IOCB 2013—2016

IOCB 2013—2016

Institute of Organic Chemistry and Biochemistry
of the Czech Academy of Sciences
September 2016


OŽÁRNÍ OCHRANA
FIRE PROTECTION

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DIRECTOR

ZDENĚK HOSTOMSKÝ
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FOREWORD

Welcome to the new IOCB yearbook.

The yearbook appears after a relatively long time since publication of the previous one in 2013. This doesn't mean, though, that not much has changed during this period to warrant a new yearbook in the meantime. On the contrary, so many changes were happening that there was simply no convenient pause in the ongoing dramatic development that would allow us to sit down and prepare one earlier.

So what has been happening? Clearly, this period was dominated by complete refurbishing of the IOCB campus, which included construction of a new building for organic synthesis and a thorough remodeling of the historic building. The progress of this endeavor (funded almost exclusively by royalty income from Antonín Holý's patents) was marked by several grand openings of the newly available spaces, including internationally noticed unveiling of a bronze bust of Antonín Holý by his former collaborators John C. Martin and Erik De Clercq in November 2015.

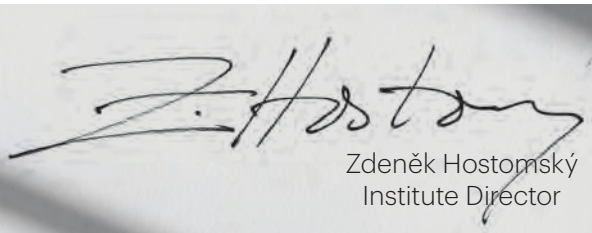
During this period we started no less than nine new junior research groups with leaders from five different countries, and with three junior group leaders being awarded prestigious and hard-to-get ERC starting grants on top of that.

As high quality basic research remains our primary objective, we consciously emphasize quality rather than quantity also in the world of scientific publishing. Our annual "Most significant IOCB publications" contest is motivating and is taken increasingly seriously.

At the same time we are also constantly on the lookout for opportunities in applied research. Our subsidiary company IOCB TTO is becoming an effective and well-respected organization that helps to identify promising projects and manage dedicated targeted research to generate commercially interesting intellectual property. It is a great news that our major industrial partner, Gilead Sciences Inc., supports this effort and has just recently renewed its funding for the third 5-year cycle of Gilead Sciences Research Centre at IOCB Prague.

As far as education goes, we take good care of our PhD students. Expressions like Bootcamp, PhD Science Club and Summer School became part of our vocabulary. IOCB also offers financial help to mothers with small children, aiming to convince them that science, work, and family can all be pursued in parallel.

To better support the research activities we have consolidated and expanded supporting functions at IOCB provided by Technical and Economic Administration, Information Technologies and Services, Human Resources, Communications, Grant Office and Legal Counsel – all of them now headed by English speaking professionals to reflect the increasingly international character of our Institute. Taken together, this helps our ambition of becoming a world-class research institution. As you go through this yearbook, you will be the judges of how far we have progressed on this bumpy road.



Zdeněk Hostomský
Institute Director

ABOUT IOCB

The Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences (IOCB Prague) is a leading scientific institution in the Czech Republic, recognized internationally. Its primary mission is basic research in the fields of chemical biology and medicinal chemistry, organic and material oriented chemistry, chemistry of natural compounds, biochemistry and molecular biology, physical chemistry, theoretical chemistry, and analytical chemistry.

Today, over 600 employees including 180 students in 45 groups are involved in a broad spectra of disciplines, which results in more than 250 publications per year, including papers in the most cited prestigious journals such as Nature or Science.

The Institute's emphasis on interaction between chemistry and other sciences leads frequently to medicinal applications. An integral part of the mission of the Institute is, therefore, to transfer the scientific results into assets which help people to live better lives.

Together with the research expertise, a system of technology transfer, IP management and commercialization have intensively been built-up. Through its subsidiary company IOCB TTO, the Institute helps scientists to transform ideas into patents and matches their research results with interests of commercial partners to bring novel ideas to human use or technology market.

