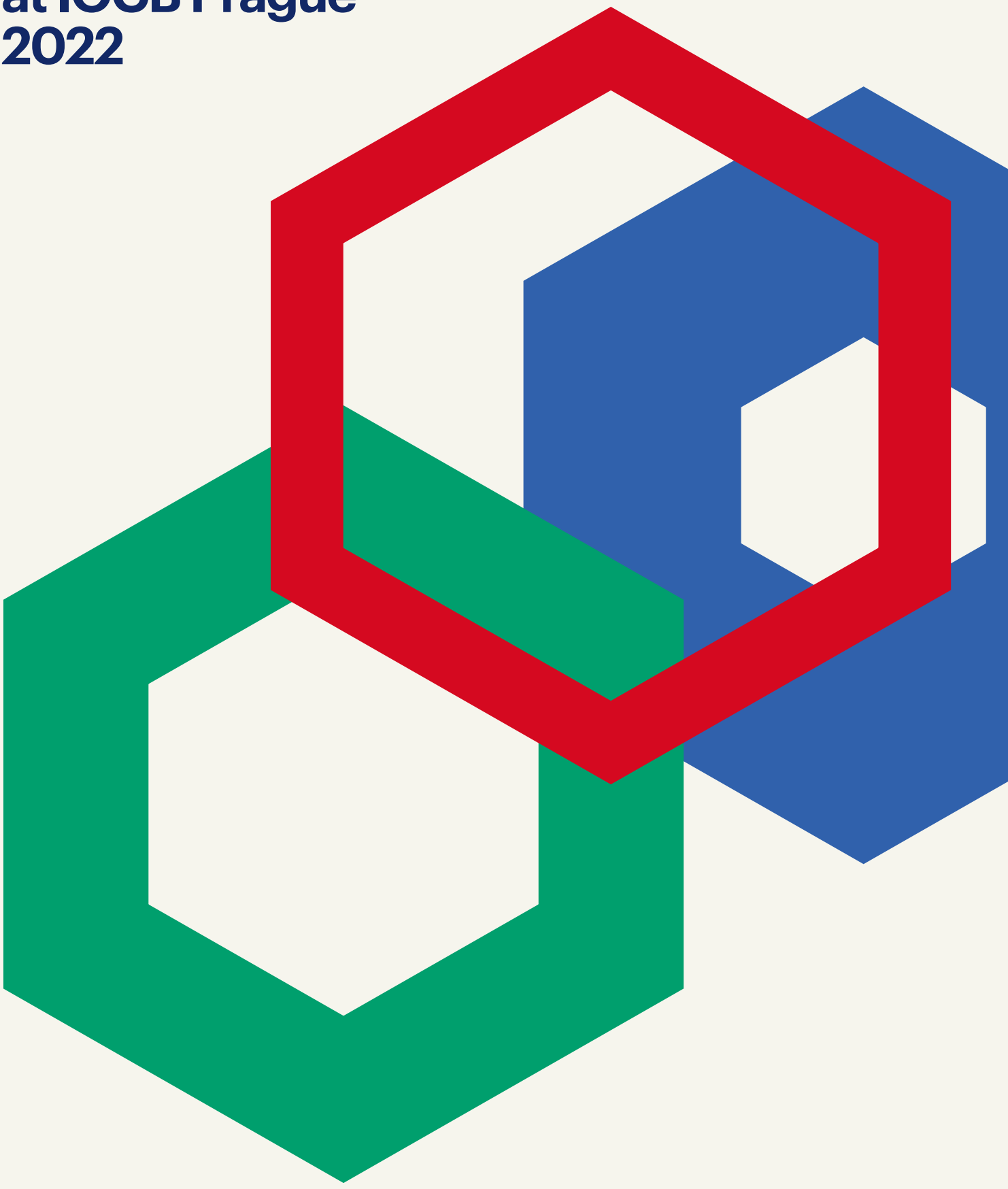
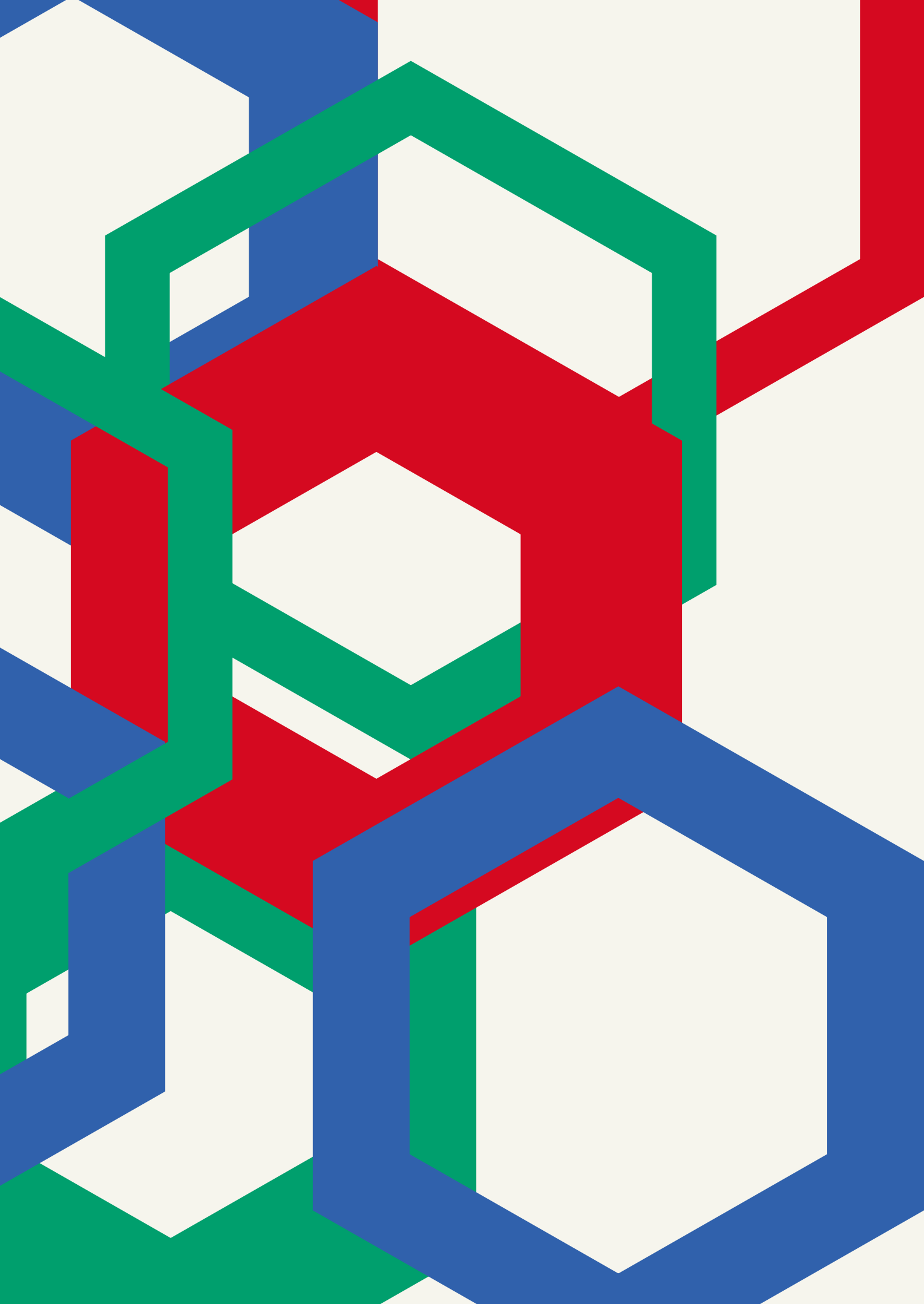
Research at IOCB Prague 2022

ÚOCHB AV ČR
IOCB PRAGUE





Contents

Foreword

As I write this introduction to the latest IOCB overview in 2022, concluding my second term as director of the institute, it is hard to resist the opportunity to look back and ponder the major developments at IOCB over the last ten years.

As you might expect, many discoveries have been made that have rewritten textbooks or inspired new chapters in them, and there are new molecules and technologies that have impacted the world beyond our walls. Some of these you will find on the following pages of this review of our latest research.

The institute has reinforced its position as a prime center for fundamental research in chemistry and biology, in large part through the legacy of previous directors, most notably František Šorm, Antonín Holý, and Zdeněk Havlas, who also demonstrated that prominent discoveries in basic research can occasionally (and with some luck) be applied to practice and can benefit society while at the same time generating considerable income to support even more discoveries. When I joined the institute in 2012, I recognized that this successful and time-tested philosophy deserved to be strengthened and systematically developed.

A critical responsibility of a successful director or scientific manager is to hire the most talented scientists available and provide them with a friendly and conducive environment with everything they need for research, and then leave the rest to them. A hands-off approach. Things are very different, however, when it comes to applied research, which is much more formalized and focused in order to satisfy industry standards. It truly requires a hands-on approach organized and coordinated by professional project managers. This functionality has been provided by IOCB Tech – a dedicated organization that over the years has become one of the most successful technology transfer companies in Central Europe.

In 2012, we introduced a concept of targeted research groups as internal incubators to fully concentrate on promising lines of research and technology that, if successful, eventually lead to the creation of external spinoffs. This is a common process at major research institutions around the world and a clear sign of strong and healthy science. Later, we established units of dedicated scientists within larger research groups with even more flexibility. These so-called SWAT teams make use of financial support from the institute to pursue specific tasks. Once their mission is complete, and regardless of whether or not they have succeeded, the scientists blend back into the original group.

In order to have thriving applied research, we must have creative and top-notch basic research, as without its discoveries there would be little to apply. The question is how to measure the performance of basic research. Intuitively, it is less about quantity and more about quality, which is why we started a competition for IOCB's most significant publications each year. This was a conscious departure from concentrating on quantitative scientometry, with focus shifting instead to quality and recognition of the gems in our scientific production.

As we have grown and become more international, our administration has adapted accordingly. We now have a professionally run English-speaking human resources department, a communications team, and a grant project office that plays an instrumental role in securing several prestigious European grants, such as EMBO Installation grants and three ERC Starting grants, for our junior scientists.

It is reassuring that with the help of the International Advisory Board we have been able to attract promising group leaders who demonstrate remarkable competitiveness and are able to secure these elusive grants. We have established approximately fifteen new junior groups, some of whom were promoted after five years to senior status, while others were not and left. Ten of the existing or new juniors were promoted to senior status during these years.

In 2013, a major breakthrough in our effort to secure the long-term financial stability of the institute was the renegotiation of intellectual property rights to a new superior prodrug of tenofovir (tenofovir alafenamide fumarate), despite the fact that the patent rights to the original form of tenofovir were due to expire in 2017. The successful negotiations, which were supported by IOCB Tech, led to a new agreement with Gilead Sciences, Inc. The arrangement extends the royalty stream through the end of 2025 and provides an opportunity to accumulate substantial resources and savings for the future.

We continued intensive cooperation with Gilead Sciences and also built strong new relationships with some of the best research institutions in the world, such as the Weizmann Institute of Science, Johns Hopkins University, Scripps Research, and MIT, creating new opportunities for our students and young researchers.

Financial security allows us to provide our scientists and international visitors with extra care and support. Following the complete refurbishment of our campus and the construction of a new building with state-of-the-art organic synthesis laboratories, we are also investing in an advanced cryo-electron microscopy facility to be built on the premises of the institute. It will allow our scientists to address important questions in structural biology and make us a sought-after center of expertise in this breakthrough technology.

We are committed to the education of the next generation of scientists, especially PhD students, who account for nearly one third of our researchers. They represent the future of science. We enthusiastically support student activities such as the PhD Student Science Club, Boot Camp, Summer Student Program, and the internationally recognized Summer School on Advances in Drug Discovery.

We follow young scientists and their families, and we know that having children can take mothers away from science and make it hard for them to return, often with consequences for their promising careers. I am proud to have introduced a program to support mothers with children up to four years of age that provides a cash bonus to cover the cost of childcare (with minimal administrative burden) and allow them stay in touch with the goings-on at the institute and in the lab. The program currently supports some forty mothers from IOCB.

The period from 2020 to 2022 has been impacted by the coronavirus epidemic. At its peak, we resisted pressure to close down and transition to the home-office mode like many other institutions. On the contrary, we remained active, and our scientists contributed to understanding the new virus and its structure and helped develop and distribute tests from domestic ingredients. They were also instrumental in the evaluation of commercial antigen tests.

Of course, not everything has worked out or been achieved according to plan. One of my biggest disappointments is that due to the byzantine bureaucratic process of obtaining a building permit, we have not yet succeeded in breaking ground for the new facilities that we have designed and are counting on. So it is that this definite positive, i.e. the institute's prosperity and growth, also has its drawbacks, namely a lack of space to accommodate new people.

Nonetheless, I am certain that my successor will find creative ways to move us forward not only through the continued development of our campus and that our future remains bright. I sincerely wish him the best of luck in his mission.

In closing, it has been an immense privilege to work alongside the so many brilliant scientists we are lucky and proud to have at the institute and to support them and watch their discoveries emerge. I have no doubt that there are many more to come.

Zdeněk Hostomský
Institute director

IOCB Prague – excellence in basic research and successful applications

IOCB 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 880 employees, of which around 220 are foreigners. Our scientists work in 47 research and service groups. More than 220 PhD students make up an essential part of the IOCB community, and we constantly seek new talents to join us.

Beginnings

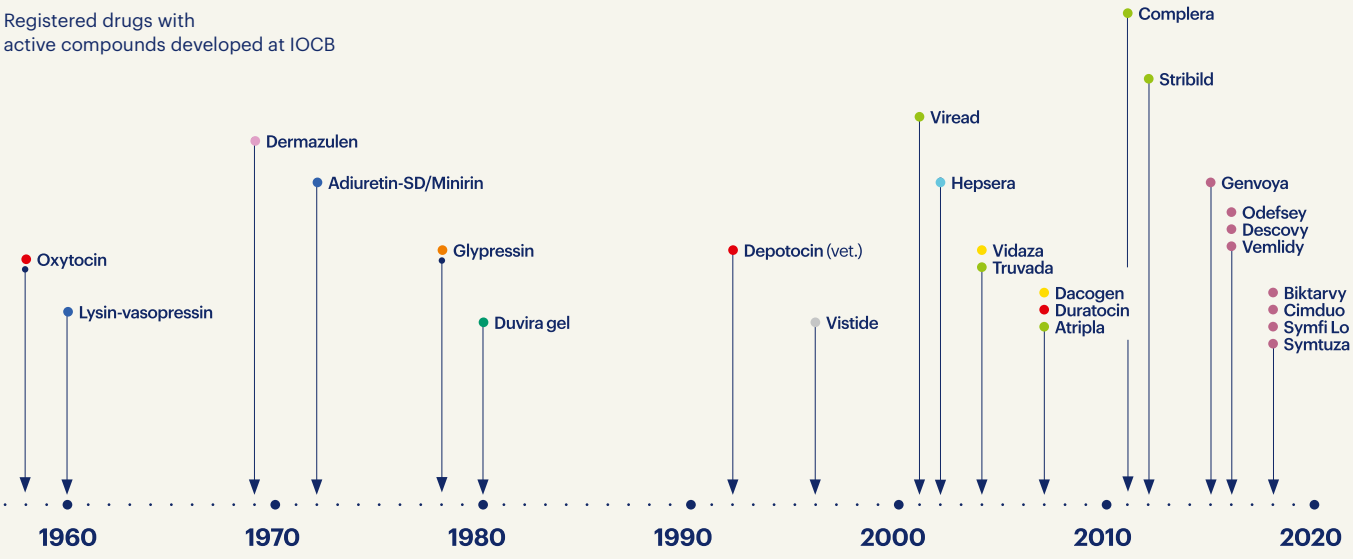
IOCB was founded in 1953 by Prof. František Šorm (1913–1980) as the Institute of Organic Chemistry, later renamed the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences (1960–1992) and, since 1993, of the Czech Academy of Sciences. From the very beginning, Prof. Šorm worked to establish IOCB as an interdisciplinary institute at the interface of chemistry, biology, and medicine with a smart combination of chemical and biological groups and teams working in the same field. He identified key areas 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

IOCB has always been very 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 the 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 excellent and groundbreaking basic research in the synthetic and medicinal chemistry of modified nucleosides and nucleotides and also to the discovery of antivirals clinically used for 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 originating from IOCB became approved drugs, such as Decitabine, which is used in the treatment of acute myeloid leukemia, and Azacytidine for myelodysplastic syndrome (both discovered by Holý's peer Dr. Alois Píškala), or 9-(2,3-dihydroxypropyl)adenine (DHPA), an example of an acyclic nucleoside analogue (discovered by A. Holý) clinically used in antiherpes 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.

Transformation

The commercial success of the drugs and 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 it was restructured with all group leader positions open to international competition. Since then, IOCB has implemented an ambitious policy of regular rigorous evaluation of the research groups by an International Advisory Board and a tenure-track program for the establishment of independent junior research groups.

The next IOCB director, Zdeněk Hostomský, further promoted out-of-the-box thinking in the sense of crossing barriers and exploring new paths emphasizing excellence in basic research together with strong support for technology transfer and capitalization on potential applications.

These new policies and strategies have transformed IOCB into an internationally recognized institute. With English as the working language, scientists at IOCB 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:

The **CHEM cluster** includes organic synthesis, medicinal chemistry, natural products chemistry, chemical biology, bioconjugate chemistry, drug design and discovery, photochemistry, materials chemistry, nanochemistry, etc. 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, bioinformatics, etc. Biochemical groups perform multidisciplinary research focused on detailed characterization of human pathogens, such as HIV, SARS-Cov-2 virus, HBV, influenza virus, different flaviviruses, *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 and methyltransferases, phosphatidylinositol kinases, carbonic anhydrases, intramembrane proteases, membrane receptors and channels, and human transcription factors as well as their complexes and interactions with cellular partners or with 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 using 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.

Technology transfer and applications

In applied research, IOCB's long tradition in 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.

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, who founded 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. Technology transfer makes those results available for human use.


Panasonic

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.

IOCB Tech has been involved in and arranged for the signing of more than twelve key license agreements with major pharma partners such as Gilead Sciences, Merck, Novo Nordisk, and SHINE Medical Technologies. In 2021, IOCB income from these licenses exceeded USD 130 mil. The current portfolio features projects focusing on CNS (epilepsy and neuropathic pain), inflammation, cancer (several projects), gene therapy, microbial resistance, and research tools.

i&i Prague

i&i Prague (www.iniprague.com) was founded in 2017 with the aim of representing IOCB in all its spinoffs and scouting 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.

In its first four years, the company supported the establishment or growth of more than 15 academic spinoffs, including Dracen Pharmaceuticals, which develops anticancer drugs, and Diana Biotechnologies, a successful IOCB startup.

In 2021, the company established i&i Biotech Fund (www.inibio.eu) in cooperation with the European Investment Fund (EIF). It currently manages more than EUR 45 mil. and specializes in investments in academic spinoffs devoted to drug discovery, diagnostics, medical devices, etc.

SARS-CoV-2 at IOCB Prague

SARS-CoV-2 and COVID-19 pandemic have become a challenge for many scientists throughout the world, and IOCB Prague has been at the forefront. Several research groups immediately began working on SARS-CoV-2, helping to expand the knowledge of the virus through their publications and contributing to the discovery of novel therapies.

During the first year of the pandemic, IOCB scientists primarily produced new findings on the structure of SARS-CoV-2 itself. The research groups of Evžen Bouřa and Radim Nencka succeeded in, among other things, deciphering the crystal structure of the nsp7-nsp8 nonstructural protein complex, which plays an important role in the activation of coronavirus RNA-dependent RNA polymerase (Konkolova, E. *et al., J. Struct. Biol*. **2020**, 211, 107548).

A great success in the laboratories of Evžen Bouřa was the elucidation of the crystal structure of viral 2'-O-RNA methyltransferase (nsp16) in complex with its cofactor protein nsp10 and sinefungin as a universal inhibitor of methyltransferases (Krafcikova, P. *et al., Nat. Commun*. **2020**, 11, 3717). A detailed understanding of the structure of 2'-O-RNA methyltransferase (nsp16) with its cofactor may be highly useful in the design of novel antiviral agents.

In collaboration with Václav Veverka, researchers from Evžen Bouřa Group studied nucleocapsid phosphoprotein (N), a structural protein whose function is to bind genomic RNA to the viral envelope (Dinesh, D. C. *et al., PLoS Pathog*. **2020**, 16, e1009100). In the fight against SARS-CoV-2 and other viruses, blocking replication of viral nucleic acid by targeting RNA polymerase appears to be an effective method of preventing the spread of infection.

In the group of Michal Hocek, which specializes in the bioorganic and medicinal chemistry of nucleic acids and modified nucleosides, a series of substituted 7-deazaadenine ribonucleosides and their monophosphate prodrugs was designed and synthesized as modified RNA building blocks, showing potent antiviral activity against RNA viruses, including SARS-CoV-2 (Milisavljevic, N. *et al., ACS Infect. Dis*. **2021**, 7, 471–478).

In collaboration with researchers from other institutes in the Czech Republic and Vienna, the Virology research-service group headed by Jan Weber participated in the testing of protective masks made of polylactic acid (PLA) (Vaňková, E. *et al., PeerJ* **2020**, 8, e10259), a polymer material produced from renewable resources that is also suitable for use in 3D printers.

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 and 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 domain and the pharma industry, the opening of transparent calls for new junior group leaders and support for productive senior groups, attracting the best PhD students from Czech universities and abroad, and promoting collaboration across groups within the institute while 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 contributing to world-class science and enable people to benefit from our discoveries and applications.

Cluster

CHEM

Research Groups

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

Targeted Research Group

Dominik Rejman Group (Antimicrobial Compounds)

Research-Service Group

Drug Discovery (Head: Pavel Majer)

Service Group

Synthesis of Radiolabeled Compounds (Head: Aleš Marek)

Michal Hocek Group

Bioorganic and Medicinal Chemistry of Nucleic Acids
(Joint Laboratory of IOCB and Charles University)
michal.hocek@uochb.cas.cz
http://hocekgroup.uochb.cas.cz

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

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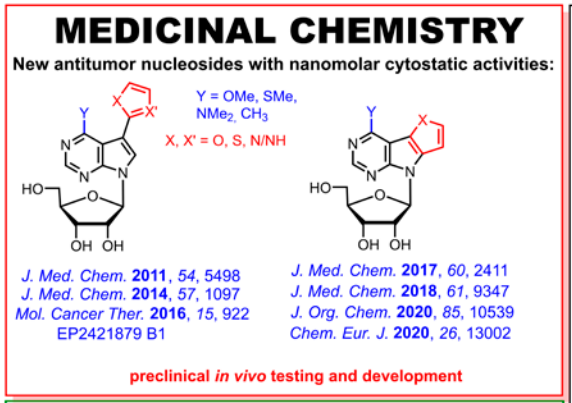

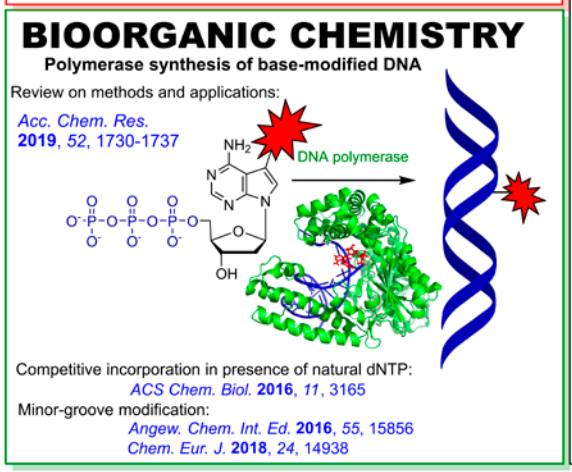

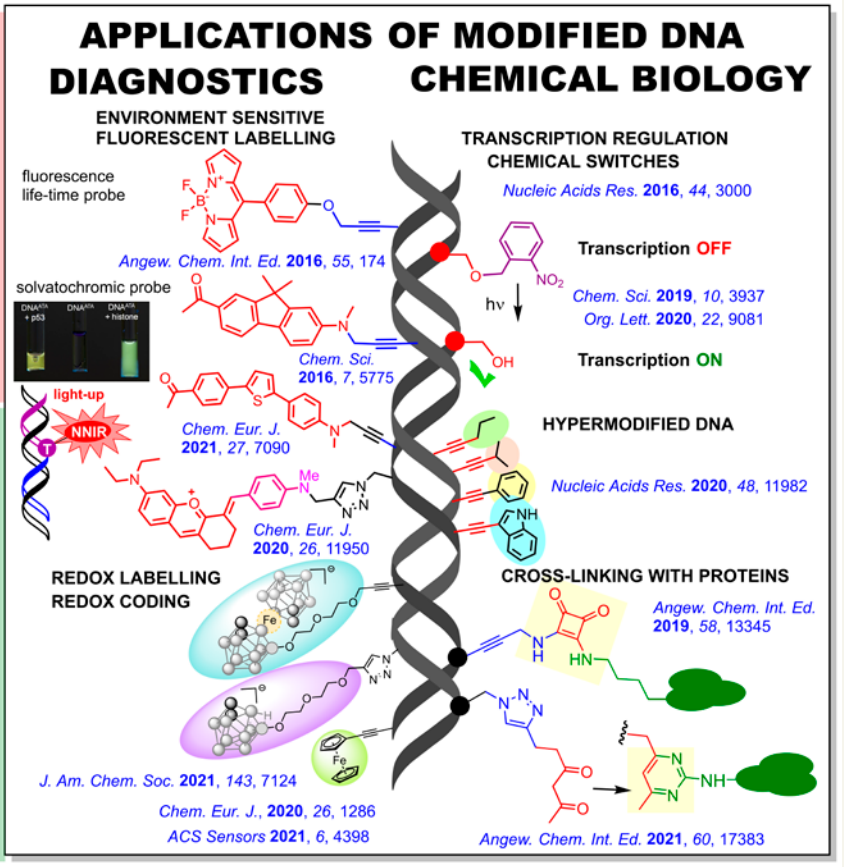

Research interests

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 activation 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
Senior scientists Tomáš Kraus, Veronika Sýkorová, Michal Tichý
Postdoctoral fellows Catherine Mulholland, Arghya Sett
Ph.D. students Mária Brunderová, Aswathi Chakrapani, Mario Dominguez Garcia, Ivana Dvořáková, Marianne Fleuti, Filip Gracias, Ivana Ivancová, Lukáš Kaiser, David Kodr, Matouš Krömer, Miroslav Kuba, Natalia Kuprikova, Denise-Liu Leone, Giammarco Liuni, Marek Ondruš, Attila Palágyi, Šimon Pospíšil, Tania Sanchez Quirante, Ambra Spampinato, Ugne Šinkeviciute, Chao Yang, Tomáš Vyskočil
Technician Tereza Schröpferová

Selected publications

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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, PI: Hocek, M.

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

Praemium Academiae to M. Hocek, Czech Academy of Sciences, 2016–2021. Gilead Sciences & IOCB Research Center, 2006–2021.

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

Awards—Michal Hocek

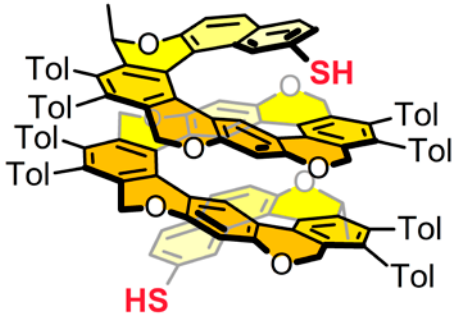
2019 – R. Lukeš Prize (Czech Chemical Society) for excellent results in organic, bioorganic or medicinal chemistry

Ivo Starý Group

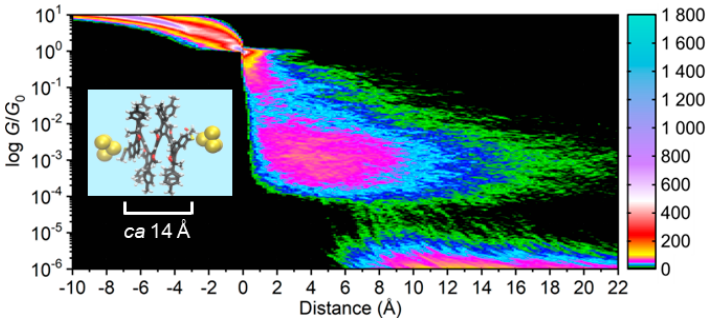
Chemistry of Functional Molecules
ivo.stary@uochb.cas.cz
www.uochb.cz/stary

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

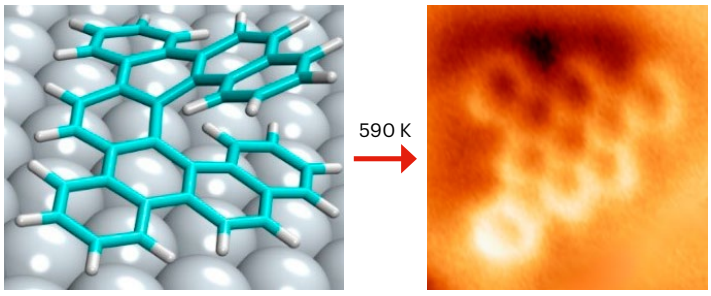
Asymmetric synthesis of long helical aromatics



Single molecule conductivity

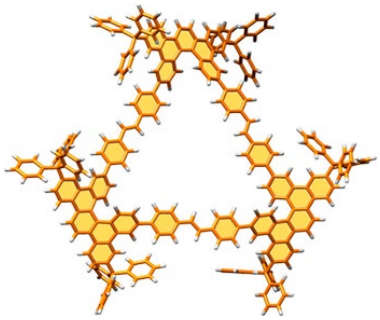


On-surface chirality transfer



Collaboration with P. Jelínek et al., Institute of Physics of the CAS

Helicene-derived shape-persistent macrocycles



Research interests

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

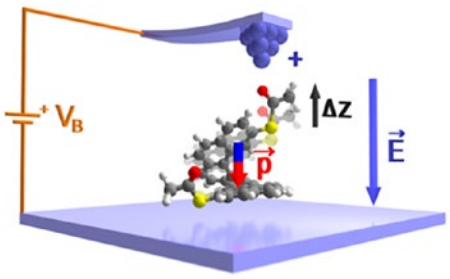
In particular, we pay attention to the synthesis of helically chiral aromatics (helicenes) that are enantiopure and properly functionalized. We systematically investigate their (chir)optical properties, self-assembly in crystals or at interfaces, charge/spin transport properties, and on-surface reactivity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

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

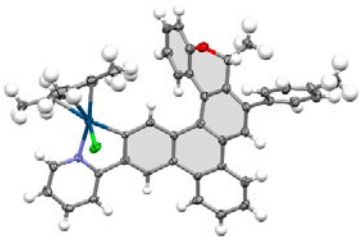
In addition, we utilize a mechanically controllable/STM break junction method to study single molecule conductivity of helical aromatics, and strive for fabrication and characterization of respective molecular devices.

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.

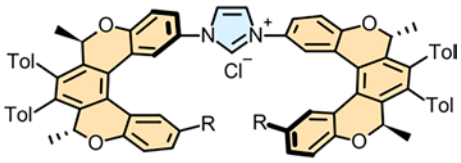
Multidisciplinary research is performed in close collaboration with experts in scanning probe microscopy techniques.



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



Helicene-based iridium catalyst



Helicene ligands in enantioselective catalysis

Group members

Group leader Ivo Starý
Senior scientists Jiří Rybáček, Ladislav Sieger, Irena G. Stará, Michal Šámal, Martin Švec, Jaroslav Vacek
Postdoctoral fellows Isabel Gay Sánchez, Jindřich Nejedlý
Ph.D. students Tereza Edlová, Jan Hanus, Václav Houska, Jiří Klívar, Katsiaryna Kutsenka
Students Daniel Bambas, Luděk Dub, Magdaléna Holasová, Vojtěch Vilím

Selected publications

Nejedlý, J.; Šámal, M.; Rybáček, J.; Gay Sánchez, I., Houska, V.; Warzecha, T.; Vacek, J.; Sieger, L.; Buděšínský, M.; Bednárová, L.; Fiedler. P.; Císařová, I.; Starý, I.; Stará, I. G. Synthesis of Racemic, Diastereopure, and Enantiopure Carba- or Oxa[5]-, [6]-, [7]-, and -[19]helicene (Di)thiol Derivatives. *J. Org. Chem.* **2020**, 85, 248–276.

Holec, J.; Rybáček, J.; Vacek, J.; Karras, M.; Bednárová, L.; Buděšínský, M.; Slušná, M.; Holý, P.; Schmidt, B.; Stará, I. G.; Starý, I. Chirality-Controlled Self-Assembly of Amphiphilic Dibenzo[6]helicenes into Langmuir–Blodgett Thin Films. *Chem. Eur. J.* **2019**, 25, 11494–11502.

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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.

Funding

Helically chiral ligands for asymmetric transition metal catalysis. Czech Science Foundation (GA ČR), No. 22-18773S, 2022–2024, PI: Starý, I.

New chiral organic TADF emitters: Towards efficient CPL OLEDs. CAS – MOST (Taiwan) MPP projects, MOST-22-01, 2022–2023, PI: Stará, I. G.

The synthesis and properties of polycyclic inherently chiral aromatics. Czech Science Foundation (GA ČR), No. 20-23566S, 2020–2022, PI: Stará, I. G.

HEL4CHIROLED: Helical systems for chiral organic light emitting diodes. European Commission, Grant agreement No. 859752, HEL4CHIROLED-MSCA-ITN Project, 2020–2023, PI: Stará, I. G.

Collaboration

- Jeanne Crassous (University of Rennes I, France)
- Karl-Heinz Ernst (Empa, Dübendorf, Switzerland)
- Matthew John Fuchter (Imperial College London, UK)
- Stefan-S. Jester (University of Bonn, Germany)
- Pavel Jelínek (Institute of Physics of the CAS, Prague, Czech Republic)
- Martin Krupička (UCT Prague, Czech Republic)
- Jérôme Lacour (University of Geneva, Switzerland)
- Nazario Martín (University Complutense of Madrid, Spain)
- Stefan Müllegger (Johannes Kepler University Linz, Austria)
- Helma Wennemers (ETH Zurich, Switzerland)
- Ken-Tsung Wong (National Taiwan University, Taipei, Taiwan)

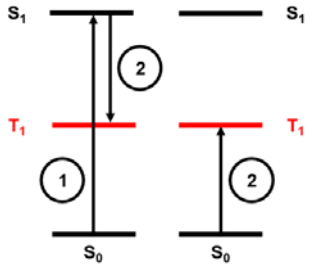
Josef Michl Group

Organic Chemistry
josef.michl@colorado.edu
www.uochb.cz/michl

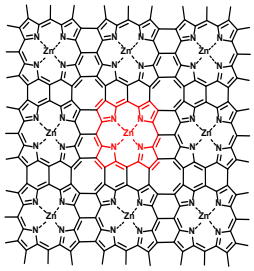
Distinguished Emeritus

alkylation of gold surfaces, singlet fission, fluorination, electrochemical synthesis, two-dimensional polymers (porphenes)

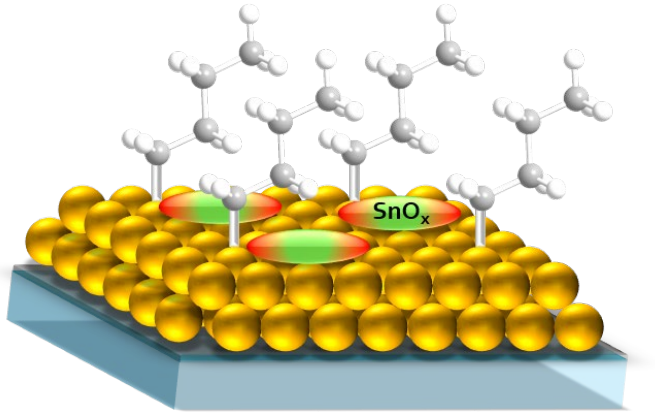
Singlet Fission
(*Chem. Rev.* **2010**, 110, 6891)



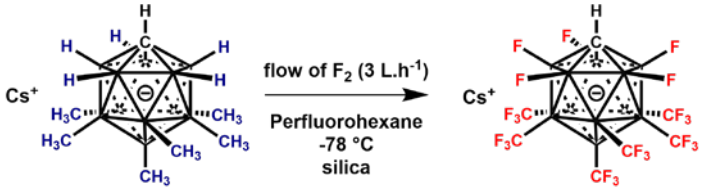
Electrochemical Synthesis of Porphene



New Ways to Molecular Surface Attachments
(*J. Am. Chem. Soc.* **2015**, 137, 12086)



Carborane Fluorination



Research interests

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 (SF) is a 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 (e.g. cibalackrots) based on calculations and concepts of molecular engineering, performed in collaboration with Dr. Zdeněk Havlas's group.

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
Porphene is a fully conjugated analog of graphene consisting of fused porphyrin instead of benzene rings. Its recent synthesis by chemical oxidative polymerization of parent porphyrin on water surface provides access to a family of 2-dimensional polymers that can be arbitrarily functionalized without taking any centers out of conjugation by inserting metals with up to two ligands into the macrocyclic rings. We are now attempting to perform the polymerization electrochemically.

Group members

Group leader Josef Michl
Senior scientists Miroslav Dudič, Jan Plutnar, Lubomír Pospíšil
Postdoctoral fellows Guillaume Bastien, Kristýna Jelínková, Lucie Ludvíková, Milan Mašát, Igor Rončević, Veronika Urbanová
Assistant Kateřina Pokorná

Selected publications

Buchanan, E. A.; Johnson, J. C.; Tan, M.; Kaleta, J.; Shtukenberg, A. G.; Bateman, G.; Benedict, J. B.; Kobayashi, S.; Wen, J.; Kahr, B.; Císařová, I.; Michl, J. Competing Singlet Fission and Excimer Formation in Solid Fluorinated 1,3-Diphenylisobenzofurans. *J. Phys. Chem. C* **2021**, 125, 27058-27071.

Rais, D.; Toman, P.; Pfleger, J.; Acharya, U.; Panthi, Y. R.; Menšík, M.; Zhigunov, A.; Thottappali, M. A.; Vala, M.; Marková, A.; Střítešký, S.; Weiter, M.; Cigánek, M.; Krajčovič, J.; Pauk, K.; Imramovský, A.; Zaykov, A.; Michl, J., Singlet Fission in Thin Solid Films of Bis(thienyl)diketopyrrolopyrroles. *ChemPlusChem* **2020**, 85, 2689.

Rončević, I.; Bastien, G.; Cvačka, J.; Kaleta, J.; Michl, J., $CB_{11}H_{10}^-$ and Related Carborenes. *Inorg. Chem.* **2020**, 59, 12453.

Ryerson, J. L.; Zaykov, A.; Aguilar Suarez, L. E.; Havenith, R. W. A.; Stepp, B. R.; Dron, P. I.; Kaleta, J.; Akdag, A.; Teat, S. J.; Magnera, T. F.; Miller, J. R.; Havlas, Z.; Broer, R.; Faraji, S.; Michl, J.; Johnson, J. C., Structure and photophysics of indigoids for singlet fission: Cibalackrot. *J. Chem. Phys.* **2019**, 151, 184903.

Zaykov, A.; Felkel, P.; Buchanan, E. A.; Jovanovic, M.; Havenith, R. W. A.; Kathir, R. K.; Broer, R.; Havlas, Z.; Michl, J., Singlet Fission Rate: Optimized Packing of a Molecular Pair. Ethylene as a Model. *J. Am. Chem. Soc.* **2019**, 141, 17729.

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.

Benkovičová, M.; Wen, D.; Plutnar, J.; Čížková, M.; Eychmüller, A.; Michl, J. Mechanism of Surface Alkylation of a Gold Aerogel with Tetra-*n*butylstannane-*d36*: 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.

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.

Funding

Electrochemical Synthesis of Porphene. Czech Science Foundation (GA ČR), No. 20-03691X, 2020–2024, PI: Michl, J.

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

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

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

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

Collaboration

Charles Roger (University of Colorado, Boulder, CO, USA)

Jiří Pfleger (Institute of Macromolecular Chemistry of the CAS, Czech Rep.)

Zdeněk Bastl & Jiří Ludvík (J. Heyrovský Institute of Physical Chemistry of the CAS, Czech Rep.)

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

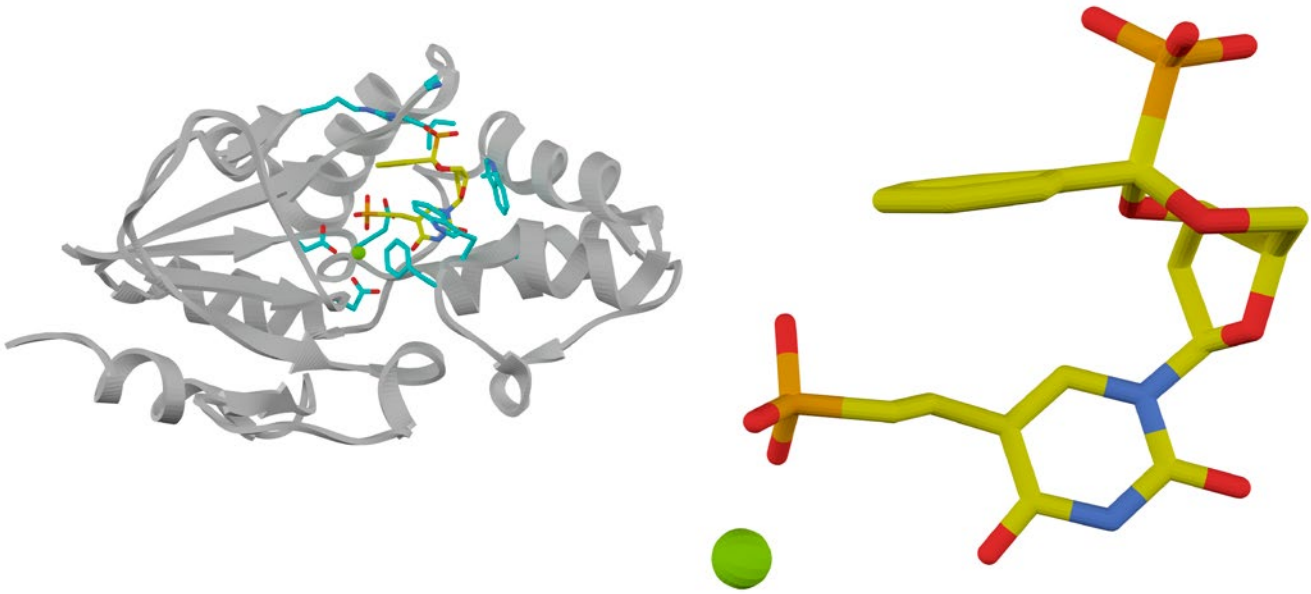
Honorary Doctorates:
- Georgetown University, 1990; University of Pardubice, 1996; Masaryk University, 2004

Ivan Rosenberg Group

Nucleotides & Oligonucleotides
ivan.rosenberg@uochb.cas.cz
www.uochb.cz/rosenberg

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

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



Research interests

The scientific program of the group centers on the design and synthesis of nucleoside phosphonic acids (NPAs) as potential antimetabolites and building units for solid phase synthesis of chimeric antisense oligonucleotides acting through the RNase H and/or steric block mechanism. Special attention has been devoted to regulatory oligonucleotides, such as phosphonate-based 2′,5′-linked oligoadenylates and CpG motif-containing oligonucleotides, and a large study has been carried out on inhibition of uracil DNA glycosylase (UDG) by uracil-containing oligonucleotides modified in the ...XUY... motif.

NUCLEOSIDE PHOSPHONIC ACIDS
We have developed many structurally diverse compounds containing classic furanose or nonoxygen heterocyclic rings. Among them, we found potent inhibitors of several salvage pathway enzymes, e.g. selective inhibitors of human recombinant mitochondrial and cytosolic pyrimidine specific 5′(3′)-deoxynucleotidases. Their biological evaluation in a prodrug form is currently underway.

OLIGONUCLEOTIDE ANALOGS
Modified oligonucleotides containing nucleoside phosphonic acids exhibit significantly increased nuclease stability, enhanced hybridization, and stimulation of RNase H activity. This makes them interesting for their potential use in biology as antisense compounds in the regulation of gene expression. We also focus on the chemistry and biology of the modified α-D and α-L-oligodeoxynucleotides. Of particular interest is a group of pyrrolidine nucleoside phosphonates and 4′-alkoxynucleosides that, upon incorporation into oligonucleotides, significantly increase duplex stability and discriminate between RNA and DNA targets. Our study on the immunostimulatory effect of CpG motif-containing oligonucleotides modified in a CpG internucleotide linkage has yielded potent compounds. Also, our study on activation of RNase L with trimeric 2′,5′-linked oligoadenylates bearing on the 5′-end uncleavable phosphonate moieties has produced potent agonists of RNase L.

Group members

Group leader Ivan Rosenberg
Senior scientists Ondřej Kostov, Ivana Markusová-Kóšiová, Šárka Rosenbergová
Research assistant Ivana Dvořáková

Selected publications

Lášek, T.; Petrová, M.; Košiová, I.; Šimák, O.; Buděšínský, M.; Kozák, J.; Snášel, J.; Vavřina, Z.; Birkuš, G.; Rosenberg, I.; Páv, O. 5′-Phosphonate modified oligoadenylates as potent activators of human RNase L. *Bioorg. Med. Chem.* **2022**, 56, 116632.

Lášek, T.; Dobiáš, J.; Buděšínský, M.; Kozák, J.; Lapuníková, B.; Rosenberg, I.; Birkuš, G.; Páv, O. Synthesis of phosphonate derivatives of 2 ′-deoxy-2 ′-fluorotetradialdose D-nucleosides and tetradialdose D-nucleosides. *Tetrahedron* **2021**, 89, 132159.

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Ligasová, A.; Rosenberg, I.; Bocková, M.; Homola, J.; Koberna, K. Anchored linear oligonucleotides: the effective tool for the real-time measurement of uracil DNA glycosylase activity. *Open Biol.* **2021**, 11, 210136.

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.

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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.

Patents

PV 2021-484. Nonisosteric isopolar phosphonate analogs of phosphorothioate CpG oligonucleotide ODN2006. Rosenberg, I.; Markusová-Košiová, I.; Štěpánek, I.; Liboska, R.; Rosenbergová, Š.; Birkuš, G.

US20190322695. 2′3′-Cyclic Dinucleotides. Birkuš, G.; Páv, O.; Rosenberg, I.; Šimák, O.

US20190322696. 3′3′-Cyclic Dinucleotides. Birkuš, G.; Páv, O.; Rosenberg, I.; Šimák, O.

US20190322697. 2′2′-Cyclic Dinucleotides. Birkuš, G.; Páv, O.; Rosenberg, I.; Šimák, O.