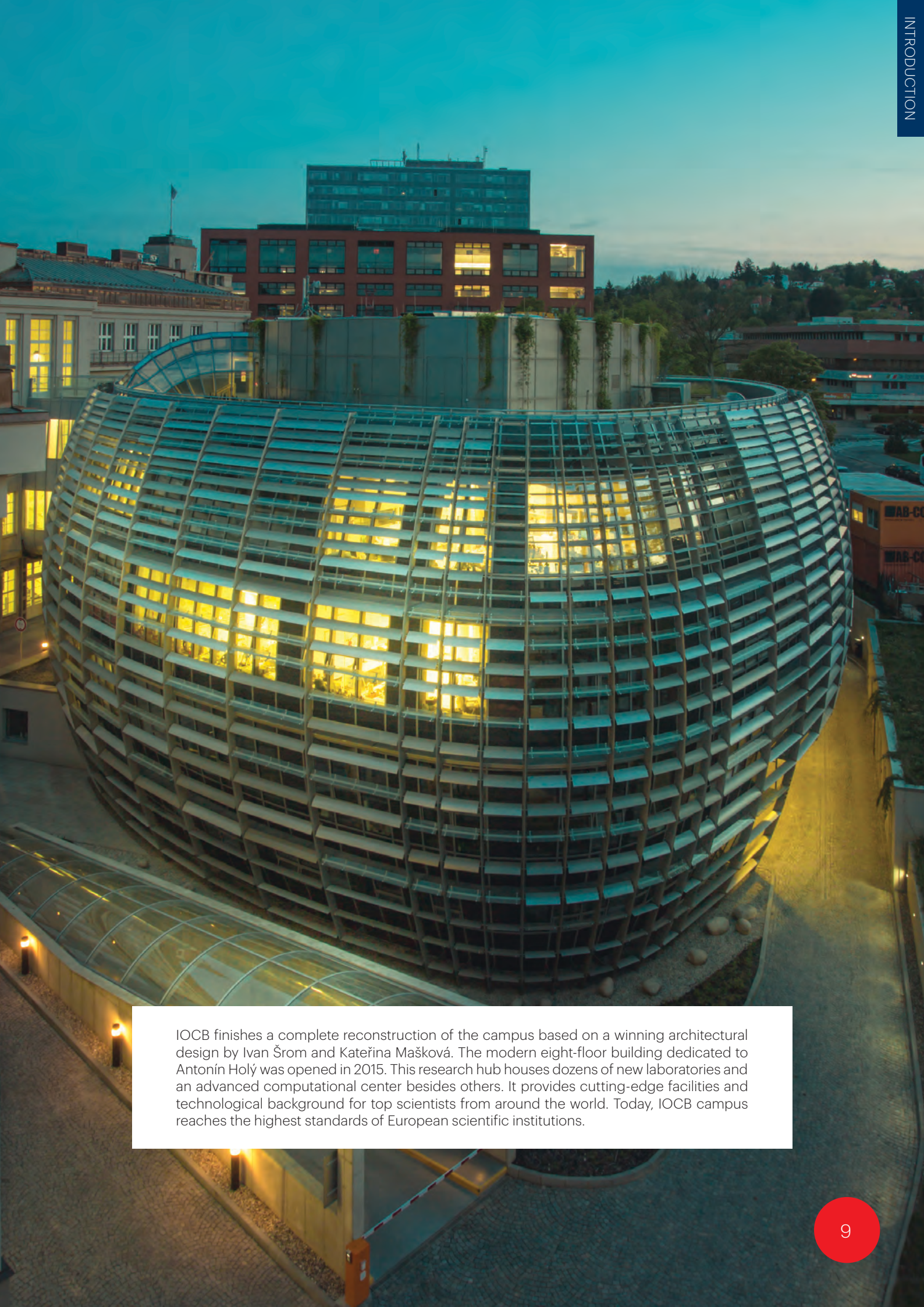
IOCB has multiple scientific collaborations worldwide with a number of research and academic institutions, e.g. Catholic University of Leuven, Johns Hopkins University, Heidelberg University, University of Queensland, Max Planck Institute for Biogeochemistry, California Institute for Biomedical Research, Helmholtz Zentrum München. A long term collaboration of IOCB with Gilead Sciences company in the field of antiviral drugs – acyclic nucleosides phosphonate analogues – which were invented, synthetized, and developed in prof. Antonín Holý's lab, continues currently within the Research Centre established in 2006.

During permanent search for new talents and future scientific leaders, IOCB pioneered progressive system of Junior groups with talented young scientists from all around the world, which is a unique case amongst academic institutes in the Czech Republic. The Institute supports each such team by providing a startup package, fixed salary resources, an equipped laboratory space and services. The new team leaders are selected in an international competition, following the selection committee recommendation and with the help of an International Advisory Board.

All the groups undergo a complex evaluation every five years by the International Advisory Board, which follows strictly transparent rules based on scientific merit. The exceptional categories of Distinguished and Honorary Chair groups are not subject to periodic evaluation anymore, as their long-term achievements are outstanding – they represent an equivalent of a permanent position. A steadily growing scientific performance of the Institute proves these strategic changes were made in the right direction.

ABOUT IOCB

ARCHITECTURE AND DEVELOPMENT



IOCB finishes a complete reconstruction of the campus based on a winning architectural design by Ivan Šrom and Kateřina Mašková. The modern eight-floor building dedicated to Antonín Holý was opened in 2015. This research hub houses dozens of new laboratories and an advanced computational center besides others. It provides cutting-edge facilities and technological background for top scientists from around the world. Today, IOCB campus reaches the highest standards of European scientific institutions.

ABOUT IOCB

WHERE THE STORY BEGAN...

After World War II, a group of chemistry enthusiasts was formed at the Czech Technical University under the leadership of Professor František Šorm, who played a crucial role in founding of the Institute. In 1951, the group moved to the current premises. The Institute was formally established in 1953 as Institute of Organic Chemistry under the auspices of The Czechoslovak Academy of Sciences.

František Šorm (1913–1980) became the Institute's first director as well as its secretary general and later a president of the Czechoslovak Academy of Sciences. This Czech chemist was recognized for synthesis of natural compounds, mainly terpenes and biologically active components found in plants. František Šorm advanced the knowledge of sesquiterpenoids and medium-ring molecules and explained the structure of different isoprenoid compounds. He initiated the study of natural peptides, especially neurohypophyseal hormones and their analogues, some of which were shown to be of major clinical importance. He was involved in establishing the primary structure of chymotrypsin and trypsin and worked also on insect juvenile hormones. His studies of antimetabolites of nucleic acid constituents as potential cancerostatics or virostatics led to synthesis and determination of the mechanism of several highly active compounds.

František Šorm published more than 1 000 papers and his work was frequently cited. His interest in cross-disciplinary research draw the future path of the Institute, which allowed its major achievements.

ANTONÍN HOLÝ AND HIS LEGACY

Antonín Holý (1936–2012) was an outstanding Czech organic chemist recognized for his work on nucleic acids analogs. He headed a research group focused on nucleic acids at IOCB and directed the Institute for eight years. From 1976 on he collaborated on the development of new antiretroviral drugs with Erik De Clercq of the Rega Institute for Medical Research at the Catholic University of Leuven, Belgium. Antonín Holý held over 60 patents and co-authored 600 scientific papers. His work has been cited more than 10 000 times. He received many significant awards and honorary degrees worldwide.