US20190185510. 2′3′ Cyclic Dinucleotides With Phosphonate Bond Activating the STING Adaptor Protein. Birkuš, G.; Páv, O.; Jandušík, T.; Rosenberg, I.; Nencka, R.

US20190183917. 3′3′ Cyclic Dinucleotides With Phosphonate Bond Activating The Sting Adaptor Protein. Birkuš, G.; Páv, O.; Jandušík, T.; Rosenberg, I.; Nencka, R.

US20190185509. 2′2′ Cyclic Dinucleotides With Phosphonate Bond Activating The Sting Adaptor Protein. Birkuš, G.; Páv, O.; Jandušík, T. ; Rosenberg, I.; Nencka, R.

Collaboration

RNDr. Karel Koberna, CSc., Institute of Molecular and Translation Medicine, Faculty of Medicine and Dentistry, Palacký University Olomouc, Czech Republic

doc. Mgr. Lukáš Trantírek, PhD., Central European Institute of Technology – Centre for Structural Biology, Brno, Czech Republic

IOCB Prague:
Mgr. Gabriel Birkuš, CSc. (HBV Cure Group)
Mgr. Jan Weber, CSc. (Virology Group)
Mgr. Miroslav Hájek, CSc. (Biochemical Pharmacology Group)
Mgr. Vladimír Sychrovský, CSc. (Biomolecular Spectroscopy Group)

Petr Beier Group

Organic Chemistry of Fluorine and Main Group Elements
petr.beier@uochb.cas.cz
www.uochb.cz/beier

Senior Research Group

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

Research interests

The central theme of our research is the development of new, selective, and convenient synthetic reagents and methods towards novel organic molecules, for which there may be applications in crop protection, drug design, and materials. We study new reactions and their mechanisms, with particular focus on the organic chemistry of the main group elements, such as fluorine, phosphorus, silicon, sulfur, and iodine.

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 were used for bioconjugation of thiols and electron-rich amino acid residues.

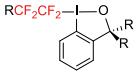
The pentafluorosulfanyl group (SF_5) is a relatively undeveloped functionality with an interesting combination of physicochemical properties. Our research is focused on the development of new methods and reactions for the synthesis and transformation of SF_5-substituted aromatic, heteroaromatic, and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

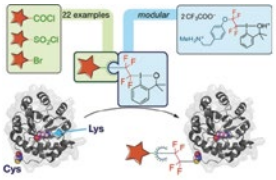
We have introduced a new class of stable organic azides – azidoperfluoroalkanes. They afford *N*-fluoroalkyl-1,2,3-triazoles through the click reaction with alkynes. These triazoles are excellent starting compounds for a variety of novel nitrogen-containing heterocycles, such as pyrroles, imidazoles, azepines, oxazoles, thiazoles, etc. A new triazole ring-opening process was discovered leading to azirines, enamines, and other *N*-alkenyl compounds.

Butenolides are natural products formed during burning vegetation with various biological activities; for example, they actively promote or inhibit seed germination and act as neuroprotectives. In our medicinal chemistry project, we study synthetic derivatives of butenolides and their biological activities.

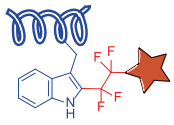
Tetrafluoroethylene group transfer

- new reagents for tetrafluoroethyle group transfer
- tagging biological thiols
- electrophilic hypervalent reagents
- Tryptophan-selective peptide labelling

Reagent	Synthon	Product
$PhSO_2CF_2CF_2SiMe_3$	$^{\ominus}CF_2CHF_2$	E-CF_2CF_2-E
$PhSCF_2CF_2SiMe_3$	$^{\cdot}CF_2CH_3^{\oplus}F_2$	R-CF_2CF_2-E
RCF_2CF_2Br	$RCF_2CF_2^{\ominus}$	RCF_2CF_2-E
	$RCF_2CF_2^{\oplus}$	RCF_2CF_2-Nu
	$RCF_2CF_2^{\cdot}$	RCF_2CF_2-R



Cysteine-selective protein labelling



Tryptophan-selective peptide labelling

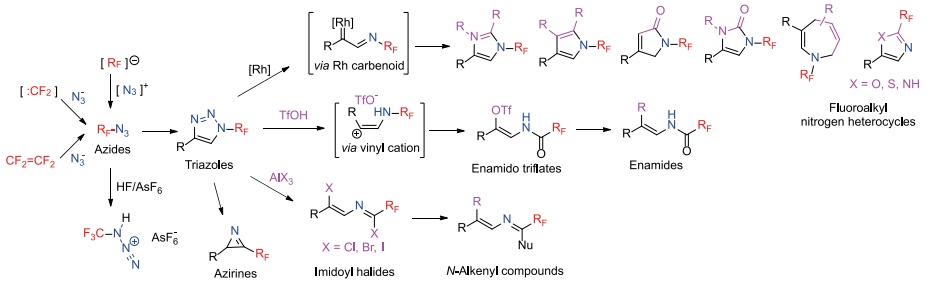
Butenolides

modifications

- smoke-derived compounds
- seed germination inhibitors/promotors
- bioactivity

Azidofluoroalkanes

- introduction of stable azidofluoroalkanes
- new triazole reactivity
- fluoroalkyl heterocycles via rhodium carbenes
- enamido triflates, enamides, imidoyl halides and *N*-alkenyl compounds via vinyl cation chemistry
- azirines via carbenes



Group members

Group leader Petr Beier
Senior scientists Svatava Voltrová, Martin Pošta, Maryam Khalili, Vladimir Motornov
Ph.D. students Olga Bakhanovich, Norbert Baris, Barbora Doksanská, Lukáš Janecký, Viktor Khutorianskyi, Anna Kubíčková, David Tichý, Mykyta Ziabko

Selected publications

Markos, A.; Janecký, L.; Klepetářová, B.; Pohl, R.; Beier, P. Stereoselective Synthesis of (*Z*)-β-Enamido Fluorides from *N*-Fluoroalkyl- and *N*-Sulfonyl-1,2,3-triazoles. *Org. Lett.* **2021**, 23, 4224–4227.

Markos, A.; Janecký, L.; Chvojka, T.; Martinek, T.; Martinez-Seara, H.; Klepetářová, B.; Beier, P. Haloalkenyl Imidoyl Halides as Multifacial Substrates in the Stereoselective Synthesis of *N*-Alkenyl Compounds. *Adv. Synth. Catal.* **2021**, 363, 3258–3266.

Khutorianskyi, V.; Baris, N.; Beier, P. Oxidative nucleophilic alkoxylation of nitrobenzenes. *Org. Chem. Front.* **2021**, 8, 77–81.

Rahimidashaghoul, K.; Klimánková, I.; Hubálek, M.; Matoušek, V.; Filgas, J.; Slavíček, P.; Slanina, T.; Beier, P. Visible-Light-Driven Fluoroalkylation of Tryptophan Residues in Peptides. *ChemPhotoChem* **2021**, 5, 43–50.

Tichý, D.; Košťál, V.; Motornov, V.; Klimánková, I.; Beier, P. Preparation of 1-Azido-2-Bromo-1,1,2,2-Tetrafluoroethane and Its Use in the Synthesis of *N*-Fluoroalkylated Nitrogen Heterocycles. *J. Org. Chem.* **2020**, 85, 11482–11489.

Saal, T.; Blastik, Z. E.; Haiges, R.; Nirmalchandar, A.; Baxter, A. F.; Christe, K. O.; Vasiliu, M.; Dixon, D. A.; Beier, P.; Prakash G. K. S. Protonation of CH_3N_3 and CF_3N_3 in Superacids: Isolation and Structural Characterization of Long-Lived Methyl- and Trifluoromethylamino Diazonium Ions. *Angew. Chem., Int. Ed.* **2020**, 59, 12520–12526.

Bakhanovich, O.; Beier, P. Synthesis, Stability and Reactivity of α-Fluorinated Azidoalkanes. *Chem. Eur. J.* **2020**, 26, 773–782.

Funding

Synthesis and reactivity of *N*-fluoroalkylated compounds. Ministry of Education, Youth and Sports (MŠMT ČR), INTERACTION LTAUSA18, 2019–2022, PI: Beier, P.

Butenolides with neuroprotective effect from plant-derived smoke and their synthetic derivatives. Czech Science Foundation (GA ČR), No. 20-11571S, 2020–2022, PI: Beier, P.

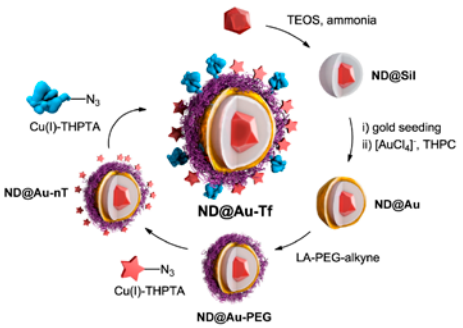
Petr Cígler Group

Synthetic Nanochemistry
petr.cigler@uochb.cas.cz
www.petrcigler.cz

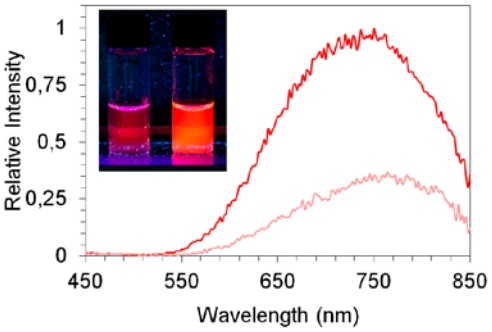
Senior Research Group
nanoparticles, bioimaging, sensing, fluorescence, nanodiamond, theranostics, plasmonics

NANOPARTICLES FOR BIOIMAGING, DIAGNOSTICS AND THERAPY

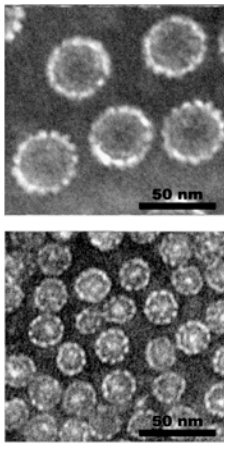
Advanced synthetic protocols



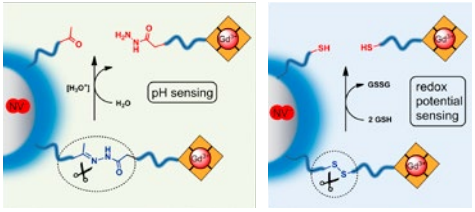
Near-infrared nanoprobes



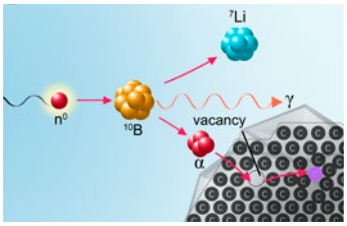
Inorganic and bioorganic nanoparticles



New sensing schemes—quantum detection



Creation of luminescent centers



Research interests

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.

We also study near-infrared emitting gold nanoclusters, plasmonic gold nanoshells, virus-like capsides, 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
Senior scientists Michal Gulka, Jiří Schimer, Volodymyr Shvadchak, Hana Španielová, Ivan Řehoř, Václav Vaněk
Postdoctoral fellows Jana Kovalčíková, Lenka Loukotová, Jitka Neburková, Chandra Prakash Epperla, Miroslava Štejfová, Pavel Švec
Research assistant Zuzana Matoušková
Ph.D. students Jakub Čopák, Maksym Galkin, Marek Kindermann, Klaudia Kvaková, Anastasiia Priss
Student Ema Fialová
Technician Petra Typoldová

Selected publications

Kvakova, K.; Ondra, M.; Schimer, J.; Petrik, M.; Novy, Z.; Raabova, H.; Hajduch, M.; Cigler, P. Visualization of Sentinel Lymph Nodes with Mannosylated Fluorescent Nanodiamonds. *Adv. Funct. Mater.* **2022**, 2109960.

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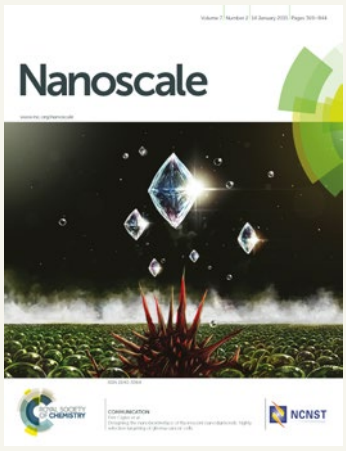
Funding

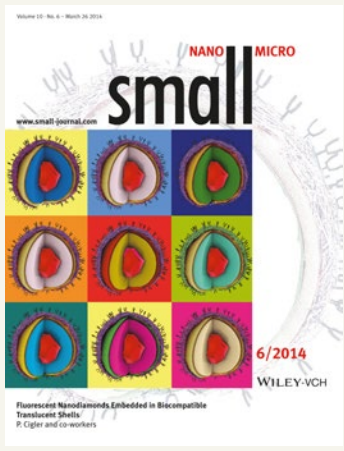
Towards precision medicine and gene therapy. Czech Academy of Sciences, Strategy AV21 grant, No. VP29, 2022–2026, co-PI: Cígler, P.

Chemistry Meets Quantum Sensing: Towards Atomic Architectures Tailored for Diamond Probes (ChemiQS). Marie Skłodowska-Curie Widening Fellowship, No. 101038045, 2022–2024, Researcher: Gulka, M., Supervisor: Cígler, P.

Carbon allotropes with rationalized nanointerfaces and nanolinks for environmental and biomedical applications (CARAT). European Regional Development Fund, OP RDE, No. CZ.02.1.01/0.0/0.0/16_026/0008382, 2018–2022, co-PI: Cígler, P.

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: Cígler, P.





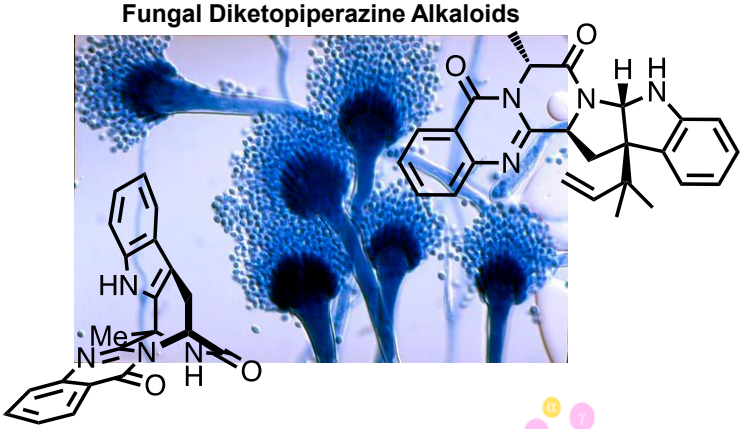
Ullrich Jahn Group

Chemistry of Natural Products
ullrich.jahn@uochb.cas.cz
www.uochb.cz/jahn

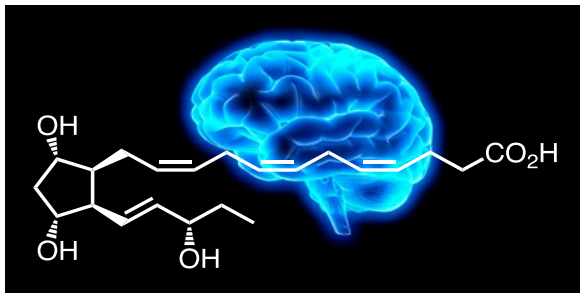
Senior Research Group

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

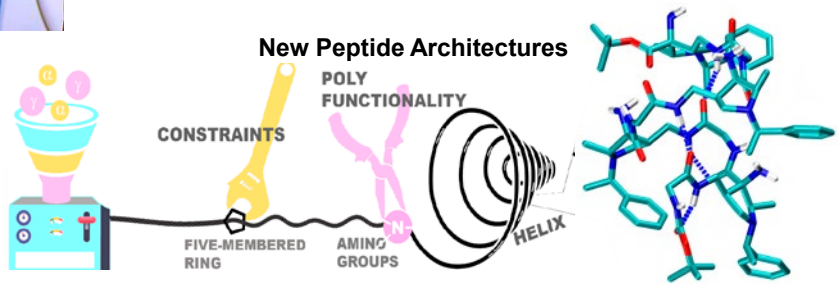
Fungal Diketopiperazine Alkaloids

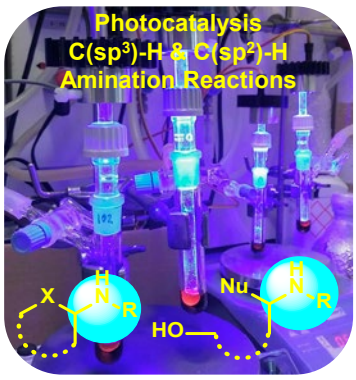


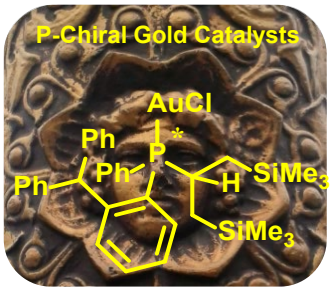
Neuroprostanes

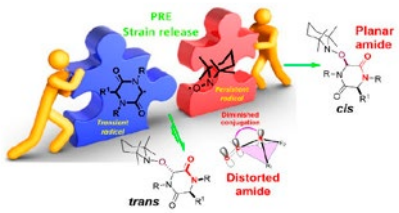


New Peptide Architectures





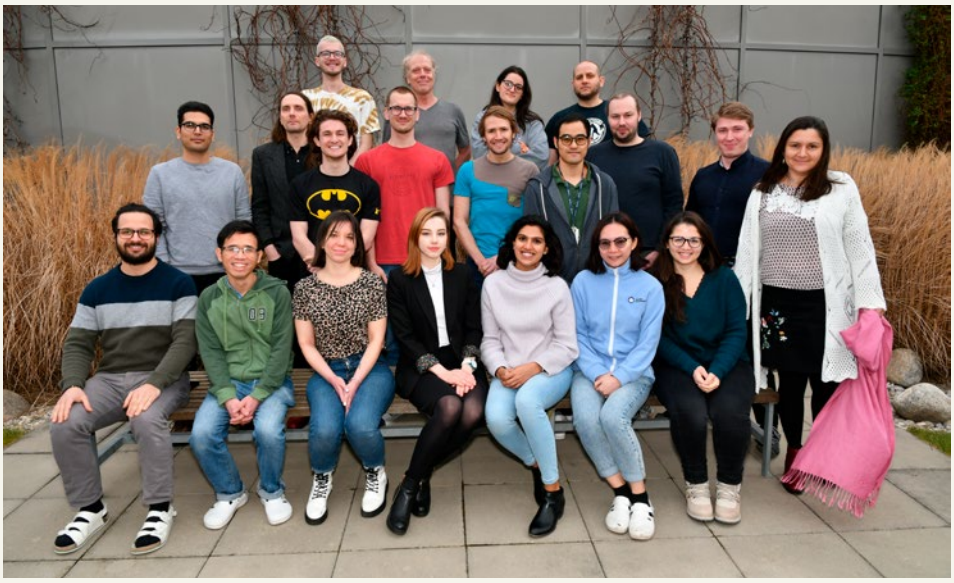




Free Radical Chemistry

Research interests

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 hybrid alkaloid terpenoid natural products to lipid metabolites, such as autoxidatively formed neuroprostanes, which are important for signaling pathways in humans. The group provides expertise in selected medicinal chemistry topics using bioinspired synthetic approaches. More recently the group started to explore new avenues in peptide chemistry using unconventional amino acids for the generation of function. An equally important area 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
Senior scientists Emanuela Jahn, Sean Coughlin
Postdoctoral fellow Jakub Smrček
Ph.D. students Saman Ahmadi, Maria Aurelia Bosi, Václav Chmela, Patsapon Chuathong, Victor Golubev, Sarah Dekoune, Trong Nguyen Phan Huu, Tomáš Mašek, Chiranan Pramthaisong, Ladislav Prener, Michal Šimek, Navyasree Venugopal, Ilaria Vespoli
Technician Anna Hlavačková
Students Tomáš Svoboda, Miroslav Stroka, Iana Raevskaia

Selected publications

Vazdar, K.; Margetič, D.; Kovacevič, B.; Sundermeyer, J.; Leito, I.; Jahn, U., Design of Novel Uncharged Organic Superbases: Merging Basicity and Functionality. *Acc. Chem. Res.* **2021**, 54, 3108–3123.

Šimek, M.; Bartová, K.; Pohl, R.; Císářová, I.; Jahn, U., Tandem Anionic oxy-Cope Rearrangement/Oxygenation Reactions as a Versatile Method for Approaching Diverse Scaffolds. *Angew. Chem. Int. Ed.* **2020**, 59, 6160–6165.

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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.

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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.

Funding

Unified Bioinspired Total Syntheses of Complex Indolodiketopiperazine Alkaloid-Terpene Hybrid Natural Products and Their Analogs. Czech Science Foundation (GA ČR), 2022–2024, PI: Jahn, U.

Unified Bioinspired Approaches to Complex Pyrazinoquinazoline Alkaloids. Czech Science Foundation (GA ČR), 2021–2023, PI: Jahn, U.

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.

Collaboration

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

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

Dr. Jan Weber (IOCB Prague): HIV Latency Reactivation

Dr. Lubomír Rulíšek (IOCB Prague): Peptidic macrocycles

Prof. Dr. Pavel Jungwirth (IOCB Prague): Peptidic foldamers

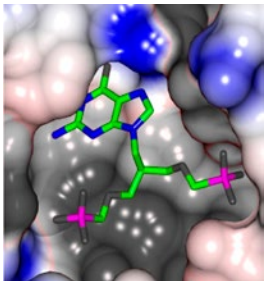
Zlatko Janeba Group

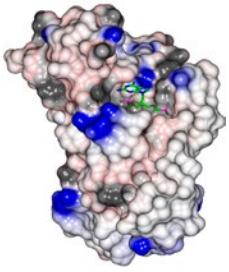
Medicinal Chemistry of Nucleotide Analogues
zlatko.janeba@uochb.cas.cz
www.uochb.cz/janeba

Senior Research Group

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

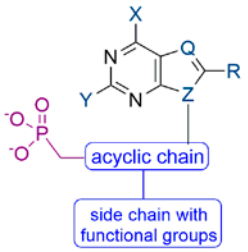
Inhibitors of phosphoribosyl transferases and purine nucleoside phosphorylases





J. Med. Chem. **2015**, 827; *J. Med. Chem.* **2015**, 4822; *J. Med. Chem.* **2017**, 7539
Eur. J. Med. Chem. **2019**, 111667; *Eur. J. Med. Chem.* **2021**, 113416; *Eur. J. Med. Chem.* **2021**, 113798

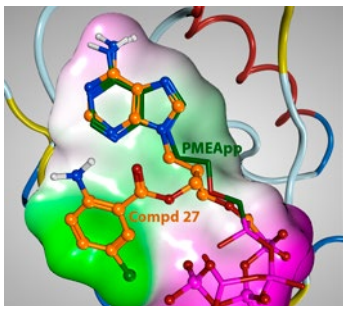
Acyclic nucleoside phosphonates (ANPs)



Antivirals

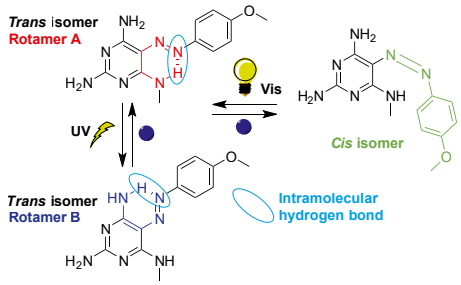
Org. Biomol. Chem. **2019**, 315; *Eur. J. Med. Chem.* **2016**, 185
Org. Biomol. Chem. **2021**, 6958; *J. Med.Chem.* **2021**, 16425

Inhibitors of adenylate cyclases



ChemMedChem **2016**, 2534; *ChemMedChem* **2018**, 199
ChemMedChem **2018**, 1779; *Eur. J. Med. Chem.* **2021**, 113581
ChemMedChem **2022**, e202100568

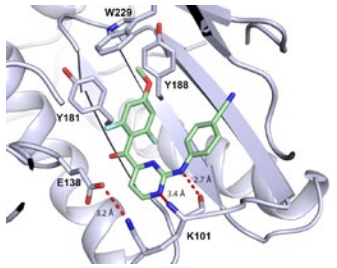
Photoswitches, 5-phenylazopyrimidines



J. Org. Chem. **2016**, 3780; *J. Org. Chem.* **2017**, 10350; *J. Org. Chem.* **2018**, 5986
Chem. Eur. J. **2018**, 492; *Angew. Chem. Int. Ed.* **2020**, 15590; *Dyes Pigm.* **2022**, 110066

Polysubstituted pyrimidines

Anti-inflammatory and immunomodulating agents



Med. Chem. Res. **2015**, 2154; *Nitric oxide* **2017**, 53
Eur. J. Med. Chem. **2018**, 295; *ChemMedChem* **2020**, 1398
Org. Process Res. Dev. **2020**, 1718; *ChemMedChem* **2021**, 2802

Research interests

We specialize in the design, development, and synthesis of biologically active antimetabolites, namely analogues of nucleic acid components, that can act as potent inhibitors of various enzymes of nucleoside and nucleotide metabolism, e.g. purine nucleoside phosphorylases (PNPs), adenylate cyclases (ACs), viral polymerases, and phosphoribosyltransferases (PRTs). Acyclic nucleoside phosphonates (ANPs) represent a key class of antimetabolites because of their potent antiviral, cytostatic, and antiparasitic properties. We develop efficient methods for the synthesis of novel types of ANPs and their prodrugs and subsequently study their biological properties. Inhibitors of PNP have the potential to treat T-cell acute lymphoblastic leukemias, while selective inhibitors of certain human ACs have the potential to treat neuropathic pain and neurodegenerative disorders. We also focus on bisphosphonate analogues, a special class of ANPs containing a second phosphonate moiety in the acyclic part of the molecule, which have been shown to be potent inhibitors of several PRTs, the purine salvage pathway enzymes essential 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/polymerase inhibitors with potent antiviral activity as well as the development of pyrimidines with significant anti-inflammatory properties for potential treatment of ulcerative colitis, rheumatoid arthritis, and colon cancer. We also design and study physicochemical properties of substituted 5-phenylazopyrimidines as molecular photoswitches for various potential applications, such as material chemistry and photopharmacology.

Group members

Group leader Zlatko Janeba
Senior scientists Michal Česnek, Viktor Kolman
Postdoctoral fellow Jan Skácel
Ph.D. students Kristína Almášiová, Marijo Čičak, Artem Chayka, Víctor Illa Fernández, Jan Frydrych, Filip Kalčic, Lucie Mužíková Čechová, Karolína Vaňková
Students Pavel Kraina, Katarína Markušová, Zuzana Palušová
Technician Adriana Struminská
Secretary Barbara Česneková

Selected publications

Kalčic, F.; Zgarbová, M.; Hodek, J.; Chalupský, K.; Dračínský, M.; Dvořáková, A.; Strmeň, T.; Šebestík, J.; Baszczyňski, O.; Weber, J.; Mertlíková-Kaiserová, H.; Janeba, Z. Discovery of modified amidate (ProTide) prodrugs of tenofovir with enhanced antiviral properties. *J. Med. Chem.* **2021**, 64, 16425–16449.

Keough, D. T.; Wun, S. J.; Baszczyňski, O.; Eng, W. S.; Špaček, P.; Panjikar, S.; Naesens, L.; Pohl, R.; Rejman, D.; Hocková, D.; Ferrero, R. L.; Guddat, L. W. *Helicobacter pylori* Xanthine–Guanine–Hypoxanthine Phosphoribosyltransferase – A Putative Target for Drug Discovery against Gastrointestinal Tract Infections. *J. Med. Chem.* **2021**, 64, 5710–5729.

Kalčic, F.; Dračínský, M.; Janeba, Z. Diverse synthetic approaches towards C1′-branched acyclic nucleoside phosphonates. *Org. Biomol. Chem.* **2021**, 19, 6958–6963.

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Skácel, J.; Dračínský, M.; Janeba, Z. Synthesis of tetrasubstituted thiophenes via direct metalation. *J. Org. Chem.* **2020**, 85, 788–797.

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Funding

Personalized medicine. Technology Agency of the Czech Republic (TA ČR), No. TN01000013, 2019–2022, co-PI: Janeba, Z.

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

Gilead Sciences & IOCB Research Center, 2006–2021, PI: Janeba, Z.

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

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

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

Collaboration

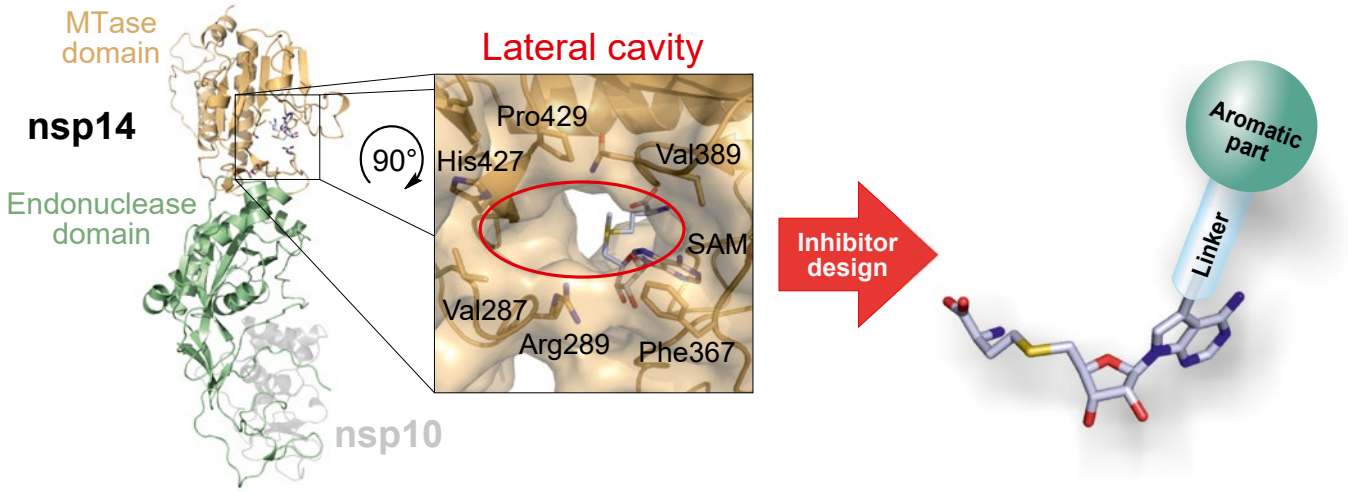
- Weizmann Institute of Science, Rehovot, Israel
- School of Chemistry & Molecular Biosciences, University of Queensland, Brisbane, Australia
- Department of Drug Evaluation, Army Malaria Institute, Enoggera, Australia
- Rega Institute for Medical Research, KU Leuven, Belgium
- College of Pharmacy, Purdue University, West Lafayette, Indiana, USA
- 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
- University of Chemistry and Technology, Prague, Czech Republic

Radim Nencka Group

Drug Design and Medicinal Chemistry
radim.nencka@uochb.cas.cz
www.uochb.cz/nencka

Senior Research Group
medicinal chemistry, chemical biology, enzyme inhibitors, phosphatidylinositol 4-kinase, STING agonists, SARS-CoV-2 inhibitors, methyltransferase, nucleosides, nucleotides

Design of novel SARS-CoV-2 methyltransferase inhibitors



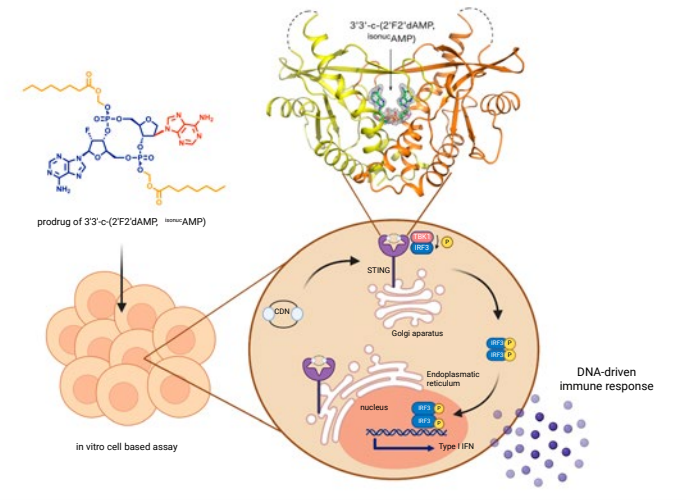
Research interests

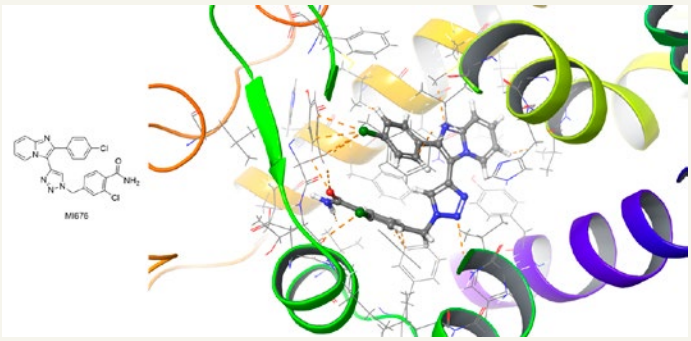
The major focus of our group is modern medicinal chemistry and chemical biology. Our priority is to discover and develop novel therapeutic agents against selected diseases and prepare chemical tools that will facilitate understanding of pathological processes and provide clues for their effective treatment. We use state-of-the-art medicinal chemistry approaches, including fragment-based drug design and extensive molecular modeling. The major part of our research focuses on the development of novel means of deciphering biological processes connected with viral replication, including involvement of viral proteins, host-virus interaction, and control of innate immunity related to viral infection and cancer. Our main targets are RNA viruses from the Coronaviridae, Flaviviridae and Picornaviridae families. Circumstances associated with the emergence of SARS-CoV-2 have led us to focus on the search for new therapeutics against COVID-19. We are part of an international team working to make a significant contribution to understanding this viral pathogen and obtaining effective therapeutic agents.

We have synthesized small molecules inhibiting coronaviral methyltransferase and RNA polymerase, respectively. These compounds effectively block SARS-CoV-2 replication and especially the methyltransferase inhibition seems to be an intriguing target for drug development. We are investigating detailed mechanism of action and SAR of our compounds that should allow for the synthesis of broad-spectrum antivirals.

We are involved in a collaborative project aimed at the development of cyclic dinucleotides acting as STING agonists. These nucleic acids act as stimulants of innate immunity response and were proven to exhibit unprecedented agonistic potency and exceptional ability to penetrate into cells thanks to unique strategy of prodrugs.

We also aim at influencing important cellular processes using small heterocyclic molecules. We discovered several agonists of human constitutive androstane receptor (CAR, NR1I3) acting at nanomolar concentrations. CAR plays a crucial regulatory role in xenobiotic and endobiotic metabolism.





(Up) Molecular docking experiment of our CAR inhibitor MI676.

(Left) Isonucleosidic CDNs acting as STING agonists. Prodrug easily enters cells and free CDN binds to STING. A sequence of steps leads to IFN secretion and DNA driven immune response.

Group members

Group leader Radim Nencka
Senior scientists Petra Břehová, Milan Dejmek, Kamil Hercík, Hubert Hřebabecký, Michal Šála
Postdoctoral fellows Jiří Böserle, Ján Kozic, Ivana Mejdrová
Research assistants Eva Dávidová, Marcela Dvořáková
Ph.D. students Anthony Allan, Mbilo Misehe, Tomáš Otava, Kryštof Škach, Milan Štefek, Luca Juliana Tóth
Technician Jaroslava Sklenářová
Students Kateřina Hakrová, Simona Horkelová, Hugo Kocek
Secretary Barbara Česneková

Selected publications

Nencka, R.; Silhan, J.; Klima, M.; Otava, T.; Kocek, H.; Krafcikova, P.; Boura, E. Coronaviral RNA-methyltransferases: function, structure and inhibition. *Nucleic Acids Res.* **2022**, 50, 635–650.

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Konkolova, E.; Dejmek, M.; Hrebabecky, H.; Sala, M.; Boserle, J.; Nencka, R.; Boura, E. Remdesivir triphosphate can efficiently inhibit the RNA-dependent RNA polymerase from various flaviviruses. *Antivir. Res.* **2020**, 182, 104899.

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Funding

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Search for novel nucleoside analogs as antivirals against medically important flaviviruses. Ministry of Education, Youth and Sports (MŠMT ČR), LTAUSA18016, 2019–2022, co-PI: Nencka, R.

Personalized Medicine – Diagnostics and Therapy. Technology Agency of the Czech Republic (TA ČR), TN01000013, 2019–2022, co-PI: Nencka, R.

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: Nencka, R.

Awards

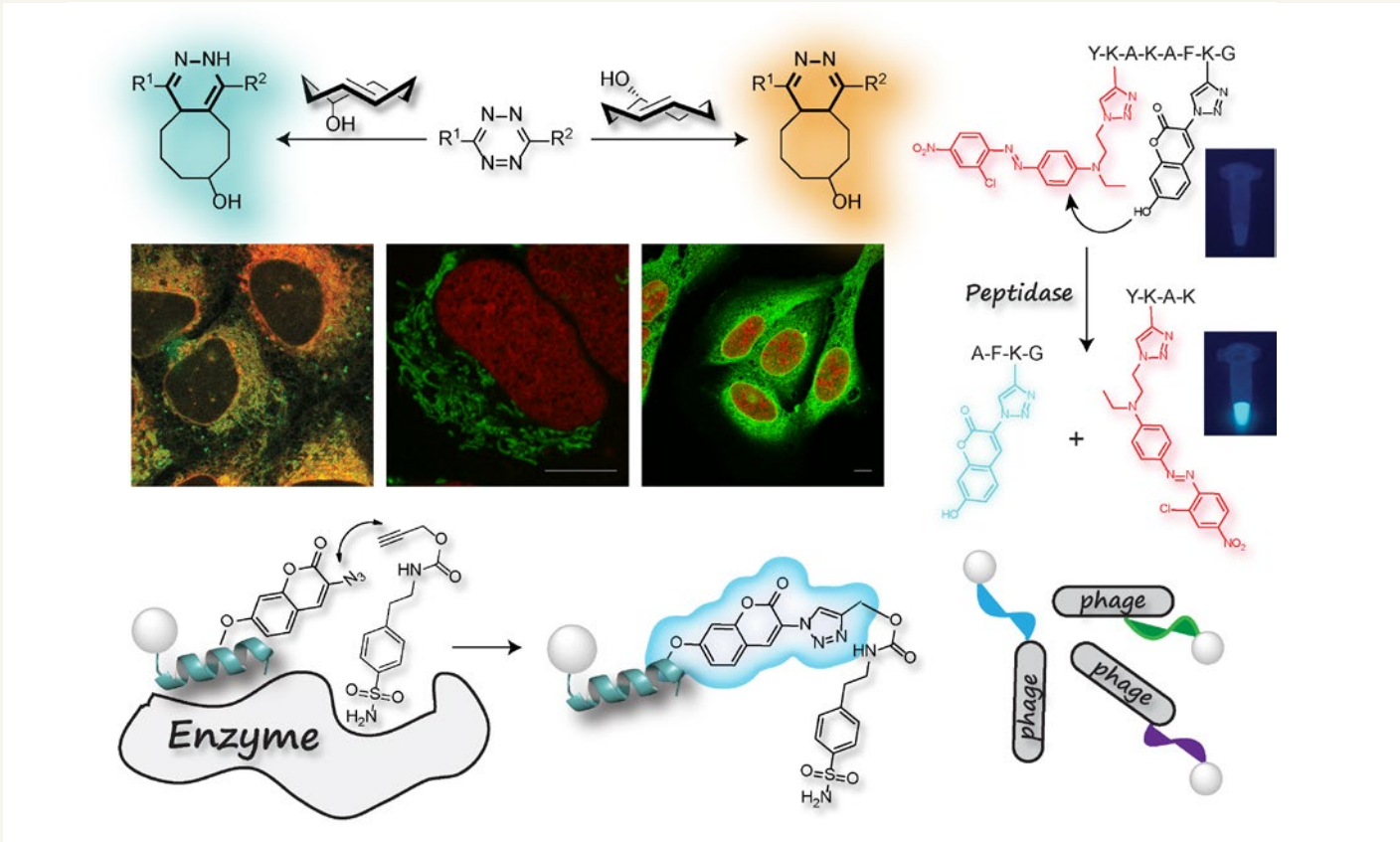
Radim Nencka – Prize of the Minister for Health for the exceptional result in research and development (antiflavivirus project, co-PI)

Milan Vrábel Group

Chemistry of Bioconjugates
milan.vrabel@uochb.cas.cz
www.uochb.cz/vrabel

Senior Research Group

bioorthogonal reactions, click chemistry, glycopeptide libraries, cancer immunology



Research interests

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.

CANCER IMMUNOTHERAPY
Our group aims to develop new approaches in cancer immunotherapy. We also focus on the development of alternative methods for cheaper and faster construction of the modified immune cells that we use in model cytolytic experiments. We employ the developed bioconjugation tools in the reengineering of cellular surfaces with molecules that enhance their function or properties.

Group members

Group leader Milan Vrábel
Senior scientists Rastislav Dzijak, Anna Kovalová, Paul Eduardo Reyes Gutierrez
Postdoctoral fellow Veronika Šlachtová
Research assistants Simona Bellová, Tereza Schröpferová
Ph.D. students Marek Chovanec, Michal Rahm, Robert Rampmaier
Students Jáchym Hrušák, Jan Vyčítal

Selected publications

Dzijak, R.; Galeta, J.; Vázquez-Alvarez, A.; Kozák, J.; Matoušová, M.; Fulka, H.; Drčínský, M.; Vrábel, M. Structurally Redesigned Bioorthogonal Reagents for Mitochondria-Specific Prodrug Activation. *JACS Au* **2021**, 1, 23–30.

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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.

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Funding

Bioorthogonal time-controlled intramitochondrial elimination (bioTime). Czech Science Foundation (GA ČR), No. GF20-30494L, 2020–2023, PI: Vrábel, M. Collaboration with Dr. Hannes Mikula from IAS TU Wien, Austria

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

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

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

Collaboration

Dr. Hannes Mikula (IAS, TU Wien, Austria)

Dr. Frédéric Friscourt (IECB, Bordeaux, France)

Dr. Michal Šmída (CEITEC, Brno, Czechia)

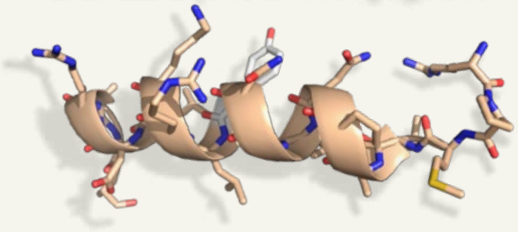
Dr. Ondřej Kuda (IPHYS CAS, Prague, Czechia)

Dr. Helena Fulka (IEM CAS, Prague, Czechia)

Dr. Martin Dračínský, Dr. Pavel Majer, Dr. Pavlína Maloy Řezáčová, Dr. Helena Mertlíková-Kaiserová (IOCB Prague)

Vrabel Group

Chemistry of Bioconjugates



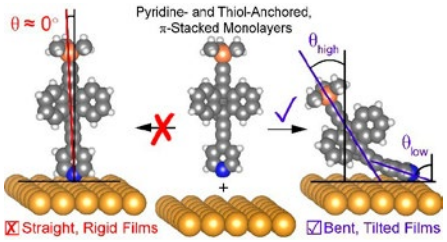
Jiří Kaleta Group

Molecular Devices
jiri.kaleta@uochb.cas.cz
www.uochb.cz/kaleta

Junior Research Group

molecular-level devices, molecular machines, molecular switches, molecular motors, organic synthesis, supramolecular chemistry, smart materials, photochemistry, reaction mechanisms

SELF-ASSEMBLED MONOLAYERS



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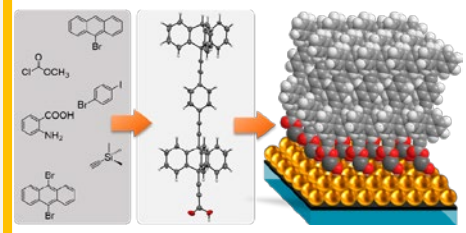
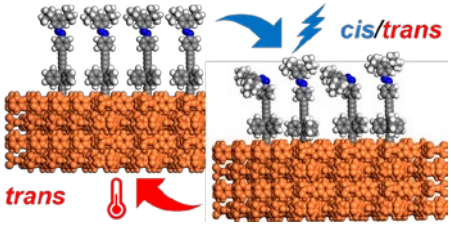
J. Phys. Chem. C
2022, DOI: 10.1021/acs.jpcc.1c10627



Kaletová *et al.*
ChemPlusChem
2022, DOI: 10.1002/cplu.202200023

SURFACE INCLUSIONS OF MOLECULAR-LEVEL DEVICES



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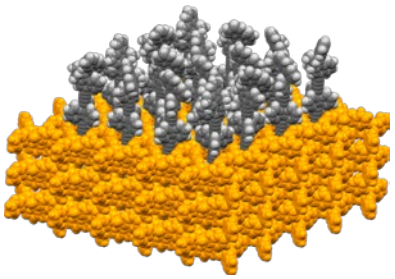
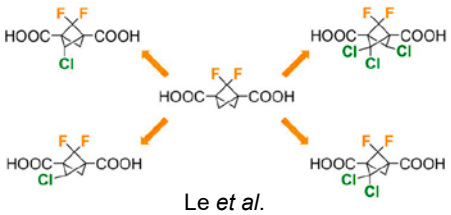
J. Am. Chem. Soc.
2020, *142*, 9337-9351



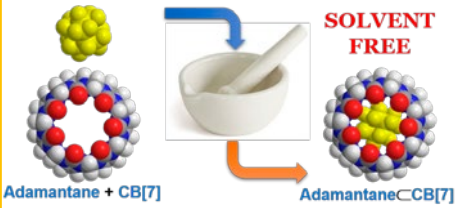
Kaleta *et al.*
J. Am. Chem. Soc.
2017, *139*, 10486-10498

REACTIVITY OF STRAINED HYDROCARBONS



Le *et al.*
J. Org. Chem. **2021**, *86*, 10303-10319
Kaleta *et al.*
J. Org. Chem. **2019**, *84*, 2448–2461

SUPRAMOLECULAR COMPLEXES



Dračínský *et al.*
Chem. Comm.
2021, *57*, 2132-2135

Research interests

REGULAR ARRAYS OF MOLECULAR MACHINES
We design, synthesize, and study advanced molecular-level devices and their complex 2D/3D assemblies. We are particularly interested in how the combination of the molecular structure, the anchoring group of the adsorbate, and the lattice parameters of a surface will affect the self-assembly process and thus the crystal structure of the formed 2D films.