Acyclic nucleoside phosphonates developed by Antonín Holý and his coworkers revolutionized the therapy of numerous viral diseases. The first active pharmaceutical ingredient to reach the market was cidofovir under a brand name Vistide®. This remedy got FDA approval for treatment of cytomegalovirus retinitis in HIV/AIDS patients in 1996. Cidofovir, however, exerts profound effect against many other DNA viruses. The second compound from the series, tenofovir, which is used as a prodrug for oral administration, meant a real breakthrough and enabled prolongation and essential life improvement of HIV and HBV patients. The first approved drug containing this substance was Viread®, which was originally approved only for treatment of HIV (2001), but showed outstanding efficiency against hepatitis B virus (HBV) in HIV/HBV co-infected patients, which led to its approval also for treatment of HBV infection (2008). Tenofovir is currently an essential component of several single pill regimens such as Truvada® (2004), Atripla® (2006), Complera® (2011), and Stribild® (2012), which combine two or more different active compounds treating HIV/AIDS with synergic effect thus reducing the pill burden for the patients. Truvada® was recently also approved as a pre-exposure prophylaxis in risk population (2012). Last but not least, a third compound from Antonín Holý's lab, adefovir, was approved in its prodrug form for treatment of chronic hepatitis B under brand name Hepsera® in 2002.

IOCB BOARDS

BOARD OF INSTITUTE

The Board of Institute serves as an advisory authority to the Director and decides on essential scientific and organizational issues. Its members are appointed by election.

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Jiří Jiráček, Ph.D.
Radek Pohl, Ph.D.

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(University of Chemistry and Technology, Prague)
prof. Tomáš Obšil, Ph.D.
(Charles University)
doc. Petr Svoboda, Ph.D.
(Institute of Molecular Genetics of the CAS)

SECRETARY
Martin Matoušek

INTERNATIONAL ADVISORY BOARD

The International Advisory Board was appointed by the Board of Institute. 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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(National Cancer Institute, USA)

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Prof. Dr. Wilhelm Boland
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Prof. Cynthia J. Burrows, Ph.D.
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(University of Bath, UK)
Prof. Dr. Frank Neese
(Max Planck Institute for Chemical Energy Conversion, Germany)

SUPERVISORY BOARD

The main task of the Supervisory Board is to monitor the financial and legal matters related to the Institute administration. Its members have been selected from Czech Academy of Sciences and business sphere representatives.

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RNDr. Hana Sychrová, DrSc.
(Institute of Physiology of the CAS)

VICE-CHAIRMAN
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(Academy Council of the CAS)
prof. Ing. Tomáš Ruml, CSc.
(University of Chemistry and Technology, Prague)
Ing. Pavel Šebek, CSc.
(Zentiva, a.s.)
doc. Ing. Pavel Mertlík, CSc.
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EMERITI

Ing. Juraj Harmatha, CSc.[1]
RNDr. Alexander Kasal, DrSc.[2]
Ing. Vladimír Špirko, DrSc.[3]

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RNDr. Ivan Hirsch, CSc.
(Department of Genetics and Microbiology, Faculty of Science, Charles University, Czech Republic)

prof. Dr. Pavel Kočovský, DSc., FRSE
(Department of Organic Chemistry, Faculty of Science, Charles University, Czech Republic)

prof. RNDr. Martin Kotora, CSc.
(Department of Organic Chemistry, Faculty of Science, Charles University, Czech Republic)

Assoc. Prof. Jiří Šrogl, Ph.D.
(Department of Chemical and Biomolecular Engineering, North Carolina State University, USA)

Dr. Aleš Svatoš
(Research Group Mass Spectrometry / Proteomics, Max Planck Institute for Chemical Ecology, Germany)

RESEARCH AT IOCB

IOCB has always understood that organic chemistry and biochemistry are not isolated and self-explaining disciplines, but rather integral parts of a complicated and much larger matrix of systems, pathways and interactions. The Institute adopted a philosophy of embracing a number of different perspectives and approaches in organic chemistry and biochemistry research including insights from biology or physics, which better reflects the complexity of living systems and grasps big questions in life sciences. Combination of interdisciplinary knowledge with cutting-edge technologies is essential for the IOCB excellent results.