ARTIFICIAL PROPULSION SYSTEMS
The next frontier in construction of smart materials involves development of systems capable of locomotion. Drawing inspiration purely from living nature, we aim to develop a new generation of fully synthetic propulsion systems using the swirling motion of flagella-like objects powered by light-driven molecular motors based on overcrowded alkenes.

BUILDING BLOCKS FOR SUPRAMOLECULAR CHEMISTRY
We also focus on systematic synthesis of small geometrically unique organic molecules that are highly attractive building blocks in supramolecular chemistry. Some of these molecules already serve as universal "pedestals" beneath molecular machines, while the others are used as spacers or rotators.

MOLECULAR MACHINES IN SUPRAMOLECULAR SYSTEMS
We are developing new types of molecular machines based on the supramolecular host-guest complexes between specifically designed molecular rods and rigid macrocyclic compounds (cucurbit[*n*]urils). These macrocycles could function as spacers enabling individual molecular machines to operate freely once the molecules are adsorbed on flat metallic surfaces.

Group members

Group leader Jiří Kaleta
Senior scientist Guillaume Bastien
Postdoctoral fellows Carina Santos Hurtado, Milan Mašát, Eva Kaletová, Igor Rončević, Lukáš Severa
Ph.D. students Kateřina Bezděková, Doroteja Lončarić
Students Adéla Křížková, Thị Phuong Lê, Lujo Matasović, Martin Škuta
Secretary Kateřina Pokorná

Selected publications

Rončević, I.; Kaletová, E.; Varga, K.; Císařová, I.; Bastl, Z.; Jiang, J.-C.; Kaleta, J. Molecular Bending - An Important Factor Affecting the Packing of Self-Assembled Monolayers of Triptycene-Based Molecular Rods on a (111) Gold Surface. *J. Phys. Chem. C* **2022**, DOI: 10.1021/acs.jpcc.1c10627.

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Funding

Could light-driven molecular motors propel microscopic objects? Czech Science Foundation (GA ČR), No. 20-13745S, 2020–2022, PI: Kaleta, J.

When cucurbit[n]urils met molecular rods: synthesis and characterization of supramolecular machines in solid state. Ministry of Education, Youth and Sport (MŠMT ČR), No. LTAUSA19120, 2020–2022, PI: Kaleta, J.

Self-assembly of molecular machines: experimental and computational study of new surface-bound structures. Czech Academy of Sciences, 2020–2021, PI: Kaleta, J.

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)

Prof. Angiolina Comotti and Prof. Piero Sozzani (University of Milano-Bicocca, Italy)

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

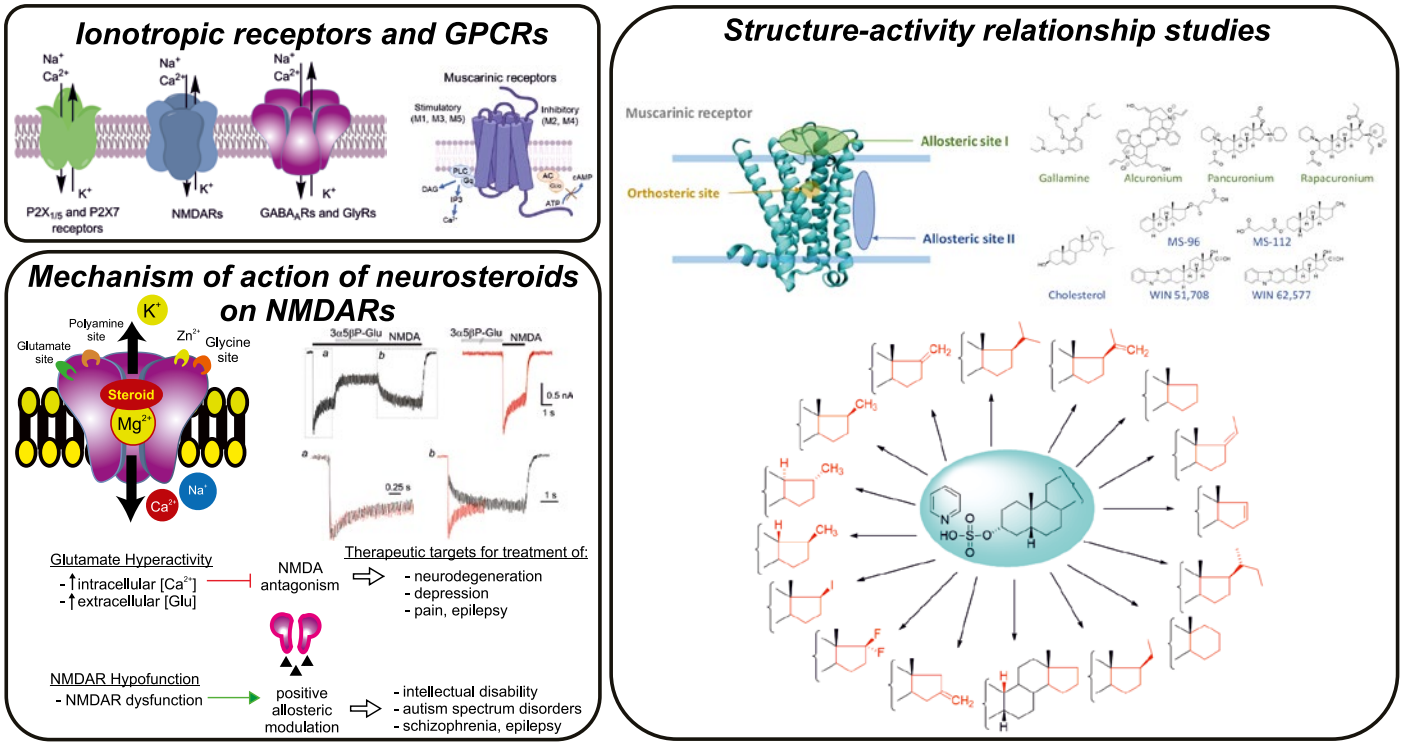
Prix de Chimie—1st Prize, awarded by the French embassy and the Rhodia, 2010

Eva Kudová Group

Neurosteroids
eva.kudova@uochb.cas.cz
www.uochb.cz/kudova

Junior Research Group

NMDA receptor, $GABA_A$ receptor, muscarinic receptor, S.M.A.R.T. steroids, NMDA hypofunction, epilepsy, neuropathic pain, excitotoxicity, neuroprotection



Research interests

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 (i.e. glutamate, GABAA, glycine) or G-protein coupled receptors (muscarinic 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
Senior scientist Hana Chodounská
Postdoctoral fellows Eszter Szánti-Pintér, Ewa Szczurowska, Mariia Vodolazhenko, Santosh Kumar Adla
Research assistants Barbora Slavíková, Kateřina Kouřilová (currently on maternity leave)
Ph.D. student Miroslav Kašpar
Intern Lada Jirkalová

Selected publications

Modulation of NMDARs:

Kudova, E.: Rapid effects of neurosteroids on neuronal plasticity and their physiological and pathological implications. *Neurosci. Lett.* **2021**, 750, 135771.

Hubalkova, P.; Ladislav, M.; Vyklicky, V.; Smejkalova, T.; Hrcka Krausova, B.; Kysilov, B.; Krusek, J.; Naimanova, Z.; Korinek, M.; Chodounska, H.; Kudova, E.; Cerny, J.; Vyklicky, L. Jr. Palmitoylation controls NMDA receptor function and steroid sensitivity. *J. Neurosci.* **2021**, 41, 2119–2134.

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Modulation of muscarinic receptors:

Dolejší, E.; Szánti-Pintér, E.; Chetverikov, N.; Nelic, D.; Randáková, A.; Doležal, V.; Kudová, E.; Jakubík, J. Neurosteroids and steroid hormones are allosteric modulators of muscarinic receptors. *Neuropharmacology* **2021**, 199, 108798.

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Modulation of farnesoid X receptors:

Stefela, A.; Kaspar, M.; Drastik, M.; Kronenberger, T.; Micuda, S.; Dracinsky, M.; Klepetarova, B.; Kudova, E.; Pavek, P. (E)-7-ethylidene-litocholic acid (7-ELCA) is a potent steroidal dual G-protein bile acid receptor 1 (GPBAR1) agonist and farnesoid X receptor (FXR) antagonist stimulating glucagon like peptide-1 secretion in intestinal enteroendocrine cells. *Front. Pharmacol.* **2021**, 12, 713149.

Stefela, A.; Kaspar, M.; Drastik, M.; Holas, O.; Hroch, M.; Smutny, T.; Skoda, J.; Hutníková, M.; Pandey, A. V.; Micuda, S.; Kudova, E.; Pavek, P. 3β-Isoobeticholic acid efficiently activates the farnesoid X receptor (FXR) due to its epimerization to 3α-epimer by hepatic metabolism. *J. Steroid Biochem. Mol. Biol.* **2020**, 202, 105702.

Modulation of GABAARs and GlyRs:

Bukanova, J.; Solntseva, E.; Kondratenko, R.; Kudova, E. Epipregnanolone as a positive modulator of GABAA receptor in rat cerebellar and hippocampus neurons. *Biomolecules* **2021**, 11, 791.

Bukanova, J. V.; Solntseva, E. I.; Kudova, E. Neurosteroids as Selective Inhibitors of Glycine Receptor Activity: Structure-Activity Relationship Study on Endogenous Androstanes and Androstenes. *Front. Mol. Neurosci.* **2020**, 13, 44.

Mareš, P.; Kudová, E.; Valeš, K.; Kubová, H. Three neurosteroids as well as GABAergic drugs do not convert immediate postictal potentiation to depression in immature rats. *Pharmacol. Rep.* **2020**, 72, 1573–1578.

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Funding

Role of the cytoplasmic domain of the NMDA receptor for its biogenesis, function, and pharmacology: Focus on disease-associated mutations. Czech Science Foundation (GA ČR), No. 20-17945S, 2020–2022, co-PI: Kudová, E.

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Project PharmaBrain. Ministry of Education, Youth and Sports (MŠMT ČR), European Structural and Investment Funds, OP RDE, No. CZ.02.1.01/0.0/0.0/16_025/0007444, 2018–2022.

Patents

Steroidal compounds for treatment of mental and neurological disorders. Vyklický, L.; Kudová, E. CZ 307648; EP 18829194.2; US 16/763,498.

Amphiphilic compounds with neuroprotective properties. Kudová, E.; Chodounská, H.; Kapras, V.; Vyklický, L.; Valeš, K.; Jahn, U. AU 2015309371; US 10,017,535; JP 6437636; CA 2.957.906; EP 3186267.

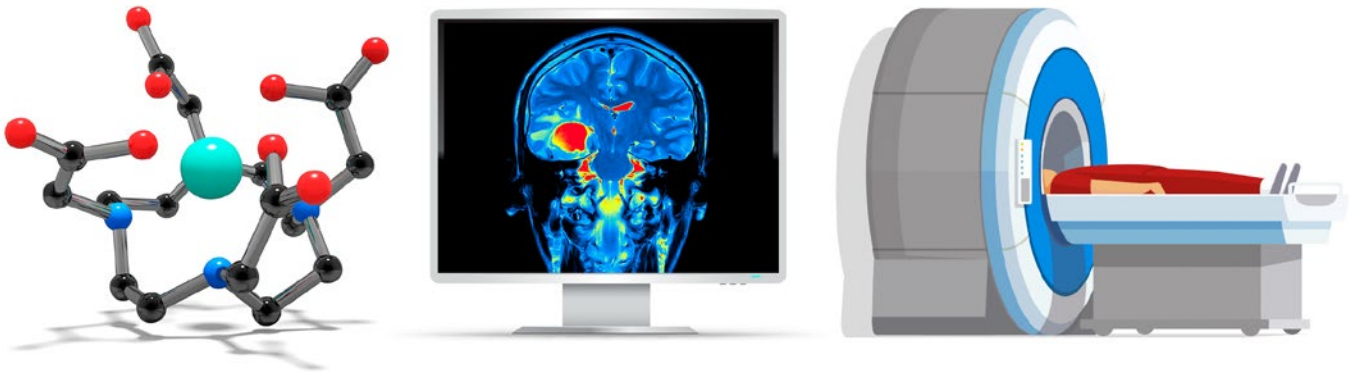
3α5β-Neuroactive steroids for treatment of mental and neurological disorders. Kudová, E.; Chodounská, H.; Mareš, P.; Valeš, K. CA 3.128.921; US 17/439688; JP 2021-558713; EP 20718527.3.

Miloslav Polášek Group

Coordination Chemistry
miloslav.polasek@uochb.cas.cz
www.uochb.cz/polasek

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

COORDINATION COMPOUNDS FOR MEDICAL IMAGING AND THERAPY



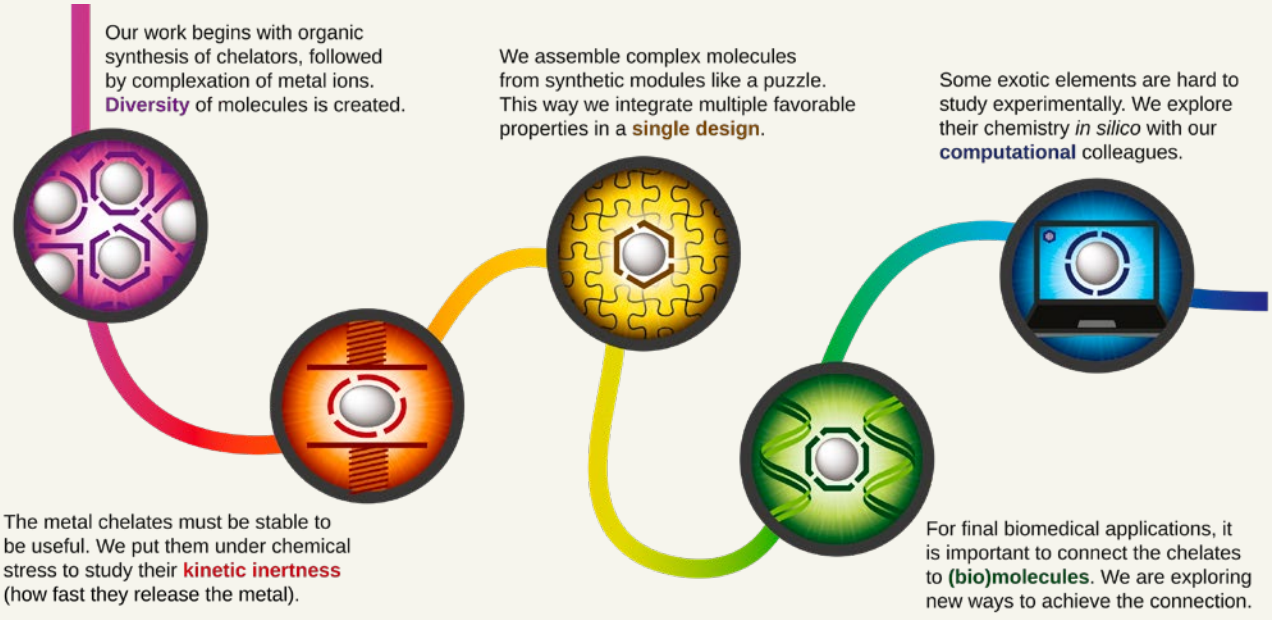
Research interests

WHY COORDINATION CHEMISTRY?
Metal elements offer magnetic, luminescent, and nuclear properties that purely organic molecules can never have. Our group specializes in the coordination compounds of lanthanides, which find a broad range of biomedical and technological applications, ranging from anti-cancer drugs to the future of information storage. We design new macrocyclic ligands that cage the metal ion and help to unlock its full potential.

METAL CHELATES IN DIAGNOSTICS
Humans naturally need to be able to see things in order to understand them. Unfortunately, pathologies in our bodies start at the molecular level, which is invisible to us. Advanced imaging techniques and molecular probes are about to change that. Our team is developing gadolinium-based probes for magnetic resonance imaging (MRI) that can visualize specific biogenic molecules. We are using combinatorial synthetic methodologies to create libraries of such probes. We are also developing probes for the newest hybrid MRI/PET scanners.

CANCER THERAPY
Radioactive metal isotopes are changing the way that cancer is treated. Targeted drugs deliver them to tumors, where the isotopes emit alpha or beta particles, damaging DNA and killing cancer cells. Lutetium-177 (^{177}Lu) is a radioisotope with excellent properties for this purpose. However, its large-scale production has been hampered by difficult separation from the chemically similar ytterbium-176. We have solved this problem with specially-designed chelators that amplify the difference between the two elements, allowing their fast and efficient separation. The technology has been licensed to SHINE Technologies (USA), who, starting in 2022, will be producing ^{177}Lu to help cancer patients around the world. We are continuing in this line of research with a focus on preparations of other medical radioisotopes.

OUT OF THE BOX
The interface between metals and organic molecules is full of opportunities to find new and unexpected properties. We are constantly exploring potential applications at the intersections of multiple fields: medicine, materials, analytical methods, and information technologies.



Group members

Group leader Miloslav Polášek
Senior scientist Tomáš David
Ph.D. students Kelsea Grace Jones, Jan Kretschmer
Technician Miroslava Šedinová

Selected publications

Kretschmer, J.; David, T.; Dračínský, M.; Socha, O.; Jirak, D.; Vít, M.; Jurok, R.; Kuchař, M.; Císařová, I.; Polasek, M. Paramagnetic encoding of molecules. *Nat. Commun.* **2022**, accepted.

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.*

Polasek, M.; Yang, Y.; Schühle, D. T.; Yaseen, M.A.; Kim, Y. R.; Sung, Y. S.; Guimaraes, A. R.; Caravan, P. Molecular MR Imaging of Fibrosis in a Mouse Model of Pancreatic Cancer. *Sci. Rep.* **2017**, 7, 8114.

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.*

** Non-IOCB article (Tomáš David, Miloslav Polášek)*

Funding

SHINE/IOCB Research Collaboration Agreement, 2022–2023, PI: Polášek, M.

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

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

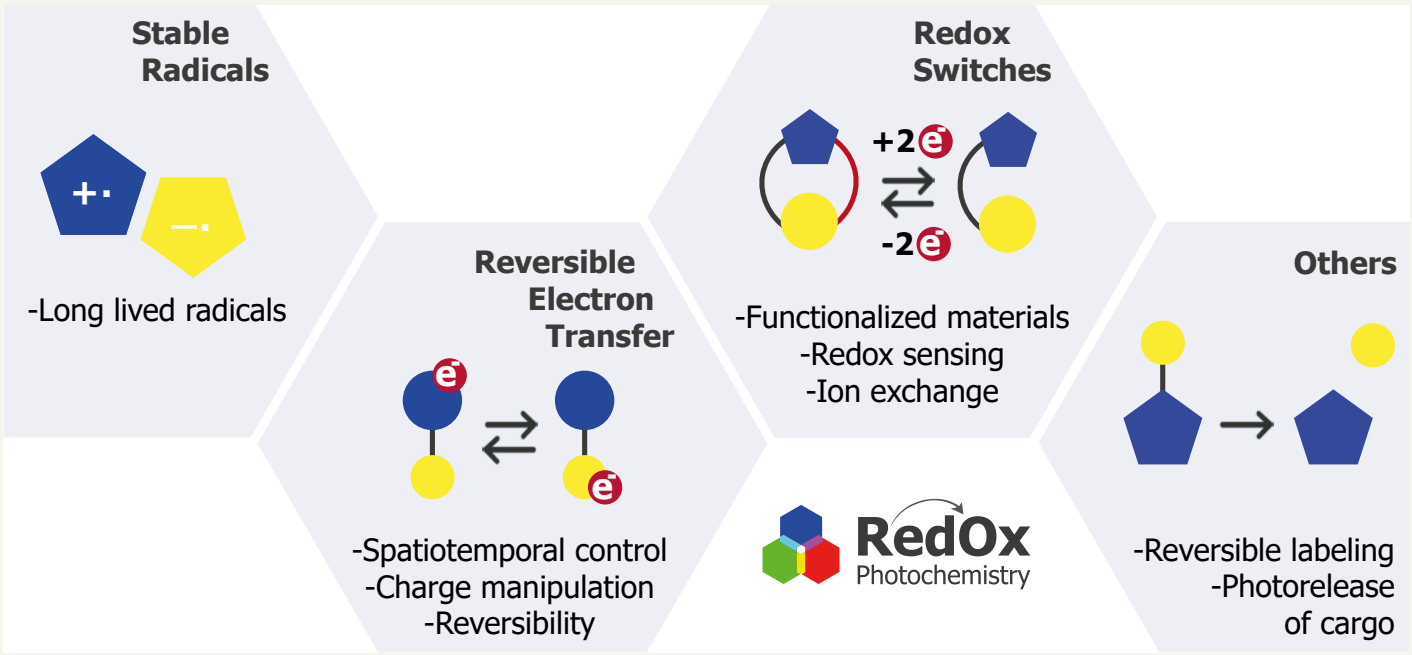
Patents

- **PCT/CZ2021/050131** (2021, pending)—Cyclen based compounds for separation of rare earth elements and method for separation of rare earth elements
- **EP21196175.0** (2021, pending)—Compounds for complexation of rare earth elements and/or s-, p-, d- block metals, their coordination compounds, peptide conjugates, method of their preparation and use thereof
- **EP19182286.5** (2019, pending)—Cyclen-based compounds, coordination compounds, peptides, pharmaceutical preparation, and use thereof
- **PCT/EP2018/083215** (2018, Granted European Patent No. 3717466)—Compounds for separation of rare earth elements and s-, p-, d- metals, method of separation, and use thereof

Tomáš Slanina Group

Redox Photochemistry
tomas.slanina@uochb.cas.cz
www.uochb.cz/slanina

Junior Research Group
electron transfer, radical ions, redox switches, stabilization of radical species, photochemical switches, photoremovable protecting groups



Research interests

REVERSIBLE ELECTRON TRANSFER
One of the goals of our group is to govern electron transfer between suitable donor-acceptor pairs by external stimuli 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 that can be regulated by the action of external stimuli (light, pH, solvent change, or temperature). They exist in two chemically stable states with different geometry, chemical, and physical properties. Redox switches are 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 labeling, and photo-click bioorthogonal reactions.

Group members

Group leader Tomáš Slanina
Senior scientist Dalimil Dvořák
Postdoctoral fellows Soňa Boháčová, Denisa Hidasová, Lucie Ludvíková, Anna Poryvai
Ph.D. students Jakub Copko, David Dunlop, Anna Vasilevska, Lucie Wohlrábová
Students Karolína Bangievská, Michal Chovanec, Ondřej Groborz, Jakub Krištof
Research assistant Tereza Černá
Assistant Alena Habartová

Selected publications

Rahimidashaghoul, K.; Klimánková, I.; Hubálek, M.; Matoušek, V.; Filgas, J.; Slavíček, P.; Slanina, T.; Beier, P. Visible-Light-Driven Fluoroalkylation of Tryptophan Residues in Peptides. *ChemPhotoChem* **2021**, 5, 43–50.

Weinstain, R.; Slanina, T.; Kand, D.; Klán, P. Visible-to-NIR-Light Activated Release: From Small Molecules to Nanomaterials. *Chem. Rev.* **2020**, 120, 13135–13272.

Slanina, T.; Ayub, R.; Toldo, J.; Sundell, J.; Rabten, W.; Nicaso, M.; Alabugin, I.; Fdez. Galván, I.; Gupta, A. K.; Lindh, R.; Orthaber, A.; Lewis, R. J.; Grönberg, G.; Bergman, J.; Ottosson, H. Impact of Excited-State Antiaromaticity Relief in a Fundamental Benzene Photoreaction Leading to Substituted Bicyclo[3.1.0] hexenes. *J. Am. Chem. Soc.* **2020**, 142, 10942–10954.

Jorner, K.; Rabten, W.; Slanina, T.; Proos Vedin, N.; Sillén, S.; Wu Ludvigsson, J.; Ottosson, H.; Norrby, P.-O. Degradation of Pharmaceuticals through Sequential Photon Absorption and Photoionization in Amiloride Derivatives. *Cell Rep. Phys. Sci.* **2020**, 1, 100274.

Čechová, L.; Filo, J.; Dračínský, M.; Slavov, C.; Sun, D.; Janeba, Z.; Slanina, T.; Wachtveitl, J.; Procházková, E.; Cigáň, M. Polysubstituted 5-Phenylazopyrimidines: Extremely Fast Non-ionic Photochromic Oscillators. *Angew. Chem., Int. Ed.* **2020**, 59, 15590–15594.

Hernández-Guerra, D.; Hlavačková, A.; Pramthaisong, C.; Vespoli, I.; Pohl, R.; Slanina, T.; Jahn, U. Photochemical C–H Amination of Ethers and Geminal Difunctionalization Reactions in One Pot. *Angew. Chem., Int. Ed.* **2019**, 58, 12440–12445.

Collaboration

Henrik Ottosson (Uppsala University, Sweden)

Sugumar Venkataramani (IISER Mohali, India)

Gopalan Rajaraman (IIT Bombay, India)

Gregor Trimmel (TU Graz, Austria)

Marek Cigáň (Univerzita Komenského, Bratislava, Slovak Republic)

Petr Klán (Masaryk University, Brno, Czech Republic)

Alexander Heckel (Goethe University Frankfurt, Germany)

Funding

Storage of Electrons into Chemical Bonds: Towards Molecular Solar Electrical Batteries (SOLBATT), ERC Starting Grant, No. 101041554, 2022–2027, PI: Slanina, T.

Photochemical Catch and Release Strategy: Towards Novel Molecular Switches and Bioorthogonal Reactions. Czech Science Foundation (GA ČR), No. 22-20319S, 2022–2024, PI: Slanina, T.

Impact of Photoinduced Charge Migration on Photochemistry of Radicals and Switches. Ministry of Education, Youth and Sports (MŠMT ČR), INTER-COST, No. LTC20076, 2020–2023, PI: Slanina, T.

Photoswitchable and Magnetic Photoswitchable Ionic Liquids: Theory and Experiments. Ministry of Education, Youth and Sports (MŠMT ČR), INTER-EXCELLENCE, INTER-ACTION, No. LTAIN19166, 2020–2022, PI: Slanina, T.

Successes

Otto Wichterle Award, 2021, Tomáš Slanina

Best oral speech (Liblice conference), 2021, Anna Poryvai

Jitka Moravcová Award for the best poster in organic chemistry section, 2021, Jakub Copko

IGRA grant, 2021, Jakub Copko

GAUK grant, 2021, David Dunlop

Master's degree, 2021, Lucie Wohlrábová, Ondřej Groborz, David Dunlop

Josef Hlávka Prize, 2020, Tomáš Slanina

3rd place at Student Scientific Conference, 2020, Lucie Wohlrábová

Alfred Bader Organic Chemistry Prize, 2019, Tomáš Slanina

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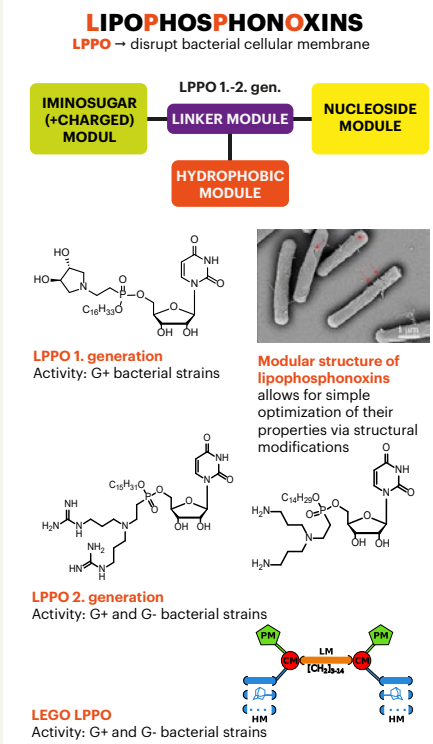
RedOx Photochemistry

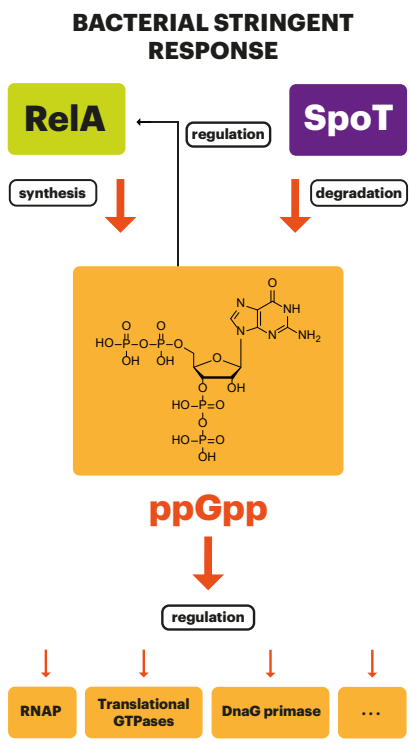
Dominik Rejman Group

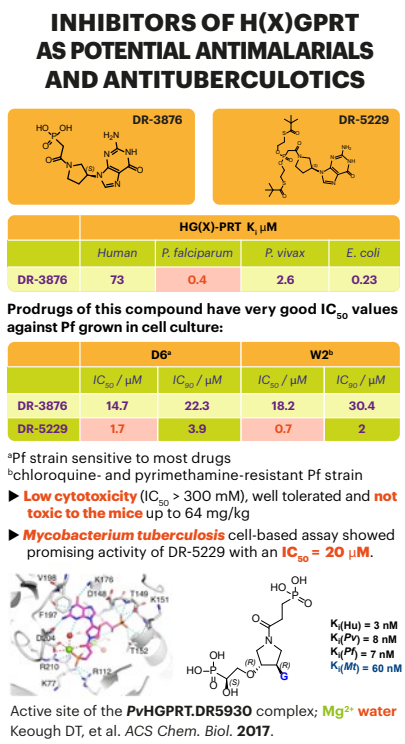
Antimicrobial Compounds
dominik.rejman@uochb.cas.cz
www.uochb.cz/rejman

Targeted Research Group

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







Research interests

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 (LPPO)—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.

Recently we have developed a new generation of these small molecule antimicrobial compounds called LEGO-LPPO with improved biological properties and a highly tunable structure. A novel composite material NANO-LPPO has also been developed, based on combination of lipophosphonoxins with nanofibrous fabric for antibacterial dressing in collaboration with Technical University Liberec, and successfully evaluated in a mouse skin wound infection model.

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. Recently we have started developing novel analogues based on boronic acids.

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
Senior scientist Magdalena Petrová
Postdoctoral fellows Duy Dinh Do Pham, Gabriela Mikušová (currently on maternal leave), Viktor Mojr, Eva Zborníková

Selected publications

Do Pham, D. D.; Jenčová, V.; Kaňuchová, M.; Bayram, J.; Grossová, I.; Šuca, H.; Urban, L.; Havlíčková, K.; Novotný, V.; Mikeš, P.; Mojr, V.; Asatiani, N.; Košťáková, E. K.; Maixnerová, M.; Vlková, A.; Vítovská, D.; Šanderová, H.; Nemec, A.; Krásný, L.; Zajíček, R.; Lukáš, D.; Rejman, D.; Gál, P. Novel lipophosphonoxin-loaded polycaprolactone electrospun nanofiber dressing reduces Staphylococcus aureus induced wound infection in mice. *Sci. Rep.* **2021**, 11, 17688.

Mojr, V.; Roghanian, M.; Tamman, H.; Do Pham, D. D.; Petrová, M.; Pohl, R.; Takada, H.; Van Nerom, K.; Ainelo, H.; Caballero-Montes, J.; Jimmy, S.; Garcia-Pino, A.; Hauryliuk, V.; Rejman, D. Nonhydrolysable Analogues of (p)ppGpp and (p)ppApp Alarmone Nucleotides as Novel Molecular Tools. *ACS Chem. Biol*. **2021**, 16, 1680–1691.

Jimmy, S.; Saha Chayan, K.; Kurata, T.; Stavropoulos, C.; Oliveira Sofia Raquel, A.; Koh, A.; Cepauskas, A.; Takada, H.; Rejman, D.; Tenson, T.; Strahl, H.; Garcia-Pino, A.; Hauryliuk, V.; Atkinson Gemma, C. A widespread toxin–antitoxin system exploiting growth control via alarmone signaling. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, 117, 10500–10510.

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.

Seydlová, G.; Pohl, R.; Zborníková, E.; Ehn, M.; Šimák, O.; Panova, N.; Kolář, M.; Bogdanová, K.; Večeřová, R.; Fišer, R.; Šanderová, H.; Vítovská, D.; Sudzinová, P.; Pospíšil, J.; Benada, O.; Křížek, T.; Sedlák, D.; Bartůněk, P.; Krásný, L.; Rejman, D. Lipophosphonoxins II: Design, Synthesis, and Properties of Novel Broad Spectrum Antibacterial Agents. *J. Med. Chem.* **2017**, 60, 6098–6118.

Beljantseva, J.; Kudrin, P.; Jimmy, J.; Ehn, M.; Pohl, R.; Varik, V.; Tozawa, Y.; Shingler, V.; Tenson, T.; Rejman, D.; Hauryliuk, V. Molecular mutagenesis of ppGpp: turning a RelA activator into an inhibitor. *Sci. Rep.* **2017**, 7, 41839.

Barvík, I.; Rejman, D.; Panova, N.; Šanderová, H.; Krásný, L. Non-canonical transcription initiation: the expanding universe of transcription initiating substrates. *FEMS Microbiol. Rev.* **2016**, 41, 131–138.

Funding

Structural determinants of membrane active antimicrobials. Czech Science Foundation (GA ČR), No. 22-08857S, 2022–2024, co-PI: Rejman, D.

Development of novel ribosome-targeting antibiotics. JPI-EC-AMR, 2019–2022, co-PI: Rejman, D.

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, PI: 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, PI: 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, co-PI: 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)

Drug Discovery

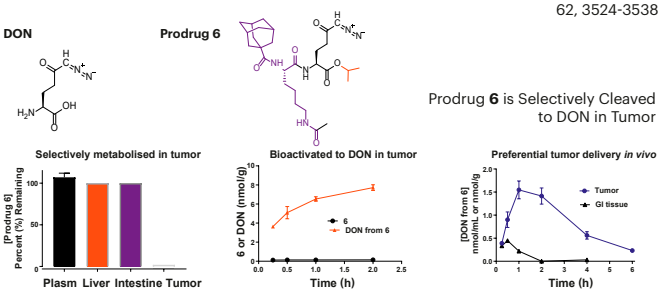
Pavel Majer
pavel.majer@uochb.cas.cz
www.uochb.cz/drugdiscovery

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

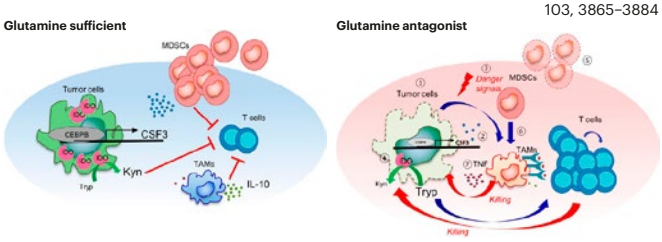
TUMOR-TARGETED DELIVERY OF 6-DIAZO-5-OXO-L-NORLEUCINE (DON)

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



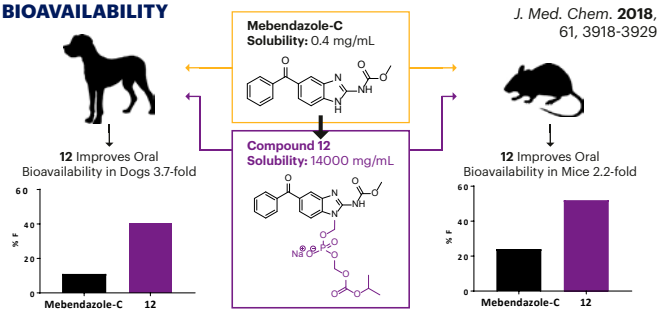
TARGETING GLUTAMINE METABOLISM ENHANCES TUMOR-SPECIFIC IMMUNITY BY MODULATING SUPPRESSIVE MYELOID CELLS

J. Clin. Invest. **2020**, 103, 3865–3884



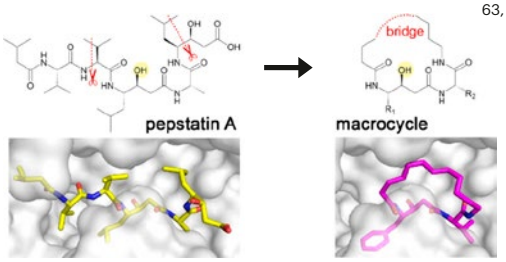
PRODRUGS OF MEBENDAZOLE IMPROVE SOLUBILITY AND ORAL BIOAVAILABILITY

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



BIOMIMETIC MACROCYCLIC INHIBITORS OF HUMAN CATHEPSIN D: STRUCTURE–ACTIVITY RELATIONSHIP AND BINDING MODE ANALYSIS

J. Med. Chem. **2020**, 63, 1576–1596



Research interests

Our main mission is the design and synthesis of biologically active compounds. Together with the Drug Discovery Group at Johns Hopkins University in Baltimore, USA, 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. One of our DON prodrugs (DRP-104, a.k.a. Sirpiglenastat), is currently being tested by Dracen Pharmaceuticals in phase 1/2a clinical trial (NCT04471415) against several types of cancer.

We also collaborate with groups at IOCB 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 Intermembrane Proteases of the Rhomboid Family (K. Stříšovský); Small Molecule Protease Inhibitors (M. Mareš); Synthesis of Communication Substances of Social Insects (R. Hanus); and Controlling Structure and Function of Biomolecules on the Molecular Scale (P. Hobza).

Our group also provides other 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
Senior scientists Marcela Krečmerová, Aleš Machara
Scientists Juraj Galeta, Martin Maxmilián Kaiser, 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, Kateřina Novotná, Robert Reiberger, Lucie Svobodová, Adéla Šimková (guest)
Technician Aleksandrina Prichodko
Students Gabriela Panýrková, Pavel Říkovský, Artem Tsalyy

Selected publications

Alt, J.; Gori, S. S.; Lemberg, M. K.; Pal, A.; Veeravalli, V.; Wu, Y.; Aguilar, M. H. J.; Dash, P. R.; Tenora, L.; Majer, P.; Sun, Q.; Slusher, S. B.; Rais, R. Glutamine Antagonist GA-607 Causes a Dramatic Accumulation of FGAR which can be used to Monitor Target Engagement. *Curr. Drug Metab.* **2021**, 22, 735–745.

Oh, M.-H.; Sun, I.-H.; Zhao, L.; Leone, R. D.; Sun, I.-M.; Xu, W.; Collins, S. L.; Tam, A. J.; Blosser, R. L.; Patel, C. H.; Englert, J. M.; Arwood, M. L.; Wen, J.; Chan-Li, Y.; Tenora, L.; Majer, P.; Rais, R.; Slusher, B. S.; Horton, M. R.; Powell, J. D. Targeting glutamine metabolism enhances tumor-specific immunity by modulating suppressive myeloid cells. *J. Clin. Investig.* **2020**, 130, 3865–3884.

Zima, V.; Radilová, K.; Kožíšek, M.; Albiñana, C. B.; Karlukova, E.; Brynda, J.; Fanfrlík, J.; Flieger, M.; Hodek, J.; Weber, J.; Majer, P.; Konvalinka, J.; Machara, A. Unraveling the anti-influenza effect of flavonoids: Experimental validation of luteolin and its congeners as potent influenza endonuclease inhibitors. *Eur. J. Med. Chem.* **2020**, 208, 112754.

Houštecká, R.; Hadzima, M.; Fanfrlík, J.; Brynda, J.; Pallová, L.; Hánová, I.; Mertlíková-Kaiserová, H.; Lepšík, M.; Horn, M.; Smrčina, M.; Majer, P.; Mareš, M. Biomimetic Macrocyclic Inhibitors of Human Cathepsin D: Structure–Activity Relationship and Binding Mode Analysis. *J. Med. Chem.* **2020**, 63, 1576–1596.

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.

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.

Funding

Discovery of small-molecule activators of the NRF1 pathway for treatment of neurodegenerative disorders. Czech Science Foundation (GA ČR), No. 22-16389S, 2022–2024, PI: Machara, A.

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

Targeting enzyme exosites by in-situ click chemistry: new strategy for anticancer drug design, Gilead Sciences Research Centre (GSRC-3), 2016-2021, co-PI: Majer, P.

Chemical Biology Tools for Drug Discovery, Gilead Sciences Research Centre (GSRC-3), 2016-2021, co-PI: Majer, P.

Czech National Node to the European Infrastructure for Translational Medicine EATRIS-CZ. Ministry of Education, Youth and Sports (MŠMT ČR), No. LM201564, 2016–2019.

Patents and patent applications

- Prodrugs of itaconate and methyl itaconate. Patent application WO/2021/087082 (2021)
- Peptidyl ketoamides as inhibitors of rhomboid proteases. United States Patent 10927146 (2021)
- Prodrug compositions and utility of hydroxamate-based GCPII inhibitors. United States Patent 11059775 (2021)
- Prodrugs of glutamine analogs. United States Patents 10336778 (2019), 10738066 (2020), 11185534 (2021), 10954257 (2021)
- Prodrugs of prostate specific membrane antigen (PSMA) inhibitor. United States Patent 10544176 (2020)
- Methods for cancer and immunotherapy using prodrugs of glutamine analogs. United States Patent 10842763 (2020)

Licenses

SPARC Ltd.—licensed itaconate prodrug technology (January 25, 2021)

Bayer AG—acquired Noria/Adarga (June 3, 2021) which licensed PSMA prodrug technology (May 29, 2019)

Dracen Pharmaceuticals—licensed prodrugs of glutamine analogues technology (December 22, 2017) and started phase 1/2a clinical trial with our compound DRP-104 (August 30, 2020)

Synthesis of Radiolabeled Compounds

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

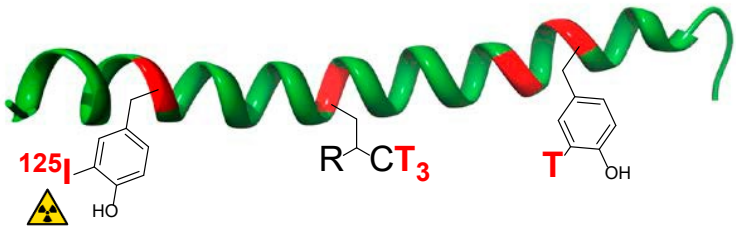
Service Group

custom synthesis of radioactive molecular tracers, γ/β⁻ emitter, ^{125}I, ^{3}H, ^{14}C, IOCB radioactive waste management, radiation protection & safety training

Peptides labeled by 125-iodine or tritium

An optimized low-cost late-stage-labeling procedure of peptides (up to 260 amino acid residues) with **IODO–GEN™ / Na[^{125}I]** system

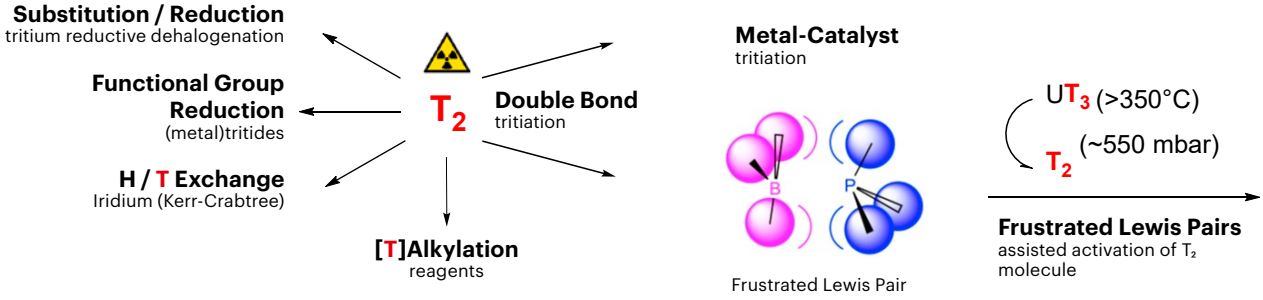
S.A. >2000 Ci/mmol



Catalyzed tritiation of suitable synthetic precursor – brominated tyrosine or dehydroaminoacids

S.A. >10–110 Ci/mmol

Commonly used techniques for tritium labeling in our lab



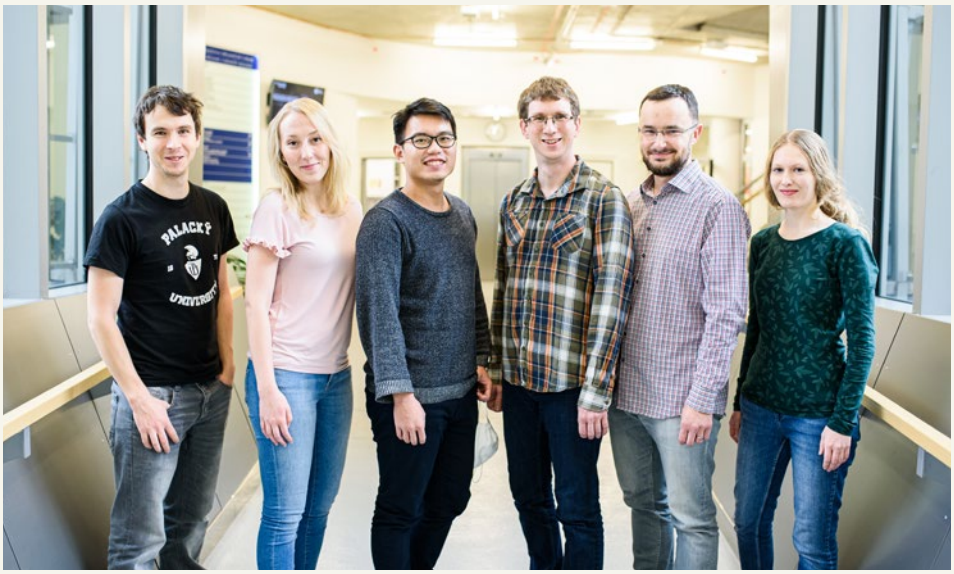
Research interests

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 and polypeptide labeling procedure 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 unlabeled 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 late-stage radiolabeling techniques using catalytic C-H activation in favor of 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 offer also [^{3}H]alkylation as a powerful tool to achieve high specific activity of prepared tracers.

The radiochemical purity of produced tracers is always checked by radio-HPLC, GC-MS, LC-MS, radio-TLC and ^{3}H NMR spectra available in lab.



Group members

Group leader Aleš Marek
Senior scientist Břetislav Brož
Postdoctoral fellows Michal Kriegelstein, Gabriela Nováková
Research assistant Jana Hojcsková
Visiting student Yongsong Tian

Selected publications

Miláček, M.; Bittová, L.; Tůmová, Š.; Lukšan, O.; Hanus, R.; Kyjáková, P.; Machara, A.; Marek, A.; Jindra, M. Binding of de novo synthesized radiolabeled juvenile hormone (JH III) by JH receptors from the Cuban subterranean termite Prorhinotermes simplex and the German cockroach Blattella germanica. Insect Biochem. *Mol. Biol.* **2021**, 139, 103671.

Liu, Y.; Ma, C.; Nováková, G.; Marek, A.; Tureček, F. Charge-Tagged Nucleosides in the Gas Phase: UV–Vis Action Spectroscopy and Structures of Cytidine Cations, Dications, and Cation Radicals. *J. Phys. Chem. A* **2021**, 125, 28, 6096–6108.

Asai, S.; Žáková, L.; Selicharová, I.; Marek, A.; Jiráček, J. A radioligand receptor binding assay for measuring of insulin secreted by MIN6 cells after stimulation with glucose, arginine, ornithine, dopamine, and serotonin. *Anal. Bioanal. Electrochem.* **2021**, 413, 4531–4543.

Polidarová, M.P.; Břehová, P.; Kaiser, M.M.; Smola, M; Dračínský, M; Smith, J; Marek, A; Dejmek, M; Šála, M; Gutten, O; Rulíšek, L.; Novotná, B.; Brázdová, A.; Janeba, Z.; Nencka, R.; Boura, E.; Páv, O.; Birkuš, G. Synthesis and Biological Evaluation of Phosphoester and Phosphorothioate Prodrugs of STING Agonist 3′,3′-c-Di(2′F,2′dAMP). *J. Med. Chem.* **2021**, 64, 11, 7596–7616.

Liu, Y.; Ma, C.; Leonen, C.J.A.; Chatterjee, C.; Nováková, G.; Marek, A.; Tureček, F. Tackling a Curious Case: Generation of Charge-Tagged Guanosine Radicals by Gas-Phase Electron Transfer and Their Characterization by UV–vis Photodissociation Action Spectroscopy and Theory. *J. Am. Soc. Mass Spectrom.* **2021**, 32, 3, 772–785.

Pražienková, V.; Marek, A.; Maletínská, L. Iodination of CART(61-102) peptide: Preserved binding and anorexigenic activity in mice. *J. Labelled Compd. Radiopharm.* **2021**, 64, 61–64.

Mžika, M.; Váňová, N.; Kriegelstein, M.; Hroch, M. Differential adsorption of an analyte and its D_4, D_5 and $^{13}C_6$ labeled analogues combined with instrument-specific carry-over issues: The Achilles' heel of ibrutinib TDM. *J. Pharm. Biomed. Anal.* **2021**, 206, 114366.

Collaboration

František Tureček (University of Washington, Seattle, WA, USA)

Petrine Wellendorph, Bente Froelund, Hans Bräuner-Osborne, Lennart Bunch (University of Copenhagen, Denmark)

Marek Jindra (Institute of Entomology, Biology Center of the CAS, České Budějovice, Czech Republic)

Jana Oklešťková, Miroslav Strnad (Institute of Experimental Botany of the CAS, Olomouc, Czech Republic)

Jan Jakubík (Institute of Physiology of the CAS, Prague, Czech Republic)

Jiří Novotný (Faculty of Science, Charles University, Prague, Czech Republic)

Miloš Hroch (Faculty of Medicine in Hradec Králové, Charles University, Czech Republic)

Ayman Hamouda (The University of Texas at Tyler, TX, USA)

Cristiano Bolchi (University of Milan, Italy)

Barbara Slusher (Johns Hopkins Drug Discovery, Baltimore, MD, USA)

Gabriel Birkuš, Lenka Maletínská, Jiří Jiráček, Helena Mertlíková Kaiserová, Jan Konvalinka, Pavel Šácha, Eva Kudová, Pavel Majer, Robert Hanuš, Josef Cvačka (IOCB Prague, Czech Republic)

Funding

Electron and proton transfer in ionized DNA fragments. Ministry of Education, Youth and Sport (MŠMT ČR), Program INTER-EXCELLENCE, No. LTAUSA19120, 2020–2022, PI: Marek, A.

Instrumentation

The laboratory is classified for handling of the open sources of ionizing radiation in quantities authorized for laboratories of II category according to Czech by law 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.

The key instrument of the laboratory is a **glove box with tritiation manifold** (RC-TRITEC AG) suitable for handling 100 to 1000 Ci of carrier-free tritium gas. Instruments for characterization of radioactively labeled compounds: **^{3}H NMR BRUKER Avance II 300 MHz**. Liquid scintillation analyzer **TriCarb 2900TR** (Perkin Elmer) for activity assays of small amounts of α, β, and γ emitters. The **Gamma Counter Wizard 1470** (Perkin Elmer) and high throughput **WIZARD^{2} 2470** (Perkin Elmer). **Radio-TLC scanner RITA** (RAYTEST). Analytical-preparative radio-HPLC Waters 600 with radio-detector Ramona. Analytical-semipreparative **radio-HPLC Waters Alliance e2695** system with radio-detector Ramona suitable also for radio-metabolite detection. **MicroBeta^{2} plate counter** – high throughput scintillation detection (LSC, SPA, FlashPlates, Filtermat, etc.) of variety of radionuclides (such as ^{3}H, ^{14}C, ^{32}P and ^{125}I-labeled compounds, etc.) directly in 96/384-well plates. Analytical **radio-LC-MS Waters Alliance e2695 system with SQ detector 2** furnished with ESI, APCI probe and radio-detector Ramona. **GC-MS Agilent 6890N** gas chromatograph with 5975B **quadrupole** mass spectrometer.

Cluster

BIO

Research Groups

Jan Konvalinka Group (Proteases of Human Pathogens) – Distinguished Chair
Evžen Bouřa Group (Structural Membrane Biology) – Senior Research Group
Edward Curtis Group (Functional Potential of Nucleic Acids) – Senior Research Group
Robert Hanus Group (Chemistry of Social Insects) – Senior Research Group
Jiří Jiráček Group (Chemistry and Biology of Insulin and Insulin-Like Growth Factors) – Senior Research Group
Lenka Maletínská Group (Pathophysiological Mechanisms of Food Intake Regulation) – Senior Research Group
Pavlína Maloy Řezáčová Group (Structural Biology) – Senior Research Group
Michael Mareš Group (Cathepsin Proteases in Pathology) – Senior Research Group
Iva Pichová Group (Viral and Microbial Proteins) – Senior Research Group
Kvido Stříšovský Group (Intramembrane Proteolysis and Biological Regulation) – Senior Research Group
Jiří Vondrášek Group (Bioinformatics) – Senior Research Group
Hana Cahová Group (Chemical Biology of Nucleic Acids) – Junior Research Group
Zuzana Kečkéšová Group (Tumor Suppressors) – Junior Research Group
Tomáš Pluskal Group (Biochemistry of Plant Specialized Metabolites) – Junior Research Group
Sebastian Zoll Group (Structural Parasitology) – Junior Research Group

Targeted Research Group

Gabriel Birkuš Group (HBV Cure)

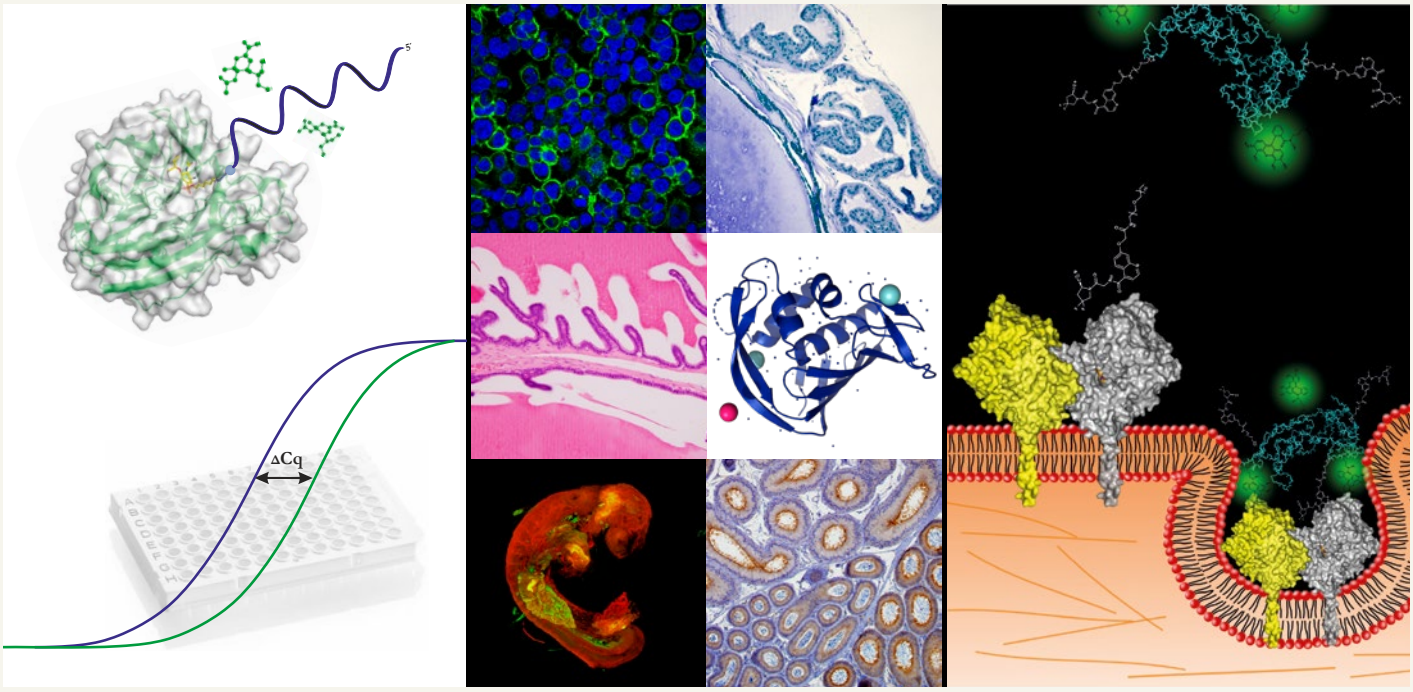
Research-Service Groups

Biochemical Pharmacology (Head: Helena Mertlíková-Kaiserová)
Virology (Head: Jan Weber)

Jan Konvalinka Group

Proteases of Human Pathogens
jan.konvalinka@uochb.cas.cz
www.uochb.cz/konvalinka

Distinguished Chair
therapeutic targets, virus replication, glutamate carboxypeptidase II, DNA damage-inducible protein, influenza neuraminidase and polymerase, affinity-based probes, lipid nanoparticles for drug delivery



Research interests

Our main mission is to identify, characterize, and exploit enzymes, predominantly proteases, as targets for therapeutic intervention. Along the way, we 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 viral processing and maturation, or glutamate carboxypeptidase II, a prostate 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 evaluate the potential of poorly characterized novel proteins with 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, enzyme kinetics, 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, an affinity anchor, and an imaging marker attached to a hydrophilic copolymer. Called iBody, this easy-to-assemble versatile scaffold is able to replace a monoclonal antibody in a number of *in vitro* and *in vivo* applications. Furthermore, we have developed a novel assay for detection of enzymes as diagnostic markers and for identification of enzyme inhibitors in drug development. The system is called DIANA, and it enables quantification of zeptomolar amounts of enzymes and high-throughput screening of potential inhibitors. Most recently, we have developed a novel platform based on lipid nanoparticles (XMANs) for the delivery of nucleic acids to target cells.

The group is engaged in a number of 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
Senior scientists Klára Grantz Šašková, Klára Hlouchová, Milan Kožíšek, Taťána Majerová, Tereza Ormsby, Jana Pokorná, Pavel Šácha
Postdoctoral fellows Kristýna Blažková, Adriana Čerešníková, Silvia Petrezsélyová, František Sedlák, Jana Staňurová
Ph.D. students Michael Adámek, Jana Beranová, Kateřina Čermáková, Lucia Ďuríčeková, Dominika Fassmannová, Jiří Gregor, Zuzana Hejdánková, Michal Kráľ, Robin Kryštůfek, Zuzana Kůtová, Adéla Marcalíková, Dominik Musil, Pavel Novotný, Kateřina Radilová, Jindřich Sedláček, Joshua Smith, Adéla Šimková, Mohammadreza Zamani Gharehchaman
Technicians & Research assistants Audrey Diederichs, Jitka Krčmářová, Jana Starková, Karolína Šrámková
Students Veronika Aulichová, Vít Bechyňský, Kateřina Daňhelová, Tereza Gistrová, Anežka Kramná, Sarah Kuchyňová, Adéla Moravcová, Veronika Nováková, Martin Pehr, Magdalena Poukarová, Pavel Říkovský, Natan Sidej, Filip Trajhan

Selected publications

Hejdánková, Z.; Vaněk, V.; Sedlák, F.; Procházka, J.; Diederichs, A.; Kereïche, S.; Novotná, B.; Buděšínský, M.; Birkuš, G.; Grantz Šašková, K.; Cígler, P. Lipid Nanoparticles for Broad-Spectrum Nucleic Acid Delivery. *Adv. Funct. Mater.* **2021**, 31, 2101391.

Kryštůfek, R.; Šácha, P.; Starková, J.; Brynda, J.; Hradilek, M.; Tloušťová, E.; Grzymska, J.; Rut, W.; Boucher, M. J.; Drąg, M.; Majer, P.; Hájek, M.; Řezáčová, P.; Madhani, H. D.; Craik, C. S.; Konvalinka, J. Re-emerging Aspartic Protease Targets: Examining Cryptococcus neoformans Major Aspartyl Peptidase 1 as a Target for Antifungal Drug Discovery. *J. Med. Chem.* **2021**, 64, 6706–6719.

Blažková, K.; Beranová, J.; Hradilek, M.; Kostka, L.; Šubr, V.; Etrych, T.; Šácha, P.; Konvalinka, J. The development of a high-affinity conformation-sensitive antibody mimetic using a biocompatible copolymer carrier (iBody). *J. Biol. Chem.* **2021**, 297.

Šimková, A.; Ormsby, T.; Sidej, N.; Slavětínská, L. P.; Brynda, J.; Beranová, J.; Šácha, P.; Majer, P.; Konvalinka, J. Structure-activity relationship and biochemical evaluation of novel fibroblast activation protein and prolyl endopeptidase inhibitors with alpha-ketoamide warheads. *Eur. J. Med. Chem.* **2021**, 224, 113717.

Hejdánek, J.; Radilová, K.; Pachl, P.; Hodek, J.; Machara, A.; Weber, J.; Řezáčová, P.; Konvalinka, J.; Kožíšek, M. Structural characterization of the interaction between the C-terminal domain of the influenza polymerase PA subunit and an optimized small peptide inhibitor. *Antiviral Res.* **2021**, 185, 104971.

Zima, V.; Radilová, K.; Kožíšek, M.; Albiñana, C. B.; Karlukova, E.; Brynda, J.; Fanfrlík, J.; Flieger, M.; Hodek, J.; Weber, J.; Majer, P.; Konvalinka, J.; Machara, A. Unraveling the anti-influenza effect of flavonoids: Experimental validation of luteolin and its congeners as potent influenza endonuclease inhibitors. *Eur. J. Med. Chem.* **2020**, 208, 112754.

Svoboda, M.; Konvalinka, J.; Trempe, J.-F.; Grantz Šašková, K. The yeast proteases Ddi1 and Wss1 are both involved in the DNA replication stress response. *DNA Repair* **2019**, 80, 45–51.

Funding

Strategies for specific targeting of brain metastasis microenvironment for diagnostic and therapy. Ministry of Health (MZ ČR), No. NU22-03-00318, 2022–2025, co-PI: Šácha, P.

New concept of enhancing receptor targeting with polymer conjugates by reversible anchoring to membranes. Czech Science Foundation (GA ČR), No. 21-04166S, 2021–2023, co-PI: Šácha, P.

Alzheimer's disease as a co-morbidity of chronic periodontitis with *Porphyromonas gingivalis* as a causative link between both diseases. Horizon 2020, ERA-NET – Joint Programming in Neurodegenerative Diseases strategic plan, No. JPND2019-466-285, 2019–2023, co-PI: 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, co-PI: Konvalinka, J.

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

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

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

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

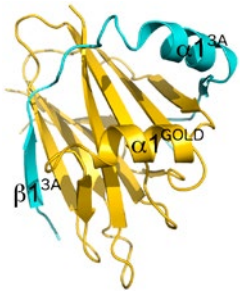
Macromolecular conjugates for targeted drug delivery, imaging, and isolation of proteins based on hydrophilic polymers decorated by functional moieties. Czech Science Foundation (GA ČR), No. 16-02938S, 2016–2018, PI: Konvalinka, J.

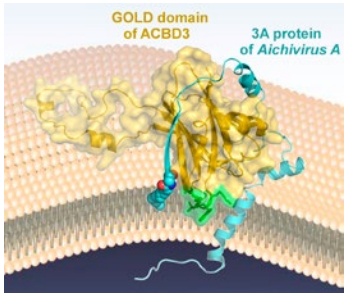
Evžen Bouřa Group

Structural Membrane Biology
evzen.boura@uochb.cas.cz
www.uochb.cz/infochem/boura

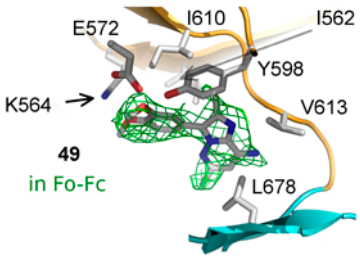
Senior Research Group

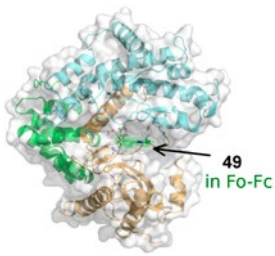
host factors for viral replication, viral polymerases, structural basis for inhibition of viral replication



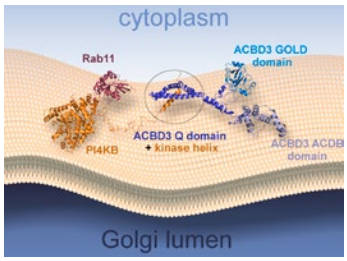


A virus is using our ACBD3 protein to hijack cellular machinery to build its replication factories. (Up center—symbolic view, upper right—detailed structural view, Klima et al. *Structure* 2017)





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)

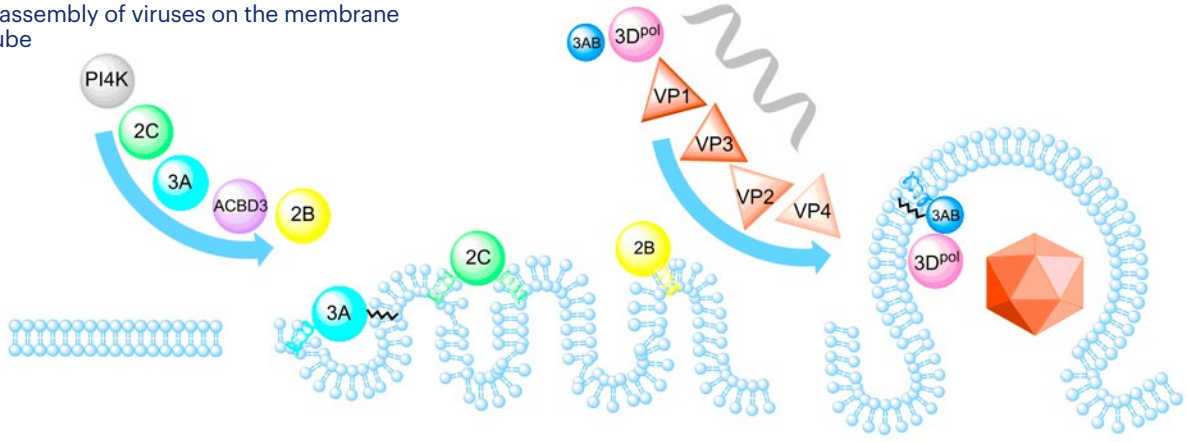
Research interests

Since its establishment in 2012, our laboratory has focused on proteins essential for viral replication. In this respect, we are interested in both host factors and viral enzymes. For instance, some lipid kinases and/or lipid transport proteins are hijacked by viral proteins. Subsequently, they assemble into large multiprotein complexes that modify the membrane; this changes the membrane's chemical composition, which leads to altered biophysical properties. We mainly use protein crystallography and other biophysical methods to understand the structure and function of these membrane-modifying enzymes in detail.

We have focused on phosphatidylinositol 4-kinase B (PI4KB), which is an essential host factor for a variety of +RNA viruses, such as HCV, poliovirus and Coxsackie virus. 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 these 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 the potential to be used as virostatics [1]. Later, we became interested in the molecular mechanism of PI4KB membrane recruitment by the Golgi resident protein ACBD3 [2].

Recently we also focused on other viral proteins, especially the methyltransferases (MTases) and polymerases (RdRp) from SARS-CoV-2 and from various flaviviruses [3-5]. We have solved a series of crystal structures of coronaviral and flaviviral polymerases in complex with inhibitors that were prepared by the Nencka group [6, 7]. We have also biophysically characterized the RdRps from SARS-CoV-2 and various flaviviruses [6, 8].

Biomimetic assembly of viruses on the membrane in the test tube



Group members

Group leader Evžen Bouřa
Senior scientists Jana Humpolíčková, Dominika Chalupská, Martin Klíma, Jan Šilhán
Postdoctoral fellows Jitka Bartošová, Dinesh Dhurvas Chandrasekaran, Pavla Fajtová, Vladimíra Horová, Eva Konkoľová, Petra Krafčíková
Ph.D. students Pavel Dostalík, Vojtěch Duchoslav, Andrea Eisenreichová, Andrea Hušková, Kateřina Krejčová, Barbora Landová, Petr Škvára
Technician Lenka Kloučková
Students Michal Fedák, Michal Hanigovský, Jana Havlíková, Dana Ivanovská, Alena Koukalová, Tomáš Ludvík, Matěj Pekárek, Matthew Todd, Pavla Trembuláková, Michal Vaško

Selected publications

[1] 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.

[2] Horova, V.; Lyoo, H.; Różycki, B.; Chalupska, D.; Smola, M.; Humpolickova, J.; Strating, J. R. P. M.; van Kuppeveld, F. J. M.; Boura, E.; Klima, M. Convergent evolution in the mechanisms of ACBD3 recruitment to picornavirus replication sites. *PLOS Pathog.* **2019**, 15, e1007962.

[3] Krafcikova, P.; Silhan, J.; Nencka, R.; Boura, E. Structural analysis of the SARS-CoV-2 methyltransferase complex involved in RNA cap creation bound to sinefungin. *Nat. Commun.* **2020**, 11, 3717.

[4] Nencka, R.; Silhan, J.; Klima, M.; Otava, T.; Kocek, H.; Krafcikova, P.; Boura, E. Coronaviral RNA-methyltransferases: function, structure and inhibition. *Nucleic Acids Res.* **2022**, 50, 635-650.

[5] Konkolova, E.; Dejmek, M.; Hřebabecký, H.; Šála, M.; Böserle, J.; Nencka, R.; Boura, E. Remdesivir triphosphate can efficiently inhibit the RNA-dependent RNA polymerase from various flaviviruses. *Antiviral Res.* **2020**, 182, 104899.

[6] Konkolova, E.; Klima, M.; Nencka, R.; Boura, E. Structural analysis of the putative SARS-CoV-2 primase complex. *J. Struct. Biol.* **2020**, 211, 107548.

[7] Otava, T.; Šála, M.; Li, F.; Fanfrlík, J.; Devkota, K.; Perveen, S.; Chau, I.; Pakarian, P.; Hobza, P.; Vedadi, M.; Boura, E.; Nencka, R. The Structure-Based Design of SARS-CoV-2 nsp14 Methyltransferase Ligands Yields Nanomolar Inhibitors. *ACS Infect. Dis.* **2021**, 7, 2214-2220.

[8] Dubankova, A.; Boura, E. Structure of the yellow fever NS5 protein reveals conserved drug targets shared among flaviviruses. *Antiviral Res.* **2019**, 169, 104536.

Funding

Czech Science Foundation (GA ČR): 21-27735K, 21-25280S, 19-18917S, 17-21649Y, 17-07058Y, 17-05200S, 15-21030Y

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.

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.

Edward Curtis Group

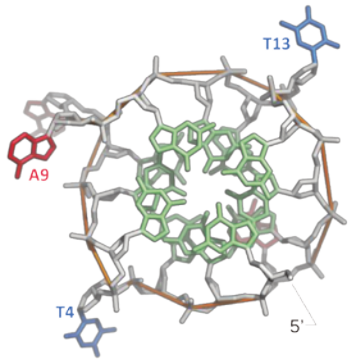
Functional Potential of Nucleic Acids
edward.curtis@uochb.cas.cz
www.uochb.cz/curtis

Senior Research Group

ribozyme, deoxyribozyme, artificial evolution, functional nucleic acid, biosensor, G-quadruplex

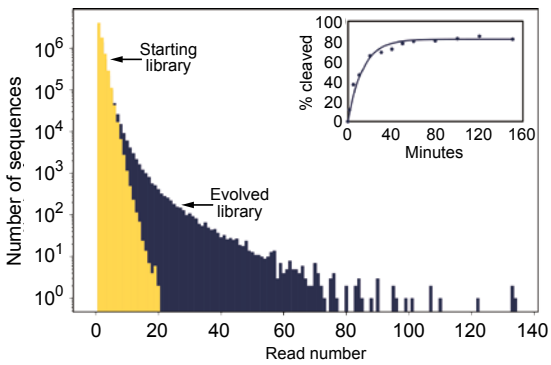
Structural basis of G4 function

Volek et al, 2021



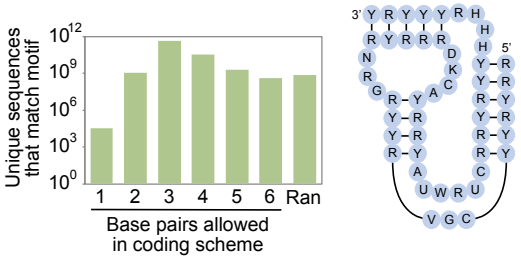
Single-step deoxyribozyme discovery

Streckerová et al, 2021



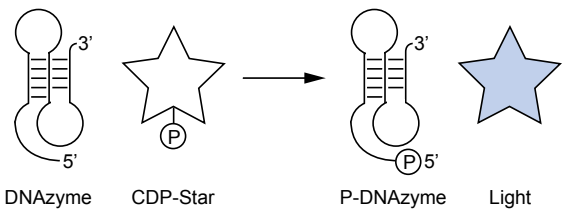
Secondary structure libraries

Sgallová and Curtis, 2021



Light-producing deoxyribozyme sensors

Svehlova et al, 2022

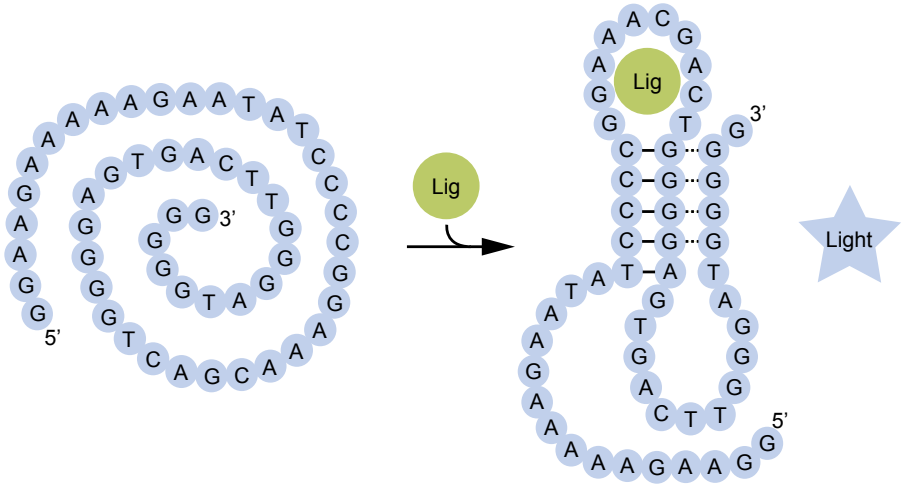


Research interests

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 methods of artificial evolution in which multiple cycles of selection and amplification are performed to isolate rare molecules with a desired function from large random sequence libraries.

We are interested in using artificial evolution 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. An exciting recent development in this area is the discovery of Supernova, a deoxyribozyme that catalyzes a chemiluminescent reaction. A second focus is to develop more powerful methods to discover and optimize functional nucleic acid motifs using new methods of library construction in combination with high-throughput sequencing. We recently used such an approach to identify new RNA-cleaving deoxyribozymes in a single round of selection rather than the ten or more which are typically required.

Light-producing deoxyribozyme sensor



Hypothetical sensor based on Supernova that produces light in the presence, but not the absence, of a ligand of interest.

Group members

Group leader Edward Curtis
Postdoctoral fellow Kateřina Dušková
Ph.D. students Martin Jakubec, Jaroslav Kurfürst, Patrik Lettrich, Ráchel Sgallová, Tereza Šrámková (Streckerová), Kateřina Švehlová, Martin Volek
Students Simona Galádová, Karolína Pšenáková
Assistant Alena Habartová

Selected publications

Svehlova, K.; Lukšan, O.; Jakubec, M.; Curtis, E.A. Supernova: a deoxyribozyme that catalyzes a chemiluminescent reaction. *Angew. Chem. Int. Ed. Engl.* **2022**, 61, e202109347.

Streckerová, T.; Kurfürst, J.; Curtis, E.A. Single-round deoxyribozyme discovery. *Nucleic Acids Res.* **2021**, 49, 6971–6981.

Volek, M.; T.; Kolesnikova, S.; Svehlova, K.; Srb, P.; Sgallová, R.; Streckerová, T.; Redondo, J.A.; Veverka, V.; Curtis, E.A. Overlapping but distinct: a new model for G-quadruplex biochemical specificity. *Nucleic Acids Res.* **2021**, 49, 1816–1827.

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Funding

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: Curtis, E.

IOCB Swat Team (DREAMMOL)

Charles University Grant Agency (GA UK) grants awarded to Martin Volek (337022), Ráchel Sgallová (152120), and Martin Jakubec (290321).

Gilead Sciences & IOCB Research Center, 2016–2021.

Collaboration

Professor Michael Lawrence (Harvard, USA)

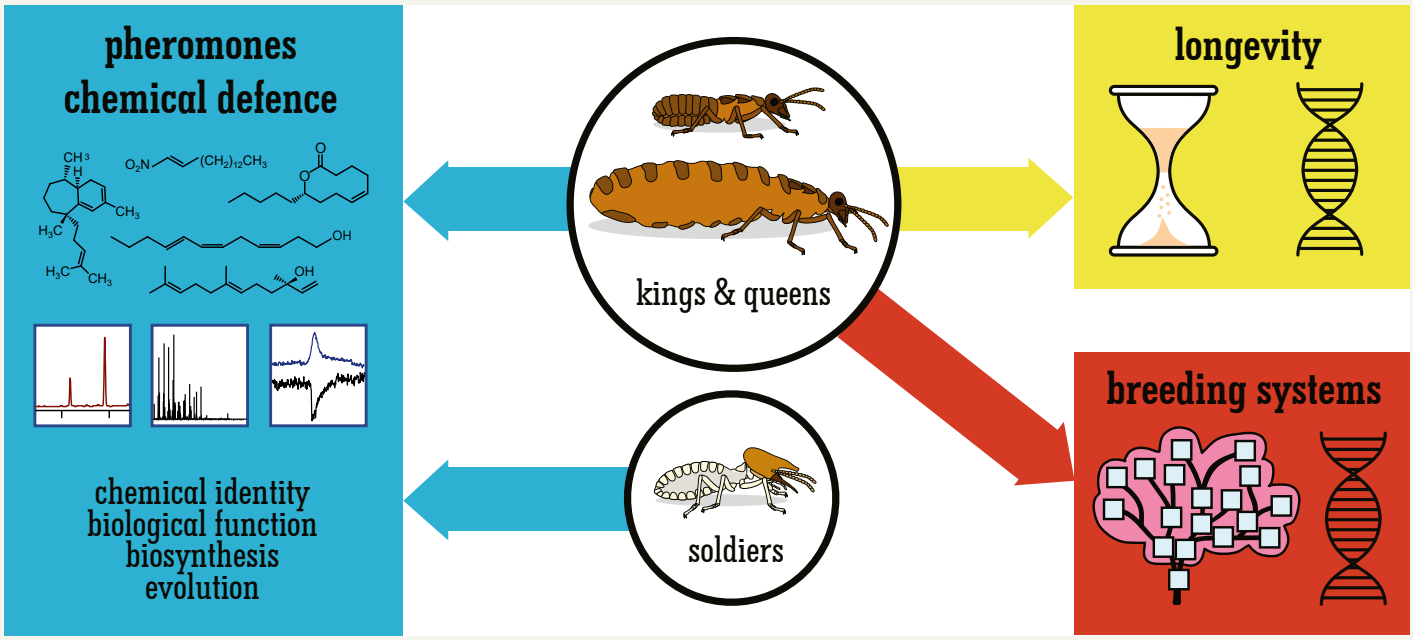
Dr. Václav Veverka (IOCB Prague, Czech Republic)

Dr. Iva Pichová (IOCB Prague, Czech Republic)

Robert Hanus Group

Chemistry of Social Insects
robert.hanus@uochb.cas.cz
www.uochb.cz/hanus

Senior Research Group
social insects, termites, chemical defence and communication, biosynthesis, pheromones, defensive chemicals, breeding systems, strategies of reproduction, endocrine signaling, ageing and longevity



Research interests

We are interested in 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.

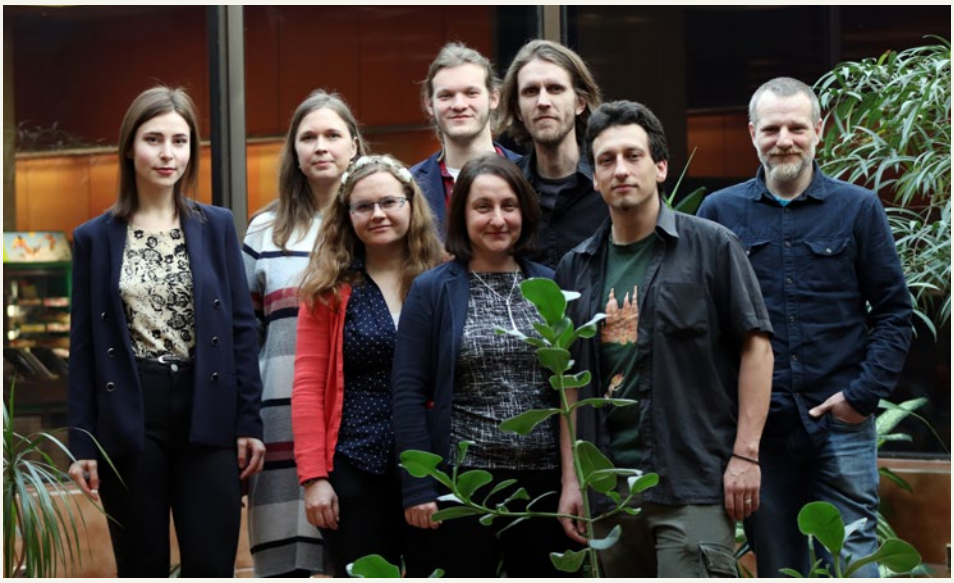
In our research, we combine the studies on established termite models kept in the long term in laboratory cultures, with field ecology studies performed in the tropics of South America, especially in the rainforests of French Guiana.

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 next generation 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 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 and long-lived colony members.



Group members

Group leader Robert Hanus
Senior scientists Pavlína Kyjaková, Ondřej Lukšan, Jitka Štáfková
Research assistant Jan Křivánek
PhD students Radka Bušovská, Natan Horáček, Marie Pangrácová
Technician Jarmila Titzenthalerová

Selected publications

Koubová, J.; Pangrácová, M.; Jankásek, M.; Lukšan, O.; Jehlík, T.; Brabcová, J.; Jedlička, P.; Křivánek, J.; Čapková Frydrychová, R.; Hanus, R. Long-lived termite kings and queens activate telomerase in somatic organs. *Proc. R. Soc. B* 288 **2021**, 20210511.

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Funding

Origin, regulation, and biological function of a termite queen pheromone. Czech Science Foundation (GA ČR), No. 22-28470S, 2022–2024, PI: Hanus, R.

Comprehensive approach to structural analysis of novel polycyclic diterpenes from termites. Charles University Grant Agency (GA UK), No. 371021, 2021–2023, PI: Horáček, N.

Evolution of chemical communication in termites. Czech Science Foundation (GA ČR), No. 20-17194S, 2020–2022, PI: Hanus, R.

Is the extraordinary longevity of termite kings and queens linked with differential expression and localization of telomerase isoforms? Charles University Grant Agency (GA UK), No. 338021, 2021–2022, PI: Pangrácová, M.

Mechanistic aspects of extended longevity of termite kings and queens. Czech Science Foundation (GA ČR), No. 18-21200S, 2018–2020, PI: Hanus, R.

Collaboration

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

Prof. Dorothea Tholl (Virginia Tech, USA)

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)

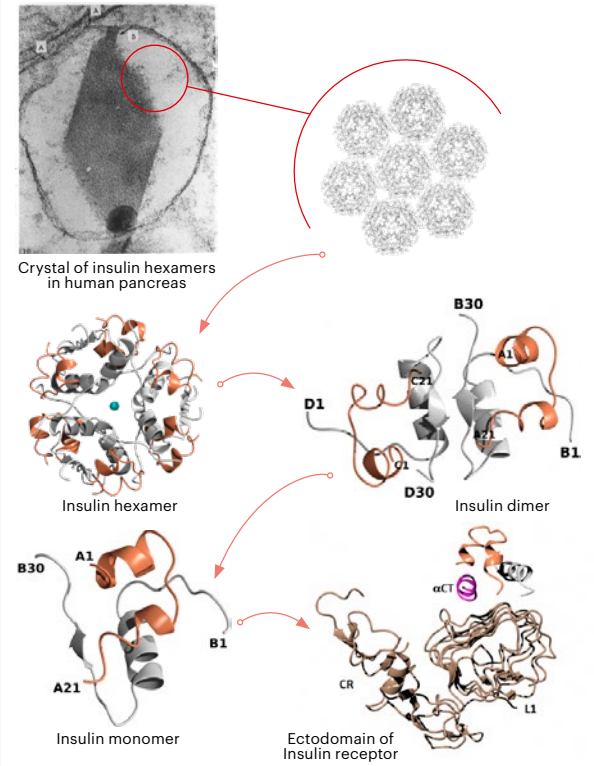
Pavel Majer Group & Iva Pichová Group (IOCB Prague, Czech Republic)

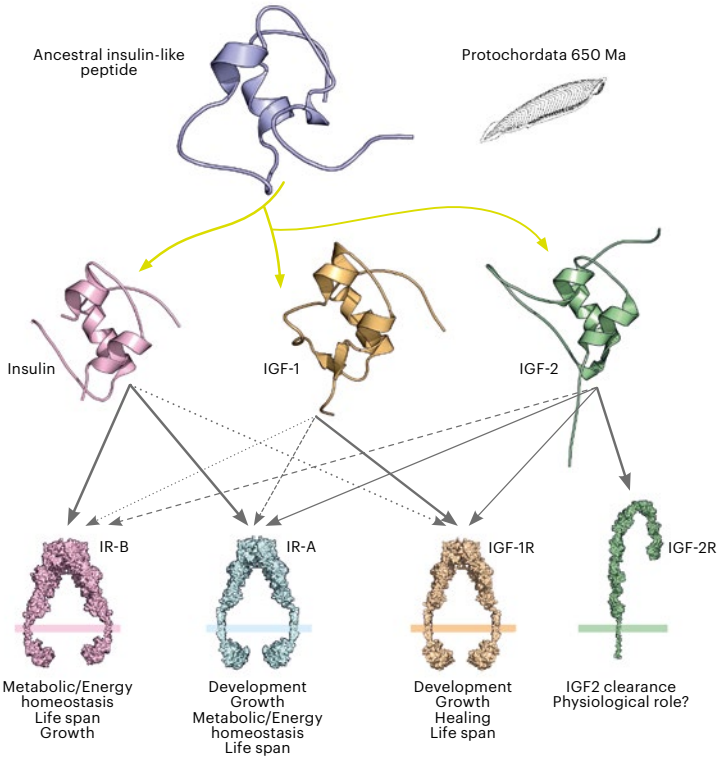
Jiří Jiráček Group

Chemistry and Biology of Insulin and Insulin-Like Growth Factors
jiri.jiracek@uochb.cas.cz
www.uochb.cz/jiracek

Senior Research Group

insulin, IGF-1, IGF-2, analogue, peptidomimetics, hormone receptor, drug discovery, medicinal chemistry, structure-activity relationship, diabetes, growth, insulin secretory granules





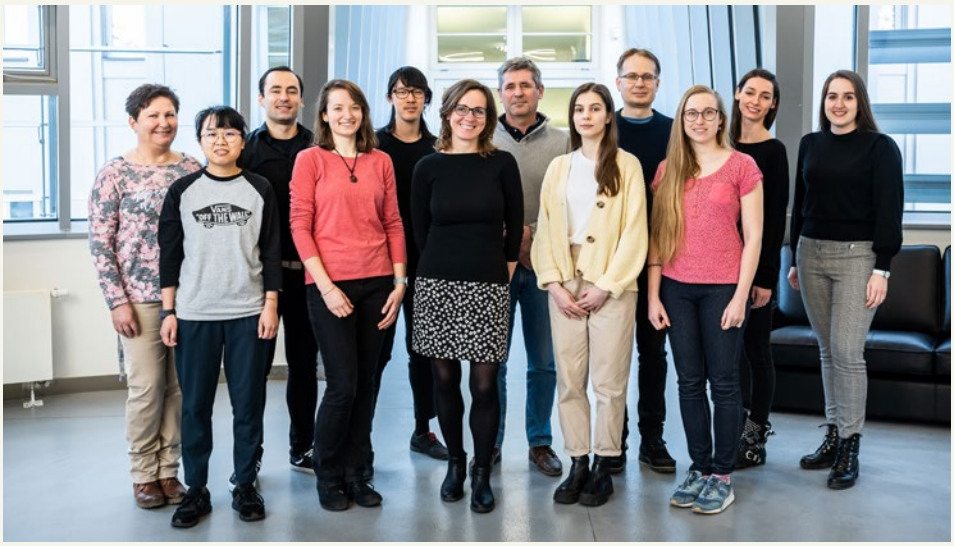
Research interests

Our research group is interested in all aspects of insulin and insulin-like growth factors 1 and 2 (IGF-1 and IGF-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 analogues 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
Senior scientists Irena Selicharová, Jan Pícha, Lenka Žáková
Postdoctoral fellows Marta Lubos, María Soledad Garre Hernández
Research assistant Katarína Mitrová
Ph.D. students Seiya Asai, Jingjing Lin, Terezie Páníková, Pavlo Potalitsyn, Tereza Turnovská
Students Anna Kertisová, Lucie Mrázková, Karolína Mrzílková, Zuzana Zápotocká

Selected publications

Páníková, T.; Mitrová, K.; Halamová, T.; Mrzílková, K.; Pícha, J.; Chrudinová, M.; Kurochka, A.; Selicharova, I.; Žáková, L.; Jiráček, J. Insulin Analogues with Altered Insulin Receptor Isoform Binding Specificities and Enhanced Aggregation Stabilities. *J. Med. Chem.* **2021**, 64, 14848.

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Funding

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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, PI: Žáková, L.