The core of IOCB scientific expertise lies in a flat structure of the research groups, of which 17 are senior groups, three are groups of Distinguished/Honorary Chairs, 13 are junior groups and ad hoc formed Targeted research groups. The research groups are complemented with six research service groups and four service groups, which support the basic research by providing cutting-edge technologies and technical expertise.

IOCB research covers disciplines in three clusters:

CHEM including organic synthesis, medicinal chemistry, natural products chemistry, chemical biology, materials chemistry, nanochemistry, drug discovery, etc. Research focuses on development of pharmaceuticals against leukemia and other types of cancer or new drugs combatting viral diseases such as AIDS, hepatitis and malaria. It investigates general principles of substances preparation, synthesis of functional molecule switch properties suitable for preparation of nano-materials and materials for molecular electronics and self-assembly.

PHYS including computational chemistry, quantum mechanics chemistry, molecular modeling, drug design, molecular spectroscopy, analytical chemistry, separation science, etc. These disciplines perform organic and bioorganic structure determination by physical methods and examine the relationship between structure and physical properties. They use quantum chemistry and molecular simulation to forecast the structure, reactivity, and properties of organic and bioorganic molecules.

BIO including biochemistry, molecular biology, structural biology, cell biology, neuroscience, physiology, chemical ecology, diagnostic tools, etc. These study structure and activity of enzymes (proteases), protein components of viruses and other pathogens (bacteria, yeasts), design and test inhibitors with potential drug development. They identify peptides with antibacterial activity. They search for substances used for chemical communication of insects; determine pheromones and other semiochemicals with subsequent utilization for pest control.

Evžen Bouřa Group

STRUCTURAL MEMBRANE BIOLOGY

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KEYWORDS / kinase, lipid, phosphatidylinositol 4-phosphate (PI4P), virus, inhibitor

Phosphatidylinositol 4-kinases (PI4Ks) are enzymes that generate phosphatidylinositol 4-phosphate (PI4P), a minor but essential regulatory lipid found in all eukaryotic cells. PI4P is the single most abundant mono phosphoinositide that defines the membranes of Golgi and TGN. It has been reported to play a key role in membrane biogenesis, vesicular transport, lipid dynamics, and protein and lipid sorting in TGN. Importantly, the replication of several +RNA viruses depends on PI4P. +RNA viruses hijack PI4Ks to produce membranous organelles (referred to as "membranous webs" or "replication factories") highly enriched in PI4P, which facilitate assembly of functional viral replication machinery. For example, hepatitis C virus (HCV) hijacks both PI4KA and PI4KB, whereas various members of the Picornaviridae family, including coxsackieviruses and rhinoviruses, and those of the Coronaviridae family were shown to depend on PI4KB.

Recently, we have crystallized several PI4K enzymes (PI4KB, PI4K2A, PI4K2B); and we have used the structural information (in collaboration with Nencka group) to develop highly potent and isoform selective inhibitors of PI4KB that have a potential to be used as virostatics. Later, we became interested in a molecular mechanism of PI4KB membrane recruitment by the Golgi resident ACBD3 protein. Currently, we are focusing on structural basis of viral hijacking of PI4Ks.

Head of the group: Evžen Bouřa[1] / Scientists: Martin Klíma[2], Jana Humpolíčková, Jan Šilhán[3]
Kamil Hercík[4] / Postdocs: Dominika Chalupská[5], Adriana Baumlová[6] / Ph.D. student: Anna Dubánková[7]
Students: Andrea Eisenreichová[8], Jiří Gregor[9] / Technician: Lenka Kloučková[10]

SELECTED PAPERS

Klíma, M., Tóth, D.J., Hexnerová, R., Baumlová, A., Chalupská, D., Tykvart, J., Řežábková, L., Sengupta, N., Man, P., Dubánková, A., Humpolíčková, J., Nencka, R., Veverka, V., Balla, T., and Bouřa, E. (2016) Structural insights and in vitro reconstitution of membrane targeting and activation of human PI4KB by the ACBD3 protein. *Sci. Rep.* **6**:23641