Collaboration

Prof. A. M. Brzozowski, York Structural Biology Laboratory, Department of Chemistry, University of York, Heslington, York, UK

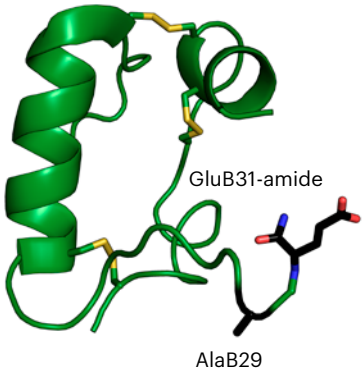
Prof. E. Altindis, Boston College, Biology Department, Higgins Hall, 140 Commonwealth Avenue Chestnut Hill, MA, 02467, USA

Prof. I. Torres-Aléman, Achucarro, Basque Center for Neuroscience, Laboratory of Neurobiology of Insulin Peptides, Leioa, Spain

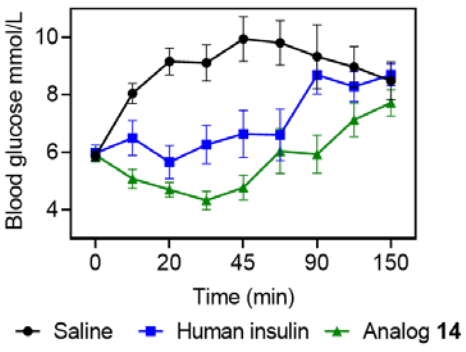
Dr. M. Rossmeisl, Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic

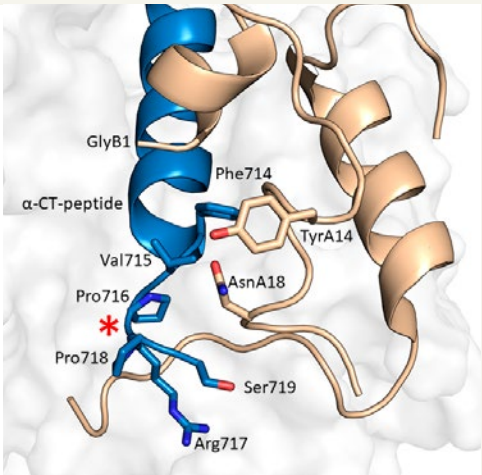
Dr. J. Nováček, Cryo-Electron Microscopy and Tomography Core Facility, CEITEC, Brno, Czech Republic

IR-B-specific insulin analog



Insulin tolerance test in mice



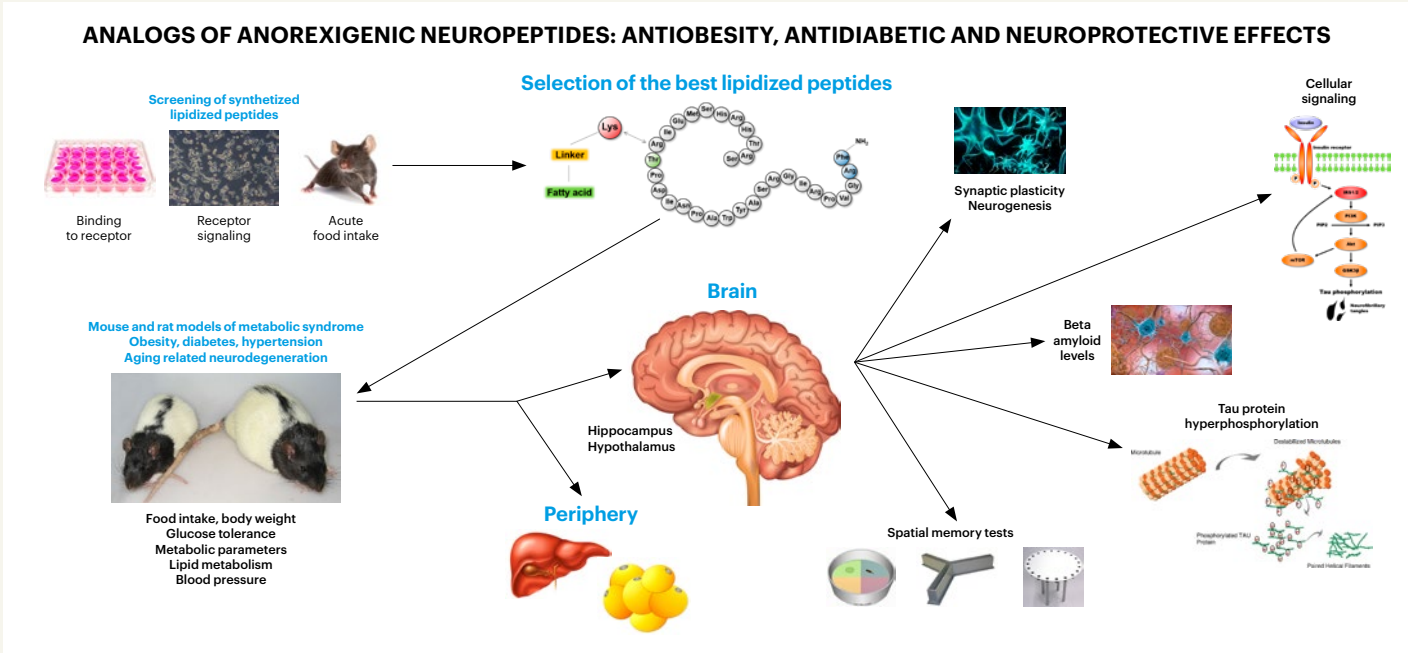


Lenka Maletínská Group

Pathophysiological Mechanisms of Food Intake Regulation
lenka.maletinska@uochb.cas.cz
www.uochb.cz/maletinska

Senior Research Group

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



Research interests

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
Senior scientists Jaroslav Kuneš, Zdenko Pirník, Blanka Železná
Junior scientists Andrea Pačesová, Veronika Strnadová
Postdoctoral fellows Leandro Ceotto Freitas Lima, Martina Holubová, Barbora Neprašová
Research assistants Martina Kojecká, Aneta Stružová
Ph.D. students Lucie Holá, Vilém Charvát, Alena Karnošová, Anna Mengr, Lucia Mráziková
Technician Hedvika Vysušilová
Students Aneta Myšková, Eliška Podoláková, Petra Vaculová

Selected publications

Mengr, A.; Hrubá, L.; Exnerová, A.; Holubová, M.; Popelová, A.; Železná, B.; Kuneš, J.; Maletínská, L. Palmitoylated Prolactin-releasing Peptide Reduced Aβ Plaques and Microgliosis in the Cerebellum: APP/PS1 Mice Study. *Curr. Alzheimer Res.* **2021**, 18, 607-622.

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Funding

Interplay between ghrelin and its novel endogenous antagonist LEAP2: possible role in the pathology of obesity. Czech Science Foundation (GA ČR), No. 22-11155S, 2022–2024, PI: Železná, B.

Neuropeptide FF-2 receptor as a potential anti-obesity target: Impact of new analogs of RFamide peptides. Czech Science Foundation (GA ČR), No. 21-03691S, 2021–2023, PI: Maletínská, L.

Obesity, diabetes and neurodegeneration crosstalk: New therapeutic potential of prolactin-releasing peptide analogs. Czech Science Foundation (GA ČR), No. 20-00546S, 2020–2022, PI: Maletínská, L.

National center of competence PerMed. Technology Agency of the Czech Republic (TA ČR), No. TN01000013, 2020–2022, PI: Fusek, M.

The role of prolactin-releasing peptide in obesity and neurodegeneration. Research collaborative project with Novo Nordisk, 2017–2022, PI: Maletínská, L.

Collaboration

Marie-Christine Galas (INSERM, Lille, France)

Jean-Alain Fehrentz, Jean-Louis Baneres (CNRS, Montpellier, France)

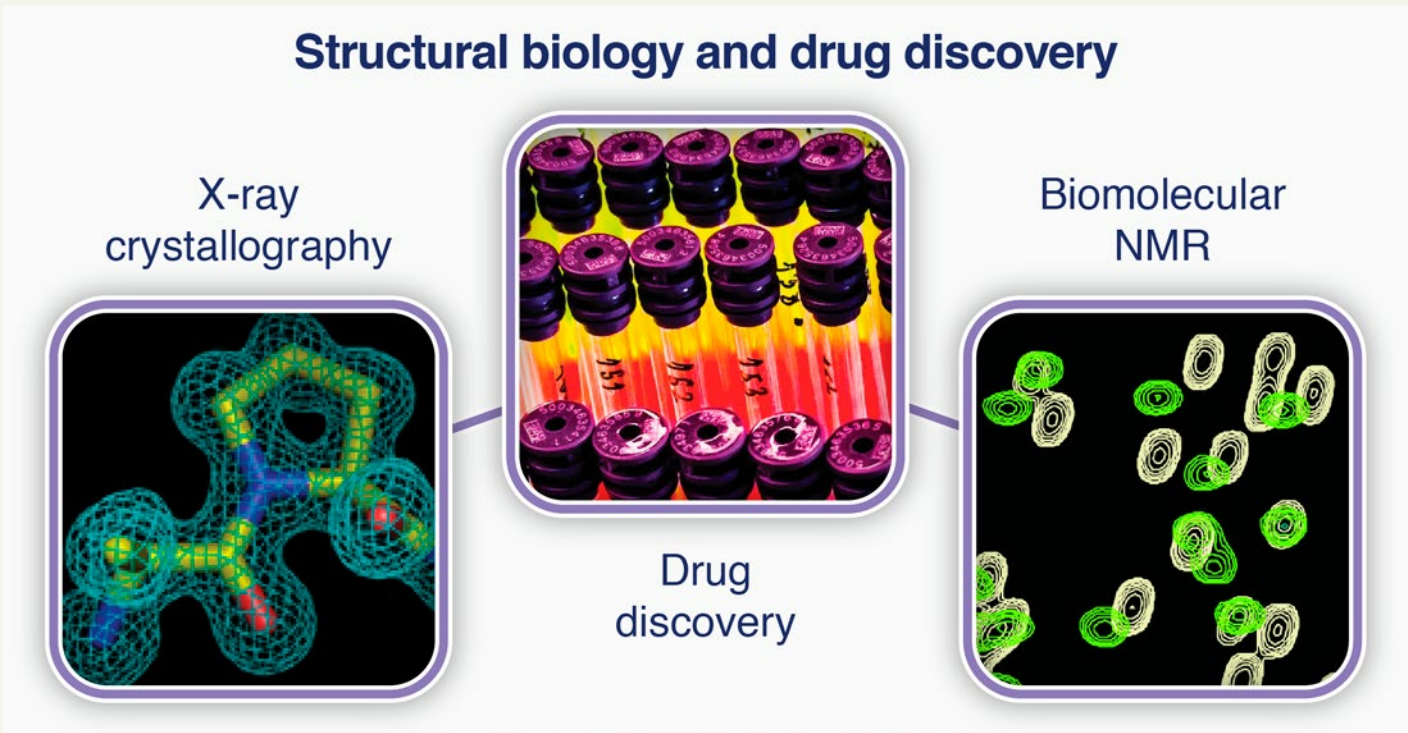
David Petřík (Cardiff University, Cardiff, UK)

Rhian Touyz, Augusto Montezano (McGill University, Montreal, Canada)

Pavlína Maloy Řezáčová Group

Structural Biology
pavlina.rezacova@uochb.cas.cz
www.uochb.cz/structbio

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



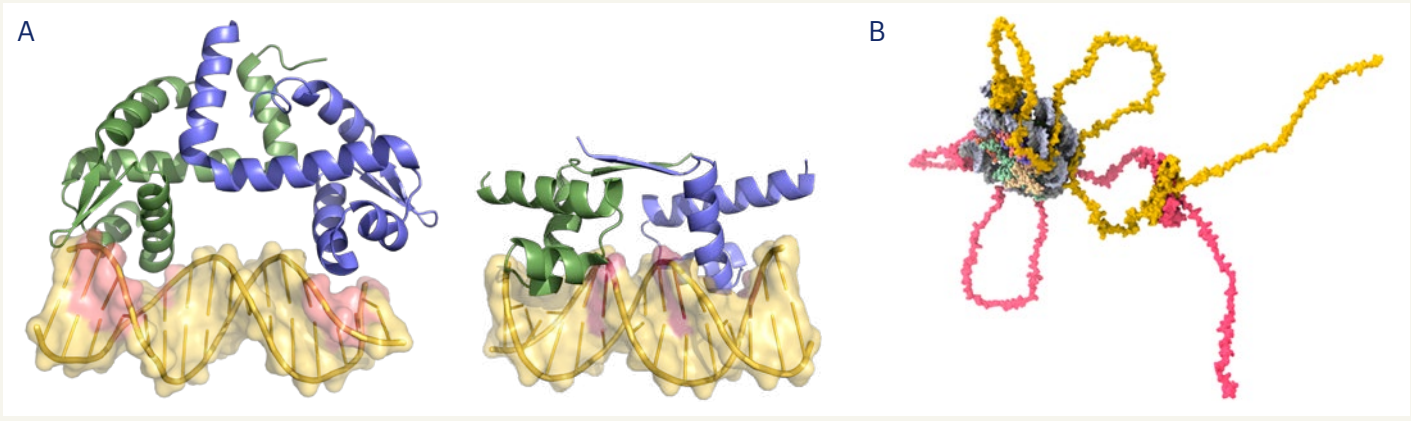
Research interests

Structural characterization of proteins and protein-protein complexes helps us address fundamental biological questions. We use structural knowledge obtained by X-ray crystallography, NMR spectroscopy and single-particle cryo-electron microscopy for understanding and modulation of biological 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*. 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, kinases, purine nucleoside phosphorylases or purine nucleotidases). The knowledge of protein structures provides a platform for the rational design of specific inhibitors. We utilize 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.



A. We performed structural studies of two members of SorC/DeoR family, each belonging to separate subgroups (left: bsCggR, right: bsDeoR). Their comparison provides the first structural evidence that hints the common mode of binding to a DNA operator most likely shared by other members of the family (Soltysova *et al.*, 2021).

B. We studied the interaction of the constitutive LEDGF dimer with a H3K36me3 nucleosome using a combination of cryo-EM and NMR spectroscopy. The hybrid approach revealed the conformational and DNA binding properties of the LEDGF central intrinsically disordered regions (Lux *et al.*, 2020).

Group members

Group leader Pavlína Maloy Řezáčová
Senior scientists Václav Veverka, Jiří Brynda, Milan Fábry, Vanda Lux, Pavel Srb
Postdoctoral fellows Petr Pachl, Jana Škerlová, Monika Nedomová, Michal Svoboda
Research assistants Matúš Drexler, Magdalena Hořejší, Blanka Klepetářová, Veronika Krejčiříková, Marcela Mádlíková, Klára Pospíšilová, Irena Sieglová, Tereza Vučková
Ph.D. students Stefan Dukic, Eliška Koutná, Markéta Nováková, Zdeněk Vavřina, Lisa-Maria Weinhold
Students Magda Havlová, Karolína Naušová
Technicians Anna Maliukova, Věra Mrkvičková

Selected publications

Cermakova, K.; Demeulemeester, J.; Lux, V.; Nedomova, M.; Goldman Seth, R.; Smith Eric, A.; Srb, P.; Hexnerova, R.; Fabry, M.; Madlikova, M.; Horejsi, M.; De Rijck, J.; Debyser, Z.; Adelman, K.; Hodges, H. C.; Veverka, V. A ubiquitous disordered protein interaction module orchestrates transcription elongation. *Science* **2021**, 374, 1113–1121.

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Grüner, B.; Brynda, J.; Das, V.; Šícha, V.; Štěpánková, J.; Nekvinda, J.; Holub, J.; Pospíšilová, K.; Fábry, M.; Pachl, P.; Král, V.; Kugler, M.; Mašek, V.; Medvedíková, M.; Matějková, S.; Nová, A.; Lišková, B.; Gurská, S.; Džubák, P.; Hajdúch, M.; Řezáčová, P. Metallacarborane Sulfamides: Unconventional, Specific, and Highly Selective Inhibitors of Carbonic Anhydrase IX. *J. Med. Chem.* **2019**, 62, 9560–9575.

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Funding

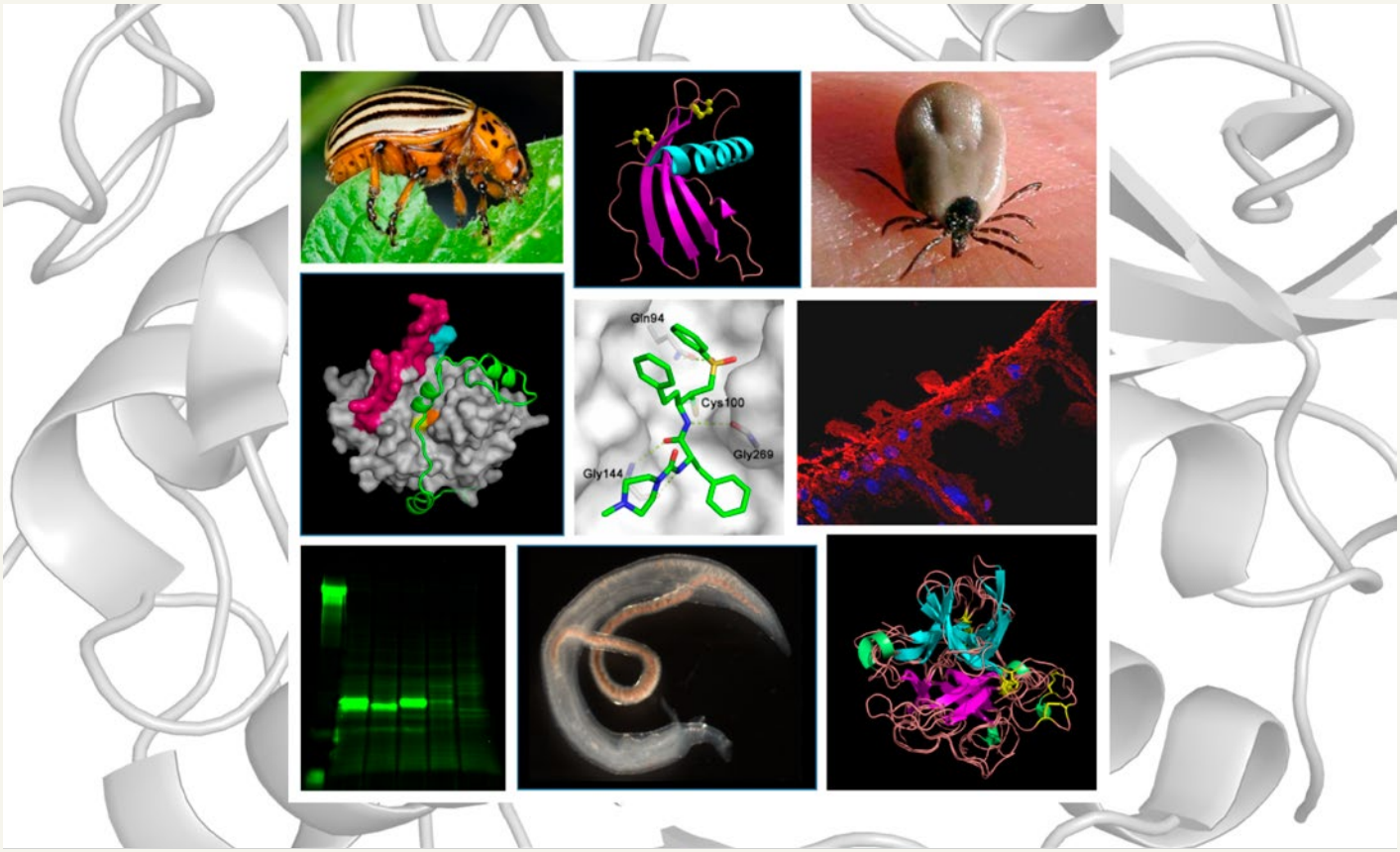
The interplay between the LEDGF chromatin reader and protein interaction modules. Czech Science Foundation (GA ČR), No. 22-03028S, 2022–2024, PI: Veverka, V.

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: Maloy Řezáčova, P.

Michael Mareš Group

Cathepsin Proteases in Pathology
michael.mares@uochb.cas.cz
www.uochb.cz/mares

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

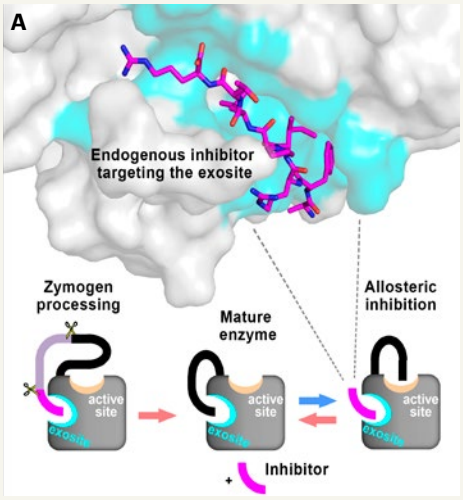


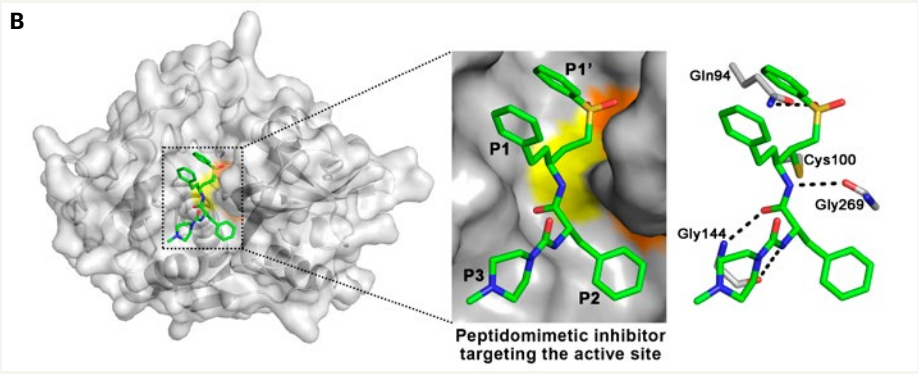
Research interests

Our research focuses on cathepsin proteases and cathepsin-driven proteolytic systems that are 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 causing 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
Senior scientists Jan Dvořák, Martin Horn, Lucie Marešová, Jana Pytelková
Postdoctoral fellows Iva Hánová, Adéla Jílková, Adrian Leontovyč, Andrea Smith, Jaroslav Srp
Research assistant Zuzana Šmotková
Ph.D. students Miloš Apeltauer, Jakub Benýšek, Mária Beňová, Lucia Bieliková, Michal Buša, Radka Houštecká, Zuzana Matoušková, Martina Mikulů, Katarína Orsághová, Petra Rubešová, Jakub Švéda, Lenka Ulrychová, Andrea Vostoupalová, Tereza Zosinčuková
Students Lenka Horáková, Filip Wichterle
Technician Milana Štajfová

Selected publications

Jílková, A.; Rubešová, P.; Fanfrlík, J.; Fajtová, P.; Řezáčová, P.; Brynda, J.; Lepšík, M.; Mertlíková-Kaiserová, H.; Emal, C. D.; Renslo, A. R.; Roush, W. R.; Horn, M.; Caffrey, C. R.; Mareš, M. Druggable hot spots in the schistosomiasis cathepsin B1 target identified by functional and binding mode analysis of potent vinyl sulfone inhibitors. *ACS Infect. Dis.* **2021**, 7, 1077–1088.

Jílková, A.; Horn, M.; Fanfrlík, J.; Küppers, J.; Pachl, P.; Řezáčová, P.; Lepšík, M.; Fajtová, P.; Rubešová, P.; Chanová, M.; Caffrey, C. R.; Gütschow, M.; Mareš, M. Azanitrile inhibitors of the SmCB1 protease target are lethal to *Schistosoma mansoni*: Structural and mechanistic insights into chemotype reactivity. *ACS Infect. Dis.* **2021**, 7, 189–201.

Lemke, C.; Benýšek, J.; Brajtenbach, D.; Breuer, Ch.; Jílková, A.; Horn, M.; Buša, M.; Ulrychová, L.; Illies, A.; Kubatzky, F.K.; Bartz, U.; Mareš, M.; Gutschow, M. An activity-based probe for cathepsin K imaging with excellent potency and selectivity. *J. Med. Chem.* **2021**, 64, 13793–13806.

Houštecká, R.; Hadzima, M.; Fanfrlík, J.; Brynda, J.; Pallová, L.; Hánová, I.; Mertlíková-Kaiserová, H.; Lepšík, M.; Horn, M.; Smrčina, M.; Majer, P.; Mareš, M. Biomimetic macrocyclic inhibitors of human cathepsin D: Structure–activity relationship and binding mode analysis. *J. Med. Chem.* **2020**, 63, 1576–1596.

Hánová, I.; Brynda, J.; Houštecká, 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.e4.

Funding

Molecular ontogeny of bloodmeal processing in the tick gut. Czech Science Foundation (GA ČR), No. 21-08826S, 2021–2023, co-PI: Mareš, M.

Novel strategies for designing antiparasitic molecules as human and veterinary drugs (Inter-Action). Ministry of Education, Youth and Sports (MŠMT ČR), No. LTAUSA19109, 2020–2022, PI: Mareš, M.

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: Mareš, M.

Proteolysis in eggs of parasitic worms: role in pathology and its regulation. Czech Science Foundation (GA ČR), No. 19-17269S, 2019–2021, PI: Horn, M.

Exopeptidase inhibitors as drugs against schistosomiasis: structure-based rational design, synthesis and functional characterization. Ministry of Health (MZ ČR), No. NV18-05-00345, 2018–2021, PI: Horn, M.

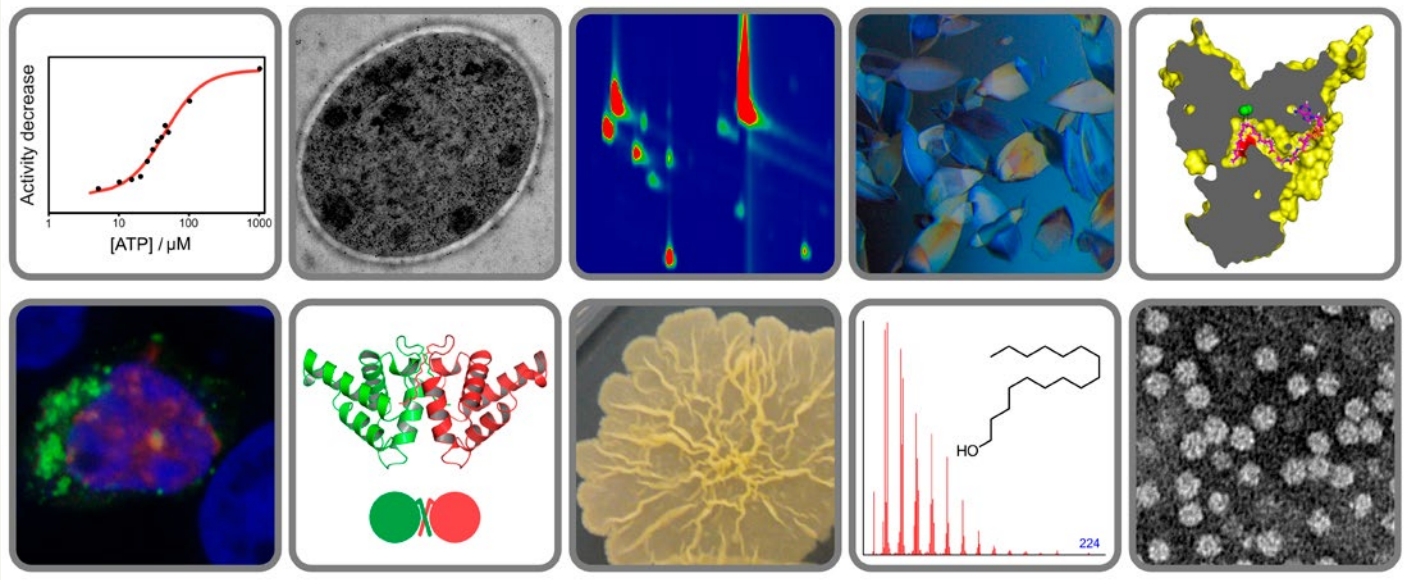
Targeting enzyme exosites by in situ click chemistry: new strategy for anticancer drug design. Gilead Sciences & IOCB Research Center, 2017–2021, co-PI: Mareš, M.

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

Iva Pichová Group

Viral and Microbial Proteins
iva.pichova@uochb.cas.cz
www.uochb.cz/pichova

Senior Research Group
hepatitis B virus, interaction of viral and cellular proteins, *Mycobacterium tuberculosis*, *Mycobacterium smegmatis*, metabolism, latent infection, desaturases and fatty acid reductases



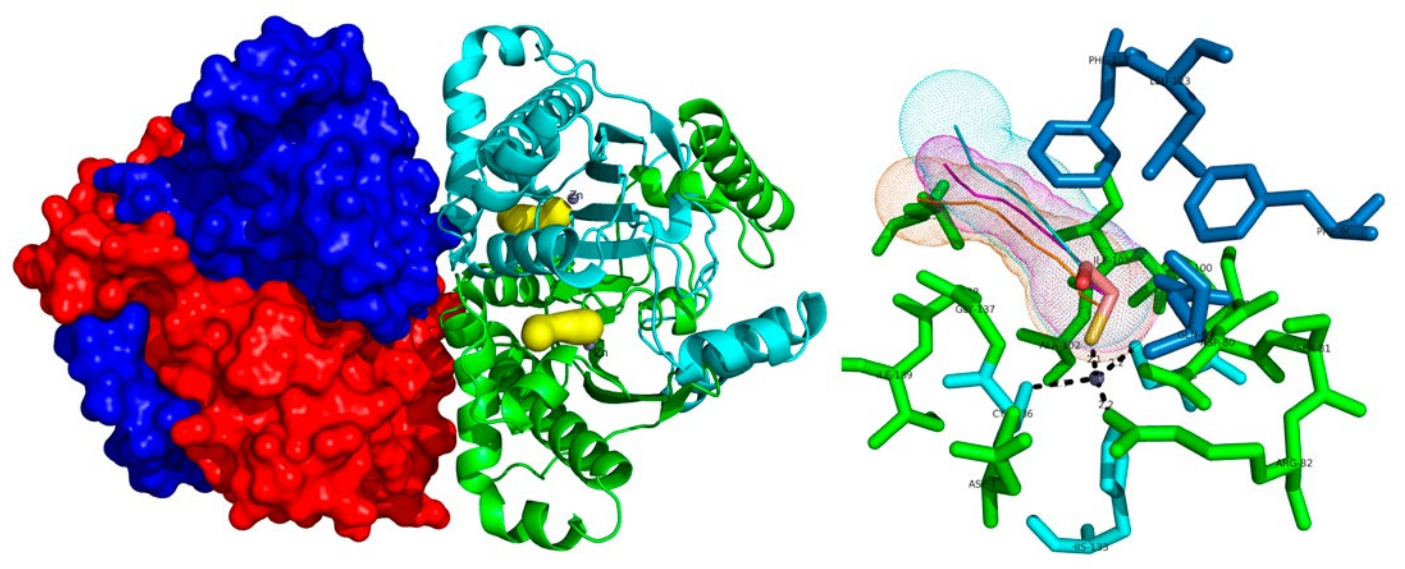
Research interests

We are oriented on investigation of different aspects of the life cycles of hepatitis B virus, mycobacteria spp., their interaction with host cells, and on regulation and evolution of enzymes involved in fatty acid biosynthesis.

We investigated interactions of hepatitis B virus proteins with cellular factors and studied maturation of precore protein HBe during the HBV life cycle. We found that the conserved Cys residues in the signal peptide of precore protein HBe serve as an auto-regulatory factor controlling proper progression of the precore-translocation process and thus preventing the mislocalisation of the precore. We have also identified the TRAP complex as a host factor required for successful translocon gating of p25 and for the support of mature p17 biogenesis.

We explored purine biosynthesis, interdependence and regulation of *de novo* and purine salvage pathways using the nonpathogenic fast-growing *Mycobacterium smegmatis* (Msme), allowing us to construct mutated strains and determine the essential enzymes involved in these processes. We discovered the novel guanosine 5´-monophosphate reductase (GMPR), which recycles guanosine monophosphate to inosine monophosphate and contains a cystathionine β-synthase domain (CBS), which is essential for enzyme activity. Currently, structural studies of essential inosine 5´-monophosphate dehydrogenase (IMPDH) complexed with ATP, GTP using cryo EM and X ray structure analysis are performed are performed. These results can be used for design of novel types of Mtb IMPDH inhibitors.

In the project focused on engineering of desaturases, we experimentally confirmed contribution of predicted mutations in the soluble Δ^9 desaturase from *Ricinus communis* (*Rco*Δ^9D) to promotion of acyl chain hydroxylation. Mutations were predicted based on a comparison with a soluble methane monooxygenase (sMMO), i.e. structurally similar $NHFe_2$ enzyme hydroxylating methane to methanol in bacteria. Functional characterization of mutated *Rco*Δ^9D revealed promotion of desaturase monohydroxylation activity. Our results broaden understanding of the origin of chemo- and stereoselectivity of the Δ^9D and provide further insight into the catalytic action of the $NHFe_2$ enzymes.



Group members

Group leader Iva Pichová
Senior scientists Jiří Dostál, Olga Heidingsfeld, Zdeněk Knejzlík, Jan Snášel, Helena Zábranská, Aleš Zábranský
Postdoctoral fellows Michal Doležal, Vicent Llopis-Torregrosa
PhD students Olena Berehovska, Ondřej Bulvas, Matteo Dedola, Stanislav Macháček, Karolína Pokorná, Michal Tupec
Research assistants Kamila Clarová, Mária Čechová, Romana Hadravová
Technicians Romana Cubínková, Elena Dolejší, Dagmar Grundová
Students Anna Amirianová, Dajána Kolářová, Magda Škrlová

Selected publications

Knejzlík, Z.; Doležal, M.; Herkommerová, K.; Clarova, K.; Klíma, M.; Dedola, M.; Zborníková, E.; Rejman, D.; Pichová, I. The mycobacterial guaB1 gene encodes a guanosine 5′-monophosphate reductase with a cystathionine-β-synthase domain. *FEBS J.* **2022**.

Tupec, M.; Culka, M.; Machara, A.; Macháček, S.; Bím, D.; Svatoš, A.; Rulíšek, L.; Pichová, I. Understanding desaturation/hydroxylation activity of castor stearoyl Δ9-Desaturase through rational mutagenesis. *Comput. Struct. Biotechnol. J.* **2022**, 20, 1378–1388.

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Buček, A.; Vazdar, M.; Tupec, M.; Svatoš, A.; Pichová, I. Desaturase specificity is controlled by the physicochemical properties of a single amino acid residue in the substrate binding tunnel. *Comput. Struct. Biotechnol. J.* **2020**, 18, 1202–1209.

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.

Funding

InterBioMed. Ministry of Education, Youth and Sports (MŠMT ČR), No. LO1302, 2014–2019, PI: 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, co-PI: Pichová, I.

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

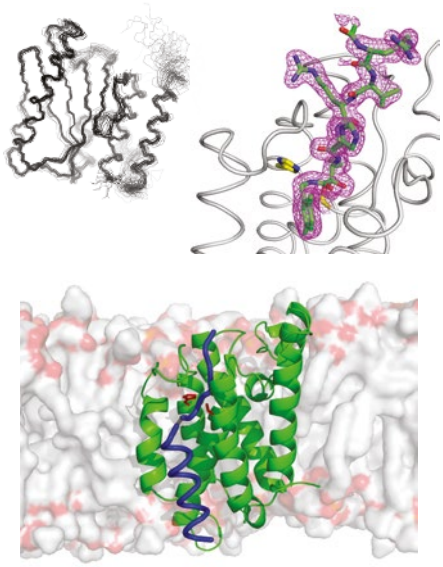
Kvido Stříšovský Group

Intramembrane Proteolysis and Biological Regulation
kvido.strisovsky@uochb.cas.cz
www.uochb.cz/strisovsky
www.strisovskylab.org

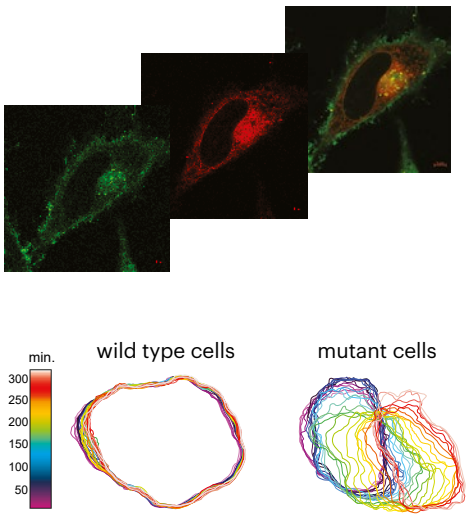
Senior Research Group

lipid membrane, membrane protein, signaling,
intramembrane proteolysis, protein structure, quality control

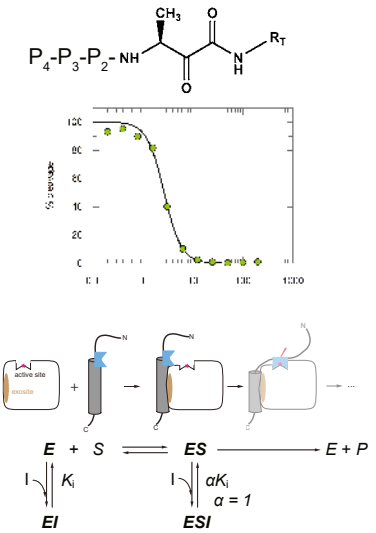
Structural biology



Cell biology



Chemical biology



Research interests

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, incl. 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. Their proteolytically inactive cousins, iRhoms, regulate membrane protein trafficking and inflammatory signaling, are another point of focus of the group.

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
Senior scientist Stancho Stanchev
Postdoctoral fellows Alma Estefania Martinez Fernandez, Monika Fliegl, Lucie Polovinkin, Jan Škerle
Research assistants Petra Rampírová, Zuzana Vaitová
Ph.D. students Kathrin Bach, Šárka Boháčová, Jana Březinová, Jan Dohnálek, Edita Poláchová, Květa Trávníčková

Selected publications

Gaspar, C. J.; Vieira, L. C.; Santos, C. C.; Christianson, J. C.; Jakubec, D.; Strisovsky, K.; Adrain, C.; Domingos, P. M. EMC is required for biogenesis of Xport-A, an essential chaperone of Rhodopsin-1 and the TRP channel. *EMBO rep.* **2022**, 23, e53210.

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Liu, G.; Beaton, S. E.; Grieve, A. G.; Evans, R.; Rogers, M.; Strisovsky, K.; Armstrong, F. A.; Freeman, M.; Exley, R. M.; Tang, C. M. Bacterial rhomboid proteases mediate quality control of orphan membrane proteins. *EMBO J.* **2020**, 39, e102922.

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Tichá, A.; Stanchev, S.; Vinothkumar, K.R.; Mikles, D.C.; Pachl, P.; Began, J.; Škerle, J.; Švehlová, K.; Nguyen, M.T.N.; Verhelst, S.H.L.; Johnson, D.C.; Bachovchin, D.A.; Lepšík, M.; Majer, P.; Strisovsky, K. General and Modular Strategy for Designing Potent, Selective, and Pharmacologically Compliant Inhibitors of Rhomboid Proteases. *Cell Chem. Biol.* **2017**, 24, 1523–1536.e4.

Zoll, S.; Stanchev, S.; Began, J.; Škerle, J.; Lepšík, M.; Peclinovská, L.; Majer, P.; Strisovsky, K. Substrate binding and specificity of rhomboid intramembrane protease revealed by substrate–peptide complex structures. *EMBO J.* **2014**, 33, 2408.

Funding

Roles of the rhomboid intramembrane protease RHBDL2 in epithelial homeostasis. Czech Science Foundation (GA ČR), No. 21-24456S, 2021–2023, PI: Stříšovský, K.

Cellular and organismal roles of the intramembrane rhomboid protease RHBDL4. Czech Science Foundation (GA ČR), No. 20-25331S, 2020–2022, PI: Stříšovský, K.

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)

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.

Collaboration

Dr. Colin Adrain (Queen's University Belfast, United Kingdom)

Prof. Rasmus Linser (University of Dortmund, Germany)

Prof. Marius Lemberg (University of Cologne, Germany)

Prof. Sonya Neal (University College San Diego, USA)

Dr. Pavel Majer (IOCB Prague, Czech Republic)

Awards—Kvido Stříšovský

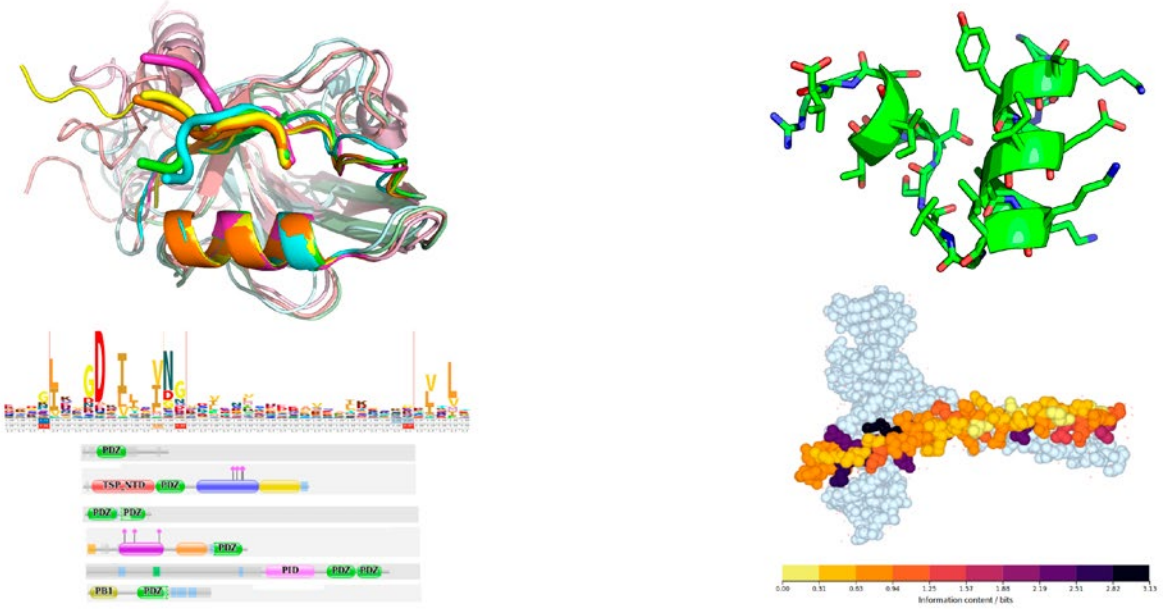
- Secretary of the International Proteolysis Society, 2019–2021
- Member of the EMBO Young Investigator Programme, EMBO, 2011
- J. E. Purkyně Fellowship, Czech Academy of Sciences, 2010
- MRC Career Development Fellowship, 2009–2012 (resigned 2011)
- EMBO Long-Term Fellowship, 2007–2009
- Marie-Curie Intra-European Fellowship, 2005–2007

Jiří Vondrášek Group

Bioinformatics
jiri.vondrasek@uochb.cas.cz
www.uochb.cz/bioinformatics

Senior Research 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 interests

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. We also provide professional computational support for users in analysis of protein sequences, modeling of protein structures, prediction of protein-protein interactions, and state-of-the-art bioinformatic analysis and tools. 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 important questions of structural biology and life sciences.

We also concentrate on computational aspects of Chemical Biology and interoperability of tools and data resources. Our recent efforts include the Integrated Database of Small Molecules (IDSM), which aims to provide a solid connection between existing chemical and biological data spaces and is used as a federated service by other bioinformatic resources and databases (Rhea, Uniprot).

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
Senior scientists Kristýna Boušová, Jakub Galgonek
Postdoctoral fellows Martin Čech, David Jakubec, Kateřina Jirásková, Jiří Vymětal
Ph.D. students Kateřina Faltejsková, Josef Šulc, Klára Poštulková, Veronika Vetýšková, Monika Zouharová
Project manager Anna Strachotová
IT specialists, programmers Pavel Dvořák, Marek Moos
Student Daniel Čermák
Assistant Natália Pižemová

Selected publications

Vymětal, J.; Jakubec, D.; Galgonek, J.; Vondrášek, J. Amino Acid Interactions (INTAA) web server v2.0: a single service for computation of energetics and conservation in biomolecular 3D structures. *Nucleic Acids Res.* **2021**, 49, W15–W20.

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Galgonek, J.; Vondrášek, J. IDSM ChemWebRDF: SPARQLing small-molecule datasets. *J. Cheminform.* **2021**, 13, 38.

Zouharova, M.; Vymetal, J.; Bednarova, L.; Vanek, O.; Herman, P.; Vetyskova, V.; Postulkova, K.; Lingstaadas, P. S.; Vondrasek, J.; Bousova, K. Intrinsically disordered protein domain of human ameloblastin in synthetic fusion with calmodulin increases calmodulin stability and modulates its function. *Int. J. Biol. Macromol.* **2021**, 168, 1–12.

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

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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.

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Stasyuk, O.A.; Jakubec, D.; Vondrasek, J.; Hobza, P. Noncovalent Interactions in Specific Recognition Motifs of Protein-DNA Complexes. *J. Chem. Theory Comput.* **2017**, 13, 877–885.

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.

Funding

ELIXIR-CONVERGE: Connect and align ELIXIR Nodes to deliver sustainable FAIR life-science data management services. European Commission (H2020-INFRADEV-2018-2020), No. 871075, 2020–2023, co-PI: Vondrášek, J.

Czech national Infrastructure for biological data. Ministry of Education, Youth and Sports (MŠMT ČR), No. LM2018130, 2020–2022, co-PI: Vondrášek, J.

Remote control: Allosteric control of PDZ3 domain selectivity from ZO-1 Protein in chimeric fusion proteins. Czech Science Foundation (GA ČR), No. 19-03488S, 2019–2021, PI: Vondrášek, J.

Czech national Infrastructure for biological data. Ministry of Education, Youth and Sports (MŠMT ČR), No. LM2015047, 2016–2019, co-PI: 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, co-PI: 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.

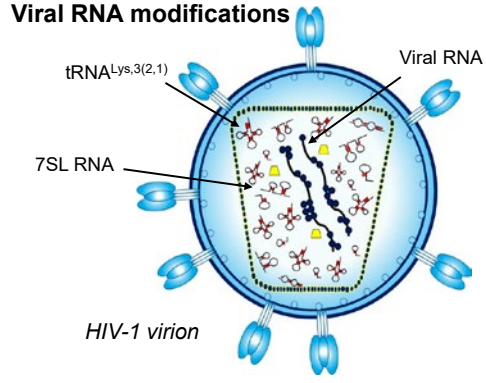
elixir
CZECH REPUBLIC

Hana Cahová Group

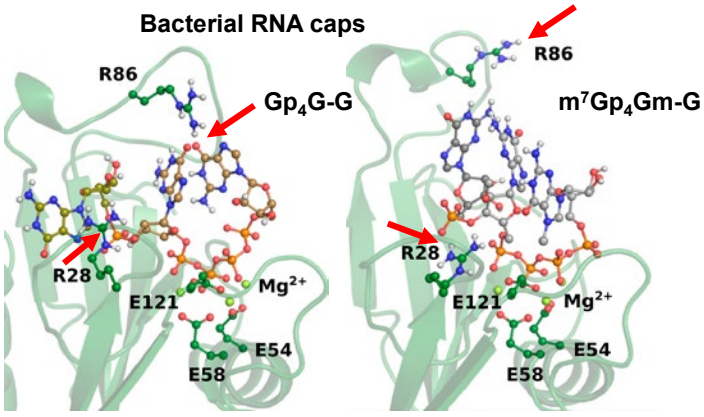
Chemical Biology of Nucleic Acids
hana.cahova@uochb.cas.cz
www.uochb.cz/cahova
www.cahovagroup.com

Junior Research Group

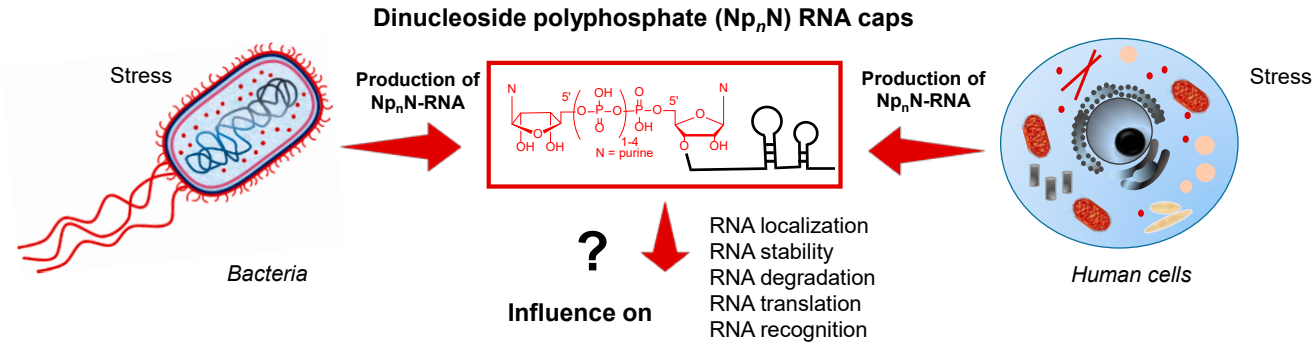
RNA caps, dinucleoside polyphosphates, RNA modifications, regulatory RNA, non-coding RNA, MS analysis of RNA, RNA-seq



Šimonová, A. et al., *Sci. Rep.* **2019,** 9, 8697



Hudeček, O., Benoni, R. et al., *Nat. Comm.* **2020,** 11, 1052



Research interests

The aim of our group is to understand the role of RNA modifications in various model systems. We believe that chemical RNA modifications are responsible for the majority of distinct RNA functions. Even though there are currently more than 170 RNA modifications known, the role of majority of them is unknown. The 5′ termini of the RNA are critical structures and are the least characterized among RNA modifications. Until recently only canonical structures, NAD or CoA have been known as 5′ RNA caps. We discovered an entirely new class of 5′RNA caps – dinucleoside polyphosphates (Np$_n$N) in bacteria. The role of free Np$_n$Ns, identified fifty years ago in all types of cells, is yet to be elucidated. Np$_n$Ns cellular concentration increases under stress conditions. We presume that their cellular effects are mediated by the RNA, where they serve as RNA caps. Therefore, we study biosynthesis, biodegradation and role of these non-canonical caps by modern molecular biological techniques in combination with RNA-seq methods and LC-MS.

In addition to bacterial and mammalian 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
Postdoctoral fellows Lenka Gahurová, Ondřej Nešuta, Anton Škríba, Pavel Vopálenský
Ph.D. students Barbora Benoni (Svojanovská), Flaminia Mancini, Maria-Bianca Mititelu, Valentina Serianni, Anna Šimonová
Students Jan Říha, Nikolas Tolar, Barbora Voleníková
Lab manager Kristína Spustová

Selected publications

Hudeček, O.; Benoni, R.; Reyes-Gutierrez, P. E.; Culka, M.; Šanderová, H.; Hubálek, M.; Rulíšek, L.; Cvačka, J.; Krásný, L.; Cahová, H. Dinucleoside polyphosphates act as 5′-RNA caps in bacteria. *Nat. Commun.* **2020**, 11, 1052.

Benoni, R.; Culka, M.; Hudeček, O.; Gahurova, L.; Cahová, H. Dinucleoside Polyphosphates as RNA Building Blocks with Pairing Ability in Transcription Initiation. *ACS Chem. Biol.* **2020**, 15, 1765–1772.

Potužník, Jiří, F.; Cahová, H. It's the Little Things (in Viral RNA). *mBio* 11, e02131-20.

Šimonová, A.; Svojanovská, B.; Trylčová, J.; Hubálek, M.; Moravčík, O.; Zavřel, M.; Pávová, M.; Hodek, J.; Weber, J.; Cvačka, J.; Pačes, J.; Cahová, H. LC/MS analysis and deep sequencing reveal the accurate RNA composition in the HIV-1 virion. *Sci. Rep.* **2019**, 9, 8697.

Cahová, H.; Winz, M.-L.; Höfer, K.; Nübel, G.; Jäschke, A. NAD captureSeq indicates NAD as a bacterial cap for a subset of regulatory RNAs. *Nature* **2015**, 519, 374–377.*

** Non-IOCB article (Hana Cahová)*

Collaboration

Francesco Di Serio (CNR, Italy)

Joanna Kowalska (Warsaw University, Poland)

Libor Krásný (MBI CAS, Prague, Czech Republic)

Joanna Kufel (Warsaw University, Poland)

Pavel Plevka (CEITEC, Brno, Czech Republic)

David Staněk (MBI CAS, Prague, Czech Republic)

Štěpánka Vaňáčová (CEITEC, Brno, Czech Republic)

Awards—Hana Cahová

Werner von Siemens Award for Women Scientific Work, 2022

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

Alfred Bader prize for young bioorganic chemist (Czech Chemical Society, Czech Republic), 2016

Otto Wichterle award for young scientist (Czech Academy of Sciences), 2015

Alexander von Humboldt Research Fellowship for Postdoctoral Researchers, IPMB Heidelberg, 2011–2013

Funding

StressRNaction: Non-canonical RNA caps – cellular reaction to environment and stress. European Research Council (ERC Starting Grant), 2022–2027, PI: Cahová, H.

Exploring RNA modifications in infectious non-coding RNAs. Bilateral cooperation project CNR-CAS, 2022–2024, PI: Cahová, H.

Virifaction: Viral RNA modifications – Essential Steps in Chemical Evolution of Protein Cofactors. Ministry of Education, Youth and Sports (MŠMT) – ERC CZ, 2017–2021, PI: Cahová, H.

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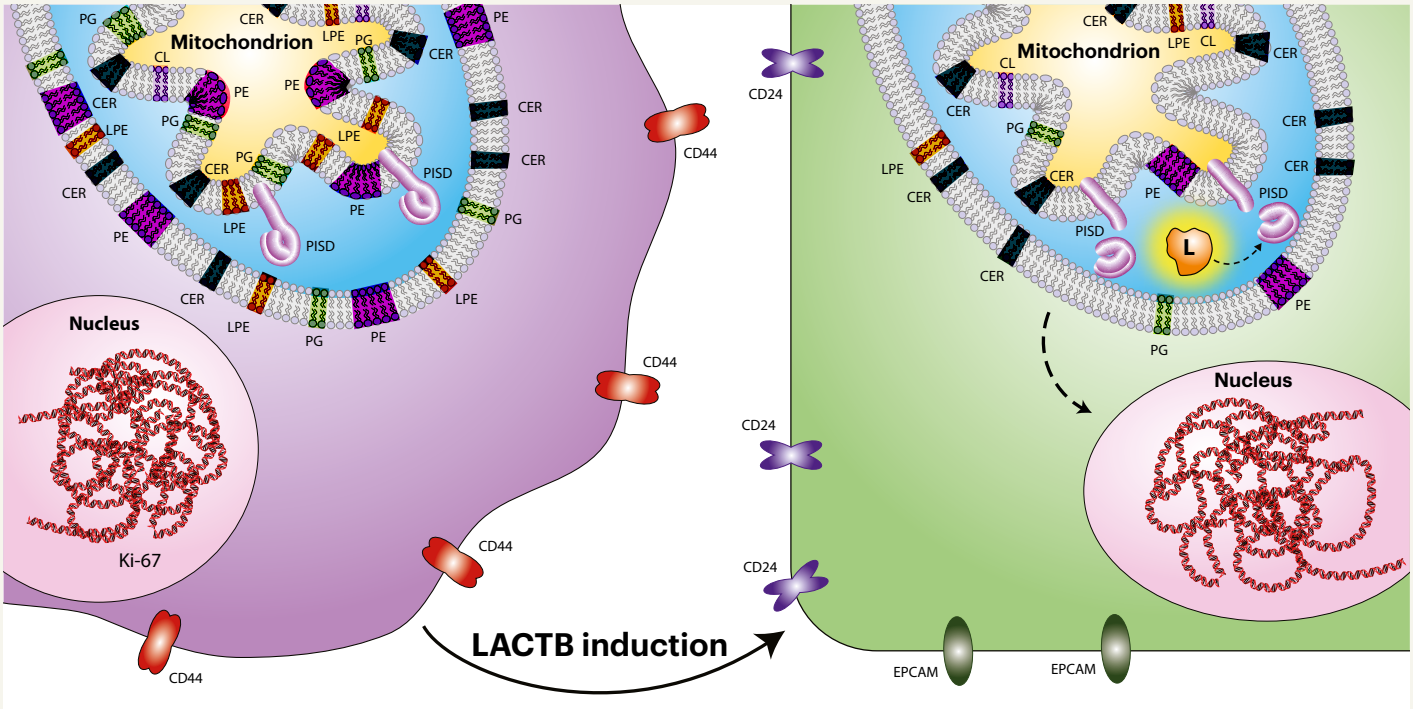
CAHOVÁ GROUP
CHEMICAL BIOLOGY IOCB PRAGUE

Zuzana Kečkéšová Group

Tumor Suppressors
zuzana.keckesova@uochb.cas.cz
www.uochb.cz/keckesova

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

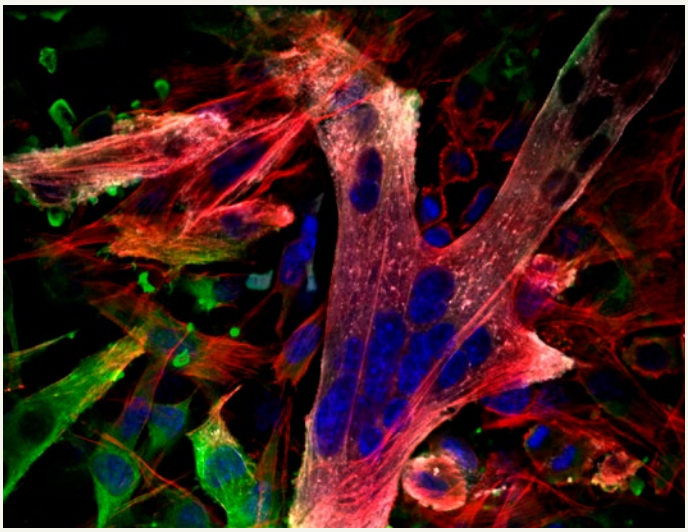


Research interests

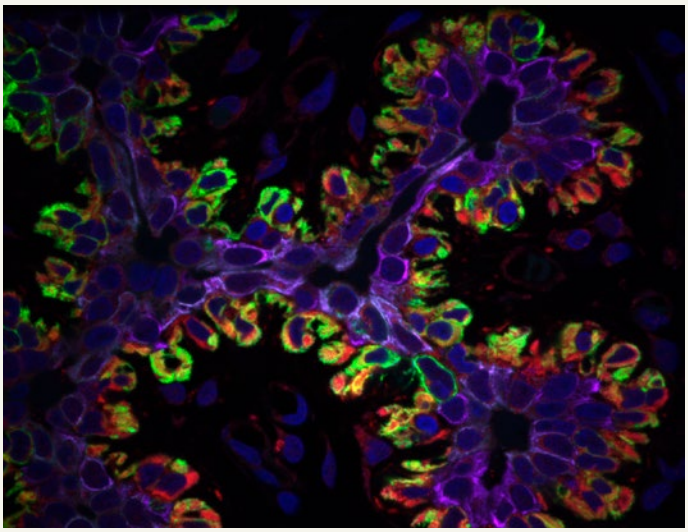
The aim of Dr. Zuzana Keckesova's lab (Zuzu Lab) is to identify and characterize new tumor suppressor pathways and circuitries in human cells with the ultimate goal of translating this new knowledge into therapeutic use. Dr. Keckesova's lab is researching tissues/cell types that rarely undergo tumorigenesis. 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). 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 Kečkéšová
Senior scientist Beata Malčeková
Postdoctoral fellows Valentina Cutano, Jessica Mariane Ferreira Mendes, Juan Manuel Gonzalez-Morena, Susana Machado, Chung Weng Phang
Students Sara Escudeiro Lopes, Pavel Jakoubě

Selected publications

Jakoube, P.; Cutano, V.; González-Morena, J. M.; Keckesova, Z. Mitochondrial Tumor Suppressors—The Energetic Enemies of Tumor Progression. *Cancer Res.* **2021**, 81, 4652.

Kečkéšová, 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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Bierie, B.; Pierce, S.E.; Kroeger, C.; Stover, D.G.; Pattabiraman, D.R.; Thiru, P.; Liu Donaher, J.; Reinhardt, F.; Chaffer, C.L.; Kečkéšová, Z.; Weinberg, R.A. Integrin-β4 identifies cancer stem cell-enriched populations of partially mesenchymal carcinoma cells. *PNAS* **2017**, 114, E2337–2346.*

De Cock, J.M.; Shibue, T.; Dongre, A.; Kečkéšová, Z.; Reinhardt, F.; Weinberg, R.A.: Inflammation triggers Zeb1-dependent escape from latency. *Cancer Res.* **2016**, 76, 6778–6784.*

Guo, W.; Kečkéšová, Z.; Donaher, J.L.; Reinhardt, F.; Shibue, T.; Itzkovitz, S.; Bell, G.; von Oudenaarden, A.; Weinberg, R.A. Slug and Sox9 cooperatively determine the mammary stem cell state. *Cell* **2012**, 148, 1015–1028.*

** Non-IOCB article (Zuzana Kečkéšová)*

Funding

Czech Academy of Sciences-National Natural Science Foundation of China (NSFC), Mobility Plus Project, 2021–2022.

Mobility Grant, MSCA-OP RDE, 2020–2022.

EMBO Installation Grant, 2018–2022.

BPD private funding, 2018–2022.

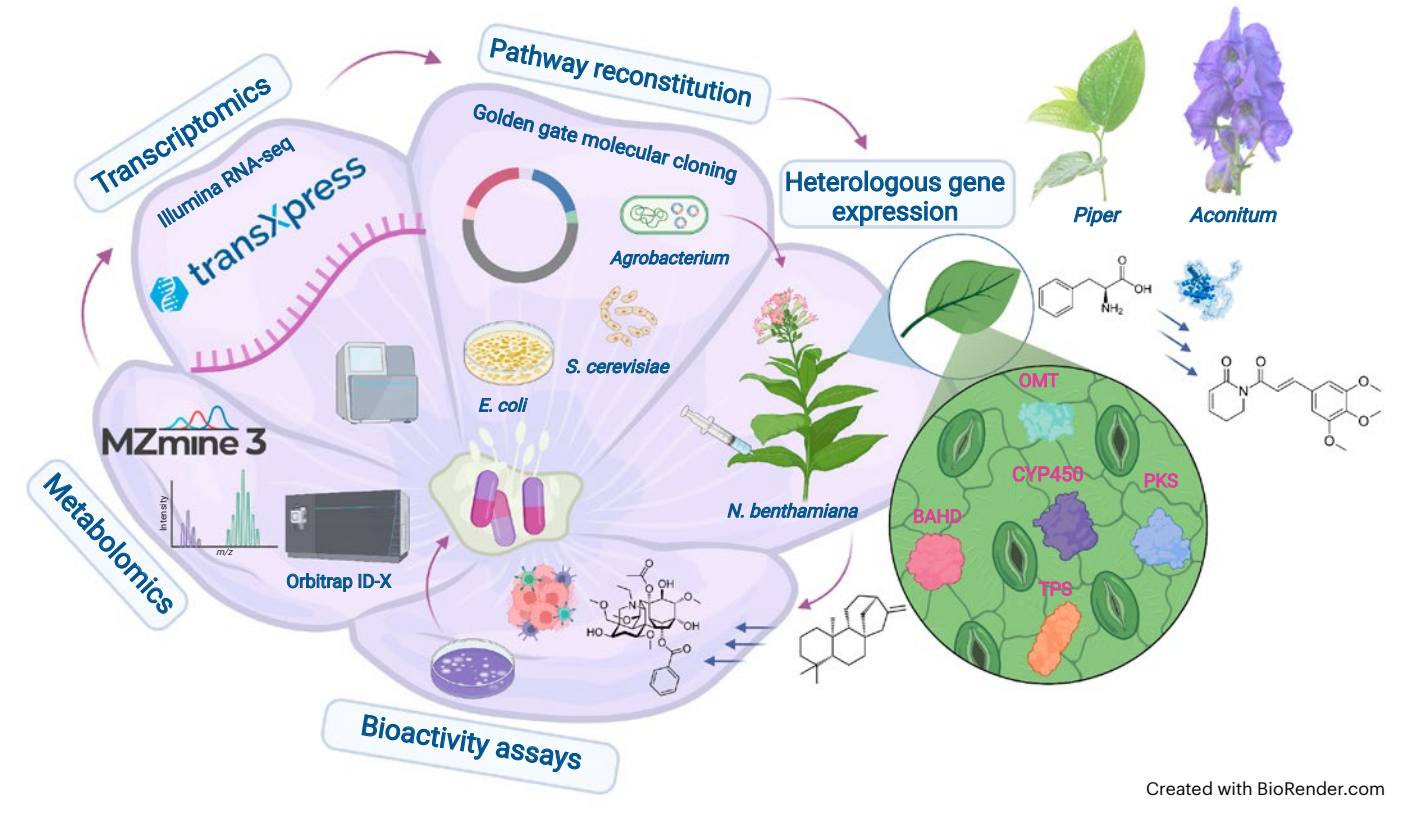
Strategies to identify the vulnerabilities of cancer cells. Czech Science Foundation (GA ČR), No. 18-24473Y, 2018–2020.

Tomáš Pluskal Group

Biochemistry of Plant Specialized Metabolites
tomas.pluskal@uochb.cas.cz
www.uochb.cz/pluskal

Junior Research Group

plant specialized metabolites, metabolomics, transcriptomics, *de novo* sequencing, bioinformatics, machine learning



Research interests

During millions of years of evolution, land plants have created an astonishing variety of bioactive specialized metabolites (also referred to as secondary metabolites or natural products) to support their defense and ecological adaptation. Such molecules often interact with human molecular receptors, thus providing an essential source of chemical scaffolds for the development of new medicines. Approximately 25% of prescription drugs currently in use originated from plants; however, the structural and stereochemical complexity of plant metabolites often renders their chemical synthesis unfeasible.

Our lab combines novel computational (e.g. machine learning) and experimental approaches (high-resolution mass spectrometry, *de novo* sequencing) to develop rapid, generally applicable workflows for the discovery and utilization of bioactive molecules derived from plants and their biosynthetic circuits. We are particularly interested in the pepper (Piper) genus of plants, which has been long recognized as a remarkable reservoir of bioactive specialized metabolites. Another exciting target is the monkshood (Aconitum) genus, which produces unique bioactive diterpenoid alkaloids such as aconitine, a molecule so complex that no chemist in the world has been able to synthesize it.

Our lab administers and develops the *MZmine* and *transXpress* projects.

Group members

Group leader Tomáš Pluskal
Lab manager Václav Čeřovský
Postdoctoral fellows Corinna Brungs, Tito Damiani, Téo Hebra
PhD students Lana Mutabdžija, Milana Perković, Raman Samusevich, Joshua Smith
Students Roman Bushuiev, Tereza Čalounová, Martin Orságh, Helena Smrčková, Andrej Tekel

MZmine 3

transXpress

Selected publications

Schmid, R., Petras, D., Nothias, LF. et al. Ion identity molecular networking for mass spectrometry-based metabolomics in the GNPS environment. *Nat. Commun.* **2021**, 12, 3832.

Nothias, L.-F. et al. Feature-based molecular networking in the GNPS analysis environment. *Nat. Methods* **2020**, 17, 905–908.*

Pluskal, T.; Torrens-Spence, M. P.; Fallon, T. R.; De Abreu, A.; Shi, C. H.; Weng, J.-K. The biosynthetic origin of psychoactive kavalactones in kava. *Nat. Plants* **2019**, 5, 867–878.*

Pluskal, T.; Weng, J.-K. Natural product modulators of human sensations and mood: molecular mechanisms and therapeutic potential. *Chem. Soc. Rev.* **2018**, 47, 1592–1637.*

Pluskal, T.; Castillo, S.; Villar-Briones, A.; Orešič, M. MZmine 2: Modular framework for processing, visualizing, and analyzing mass spectrometry-based molecular profile data. *BMC Bioinform.* **2010**, 11, 395.*

** Non-IOCB article (Tomáš Pluskal)*

Funding

Mapping the chemodiversity of Piperaceae plants using next-generation MZmine platform. Czech Science Foundation (GA ČR), No. 21-11563M, 2021–2025, PI: Pluskal, T.

KavaTarget – Identification of molecular targets of psychoactive kavalactones using iBodies. Horizon 2020, No. 891397, 2021–2024, PI: Pluskal, T.

EpiLipidNet – Pan-European Network in Lipidomics and EpiLipidomics, EU COST Action, No. CA19105, 2020–2024.

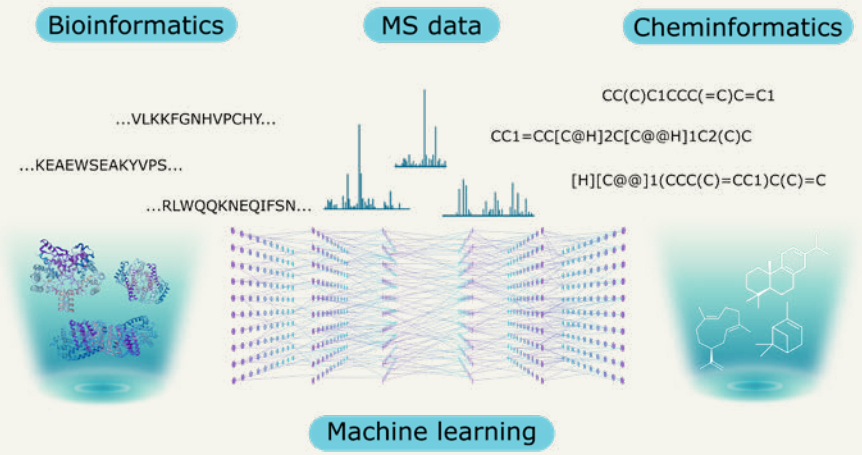
Collaboration

Pieter Dorrestein (University of California San Diego, CA, USA)

Xiuxia Du (University of North Carolina at Charlotte, NC, USA)

Cathie Martin (John Innes Centre, UK)

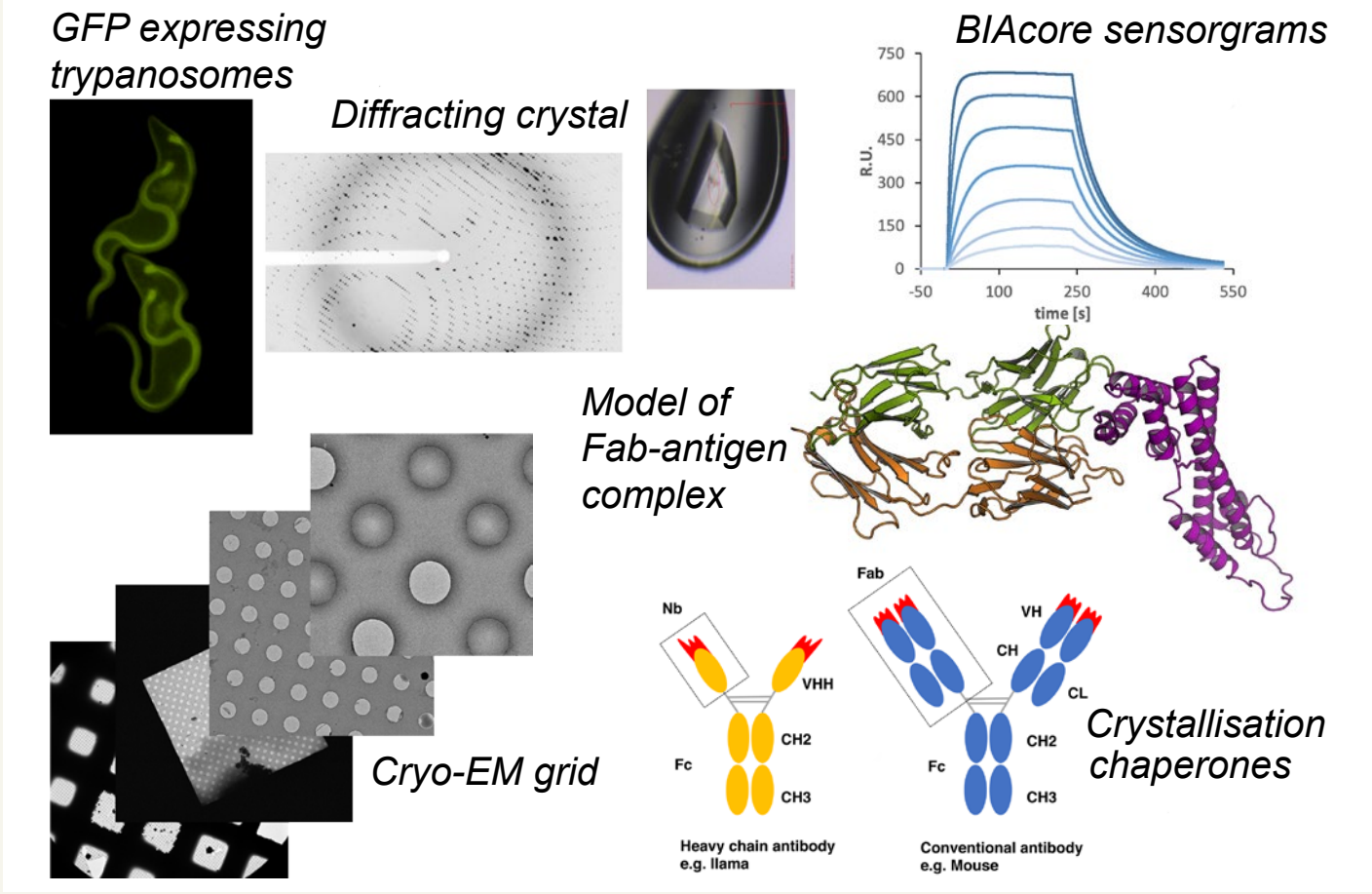
Uwe Karst (University of Münster, Germany)



Sebastian Zoll Group

Structural Parasitology
sebastian.zoll@uochb.cas.cz
www.uochb.cz/zoll

Junior Research Group
host-pathogen interactions, human parasites, neglected tropical diseases, cryo-EM, crystallography, small-angle X-ray scattering, protein-protein interactions, anti(nano)body engineering



Research interests

Our group is interested in understanding the structural basis of interaction between surface proteins of eukaryotic parasites and human host factors. Our goal is to use these structural insights to provide a foundation for the development of novel therapeutic strategies against neglected parasitic diseases.

We use an integrated structural biology approach, including X-ray crystallography, small-angle X-ray scattering, and single-particle Cryo-EM, together with a wide range of biophysical techniques for characterisation of protein-protein/ligand interactions.

Surface proteins of eukaryotic parasites often adopt unusual folds. To obtain structural information, we use cutting-edge recombinant antibody and nanobody technology to create adaptor proteins for crystallisation as well as applications in single-particle Cryo-EM. In addition, our group is adapting this technology for the development of nanobody-based therapeutics to overcome the limitations of current antiparasitic drugs.

Our group works closely with the IOCB Cryo-EM facility.

Group members

Group leader Sebastian Zoll
Postdoctoral fellows Sami Kereiche, Hanna Tulmin, Arun Dhillon
PhD student Hagen Sülzen
Technicians Alžběta Lacinová, Marie Šafner, Jitka Votrubová
Students Kateřina Čápová, Adriána Merčiaková

Selected publications

Magez, S.; Li, Z.; Nguyen, H. T.; Pinto Torres, J. E.; Van Wielendaele, P.; Radwanska, M.; Began, J.; Zoll, S.; Sterckx, Y. G. J. The History of Anti-Trypanosome Vaccine Development Shows That Highly Immunogenic and Exposed Pathogen-Derived Antigens Are Not Necessarily Good Target Candidates: Enolase and ISG75 as Examples. *Pathogens* **2021**, 10.

Zoll, S.; Lane-Serff, H.; Mehmood, S.; Schneider, J.; Robinson, C. V.; Carrington, M.; Higgins, M. K. The structure of serum resistance-associated protein and its implications for human African trypanosomiasis. *Nat. Microbiol.* **2018**, 3, 295-301.*

Zoll, S.; Stanchev, S.; Began, J.; Škerle, J.; Lepšík, M.; Peclinovská, L.; Majer, P.; Strisovsky, K. Substrate binding and specificity of rhomboid intramembrane protease revealed by substrate–peptide complex structures. *EMBO J.* **2014**, 33, 2408-2421.

Büttner, F. M.; Zoll, S.; Nega, M.; Götz, F.; Stehle, T. Structure-Function Analysis of Staphylococcus aureus Amidase Reveals the Determinants of Peptidoglycan Recognition and Cleavage. *J. Biol. Chem.* **2014**, 289, 11083-11094.*

Zoll, S.; Schlag, M.; Shkumatov Alexander, V.; Rautenberg, M.; Svergun Dmitri, I.; Götz, F.; Stehle, T. Ligand-Binding Properties and Conformational Dynamics of Autolysin Repeat Domains in Staphylococcal Cell Wall Recognition. *J. Bacteriol.* **2012**, 194, 3789-3802.*

Zoll, S.; Pätzold, B.; Schlag, M.; Götz, F.; Kalbacher, H.; Stehle, T. Structural Basis of Cell Wall Cleavage by a Staphylococcal Autolysin. *PLoS Pathog.* **2010**, 6, e1000807.*

Schlag, M.; Biswas, R.; Krismer, B.; Kohler, T.; Zoll, S.; Yu, W.; Schwarz, H.; Peschel, A.; Götz, F. Role of staphylococcal wall teichoic acid in targeting the major autolysin Atl. *Mol. Microbiol.* **2010**, 75, 864-873.*

Lützner, N.; Pätzold, B.; Zoll, S.; Stehle, T.; Kalbacher, H. Development of a novel fluorescent substrate for Autolysin E, a bacterial type II amidas. *Biochem. Biophys. Res. Commun.* **2009**, 380, 554-558.*

** Non-IOCB article (Sebastian Zoll)*

Funding

Understanding the mechanism of ISG65-mediated complement control by the human parasite *Trypanosoma brucei gambiense*. Czech Science Foundation (GA ČR), No. 22-21612S, 2022–2024, PI: Zoll, S.

Collaboration

Prof. Yann G. J. Sterckx, University of Antwerp, Antwerp, Belgium

Dr. Dirk M. Reiter, VIB-VUB, Brussels, Belgium

Dr. Martin Zoltner, BIOCEV, Vestec, Czech Republic

Dr. Petr Pompach, BIOCEV, Vestec, Czech Republic

Prof. Niklas Arnberg, Umeå University, Umea, Sweden

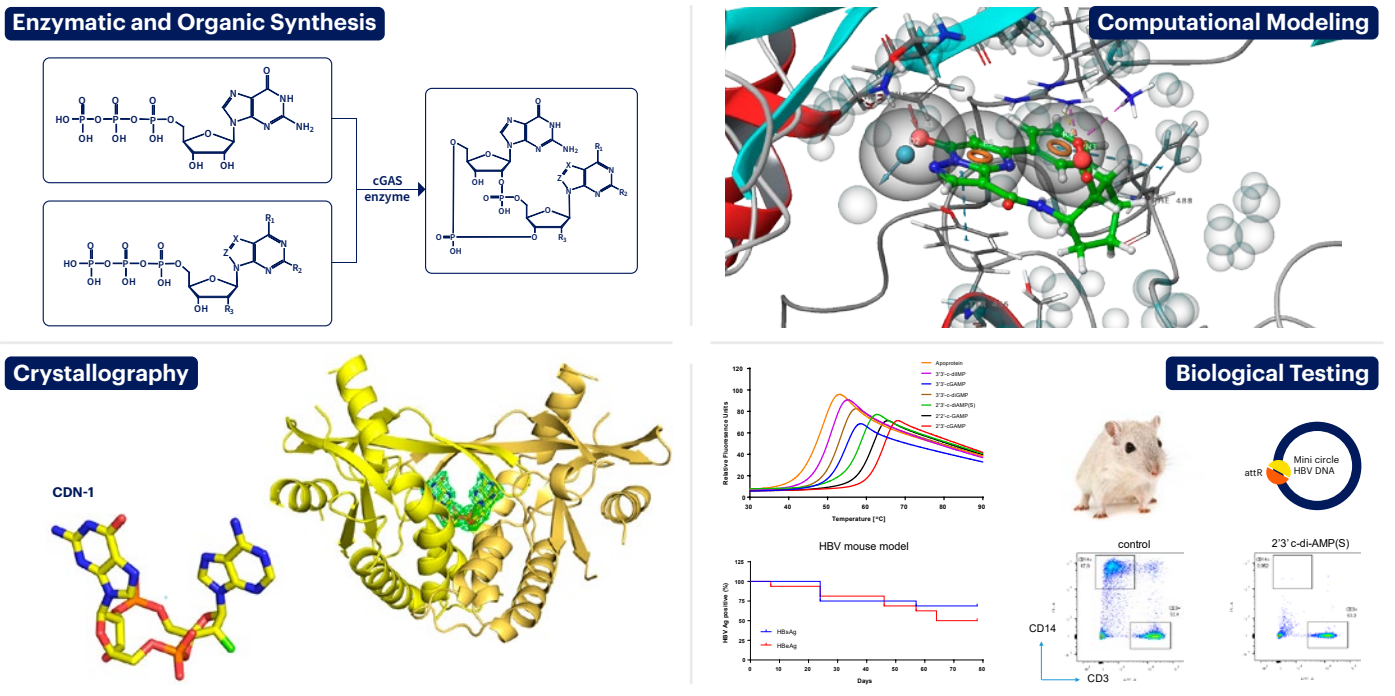
Prof. Mark C. Field, Drug Discovery Unit, University of Dundee, Dundee, United Kingdom

Gabriel Birkuš Group

HBV Cure
gabriel.birkus@uochb.cas.cz
www.uochb.cz/birkus

Targeted Research Group

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



Research interests

Our cross-functional team, comprising medicinal chemists, virologists, immunologists, computational chemists, and biochemists, specializes in discovery of novel therapies to treat chronic hepatitis B, cancer, and inflammatory disorders.

In collaboration with 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, 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 in relation to all STING haplotypes. In addition to employing conventional chemical synthesis, we have also used enzymatic preparation of CDNs, identifying several promiscuous bacterial and vertebrate cyclic dinucleotide synthases that allowed for efficient one-step preparation of CDNs from NTP analogues. We have also developed methods for the synthesis of lipophilic prodrugs of CDNs with cellular activity improved by three orders of magnitude as compared with their parent CDNs. Consistently with their *in vitro* profile, the lead CDNs show potent activity in mouse models of chronic hepatitis B and cancer. More recently, we have prepared antibody CDN conjugates with excellent *in vivo* activity and minimal toxicity. Finally, we apply our expertise in drug discovery to the identification of inhibitors of the cGAS enzyme and antagonists of the STING adaptor protein.

Group members

Group leader Gabriel Birkuš
Senior scientists Andrea Brázdová, Vlastimil Král, Radek Liboska, Ondřej Páv, Ondřej Šimák, Ivan Štěpánek
Junior scientists Florian Chevrier, Juraj Dobiaš
Postdoctoral fellows Mikhail Klychnikov, Tomáš Lášek, Markéta Polidarová
Ph.D. students Lenka Vaneková, Zdeněk Vavřina, Barbora Vinšová
Technicians Milan Drška, Jana Hricová, Markéta Koutová, Anna Kratochvílová, Karin Krýcha, Hana Prouzová, Petra Prouzová, Jana Řeháková, Josef Uskoba, Klára Vernerová
Student Michaela Mochánová

Selected publications

Pimkova Polidarova, M.; Brehova, P; Dejmek, M.; Birkus, G.; Brazdova, A. STING Agonist-Mediated Cytokine Secretion Is Accompanied by Monocyte Apoptosis. *ACS Infect. Dis.* **2022**, 8, 463.

Novotná, B.; Holá, L.; Staś, M.; Gutten, O.; Smola, M.; Zavřel, M.; Vavřina, Z.; Buděšínský, M.; Liboska, R.; Chevrier, F.; Dobiaš, J.; Boura, E.; Rulíšek, L.; Birkuš, G. Enzymatic Synthesis of 3′-5′, 3′-5′ Cyclic Dinucleotides, Their Binding Properties to the Stimulator of Interferon Genes Adaptor Protein, and Structure/Activity Correlations. *Biochemistry* **2021**, 60, 3714.

Vavřina, Z.; Gutten, O.; Smola, M.; Zavřel, M.; Aliakbar, Tehrani, Z.; Charvát, V.; Kožíšek, M.; Boura, E.; Birkuš, G.; Rulíšek L. Protein-Ligand Interactions in the STING Binding Site Probed by Rationally Designed Single-Point Mutations: Experiment and Theory. *Biochemistry* **2021**, 60, 607.

Pimková Polidarová, M.; Břehová, P.; Kaiser, M. M.; Smola, M.; Dračínský, M.; Smith, J.; Marek, A.; Dejmek, M.; Šála, M.; Gutten, O.; Rulíšek, L.; Novotná, B.; Brázdová, A.; Janeba, Z.; Nencka, R.; Boura, E.; Páv, O.; Birkuš, G. Synthesis and Biological Evaluation of Phosphoester and Phosphorothioate Prodrugs of STING Agonist 3′,3′-c-Di(2′F,2′dAMP). *J. Med. Chem.* **2021**, 64, 7596.

Novotná, B.; Vaneková, L.; Zavřel, M.; Buděšínský, M.; Dejmek, M.; Smola, M.; Gutten, O.; Tehrani, Z.A.; Pimková Polidarová, M.; Brázdová, A.; Liboska, R.; Štěpánek, I.; Vavřina, Z.; Jandušík, T.; Nencka, R.; Rulíšek, L.; Bouř, E.; Brynda, J.; Páv, O.; Birkuš, G. Enzymatic Preparation of 2′-5′,3′-5′-Cyclic Dinucleotides, Their Binding Properties to Stimulator of Interferon Genes Adaptor Protein, and Structure/Activity Correlations. *J. Med. Chem.* **2019**, 62, 10676.

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.

Funding

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.

Patents

Birkus, G.; Pav, O.; Rosenberg, I.; Simak, O. 2′3′-cyclic dinucleotides. (2020) US patent US11149052.

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 US11203610.

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 US10966999.

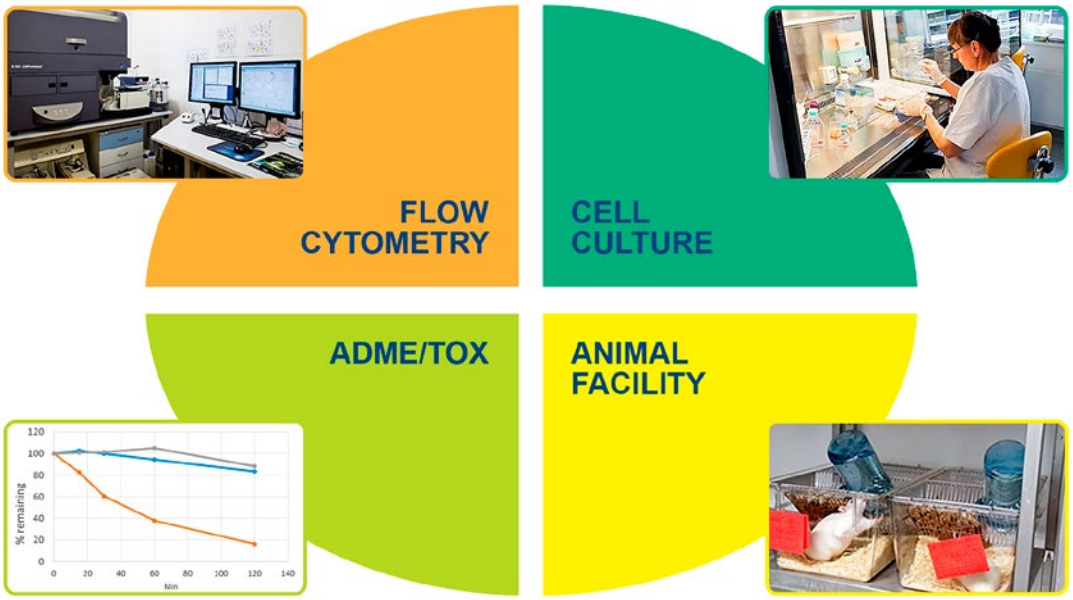
Collaboration

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

Biochemical Pharmacology

Helena Mertlíková-Kaiserová
helena.kaiserova@uochb.cas.cz
www.uochb.cz/pharmacology

Research-Service Group
drug discovery, cell culture, assay development, screening, DMPK, cancer, inflammation



Research interests

Biochemical Pharmacology is a research-service group aiming to support early phase drug discovery projects based on original compounds synthesized at IOCB. The team provides assay development and screening services and assists in target identification and validation (receptors, enzymes, signaling molecules). Compounds with biological activity are further investigated for their bioavailability in a battery of *in vitro* ADME tests and eventually, lead compounds are subjected to early PK studies in mice. The research is strongly collaborative, especially with medicinal chemistry and structural biology groups as well as IOCB compound library and technology transfer office.

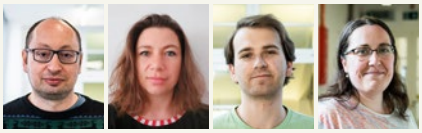
Most of our projects fall into the fields of oncology/inflammation, anti-microbials or neuropharmacology.

The group runs central cell culture facility, which ensures regular cytotoxicity screening services, mycoplasma testing and provides ready-to-use cells to the researchers who wish to perform the experiments on their own. We are also in charge of a small animal facility (mice, rats) dedicated primarily to short-term experiments. Our staff is responsible for housing and well-being of the animals, the experiments are performed by the researchers themselves, unless this is a part of the research project in which group members are involved. The team also operates three flow cytometers – two analyzers and a sorter and provides user training, consultancy in experimental design (multiparametric panels) and assistance in cell sorting including single-cell sorting in multiwell plates. Data evaluation software license (FlowJo) is available to the users.

We are open to new ideas and challenges in assay development, miniaturization, and automatization for HTS screening and ready to customize the assays to fit the needs of our partners.

Group members

Group leader Helena Mertlíková-Kaiserová
Deputy leader Miroslav Hájek
Senior scientists Karel Chalupský, Jaroslav Kozák, Erika Kužmová, Marika Matoušová, Markéta Šmídková, Martin Zavřel
Postdoctoral fellow Timotej Strmeň
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 Valeriia Domochka, Zuzana Kráľová, Tomáš Sanislo, Martin Žáček



Selected publications

Kalčic, F.; Zgarbová, M.; Hodek, J.; Chalupský, K.; Dračínský, M.; Dvořáková, A.; Strmeň, T.; Šebestík, J.; Baszczyński, O.; Weber, J.; Mertlíková-Kaiserová, H.; Janeba, Z. Discovery of Modified Amidate (ProTide) Prodrugs of Tenofovir with Enhanced Antiviral Properties. *J. Med. Chem.* **2021**, 64,16425–16449.

Dzijak, R.; Galeta, J.; Vázquez, A.; Kozák, J.; Matoušová, M.; Fulka, H.; Dračínský, M.; Vrabel, M. Structurally Redesigned Bioorthogonal Reagents for Mitochondria-Specific Prodrug Activation. *JACS Au* **2021**, 1, 23–30.

Smrček, J.; Hájek, M.; Hodek, O.; Čížek, K.; Pohl, R.; Jahn, E.; Galano, J.M.; Oger, C.; Durand, T.; Cvačka, J.; Jahn, U. First Total Synthesis of Phytoprostanes with Prostaglandin-Like Configuration, Evidence for Their Formation in Edible Vegetable Oils and Orienting Study of Their Biological Activity. *Chemistry* **2021**, 27, 9556–9562.

Břehová, P.; Chaloupecká, E.; Česnek, M.; Skácel, J.; Dračínský, M.; Tloušťová, E.; Mertlíková-Kaiserová, H.; Soto-Velasquez, M.P.; Watts, V.J.; Janeba, Z. Acyclic nucleoside phosphonates with 2-aminothiazole base as inhibitors of bacterial and mammalian adenylate cyclases. *Eur. J. Med. Chem.* **2021**, 15, 222:113581.

Kužmová, E.; Zawada, Z.; Navrátil, M.; Günterová, J.; Kraus, T. Flow cytometric determination of cell cycle progression via direct labeling of replicated DNA. *Anal. Biochem.* **2021**, 1, 614:114002.

Dostalik, P.; Krafcikova, P.; Silhan, J.; Kozic, J.; Chalupska, D.; Chalupsky, K.; Boura, E. Structural Analysis of the OC43 Coronavirus 2′-O-RNA Methyltransferase. *J. Virol.* **2021**, 12, 95:e0046321.

Funding

Development of DIANAbased *in vitro* ADME methods for new drug discovery. Technology Agency of the Czech Republic (TA ČR), No. TJ02000276, 2019–2021, co-PI: Mertlíková-Kaiserová, H.

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

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

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

Collaboration

We support these IOCB projects:

—Anti-inflammatory effects of substituted pyrimidine analogs (Z. Janeba, IOCB Tech)

—Inhibitors of purine nucleoside phosphorylase to treat Tcell leukemias (Z. Janeba, IOCB Tech)

—Kinase inhibitors to treat myeloid leukemias (M. Hocek, IOCB Tech)

—Neuroprotective effects of steroidal inhibitors of NMDA receptors (E. Kudová, IOCB Tech)

—Galectin1/3 inhibitors for cancer treatment (R. Pohl)

—Adenylate cyclase inhibitors as antimicrobial drugs (Z. Janeba)

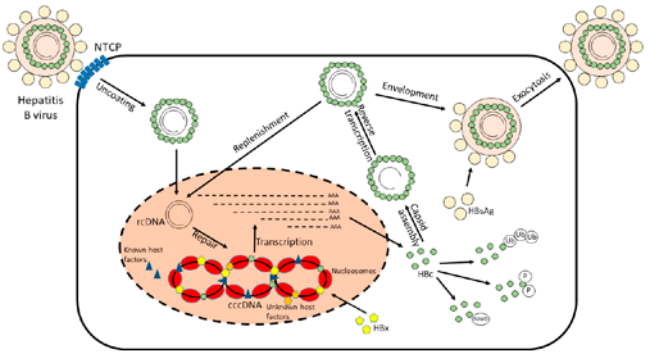
—α2 Adrenergic receptor antagonists for mitigation of ACLF (acute-on-chronic liver failure) (Z. Janeba)

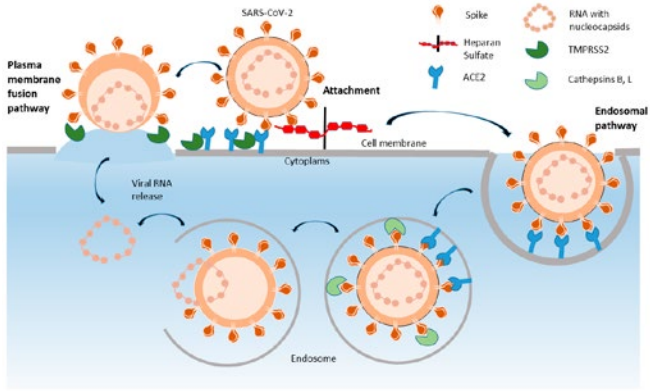
Virology

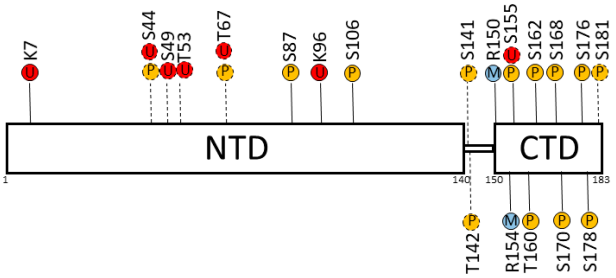
Jan Weber
jan.weber@uochb.cas.cz
www.uochb.cz/virology

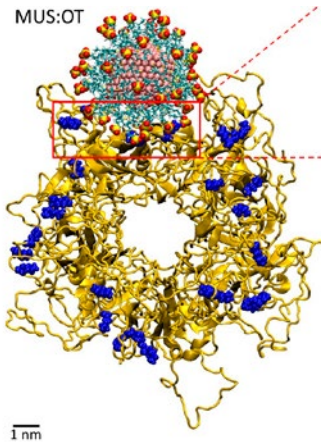
Research-Service Group

antiviral screening, drug discovery, human immunodeficiency virus, hepatitis B virus, replication, latency, reactivation, virucidal nanoparticles, virus attachment, virus entry, adhesion GPCR





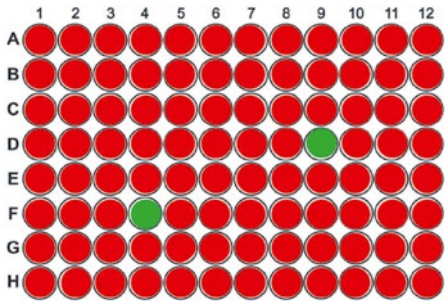


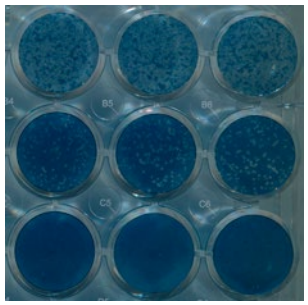
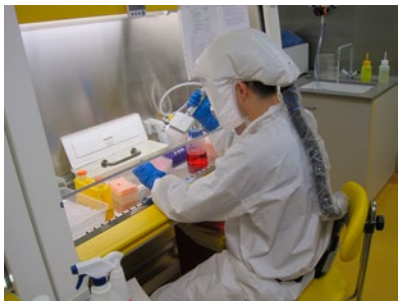
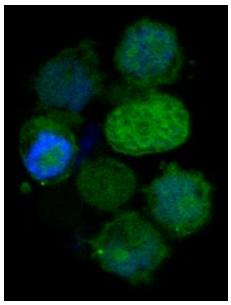


Research interests

The group 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, zika virus, herpes simplex virus, coxsackie virus, and SARS-CoV-2. Furthermore, we collaborate with other groups to improve entry of active compounds into cells using liposomal and macrocyclic delivery systems. We are also involved in the search for nanoparticles and nanomaterials with antiviral and virucidal activity.

In our research, we are focused 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. Furthermore, we are particularly interested in the effect of microenvironment of HBV-infected hepatocytes on the function of plasmacytoid dendritic cells. In addition, we examine new strategies for HIV inhibition, reactivation and latency. We also explore strategies to target the virus attachment and entry to the cells. Many viruses use heparan sulfate proteoglycan for initial attachment on the cell surface. Using various gold and silver nanoparticles with multi-sulfonated ligands we characterize this attachment process to find new ways to block the virus entry in the cells. Finally, we started project focusing on the role of specific aGPCR and cellular proteins in aGPCRs pathways involved in viral infections of mammalian cells.



Group members

Group leader Jan Weber
Senior scientists Jan Hodek, Barbora Lubyová
Postdoctoral fellows Ludovic Aillot, Marcela Pávová, Jana Trylčová
Research assistants Václav Janovec, Barbora Lapuníková, Eva Tikalová, Michala Zgarbová
Ph.D. students Kristýna Krulová, Lucie Ulrychová, Sandra Žáčková
Technician Jitka Weberová
Students Jitka Chalupová, Tereza Starková

Selected publications

Lubyova, B.; Tikalova, E.; Krulova, K.; Hodek, J.; Zabransky, A.; Hirsch, I.; Weber, J. ATM-Dependent Phosphorylation of Hepatitis B Core Protein in Response to Genotoxic Stress. *Viruses* **2021**, 13.

Hejdánek, J.; Radilová, K.; Pachl, P.; Hodek, J.; Machara, A.; Weber, J.; Řezáčová, P.; Konvalinka, J.; Kožíšek, M. structural characterization of the interaction between the C-terminal domain of the influenza polymerase PA subunit and an optimized small peptide inhibitor. *Antiviral Res.* **2021**, 185, 104971.

Kalčic, F.; Zgarbová, M.; Hodek, J.; Chalupský, K.; Dračínský, M.; Dvořáková, A.; Strmeň, T.; Šebestík, J.; Baszczyňski, O.; Weber, J.; Mertlíková-Kaiserová, H.; Janeba, Z. Discovery of Modified Amidate (ProTide) Prodrugs of Tenofovir with Enhanced Antiviral Properties. *J. Med. Chem.* **2021**, 64, 16425–16449.

Vaňková, E.; Kašparová, P.; Khun, J.; Machková, A.; Julák, J.; Sláma, M.; Hodek, J.; Ulrychová, L.; Weber, J.; Obrová, K.; Kosulin, K.; Lion, T.; Scholtz, V. Polylactic acid as a suitable material for 3D printing of protective masks in times of COVID-19 pandemic. *PeerJ* **2020**, 8, e10259.

Janovec, V.; Hodek, J.; Clarova, K.; Hofman, T.; Dostalik, P.; Fronek, J.; Chlupac, J.; Chaperot, L.; Durand, S.; Baumert, T. F.; Pichova, I.; Lubyova, B.; Hirsch, I.; Weber, J. Toll-like receptor dual-acting agonists are potent inducers of PBMC-produced cytokines that inhibit hepatitis B virus production in primary human hepatocytes. *Sci. Rep.* **2020**, 10, 12767.

Zacheo, A.; Hodek, J.; Witt, D.; Mangiatordi, G. F.; Ong, Q. K.; Kocabiyik, O.; Depalo, N.; Fanizza, E.; Laquintana, V.; Denora, N.; Migoni, D.; Barski, P.; Stellacci, F.; Weber, J.; Krol, S. Multi-sulfonated ligands on gold nanoparticles as virucidal antiviral for Dengue virus. *Sci. Rep.* **2020**, 10, 9052.

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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.* **2018**, 17, 195–203.

Funding

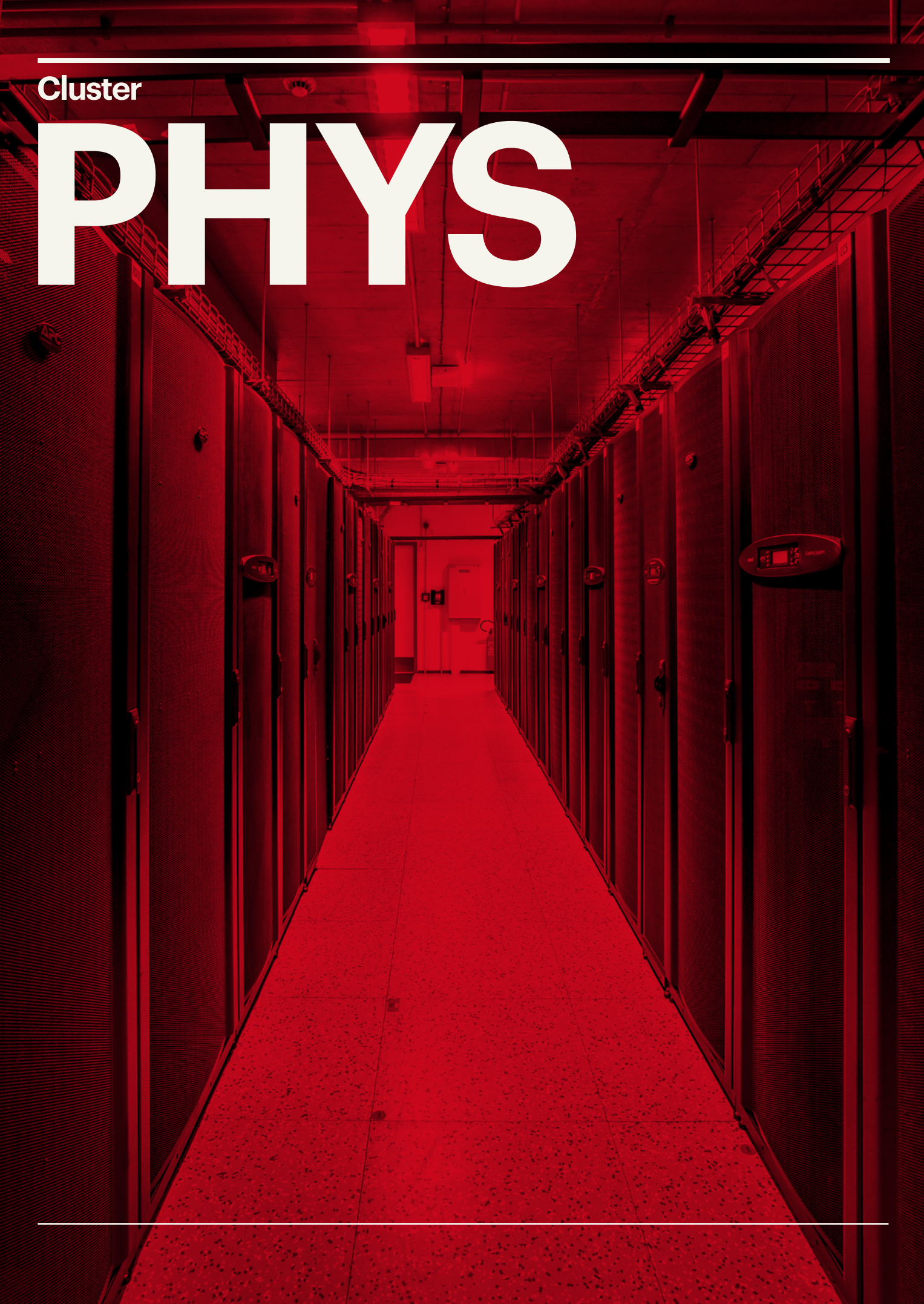
Embedding Antiviral Nanoparticles in Water and/or Air for Cleaning the Environment. INTER-EXCELLENCE, INTER-ACTION, Ministry of Education, Youth and Sports (MŠMT ČR), No. LTAIZ19017, 2019–2022, PI: Weber, J.

Role of adhesion-GPCRs during viral infection of mammalian cells. INTER-EXCELLENCE, INTER-COST, Ministry of Education, Youth and Sports (MŠMT ČR), No. LTC20065, 2020–2023, PI: Weber, 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.

Cluster

PHYS



Research Groups

Pavel Hobza Group (Non-Covalent Interactions) – Distinguished Chair
Pavel Jungwirth Group (Molecular Modeling) – Distinguished Chair
Zdeněk Havlas Group (Computational Chemistry) – Honorary Chair
Petr Bouř Group (Biomolecular Spectroscopy) – Senior Research Group
Lubomír Rulíšek Group (Theoretical Bioinorganic Chemistry) – Senior Research Group

Research-Service Groups

Electromigration Methods (Head: Václav Kašička)
Mass Spectrometry (Head: Josef Cvačka)
NMR Spectroscopy (Head: Martin Dračínský)

Service Group

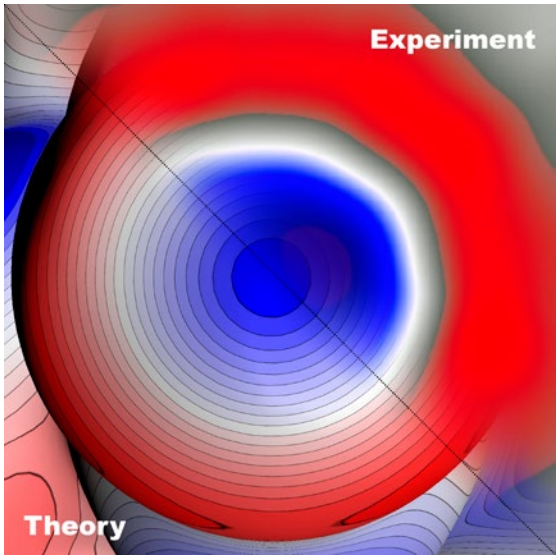
Analytical Laboratory (Head: Stanislava Matějková)

Pavel Hobza Group

Non-Covalent Interactions
pavel.hobza@uochb.cas.cz
www.uochb.cz/hobza

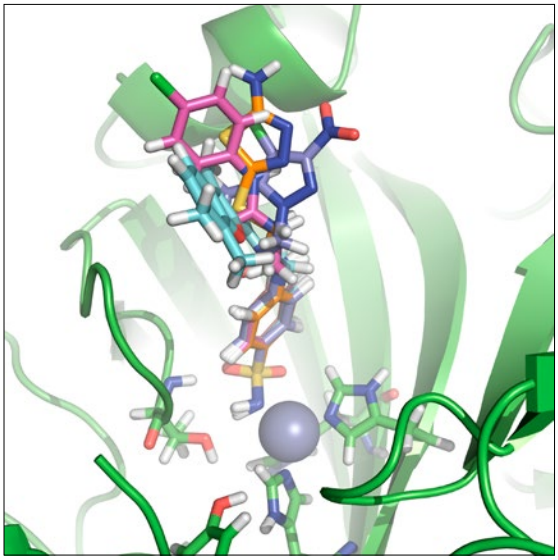
Distinguished Chair
non-covalent interactions, quantum chemistry, material design, drug design, protein-ligand binding, molecular dynamics

MATERIAL DESIGN



Experimental verification of theoretically described σ-hole

DRUG DESIGN



Challenging system for scoring: thiolate group of ligand binding to metalloenzyme

Research interests

The overarching theme of the group has been the computational description of non-covalent interactions in biomolecules. We use advanced quantum chemical (QM) methods to develop accurate and efficient semiempirical QM (SQM) methods capable of treating large protein-ligand complexes. Our SQM-based scoring function has been applied in ranking, sampling, and virtual screening for dozens of targets, such as cyclin-dependent kinases and HIV-1 protease or insulin receptor. Our SQM-based scoring function has been nonexclusively licensed to a leading US-based pharmaceutical company and is being further developed by a dedicated SWAT team with the aim of commercialization. It is currently being tested on an extended dataset of diverse protein-ligand complexes and has been shown to outperform widely used scoring functions from both academia and industry.

The halogen bond, the most famous example of σ-hole interactions, is a specific noncovalent interaction between the σ-hole of a halogen atom (region of positive charge) and an electronegative site. The existence of σ-holes was predicted theoretically thirty years ago. We are the first to prove the existence of the σ-hole with experimental evidence using Kelvin probe force microscopy. This achievement opens the door to new ways of characterizing biological and chemical systems in which anisotropic electron density distribution plays a decisive role.

Recently, we have also investigated the character of the dative bond in complexes between different electron acceptors (C60, graphene, and single-wall nanotubes) and electron donors (amines, piperidine). Further studies on various types of dative bonds (N→C, P→B) led to unexpected findings on the solvent effect. While all systems with covalent or noncovalent bonds become destabilized with increasing polarity of the solvent, systems with the dative bond exhibit the exact opposite behavior.

Group members

Group leader Pavel Hobza
Senior scientists Ota Bludský, Jindřich Fanfrlík, Martin Lepšík, Dana Nachtigallová, Adam Pecina, Miroslav Rubeš, Jan Řezáč
Postdoctoral fellows Dominik Farka, Cemal Köprülüoğlu, Rabindranath Lo, Vijay Madhav Miriyala, Amrit Sarmah, Yevgen Yurenko
Ph.D. students Maximilián Lamanec, Michal Trachta, Jaroslav Vacek
Students Mikuláš Klenor, Anna Mašínová
Secretary Helena Černá

Selected publications

Mallada, B.; Gallardo, A.; Lamanec, M.; de la Torre, B.; Špirko, V.; Hobza, P.; Jelinek, P. Real-space imaging of anisotropic charge of σ-hole by means of Kelvin probe force microscopy. *Science* **2021**, 374, 863–867.

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Lo, R.; Lamanec, M.; Wang, W.; Manna, D.; Bakandritsos, A.; Dračínský, M.; Zbořil, R.; Nachtigallová, D.; Hobza, P. Structure-directed formation of the dative/covalent bonds in complexes with C_{70}···piperidine. *Phys. Chem. Chem. Phys.* **2021**, 23, 4365–4375.

Vrána, J.; Holub, J.; Samsonov, M. A.; Růžičková, Z.; Cvačka, J.; McKee, M. L.; Fanfrlík, J.; Hnyk, D.; Růžička, A. Access to cationic polyhedral carboranes via dynamic cage surgery with N-heterocyclic carbenes. *Nat. Commun.* **2021**, 12, 4971.

Pecina, A.; Eyrilmez, S. M.; Köprülüoğlu, C.; Miriyala, V. M.; Lepšík, M.; Fanfrlík, J.; Řezáč, J.; Hobza, P. SQM/COSMO Scoring Function: Reliable Quantum-Mechanical Tool for Sampling and Ranking in Structure-Based Drug Design. *ChemPlusChem* **2020**, 85, 2361–2361.

Antalík, A.; Nachtigallová, D.; Lo, R.; Matoušek, M.; Lang, J.; Legeza, Ö.; Pittner, J.; Hobza, P.; Veis, L. Ground state of the Fe(ii)-porphyrin model system corresponds to quintet: a DFT and DMRG-based tailored CC study. *Phys. Chem. Chem. Phys.* **2020**, 22, 17033–17037.

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Funding

Boron-containing catalysts for alkanes oxidative dehydrogenation. Czech Science Foundation (GA ČR), No. 22-23120S. 2022–2024, co-PI: Bludský

Data-driven approach to the development of next-generation semiempirical QM methods. Czech Science Foundation (GA ČR), No. 22-17063S, 2022–2024, PI: J. Řezáč

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, PI: Hobza, P.

Exploring Zeolites with Nanoscale Architecture: Synergy Between Experiment and Theory. Czech Science Foundation (GA ČR), No. 20-12735S, 2020–2022, co-PI: Bludský, O.

Chemical biology for drugging undruggable targets. Ministry of Education, Youth and Sports (MŠMT ČR), No. CZ.02.1.01/0.0/0.0/16_019/0000729, 2018–2022.

Pavel Jungwirth Group

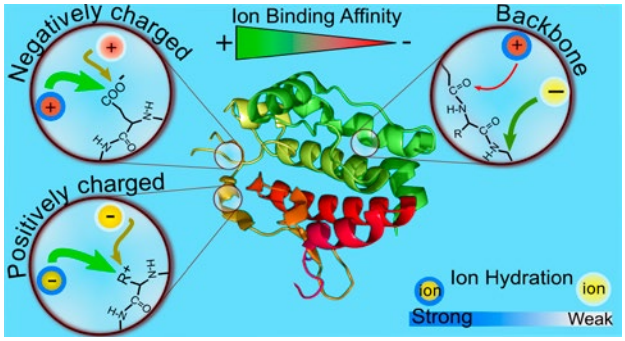
Molecular Modeling
pavel.jungwirth@uochb.cas.cz
www.uochb.cz/jungwirth

Distinguished Chair

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

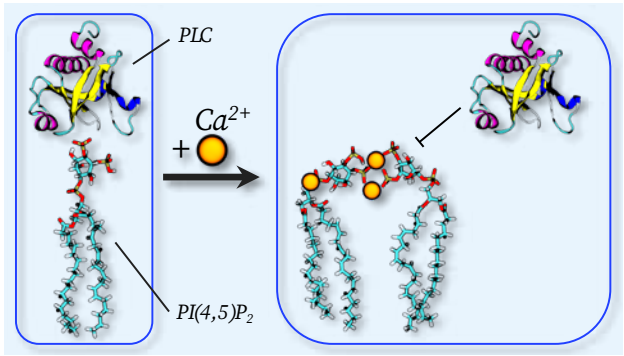
Ion Protein Interactions in Solution

J. Chem. Phys. **153** (2020), 050901; *J. Phys. Chem. B* **121** (2017), 1997–2014



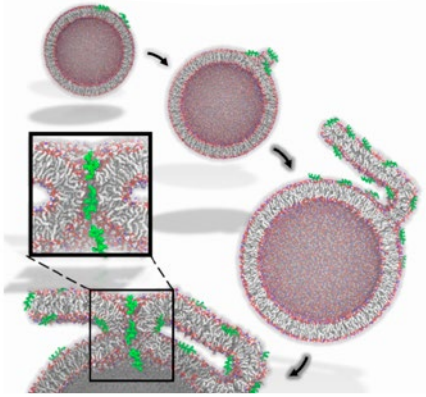
Calcium Signaling at Cell Membranes

Phys. Chem. Chem. Phys. **22** (2020), 24014–24027; *J. Am. Chem. Soc.* **139** (2017), 4019–402



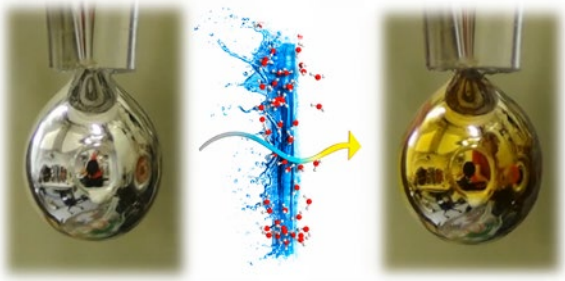
Cell Penetrating peptides and Membrane Fusion

Langmuir **36** (2020), 10438–10447; *PNAS* **115** (2018), 11923–11928



Structure, Dynamics, and Reactivity of Solvated Electrons

Nature **595** (2021), 673–676; *Science* **368** (2020), 1086–1091



Research interests

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
Senior scientists Lukasz Cwiklik, Phil Mason, Hector Martinez-Seara Monne
Postdoctoral fellows Denys Biriukov, Balázs Fábián, Christian Schewe
Research assistant Barbara Jagoda-Cwiklik
Ph.D. students Katarína Baxová, Nguyen Man, Tomáš Martinek, Tatiana Nemirovich, Vladimír Palivec, Miguel Riopedre, Ondřej Ticháček, Marco Vítek
Students Kryštof Březina, Martin Crhán, Vojtěch Košťál, Itay Schachter

Selected publications

Mason, P. E.; Schewe, H. C.; Buttersack, T.; Kostal, V.; Vitek, M.; McMullen, R. S.; Ali, H.; Trinter, F.; Lee, C.; Neumark, D. M.; Thürmer, S.; Seidel, R.; Winter, B.; Bradforth, S. E.; Jungwirth, P. Spectroscopic evidence for a gold-coloured metallic water solution. *Nature* **2021**, 595, 673–676.

Ben Abu, N.; Mason, P. E.; Klein, H.; Dubovski, N.; Ben Shoshan-Galeczki, Y.; Malach, E.; Pražienková, V.; Maletínská, L.; Tempra, C.; Chamorro, V. C.; Cvačka, J.; Behrens, M.; Niv, M. Y.; Jungwirth, P. Sweet taste of heavy water. *Commun. Biol.* **2021**, 4, 440.

Buttersack, T.; Mason, P. E.; McMullen, R. S.; Schewe, H. C.; Martinek, T.; Brezina, K.; Crhan, M.; Gomez, A.; Hein, D.; Wartner, G.; Seidel, R.; Ali, H.; Thürmer, S.; Marsalek, O.; Winter, B.; Bradforth, S. E.; Jungwirth, P. Photoelectron spectra of alkali metal–ammonia microjets: From blue electrolyte to bronze metal. *Science* **2020**, 368, 1086–1091.

Duboué-Dijon, E.; Javanainen, M.; Delcroix, P.; Jungwirth, P.; Martinez-Seara, H. A practical guide to biologically relevant molecular simulations with charge scaling for electronic polarization. *J. Chem. Phys.* **2020**, 153, 050901.

Kirby, B. J.; Jungwirth, P. Charge Scaling Manifesto: A Way of Reconciling the Inherently Macroscopic and Microscopic Natures of Molecular Simulations. *J. Phys. Chem. Lett.* **2019**, 10, 7531–7536.

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.

Funding

Concert of lipids, ions, and proteins in cell membrane dynamics and function. Czech Science Foundation (GA ČR), EXPRO, No. 19-26854X, 2018–2023, co-PI: Jungwirth, P.

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.

Awards—Pavel Jungwirth

Humboldt Research Award (2020)

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

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

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

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

Service to the scientific community

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

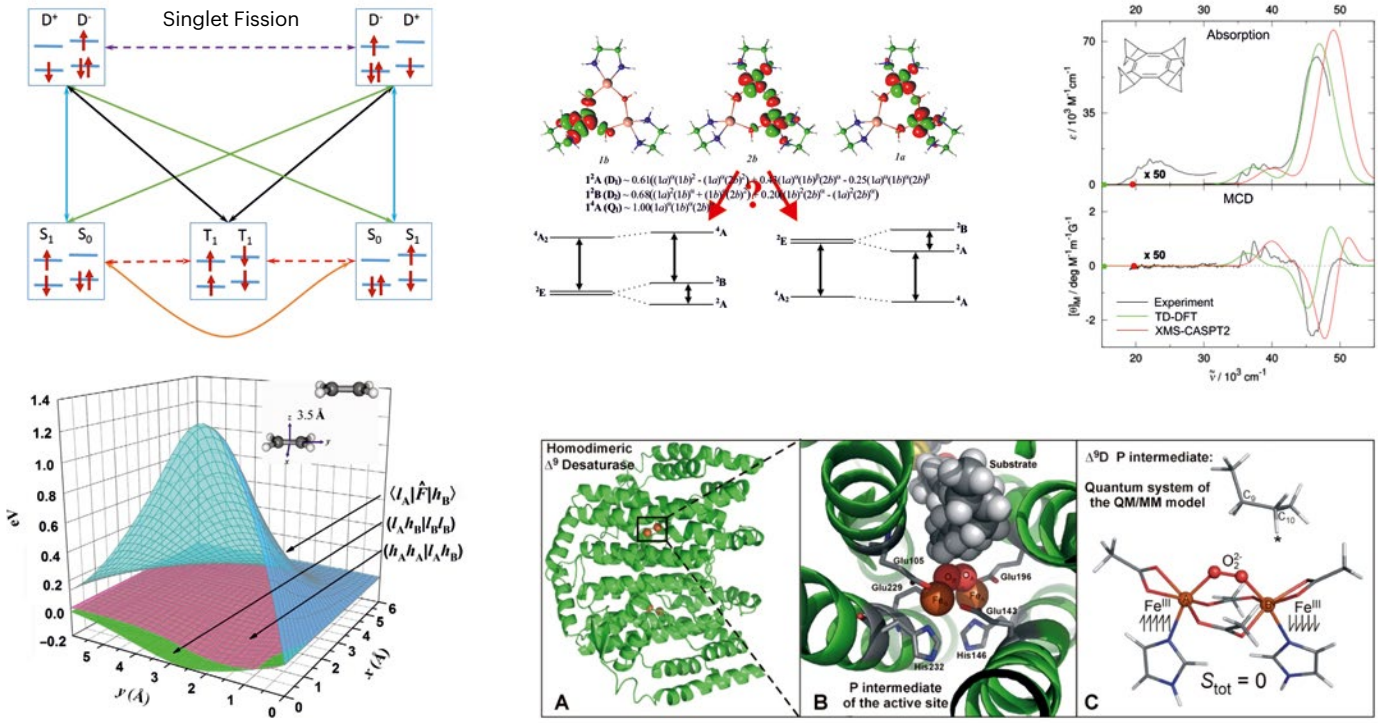
Popularization of science—regular articles in Czech newspapers and magazines on science and society. Numerous radio and TV shows on popular science.

Zdeněk Havlas Group

Computational Chemistry
zdenek.havlas@uochb.cas.cz
www.uochb.cz/havlas

Honorary Chair

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



Research interests

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
Senior scientists Jakub Chalupský, Mojmír Kývala
Postdoctoral fellows Gaurab Ganguly, Paul Ionut Dron
Students Kateřina Fatková, Alexandr Zaykov
Secretary Anna Kozáková

Selected publications

Chalupský, J.; Srnec, M.; Yanai, T. Interpretation of Exchange Interaction through Orbital Entanglement. *J. Phys. Chem. Lett.* **2021**, 12, 1268–1274.

Bím, D.; Chalupský, J.; Culka, M.; Solomon, E.I.; Rulíšek, L.; Srnec, M. Proton–Electron Transfer to the Active Site Is Essential for the Reaction Mechanism of Soluble Δ9-Desaturase. *J. Am. Chem. Soc.* **2020**, 142, 10412–10423.

Zaykov, A.; Felkel, P.; Buchanan, E.A.; Jovanovic, M.; Havenith, R.W.A.; Kathir, R.K.; Broer, R.; Havlas, Z.; Michl, J. Singlet Fission Rate: Optimized Packing of a Molecular Pair. Ethylene as a Model. *J. Am. Chem. Soc.* **2019**, 141, 17729–17743.

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.

Schrauben, J.N.; Akdag, A.; Wen, J.; Havlas, Z.; Ryerson, J. L.; Smith, M.B.; Michl, J.; Johnson, J. C. Excitation Localization/Delocalization Isomerism in a Strongly Coupled Covalent Dimer of 1,3-Diphenylisobenzofuran. *J. Phys. Chem. A* **2016**, 120, 3473–3483.

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.

Funding

Spectroscopic properties of molecules with complex electronic structure. Czech Science Foundation (GA ČR), No. 20-06451Y, 2020–2022, PI: Chalupský, J.

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

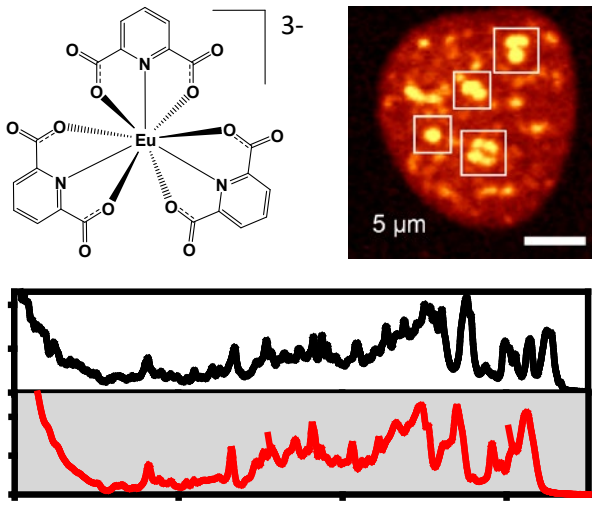
Award of the Learned Society of the Czech Republic, 2001

Petr Bouř Group

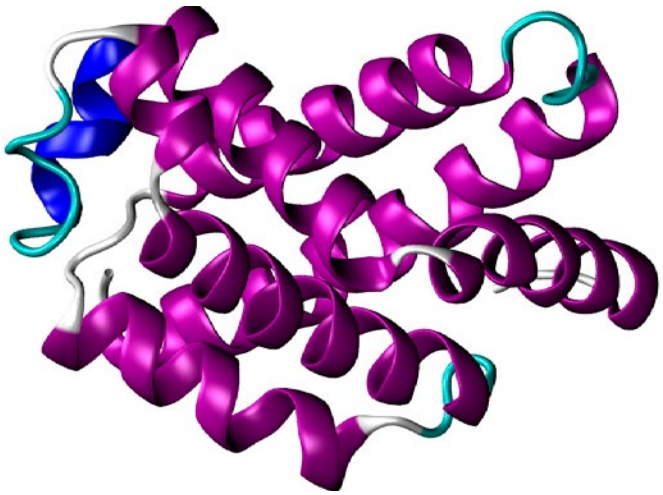
Biomolecular Spectroscopy
petr.bour@uochb.cas.cz
www.uochb.cz/bour

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

Spectroscopy / Imaging



Applications



Theory

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

Research interests

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
Senior scientists Valery Andrushchenko, Jakub Kaminský, Jiří Kessler, Radek Pelc, Vladimír Sychrovský, Jaroslav Šebestík
Postdoctoral fellows Debraj Gangopadhyay, Jakub Šebera, Tao Wu
Ph.D. students Moumita Das, Jiří Fukal, Mohamed Hamissa, Andrii Kurochka, Petr Niederhafner, Jiří Průša, Olga Rybakova, Věra Schrenková, Mohammed Siddhique, Adam Sklenář, Jiří Zdráhala
Technician Martin Šafařík
Students Petra Gwozdiaková, Františka Horáčková

Selected publications

Li, G.; Alshalalfeh, M.; Yang, Y.; Cheeseman, J. R.; Bouř, P.; Xu, Y. Can One Measure Resonance Raman Optical Activity? *Angew. Chem. Int. Ed.* **2021**, 60, 22004–22009.

Kurochka, A.; Průša, J.; Kessler, J.; Kapitán, J.; Bouř, P. α-Synuclein conformations followed by vibrational optical activity. Simulation and understanding of the spectra. *Phys. Chem. Chem. Phys.* **2021**, 23, 16635–16645.

Wu, T.; Li, G.; Kapitán, J.; Kessler, J.; Xu, Y.; Bouř, P. Two Spectroscopies in One: Interference of Circular Dichroism and Raman Optical Activity. *Angew. Chem. Int. Ed.* **2020**, 59, 21895–21898.

Tomeček, J.; Bouř, P. Density Functional Computations of Vibrational Circular Dichroism Spectra beyond the Born–Oppenheimer Approximation. *J. Chem. Theory Comput.* **2020**, 16, 2627–2634.

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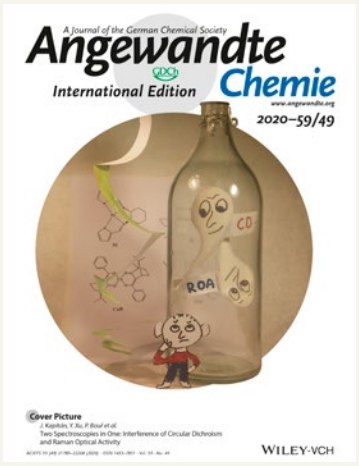
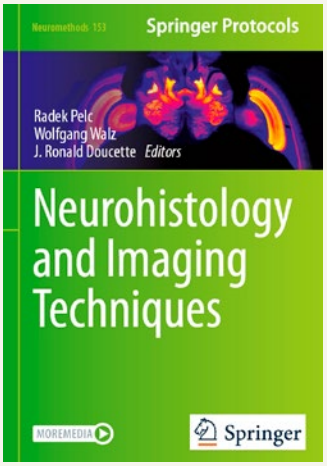




Funding

Sensitivity Enhancement of Vibrational Optical Activity Spectroscopy for Biomolecules. Czech Science Foundation (GA ČR), No. 22-04669S, 2022–2024, PI: Bouř, P.

Instrumentation and theory for measurement of terahertz optical activity of biomolecules. Czech Science Foundation (GA ČR), No. 22-33060S, 2022–2024, PI: Postava, K.

Development of Chiral Spectroscopic Methods for Intermolecular Interaction Studies. Czech Science Foundation (GA ČR), 2020–2022, No. 20-10144S.

Poly-β-malic acid and its role as a possible primitive predecessor of nucleic acids. Ministry of Education, Youth and Sports (MŠMT ČR), No. LTAUSA18085, 2019–2022, PI: Kaminský, J.

Development of Lanthanide Raman Probes for Biomedical Analyses and Imaging. Czech Science Foundation (GA ČR), No. 19-05974Y, 2019–2021, PI: Wu, T.

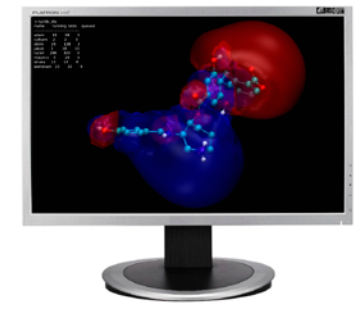
Exploring Resonance and Anharmonic Phenomena in Biomolecular Spectroscopy. Czech Science Foundation (GA ČR), No. 18-05770S, 2018–2020, PI: Bouř, P.

An integrative action for multidisciplinary studies on cellular structural networks (EuroCellNet). EU COST Action CA 15214, Ministry of Education, Youth and Sports (MŠMT ČR), No. LTC17012, 2017–2020, PI: Bouř, P.

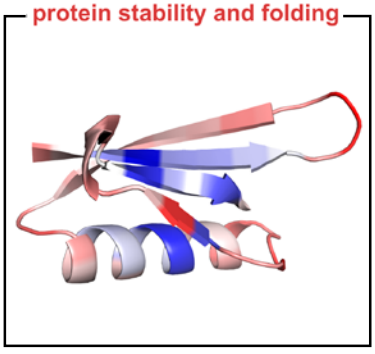
Lubomír Rulíšek Group

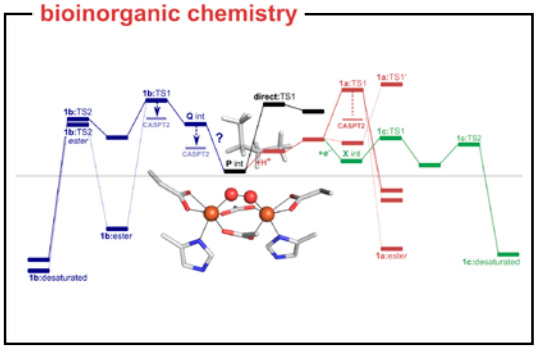
Theoretical Bioinorganic Chemistry
lubomir.rulisek@uochb.cas.cz
www.uochb.cz/rulisek

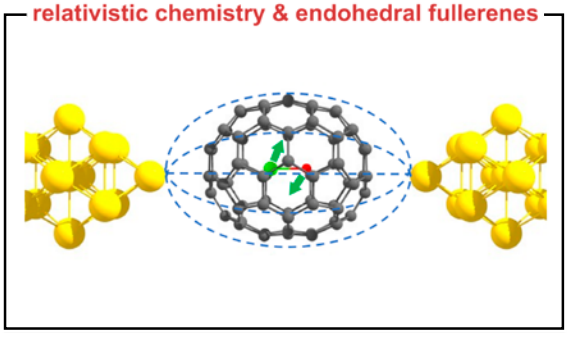
Senior Research Group
metalloenzymes, catalysis, molecular design, structure-function correlations, molecular switches, principles of protein folding, ligand binding, relativistic effects in chemistry, theoretical spectroscopy

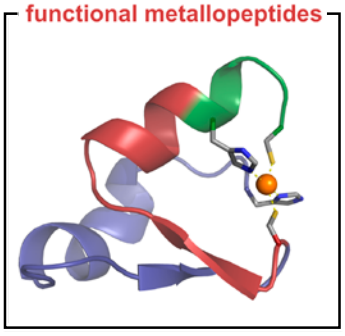


> COMPUTATIONAL CHEMISTRY_









Research interests

Computational (bio)chemistry has become an integral part of our understanding of chemical and biological systems and processes. 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, artificial-intelligence driven approaches, 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, highly specific metal chelators, and various folded protein structures *de novo*. This is closely related to understanding the underlying principles of protein structure *ab initio*. To this aim, the group focuses on the complete mapping of conformational space of protein building blocks, employing quantum chemical and solvation methods.

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 a chemical theory 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
Senior scientist Michal Straka
Postdoctoral fellow Erik Andris
Ph.D. students Hana Bušková, Adam Jaroš, Tadeáš Kalvoda, Michael Kormaník, Agnieszka Stanczak
Undergraduate student Lucie Tučková

Selected publications

Kipouros, I.; Stańczak, A.; Culka, M.; Andris, E.; Machonkin, T. R.; Rulíšek, L.; Solomon. E. I. Evidence for H-bonding interactions to the μ-η^2:η^2-peroxide of oxy-tyrosinase that activate its coupled binuclear copper site. *Chem. Commun.* **2022**, 58, 3913–3916.

Smola, M.; Gutten, O.; Dejmek, M.; Kožíšek, M.; Evangelidis, T.; Aliakbar Tehrani, Z.; Novotná, B.; Nencka, R.; Birkuš, G.; Rulíšek, L.; Boura, E. Ligand Strain and Its Conformational Complexity Is a Major Factor in the Binding of Cyclic Dinucleotides to STING Protein. *Angew. Chem. Int. Ed.* **2021**, 60, 10172–10178.

Culka, M.; Kalvoda, T.; Gutten, O.; Rulíšek, L. Mapping Conformational Space of All 8000 Tripeptides by Quantum Chemical Methods: What Strain is Affordable within Folded Protein Chains? *J. Phys. Chem. B* **2021**, 125, 58–69.

Bím, D.; Chalupský, J.; Culka, M.; Solomon, E. I.; Rulíšek, L.; Srnec, M. Proton-Electron Transfer to the Active Site Is Essential for the Reaction Mechanism of Soluble Δ^9-Desaturase. *J. Am. Chem. Soc.* **2020**, 142, 10412–10423.

Vícha, J.; Novotný, J.; Komorovsky, S.; Straka, M.; Kaupp, M.; Marek, R. Relativistic Heavy-Neighbor-Atom Effects on NMR Shifts: Concepts and Trends Across the Periodic Table. *Chem. Rev.* **2020**, 120, 7065–7103.

Andris, E.; Segers, K.; Mehara, J.; Rulíšek, L. Roithová, J. Closed Shell Iron(IV) Oxo Complex with an Fe–O Triple Bond: Computational Design, Synthesis, and Reactivity. *Angew. Chem. Int. Ed.* **2020**, 59, 23137–23144.

Jaroš, A.; Bonab, E.F.; Straka M.; Foroutan-Nejad, C. Fullerene-Based Switching Molecular Diodes Controlled by Oriented External Electric Fields. *J. Am. Chem. Soc.* **2019**, 141, 19644–19654.

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.

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

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.

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.

Funding

Endohedral Fullerenes for Molecular Components: Memristors and Spinristors. Czech Science Foundation (GA ČR), No. 21-17806S, 2021–2023, PI: Straka, M.

Interconnected azamacrocyclic complexes – new kind of molecular electronics. Czech Science Foundation (GA ČR), No. 21-23261S, 2021–2023, co-PI: Straka, M.

Fundamental Principles of Protein Folding and Protein-Ligand Interactions Revealed by High-Level Quantum Chemical Calculations. Czech Science Foundation (GA ČR), No. 20-08772S, 2020–2022, PI: Rulíšek, L.

Mono- and binuclear Fe, Cu active sites in biological systems: interplay between theory and experiment. Ministry of Education, Youth and Sports (MŠMT ČR), Program Inter-Excellence, No. LTAUSA19, 2020–2022, PI: Rulíšek, L.

Gilead Sciences & IOCB Research Center, 2016–2021, PI: Rulíšek, L.

Collaboration

IOCB Prague: Petr Beier, Michal Hocek, Ullrich Jahn, Jan Konvalinka, Josef Michl, Jan Řezáč, Miloslav Polášek, Evžen Bouřa, Gabriel Birkuš, Jiří Vondrášek, Pavel Kočovský

Domestic: Cyril Bařinka (*Inst. Biotechnology, CAS, BIOCEV, Vestec*), Martin Srnec (*J. H. Inst. Physical Chemistry, CAS, Prague*), Radek Marek (*Masaryk Univ., CEITEC, Brno*), Milan Pour (*Faculty of Pharmacy, Charles University, Hradec Králové*), 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*), František Tureček (*Univ. Washington, Seattle, USA*), Michal S. Shoshan (*Univ. Zürich, Switzerland*), Juha Vaara (*Univ. Oulu, Finland*), Martin Kaupp (*TU Berlin, Germany*), Gernot Frenking (*Philipps-Universität Marburg, Germany*)

Awards—Lubomír Rulíšek

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

Fulbright Fellowship (2014)—Stanford University

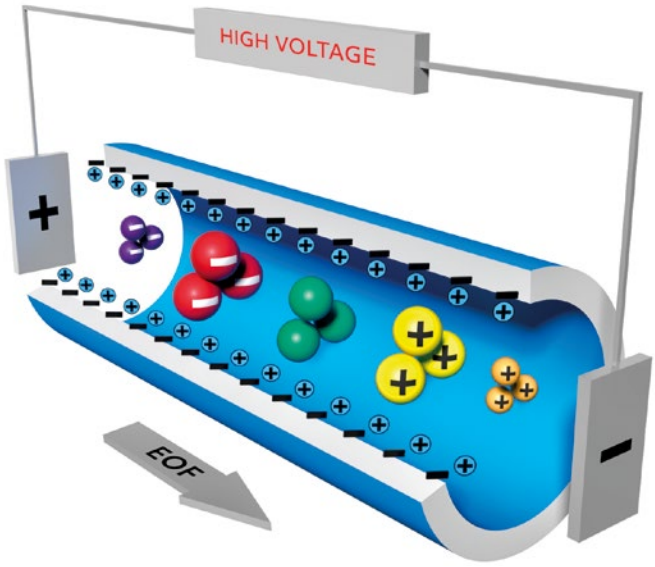
Werner von Siemens Prize (2020)—with Martin Srnec

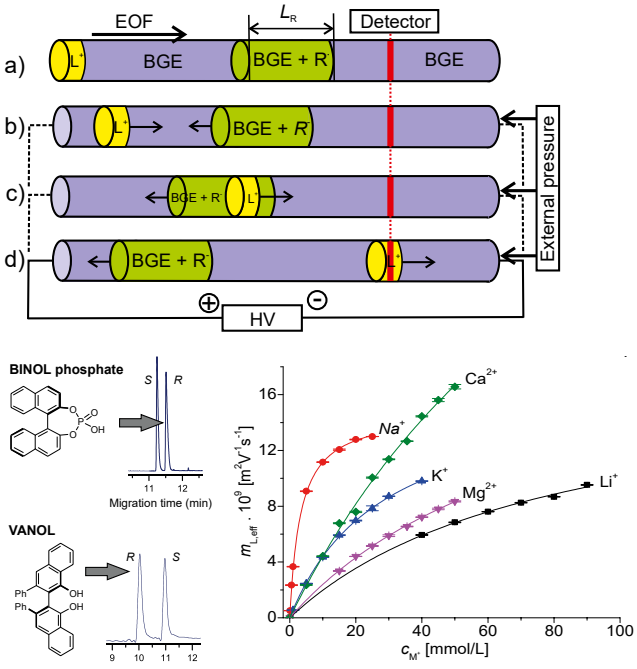
Electromigration Methods

Václav Kašička
vaclav.kasicka@uochb.cas.cz
www.uochb.cz/electromigration

Research-Service Group

electroseparation methods, capillary electrophoresis, affinity electrophoresis, isotachophoresis, isoelectric focusing, electrokinetic chromatography, electrochromatography, separation sciences





Research interests

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
Senior scientists Jana Jaklová Dytrtová, Dušan Koval, Petra Sázelová, Veronika Šolínová, Sille Štěpánová
Postdoctoral fellow Renáta Konášová
Ph.D. students Maria Butnariu, Ishak Kovač

Selected publications

Konášová, R.; Butnariu, M.; Šolínová, V.; Kašička, V.; Koval, D. Covalent cationic copolymer coatings allowing tunable electroosmotic flow for optimization of capillary electrophoretic separations. *Anal. Chim. Acta* **2021**, 1178, 338789.

Šolínová, V.; Brynda, J.; Šícha, V.; Holub, J.; Grűner, B.; Kašička, V. Determination of acidity constants, ionic mobilities, and hydrodynamic radii of carborane-based inhibitors of carbonic anhydrases by capillary electrophoresis. *Electrophoresis* **2021**, 42, 910-919.

Šolínová, V.; Sázelová, P.; Mášová, A.; Jiráček, J.; Kašička, V. Application of capillary and free-flow zone electrophoresis for analysis and purification of antimicrobial β-alanyl-L-tyrosine from hemolymph of fleshfly *Neobellieria bullata*. *Molecules* **2021**, 26, 5636.

Konášová, R.; Koval, D.; Hošek, J.; Kašička, V. Investigating the position of the separation capillary and emitter tube tips in a nanoflow sheath-liquid CE-ESI-MS interface to decouple the ESI potential. *Talanta* **2021**, 228, 122212.

Vitorino, R.; Guedes, S.; Pinto da Costa, J.; Kašička, V. Microfluidics for peptidomics, proteomics, and cell analysis. *Nanomaterials* **2021**, 11, 1118.

Tůma, P.; Hložek, T.; Sommerová, B.; Koval, D. Large volume sample stacking of antiepileptic drugs in counter current electrophoresis performed in PAMAPTAC coated capillary. *Talanta* **2021**, 221, 121626.

Kovač, I.; Jakl, M.; Šolínová, V.; Konášová, R.; Kašička, V.; Jaklová Dytrtová, J. Micellar electrokinetic chromatography in the determination of triazoles in fruit peel. *J. Chromatogr. A* **2021**, 1652, 462385.

Kašička, V. Recent developments in capillary and microchip electroseparations of peptides (2017–mid 2019). *Electrophoresis* **2020**, 41, 10-35.

Sázelová, P.; Koval, D.; Severa, L.; Teplý, F.; Vigh, G.; Kašička, V. Determination of binding constants of multiply charged cyclodextrin complexes by ACE using uncorrected and ionic strength corrected actual mobilities of the species involved. *Electrophoresis* **2020**, 41, 523-535.

Michalusová, I.; Sázelová, P.; Cejnar, P.; Kučková, Š.; Hynek, R.; Kašička, V. Capillary electrophoretic profiling of in-bone tryptic digests of proteins as a potential tool for the detection of inflammatory states in oral surgery. *J. Sep. Sci.* **2020**, 43, 3949-3959.

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.; Kašička, V. Recent developments and applications of capillary and microchip electrophoresis in proteomics and peptidomics (2015-mid 2018). *J. Sep. Sci.* **2019**, 42, 398-414.

Funding

Affinity capillary electrokinetic methods for selective analysis of biopolymers and metabolites and for study of their interactions. Czech Science Foundation (GA ČR), No. 20-03899S, 2020–2022, PI: Kašička, V.

European network for promotion of portable, affordable and simple analytical platforms (PortASAP). COST Association (European Cooperation in Science and Technology), Horizon 2020, COST Action, CA 16215, 2017–2022, co-PI: Kašička, V.

New multibinding (pseudo)stationary phases for chromatographic and electromigration separations of (bio)molecules. Czech Science Foundation (GA ČR), No. 18-02597S, 2018–2021, co-PI: Kašička, V.

Group interactions of azol pesticides and their effects on essential enzymes. Czech Science Foundation (GA ČR), No. 18-01710S, 2018–2021, PI: Jaklová Dytrtová, J.

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, PI: Kašička, V.

Tools for separation optimization in capillary electrophoresis. Czech Science Foundation (GA ČR), No. 17-12648S, 2017–2019, PI: Koval, D.

Novel stationary phases for chromatographic separation of chiral compounds. Ministry of Industry and Trade (MPO), Program Trio, 2016–2019, co-PI: Koval, D.

Awards

Václav Kašička
Prof. Andrzej Waksmundzki Medal Award (2021) – a prize awarded by the Polish Academy of Sciences for the important achievements in the field of separation methods

Renáta Konášová, Jana Jaklová Dytrtová, Václav Kašička
Karel Preis Award (2013) – a prize awarded by the Czech Chemical Society for the best paper in the journal Chemické listy

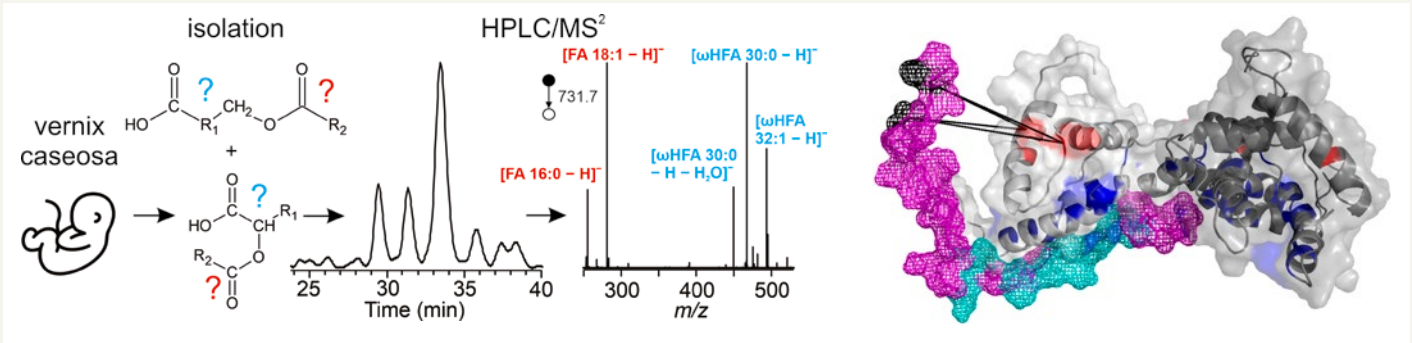
Dušan Koval
Wichterle Prize of the CAS (2011) – a prize awarded by the Czech Academy of Sciences for outstanding young researchers

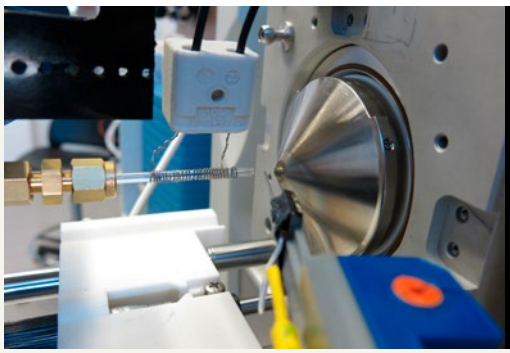
Mass Spectrometry

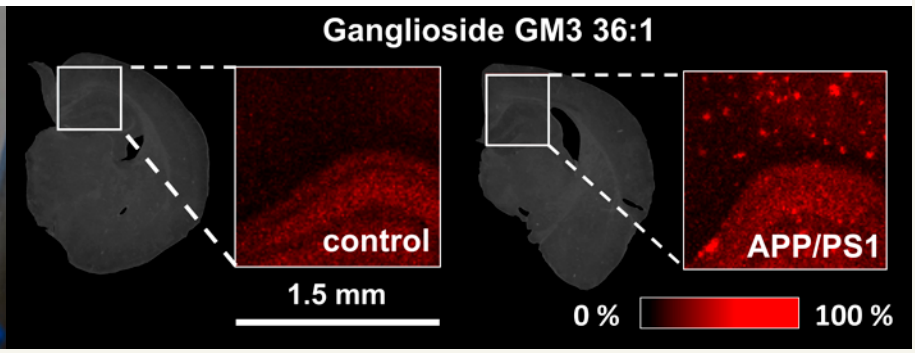
Josef Cvačka
josef.cvacka@uochb.cas.cz
www.uochb.cz/ms

Research-Service Group

mass spectrometry, organic compounds, structure elucidation, development of methods and instrumentation







Research interests

Our group uses mass spectrometry to answer diverse scientific questions. Mass spectrometry (MS) is applied in structure elucidation, identification, and quantification of organic compounds ranging from small to large biomacromolecules. Because the current approaches are sometimes unsuitable for particular tasks, new methods, applications, and devices are being developed. As regards instrumentation, we pursue the development of new types of ion sources for sensitive detection of various analytes. In addition to our own research program, group members perform routine analyses for the IOCB scientific community, maintain open-access instruments, and provide collaborative support.

The group's projects often focus on lipids. Lipids are characterized using chromatography and MS with the aim of understanding their biological 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, establishment of double bond position(s). Our long-term involvement in vernix caseosa research has led to the discovery of several new lipid classes. Additionally, we use MS imaging to visualize the spatial distribution of various lipids on the surfaces of insect and plant samples, or in tissue sections.

We are also involved in numerous projects requiring identification, characterization, and quantification of proteins. In addition to routinely used classical workflows, methods relevant for structural biology, including native MS, protein covalent labelling, protein crosslinking, and hydrogen exchange MS, are being implemented. These complementary methods allow us to study protein structures and characterize not only protein-protein interactions but also interactions of proteins and other biological molecules.

We also perform qualitative and quantitative analysis of nucleic acids, various metabolites, and synthetic compounds.

Group members

Group leader Josef Cvačka
Senior scientists Martin Hubálek, Vladimír Vrkoslav
Postdoctoral fellow Petra Junková
Research assistants Karel Čížek, Marta Kadeřábková, Květoslava Kertisová, Edita Kofroňová, Alena Křenková, Kateřina Nováková, Štěpán Strnad, Martin Svoboda
Ph.D. students Swati Banerjee, Jana Březinová, Lukáš Cudlman, Adéla Pravdová, Barbora Rumlová, Simona Sedláčková, Jakub Sýs, Mikuláš Vlk
Technician Michal Korecký
Student Lucie Lebertová

Selected publications

Horká, P.; Vrkoslav, V.; Kindl, J.; Schwarzová-Pecková, K.; Cvačka J. Structural Characterization of Unusual Fatty Acid Methyl Esters with Double and Triple Bonds Using HPLC/APCI-MS2 with Acetonitrile In-Source Derivatization. *Molecules* **2021**, 26, 6468.

Prchal, J.; Sýs, J.; Junková, P.; Lipov, J.; Ruml, T. Interaction interface of Mason-Pfizer monkey virus matrix and envelope proteins. *J. Virol.* **2020**, 94, e01146-20.

Junková, P.; Pleskot, R.; Prchal, J.; Sýs, J.; Ruml T. Differences and commonalities in plasma membrane recruitment of the two morphogenetically distinct retroviruses HIV-1 and MMTV. *J. Biol. Chem.* **2020**, 295, 8819–8833.

Strnad, Š.; Pražienková, V.; Holubová, M.; Sýkora, D.; Cvačka, J.; Maletínská, L.; Železná, B.; Kuneš, J.; Vrkoslav, V. Mass spectrometry imaging of free-floating brain sections detects pathological lipid distribution in a mouse model of Alzheimer's-like pathology. *Analyst* **2020**, 145, 4595–4605.

Vrkoslav, V.; Rumlová, B.; Strmeň, T.; Cvačka, J. Temperature-programmed capillary high-performance liquid chromatography with atmospheric pressure chemical ionization mass spectrometry for analysis of fatty acid methyl esters. *J. Sep. Sci.* **2020**, 43, 2579–2588.

Strmeň, T.; Vrkoslav, V.; Bosáková, Z.; Cvačka, J. Atmospheric pressure chemical ionization mass spectrometry at low flow rates: Importance of ion source housing. Rapid Commun. *Mass Spectrom.* **2020**, 34, e8722.

Vavrušová, A.; Vrkoslav, V.; Plavka, R.; Bosáková, Z.; Cvačka, J. Analysis of (*O-acyl*) alpha- and omega-hydroxy fatty acids in vernix caseosa by high-performance liquid chromatography-Orbitrap mass spectrometry. *Anal. Bioanal. Chem.* **2020**, 412, 2291–2302.

Hudeček, O.; Benoni, R.; Reyes-Gutierrez, P.E.; Culka, M.; Šanderová, H.; Hubálek, M.; Rulíšek, L.; Cvačka, J.; Krásný, L.; Cahová, H. Dinucleoside polyphosphates act as 5'-RNA caps in bacteria. *Nat. Commun.* **2020**, 11, 1052.

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.

Equipment

SELECT SERIES Cyclic IMS ion mobility MS with ESI, nano-ESI, APCI and UniSpray sources (Waters)

7250 GC/Q-TOF system with EI/CI sources (Agilent), equipped with a direct inlet probe (SIM)

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)

SYNAPT G2 quadrupole-ion mobility-TOF hybrid MS with ESI, nano-ESI, APCI and MALDI 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)

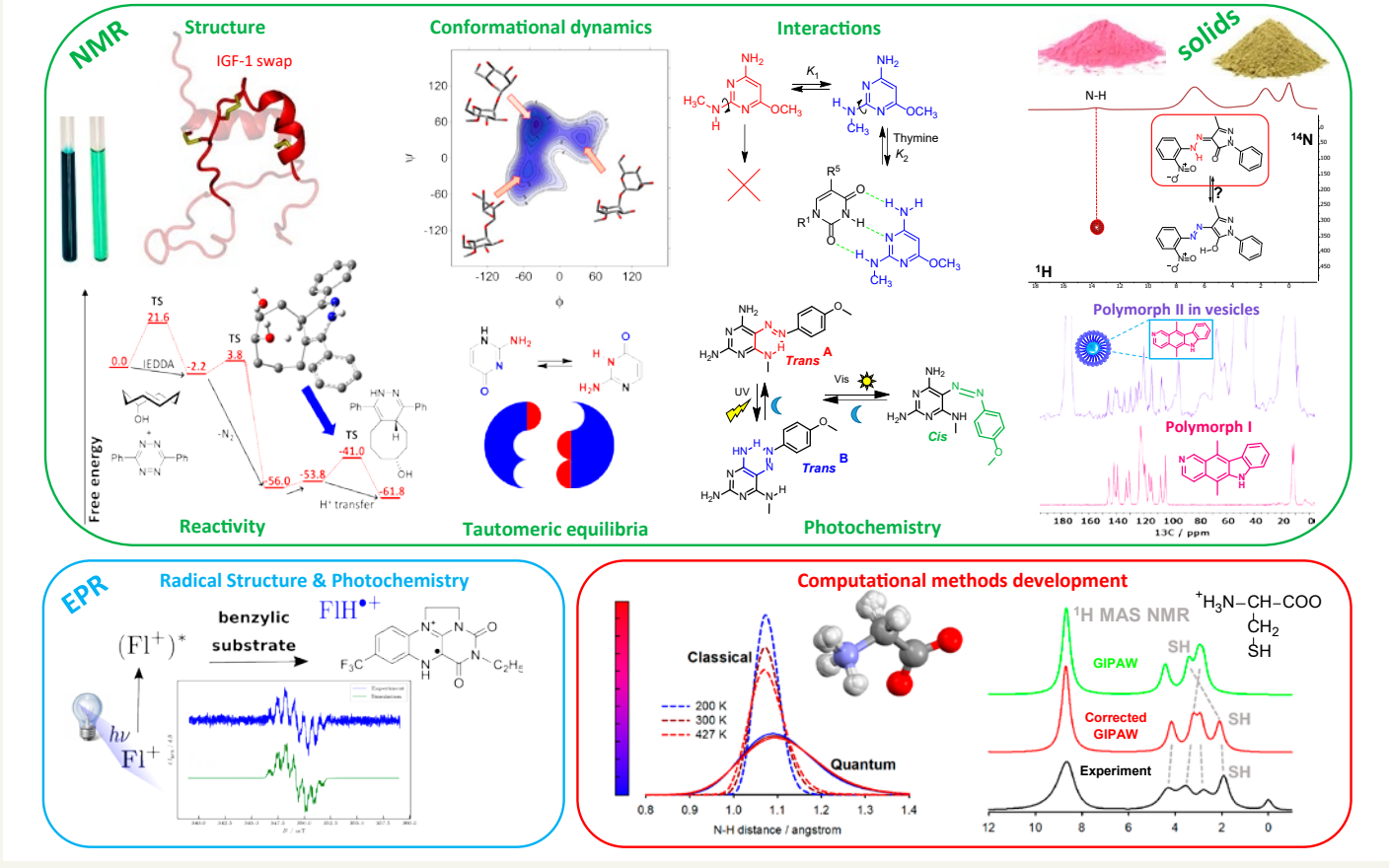
LCQ Fleet quadrupole ion trap MS with ESI, nano-ESI and APCI sources (Thermo Fisher Scientific)

NMR Spectroscopy

Martin Dračínský
martin.dracinsky@uochb.cas.cz
www.uochb.cz/nmr

Research-Service Group

NMR and EPR spectroscopy, structural analysis, theoretical calculations



Research interests

Our research deals with many aspects of experimental NMR/EPR spectroscopy in solutions and solids, molecular modelling, and theoretical calculations of spectroscopic parameters and molecular properties. We apply both experimental and theoretical methods in studies of the structure and properties of biologically active compounds, of intra- and inter-molecular interactions, and of reaction mechanisms. We also provide NMR and EPR services to IOCB researchers. We utilize modern one- and two-dimensional NMR techniques for structure elucidation of compounds synthesized in IOCB laboratories or isolated from natural sources. We work to determine the configuration of chiral molecules and conduct studies on conformational dynamics in flexible molecules as well as on noncovalent interactions, particularly hydrogen bonding (both intra- and inter-molecular). We have implemented a methodology for continuous UV or visible light irradiation during NMR and EPR experiments, which makes it possible to investigate photochemical processes in real time. We also develop new methods of NMR crystallography that combine experimental solid-state NMR data with theoretical calculations for gaining new insights into the structure and dynamics of solids. We apply EPR spectroscopy together with quantum chemical calculations to solve structures of paramagnetic molecules in organic and nanomaterial chemistry.

Group members

Group leader Martin Dračínský
Senior scientists Miloš Buděšínský, Radek Pohl, Lenka Poštová Slavětínská, Eliška Procházková, Serhii Suikov, David Šaman, Ján Tarábek
Postdoctoral fellow Jan Blahut
Ph.D. students Nina Habanová, Anna Hruzíková, Ema Chaloupecká, Zuzana Osifová, Ondřej Socha, Jakub Radek Štoček, Markéta Tichotová
Technician Marie Snopková

Selected publications

Procházková, E.; Filo, J.; Mužíková Čechová, L.; Dračínský, M.; Císařová, I.; Janeba, Z.; Kawamura, I.; Naito, A.; Kuběna, I.; Nádaždy, P.; Šiffalovič, P.; Cigáň, M. Photoswitching of 5-Phenylazopyrimidines in Crystalline Powders and Thin Films. *Dyes Pigm.* **2022**, 199, 110066.

Dračínský, M.; Hurtado, C. S.; Masson, E.; Kaleta, J. Stuffed pumpkins: mechanochemical synthesis of host–guest complexes with cucurbit[7]uril. *Chem. Commun.* **2021**, 57, 2132–2135.

Procházková, E.; Kucherak, O.; Stodůlková, E.; Tošner, Z.; Císařová, I.; Flieger, M.; Kolařík, M.; Baszczyňski, O. NMR Structure Elucidation of Naphthoquinones from Quambalaria cyanescens. *J. Nat. Prod.* **2021**, 84, 1, 46–55.

Procházková, E.; Šimon, P.; Straka, M.; Filo, J.; Májek, M.; Cigáň M.; Baszczyňski, O. Phosphate Linkers with Traceable Cyclic Intermediates for Self-Immolation Detection and Monitoring. *Chem. Commun.* **2021**, 57, 211–214.

Čechová, L.; Filo, J.; Dračínský, M.; Slavov, C.; Sun, D.; Janeba, Z.; Slanina, T.; Wachtveitl, J.; Procházková, E.; Cigáň, M. Polysubstituted 5-Phenylazopyrimidines Extremely Fast Non-Ionic Photochromic Oscillators. *Angew. Chem. Int. Ed.* **2020**, 59, 15590–15594.

Vícha, J.; Švec, P.; Růžičková, Z.; Samsonov, M.; Bártová, K.; Růžička, A.; Straka, M.; Dračínský, M. Experimental and Theoretical Evidence of Spin-Orbit Heavy Atom on the Light Atom ^{1}H NMR Chemical Shifts Induced through H···I^{-} Hydrogen Bond. *Chem. Eur. J.* **2020**, 26, 8698–8702.

Barton, J.; Gulka, M.; Tarabek, J.; Mindarava, Y.; Wang, Z.; Schimer, J.; Raabova, H.; Bednar, J.; Plenio, M. B.; Jelezko, F.; Nesladek, M.; Cigler, P. Nanoscale Dynamic Readout of a Chemical Redox Process Using Radicals Coupled with Nitrogen-Vacancy Centers in Nanodiamonds. *ACS Nano* **2020**, 14, 12938–12950.

Štoček, J. R.; Bártová, K.; Čechová, L.; Šála, M.; Socha, O.; Janeba, Z.; Dračínský, M. Determination of nucleobase-pairing free energies from rotamer equilibria of 2-(methylamino)pyrimidines. *Chem. Commun.* **2019**, 55, 11075–11078.

Dračínský, M.; Unzueta, P.; Beran, G.J.O. Improving the accuracy of solid-state nuclear magnetic resonance chemical shift prediction with a simple molecular correction. *Phys. Chem. Chem. Phys.* **2019**, 21, 14992–15000.

Zelenka, J.; Svobodová, E.; Tarábek, J.; Hoskovcová, I.; Boguschová, V.; Bailly, S.; Sikorski, M.; Roithová, J.; Cibulka, R. Combining Flavin Photocatalysis and Organocatalysis: Metal-Free Aerobic Oxidation of Unactivated Benzylic Substrates. *Org. Lett.* **2019**, 21, 114–119.

Funding

Proton transfer reactions studied by NMR spectroscopy and advanced quantum-chemical calculations. Czech Science Foundation (GA ČR), No. 22-15374S, 2022–2024, PI: Dračínský, M.

^{15}N isotopic labeling in NMR structural analysis of N-disaccharides. Czech Science Foundation (GA ČR), No. 22-17586S, 2022–2024, PI: Pohl, R.

NMR Toolbox for probing stereochemistry in phosphorus-containing bioactive molecules. Czech Science Foundation (GA ČR), No. 21-23014S, 2021–2023, PI: Procházková, E.

NMR crystallography of disordered systems. Czech Science Foundation (GA ČR), No. 20-01472S, 2020–2022, PI: Dračínský, M.

Instrumentation

NMR spectroscopy
- 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 variable temperature NMR experiments
- Bruker Avance III HD 400 MHz with PRODIGY cryoprobe
- Bruker Avance III HD 400 MHz
- JEOL ECZ600R/M1 600 MHz—for solid-state NMR experiments
- JEOL ECZ500R/S3 500 MHz

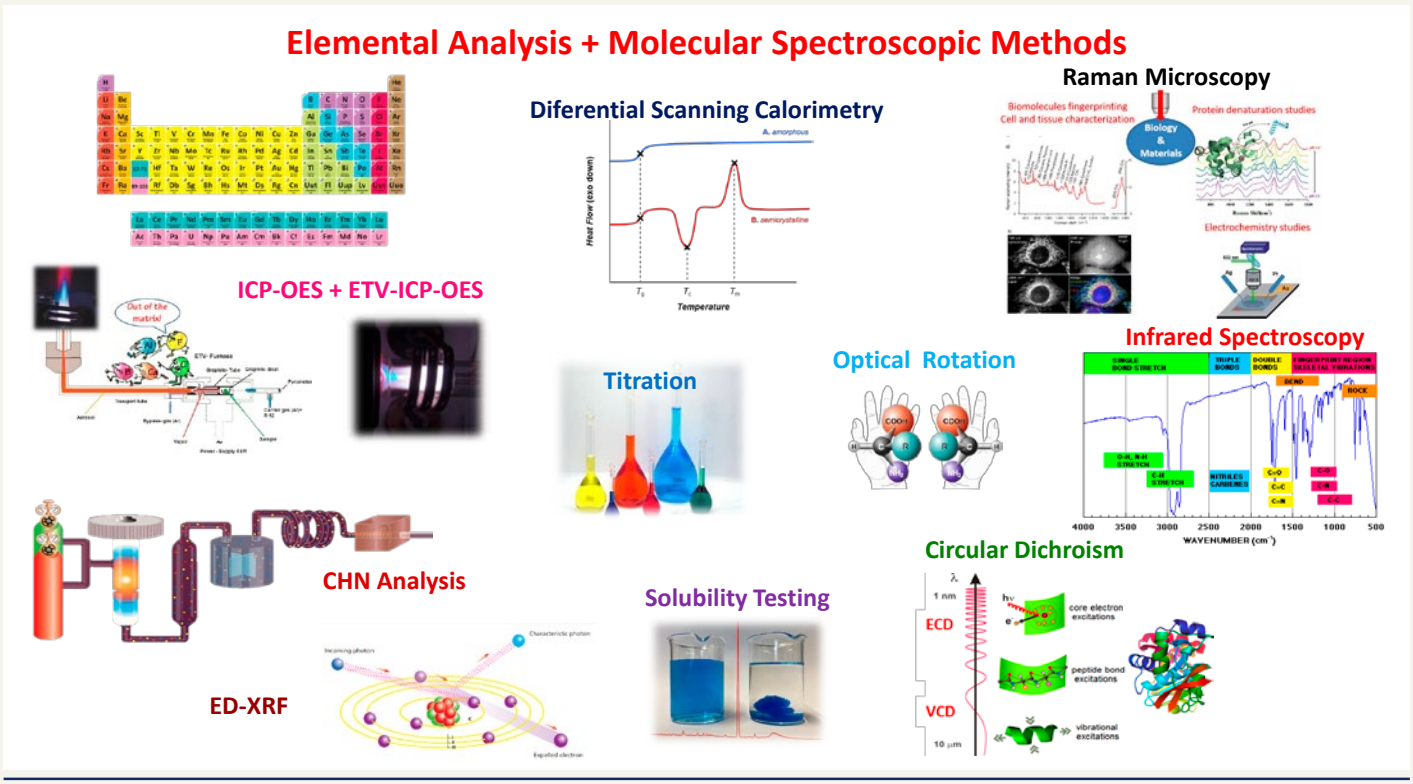
EPR spectroscopy
- Bruker EMX Plus

Analytical Laboratory

Stanislava Matějková
stanislava.matejkova@uochb.cas.cz
www.uochb.cz/analysis

Service Group

elemental analysis, optical emission spectrometry, ED-XRF, (ETV)-ICP-OES, vibrational spectroscopy (IR, Raman), chiroptical spectroscopy (ECD, VCD, ROA), optical rotation, DSC, solubility screening



Research interests

We provide complete elemental analysis of various sample types using a minimal amount of material for basic sample characterization. This information, together with a 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. We routinely perform C, H, and N determination as well as identification or quantitative determination of almost all elements of the periodic table by means of X-ray fluorescence spectroscopy and inductively coupled plasma optical emission spectrometry, optionally in combination with electrothermal evaporation of the sample. The F content is determined using an ion-selective electrode. The classic titration methods for determination of S, P, Cl, Br, and I can also be applied.

We also use the methods of molecular spectroscopy for the structural characterization of different molecular systems and their dynamic studies. We perform experiments using infrared spectroscopy in a standard experimental setup as well as in combination with gas chromatography. Raman microscopy can also be applied to various types of materials. Variability in the experimental setup allow investigation of a broad range of organic and biological samples under different conditions. In addition, chiral samples can be characterized using chiroptical spectroscopy methods and optical rotation. We can also characterize thermal transitions in materials using differential scanning calorimetry and run solubility screening. Finally, we perform precise weighing of small sample quantities and determination of water in organic solvents.

Group members

Group leader Stanislava Matějková
Research assistants Lucie Bednárová, Lenka Borovičková, Pavel Fiedler, Michaela Gazdurová, Jaroslava Hniličková, Lucie Holasová, Martin Král, Lenka Krepsová, Karel Kudláček, Martin Loula, Markéta Pazderková, Luisa Šerá, Adéla Šimůnková, Jana Šplíchalová
Technicians Magdalena Hošková, Marina Morozovová, Miroslava Otrubová

Selected publications

Giacobelli, V. G.; Fujishima, K.; Lepšík, M.; Tretyachenko, V.; Kadavá, T.; Makarov, M.; Bednárová, L.; Novák, P.; Hlouchová, K. In Vitro Evolution Reveals Noncationic Protein–RNA Interaction Mediated by Metal Ions. *Mol. Biol. Evol.* **2022**, 39, msac032.

Vaghasiya, J. V.; Mayorga-Martinez, C. C.; Matějková, S.; Pumera, M. Pick up and dispose of pollutants from water via temperature-responsive micellar copolymers on magnetite nanorobots. *Nat. Commun.* **2022**, 13, 1026.

Dvořanová, J.; Kugler, M.; Holub, J.; Šícha, V.; Das, V.; Nekvinda, J.; El Anwar, S.; Havránek, M.; Pospíšilová, K.; Fábry, M.; Král, V.; Medvedíková, M.; Matějková, S.; Lišková, B.; Gurská, S.; Džubák, P.; Brynda, J.; Hajdúch, M.; Grüner, B.; Řezáčová, P. Sulfonamido carboranes as highly selective inhibitors of cancer-specific carbonic anhydrase IX. *Eur. J. Med. Chem.* **2020**, 200, 112460.

Kaufman, F.; Dostálková, A.; Pekárek, L.; Thanh, T. D.; Kapisheva, M.; Hadravová, R.; Bednárová, L.; Novotný, R.; Křížová, I.; Černý, J.; Grubhoffer, L.; Ruml, T.; Hrabal, R.; Rumlová, M. Characterization and in vitro assembly of tick-borne encephalitis virus C protein. *FEBS Lett.* **2020**, 594, 1989–2004.

Nejedlý, J.; Šámal, M.; Rybáček, J.; Sánchez, I. G.; Houska, V.; Warzecha, T.; Vacek, J.; Sieger, L.; Buděšínský, M.; Bednárová, L.; Fiedler, P.; Císařová, I.; Starý, I.; Stará, I. G. Synthesis of Racemic, Diastereopure, and Enantiopure Carba- or Oxa[5]-, [6]-, [7]-, and -[19]helicene (Di)thiol Derivatives. *J. Org. Chem.* **2020**, 85, 248–276.

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Ondruš, M.; Sýkorová, V.; Bednárová, L.; Pohl, R.; Hocek, M. Enzymatic synthesis of hypermodified DNA polymers for sequence-specific display of four different hydrophobic groups. *Nucleic Acids Res.* **2020**, 48, 11982–11993.

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.

Collaboration

Charles University, Prague, Czech Republic
Faculty of Sciences: Department of Inorganic Chemistry, Department of Zoology, Department of Cell Biology
Faculty of Mathematics and Physics: Biophysics Department

University of Chemistry and Technology, Prague, Czech Republic
Department of Inorganic Chemistry, Department of Biotechnology

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 vaporization unit ETV 4000c Spectral Systems P. Perzl

ICP-OES spectrometer SPECTRO Arcos MultiView

Vibrational spectroscopy
FT-IR spectrometer Nicolet 6700 with additional accessories and coupled with gas chromatograph Agilent 6850 interfaced to FTIR for GC-IR measurements (thermally controlled capillary cell with optical path length 200 mm)

Renishaw inVia QONTOR Micro-Raman Spectroscopy System coupled to Leica DMi8 inverted microscope equipped with laser excitation 325 nm, 532 nm, 633 nm, 785 nm, and 1064 nm, polarization accessories for all lasers and various additional accessories

Electronic circular dichroism
CD spectrometer Jasco 815 with additional accessories (Peltier element allowing temperature dependent measurements [5–95 °C]), permanent magnet 1T for MCD

CD spectrometer Jasco 1500 with additional accessories (Peltier element allowing temperature dependent measurements [5–95 °C]), stop flow

Optical activity
Autopol IV Polarimeter Rudolph Research

Diferencial scanning calorimetry
DSC TA 250 (possible temperature range –180–500 °C)

Solubility testing
Determination of kinetic and thermodynamic solubility using Thermo UHPLC-UV/VIS-CAD and PAL-RTC system

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

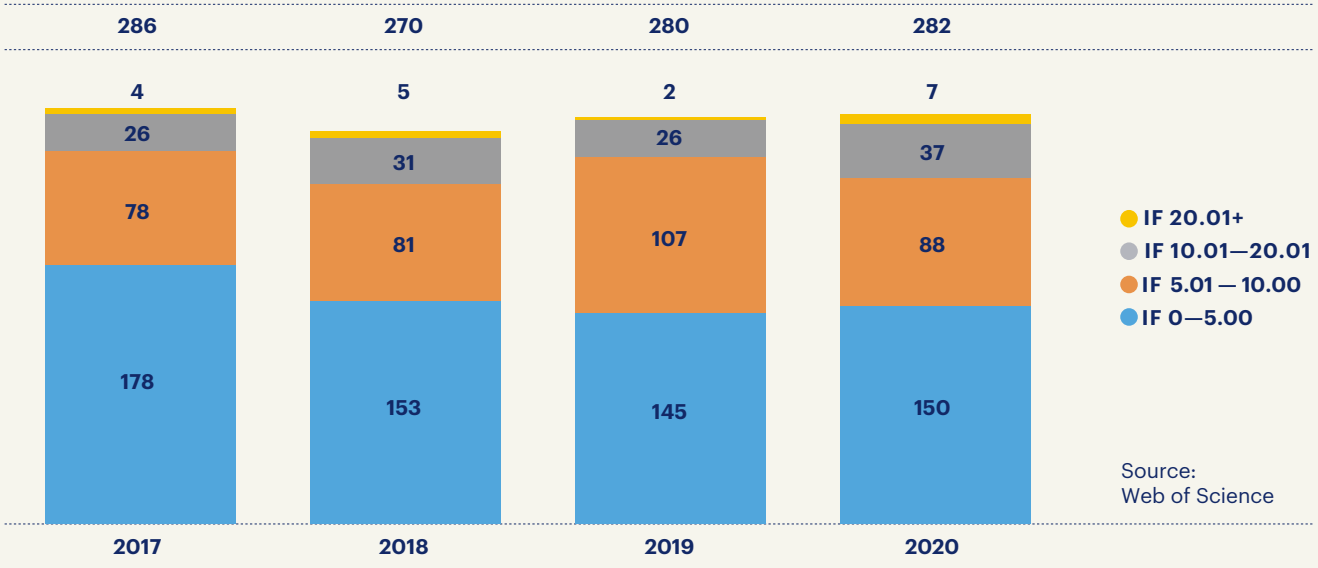
Other instruments
Coulometer WTD Diram – Karl Fischer moisture determination


22
82
23
83
24
84
25
85

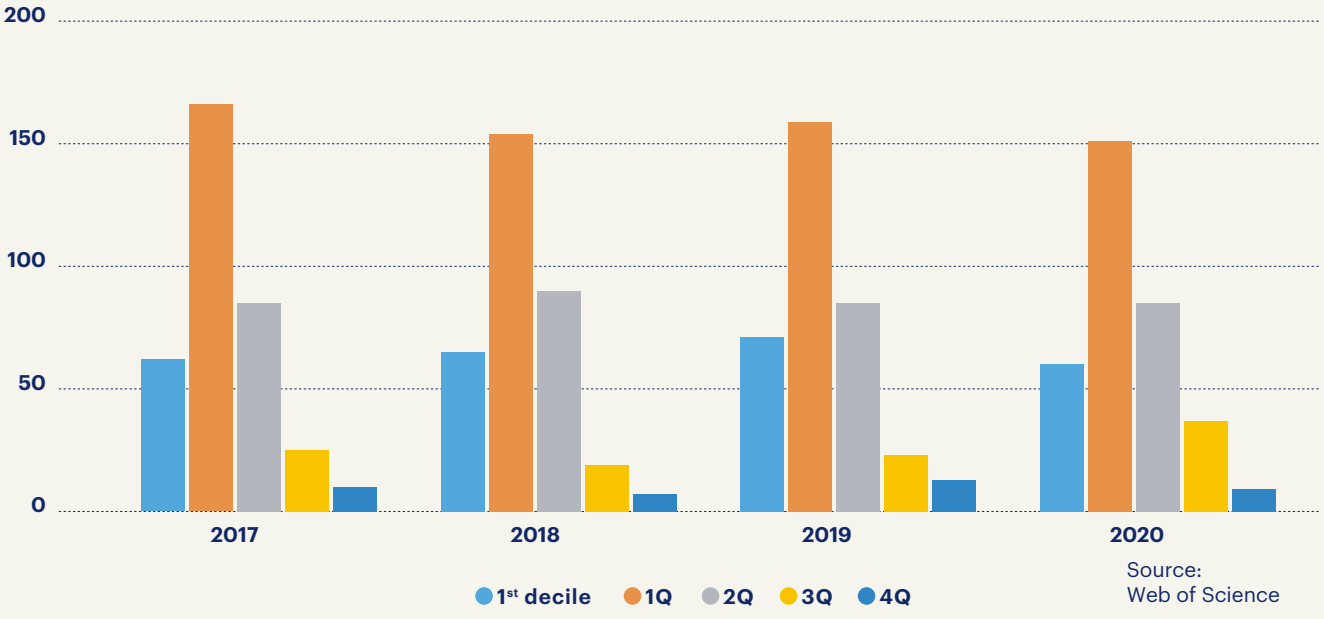
Publications

When it comes to publications, we focus on quality rather than quantity. Today, IOCB scientists publish approximately 280 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



IOCB Most Significant Publications

The most significant publications in three categories are selected each year by both external (international) and internal panels of reviewers. Winning papers are awarded prizes. (The publications are listed alphabetically by title.)

2020

Houštecká, R. *et al.* Biomimetic Macrocyclic Inhibitors of Human Cathepsin D: Structure–Activity Relationship and Binding Mode Analysis. *J. Med. Chem.* **2020**, 63, 1576–1596. **BIO**

Hudeček, O. *et al.* Dinucleoside polyphosphates act as 5′-RNA caps in bacteria. *Nat. Commun.* **2020**, 11, 1052. **BIO**

Myšková, J. *et al.* Directionality of light absorption and emission in representative fluorescent proteins. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, 117, 32395–32401. **PHYS**

Lux, V. *et al.* Molecular Mechanism of LEDGF/p75 Dimerization. *Structure* **2020**, 28, 1288–1299.e7. **BIO**

Barton, J. *et al.* Nanoscale Dynamic Readout of a Chemical Redox Process Using Radicals Coupled with Nitrogen-Vacancy Centers in Nanodiamonds. *ACS Nano* **2020**, 14, 12938–12950. **PHYS**

Šála, M. *et al.* Novel Human Neutral Sphingomyelinase 2 Inhibitors as Potential Therapeutics for Alzheimer's Disease. *J. Med. Chem.* **2020**, 63, 6028–6056. **CHEM**

Buttersack, T. *et al.* Photoelectron spectra of alkali metal–ammonia microjets: From blue electrolyte to bronze metal. *Science* **2020**, 368, 1086–1091. **PHYS**

Čechová, L. *et al.* Polysubstituted 5-Phenylazopyrimidines: Extremely Fast Non-ionic Photochromic Oscillators. *Angew. Chem. Int. Ed.* **2020**, 59, 15590–15594. **CHEM**

Bím, D. *et al.* Proton–Electron Transfer to the Active Site Is Essential for the Reaction Mechanism of Soluble 9-Desaturase. *J. Am. Chem. Soc.* **2020**, 142, 10412–10423. **PHYS**

Santos Hurtado, C. *et al.* Regular Two-Dimensional Arrays of Surface-Mounted Molecular Switches: Switching Monitored by UV–vis and NMR Spectroscopy. *J. Am. Chem. Soc.* **2020**, 142, 9337–9351. **CHEM**

Began, J. *et al.* Rhomboid intramembrane protease YqgP licenses bacterial membrane protein quality control as adaptor of FtsH AAA protease. *EMBO J.* **2020**, 39, e102935. **BIO**

Krafcikova, P. *et al.* E. Structural analysis of the SARS-CoV-2 methyltransferase complex involved in RNA cap creation bound to sinefungin. *Nat. Commun.* **2020**, 11, 3717. **BIO**

Galeta, J. *et al.* A Systematic Study of Coumarin–Tetrazine Light-Up Probes for Bioorthogonal Fluorescence Imaging. *Chem. Eur. J.* **2020**, 26, 9945–9953. **CHEM**

Wu, T. *et al.* Two Spectroscopies in One: Interference of Circular Dichroism and Raman Optical Activity. Angew. *Chem. Int. Ed.* **2020**, 59, 21895–21898. **PHYS**

Zima, V. *et al.* Unraveling the anti-influenza effect of flavonoids: Experimental validation of luteolin and its congeners as potent influenza endonuclease inhibitors. *Eur. J. Med. Chem.* **2020**, 208, 112754. **CHEM**

2019

Hellerstedt, J. *et al.* Aromatic Azide Transformation on the Ag(111) Surface Studied by Scanning Probe Microscopy. *Angew. Chem. Int. Ed.* **2019**, 58, 2266–2271. **PHYS**

Novotná, B. *et al.* Enzymatic Preparation of 2′–5′,3′–5′-Cyclic Dinucleotides, Their Binding Properties to Stimulator of Interferon Genes Adaptor Protein, and Structure/Activity Correlations. *J. Med. Chem.* **2019**, 62, 10676–10690. **CHEM**

Jaroš, A. *et al.* Fullerene-Based Switching Molecular Diodes Controlled by Oriented External Electric Fields. *J. Am. Chem. Soc.* **2019**, 141, 19644–19654. **PHYS**

Eyrilmez, S. M. *et al.* Impressive Enrichment of Semiempirical Quantum Mechanics-Based Scoring Function: HSP90 Protein with 4541 Inhibitors and Decoys. *ChemPhysChem* **2019**, 20, 2759–2766. **PHYS**

Šimonová, A. *et al.* LC/MS analysis and deep sequencing reveal the accurate RNA composition in the HIV-1 virion. *Sci. Rep.* **2019**, 9, 8697. **BIO**

Holubová, M. *et al.* Liraglutide and a lipidized analog of prolactin-releasing peptide show neuroprotective effects in a mouse model of β-amyloid pathology. *Neuropharmacology* **2019**, 144, 377–387. **BIO**

Grüner, B. *et al.* Metallacarborane Sulfamides: Unconventional, Specific, and Highly Selective Inhibitors of Carbonic Anhydrase IX. *J. Med. Chem.* **2019**, 62, 9560–9575. **CHEM**

Macháčková, K. *et al.* Mutations at hypothetical binding site 2 in insulin and insulin-like growth factors 1 and 2 result in receptor- and hormone-specific responses. *J. Biol. Chem.* **2019**, 294, 17371–17382. **BIO**

Hernández-Guerra, D. *et al.* Photochemical C–H Amination of Ethers and Geminal Difunctionalization Reactions in One Pot. *Angew. Chem. Int. Ed.* **2019**, 58, 12440–12445. **CHEM**

Mason, P. E. *et al.* Quantifying the Strength of a Salt Bridge by Neutron Scattering and Molecular Dynamics. *J. Phys. Chem. Lett.* **2019**, 10, 3254–3259. **PHYS**

Vaníková, Z. *et al.* Switching transcription with bacterial RNA polymerase through photocaging, photorelease and phosphorylation reactions in the major groove of DNA. *Chem. Sci.* **2019**, 10, 3937–3942. **BIO**

Li, G. *et al.* Transfer and Amplification of Chirality Within the “Ring of Fire” Observed in Resonance Raman Optical Activity Experiments. *Angew. Chem. Int. Ed.* **2019**, 58, 16495–16498. **PHYS**

Tenora, L. *et al.* Tumor-Targeted Delivery of 6-Diazo-5-oxo-l-norleucine (DON) Using Substituted Acetylated Lysine Prodrugs. *J. Med. Chem.* **2019**, 62, 3524–3538. **CHEM**

2018

Sharma, S. *et al*. Affinity switching of the LEDGF/p75 IBD interactome is governed by kinase-dependent phosphorylation. *PNAS* **2018**, 115, E7053–E7062. **BIO**

Allolio, C. *et al*. Arginine-rich cell-penetrating peptides induce membrane multilamellarity and subsequently enter via formation of a fusion pore. *PNAS* **2018**, 115, 11923–11928. **PHYS**

Havlik, J. *et al*. Extremely rapid isotropic irradiation of nanoparticles with ions generated in situ by a nuclear reaction. *Nat. Commun.* **2018**, 9, 4467. **PHYS**

Šimon, P. *et al*. Identification of Protein Targets of Bioactive Small Molecules Using Randomly Photomodified Probes. *ACS Chem. Biol*. **2018**, 13, 3333–3342. **BIO**

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. **PHYS**

de la Torre, B. *et al*. Non-covalent control of spin-state in metal-organic complex by positioning on N-doped graphene. *Nat. Commun*. **2018**, 9, 2831. **PHYS**

Hánová, I. *et al*. Novel Structural Mechanism of Allosteric Regulation of Aspartic Peptidases via an Evolutionarily Conserved Exosite. *Cell Chem. Biol*. **2018**, 25, 318–329.e4. **BIO**

Procházková, E. *et al*. Photoswitchable Intramolecular Hydrogen Bonds in 5-Phenylazopyrimidines Revealed By In Situ Irradiation NMR Spectroscopy. *Chem. Eur. J.* **2018**, 24, 492–498. **CHEM**

Vícha, J. *et al*. Relativistic Spin–Orbit Heavy Atom on the Light Atom NMR Chemical Shifts: General Trends Across the Periodic Table Explained. *J. Chem. Theory Comput*. **2018**, 14, 3025–3039. **PHYS**

Motornov, V. *et al*. A rhodium-catalyzed transannulation of N-(per)fluoroalkyl-1,2,3-triazoles under microwave conditions – a general route to N-(per)fluoroalkyl-substituted five-membered heterocycles. *ChemComm* **2018**, 54, 3258–3261. **CHEM**

Tokarenko, A. *et al*. Synthesis and Cytotoxic and Antiviral Profiling of Pyrrolo- and Furo-Fused 7-Deazapurine Ribonucleosides. *J. Med. Chem*. **2018,** 61, 9347–9359. **CHEM**

Zawada, Z. *et al*. Transport of Nucleoside Triphosphates into Cells by Artificial Molecular Transporters. *Angew. Chem. Int. Ed*. **2018**, 57, 9891–9895. **BIO**


21

Leadership

Institute Directors

Zdeněk Hostomský, Ph.D. (2012—2022)
Prof. Jan Konvalinka, Ph.D. (2022—)

Board of the Institute

The IOCB Board together with the Director decide
on essential scientific and organizational matters of the Institute.

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Vice-chairman
Prof. Michal Hocek, Ph.D., DSc.

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Prof. Jan Černý, Ph.D. (Faculty of Science, Charles University)
Prof. Petr Slavíček, Ph.D. (Faculty of Chemical Engineering, UCT Prague)

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The main task of the Supervisory Board is to monitor
the financial and legal matters related to the Institute administration.

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Institute of Microbiology of the CAS)

Vice-chairman
Zlatko Janeba, Ph.D. (IOCB Prague)

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Prof. Josef Lazar, Ph.D. (Institute of Scientific Instruments of the CAS)
Pavel Mertlík, Ph.D. (ŠKODA AUTO University)

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The main task of the International Advisory Board is to evaluate the research groups at IOCB, provide constructive feedback and suggest future goals and strategies.

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