Mejdrová, I., Chalupská, D., Kögler, M., Šála, M., Plačková, P., Baumlová, A., Hřebabecký, H., Procházková, E., Dejmek, M., Guillon, R., Strunin, D., Weber, J., Lee, G., Birkus, G., Mertlíková-Kaiserová, H., Bouřa, E., and Nencka, R. (2015) Highly Selective Phosphatidylinositol 4-Kinase III beta Inhibitors and Structural Insight into Their Mode of Action. *J. Med. Chem.* **58**, 3767-3793

Klíma, M., Baumlová, A., Chalupská, D., Hřebabecký, H., Dejmek, M., Nencka, R., and Bouřa, E. (2015) The high-resolution crystal structure of phosphatidylinositol 4-kinase II beta and the crystal structure of phosphatidylinositol 4-kinase II alpha containing a nucleoside analogue provide a structural basis for isoform-specific inhibitor design. *Acta Crystallogr. Sect. D-Struct. Biol.* **71**, 1555-1563

Baumlová, A., Chalupská, D., Różycki, B., Jovic, M., Wisniewski, E., Klima, M., Dubánková, A., Kloer, D. P., Nencka, R., Balla, T., and Bouřa, E. (2014) The crystal structure of the phosphatidylinositol 4-kinase II alpha. *EMBO Rep.* **15**, 1085-1092

Różycki, B., and Bouřa, E. (2014) Large, dynamic, multi-protein complexes: a challenge for structural biology. *J. Phys.-Condes. Matter* **26**, 11

CURRENT GRANTS

In vitro reconstitution of viral "replication factories", Project no. 15-21030Y, Czech Science Foundation (GA ČR), 2014–2016, Bouřa, E.

Sustainability grant to research centers of excellence (NPU I), Project no. LO1302 (InterBioMed), Ministry of Education, Youth and Sports (MŠMT ČR), 2013–2016, Bouřa, E.

Structural targeting of PI4 kinases (StarPI4K), Project no. 333916, European Commission (FP7-PEOPLE-2012-CIG - Marie-Curie Action: "Career Integration Grants"), 2013–2016, Bouřa, E.

Hana Cahová Group

CHEMICAL BIOLOGY

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Head of the group: Hana Cahová[1] / Postdocs: Babek Alibayev
Roberto Benoni, Oldřich Hudeček[2] / Ph.D. student: Anna Šimonová[3]

KEYWORDS / virus, RNA cap, RNA modification cofactors, MS analysis of RNA

Viruses are a major force that shapes the evolution of both prokaryotic and eukaryotic organisms. The mechanism of action of various viruses has been a primary focus of many studies, yet, there are surprisingly scarce data on RNA modifications or RNA conjugates in any type of viruses. Development of vitally important methods for sensitive analysis of RNA modification enabling detailed studies of the chemical structure of various RNA entities began only recently and the methods have never been applied to viral RNA.

Recent discovery of nicotinamide adenine dinucleotide (NAD) attached to plasmid encoded RNA molecules responsible for replication of plasmids in *E. coli* hints that other episomes such as herpesvirus, adenovirus (ds DNA viruses) and even other simple forms of life could also employ RNA molecules with covalently attached coenzymes or other conjugates. The simplicity of their genomes and well described structure and machinery of various viruses make them a perfect model system for studying the role of new RNA conjugates such as NAD-RNA.

The goal of our group is an in-depth study of the chemical structure of viral RNA molecules (both coding and non-coding) of mammalian viruses (DNA and RNA) by means of mass spectrometry (MS) and chemical biology. After detection of any modification or conjugate, new chemical or chemo-enzymatic methods will be employed or developed to identify modified RNA sequences. Once the function of modified RNA has been elucidated, biogenesis, biodegradation and mechanisms of interaction of viral RNA with host cell targets will be the objective of further studies.

We believe that our research will comprehensively provide new insight into the mechanism of action of various viral RNAs in host cells and will have the potential to employ these findings in the development of new RNA-based antiviral treatments or viral infection sensors.

SELECTED PAPERS

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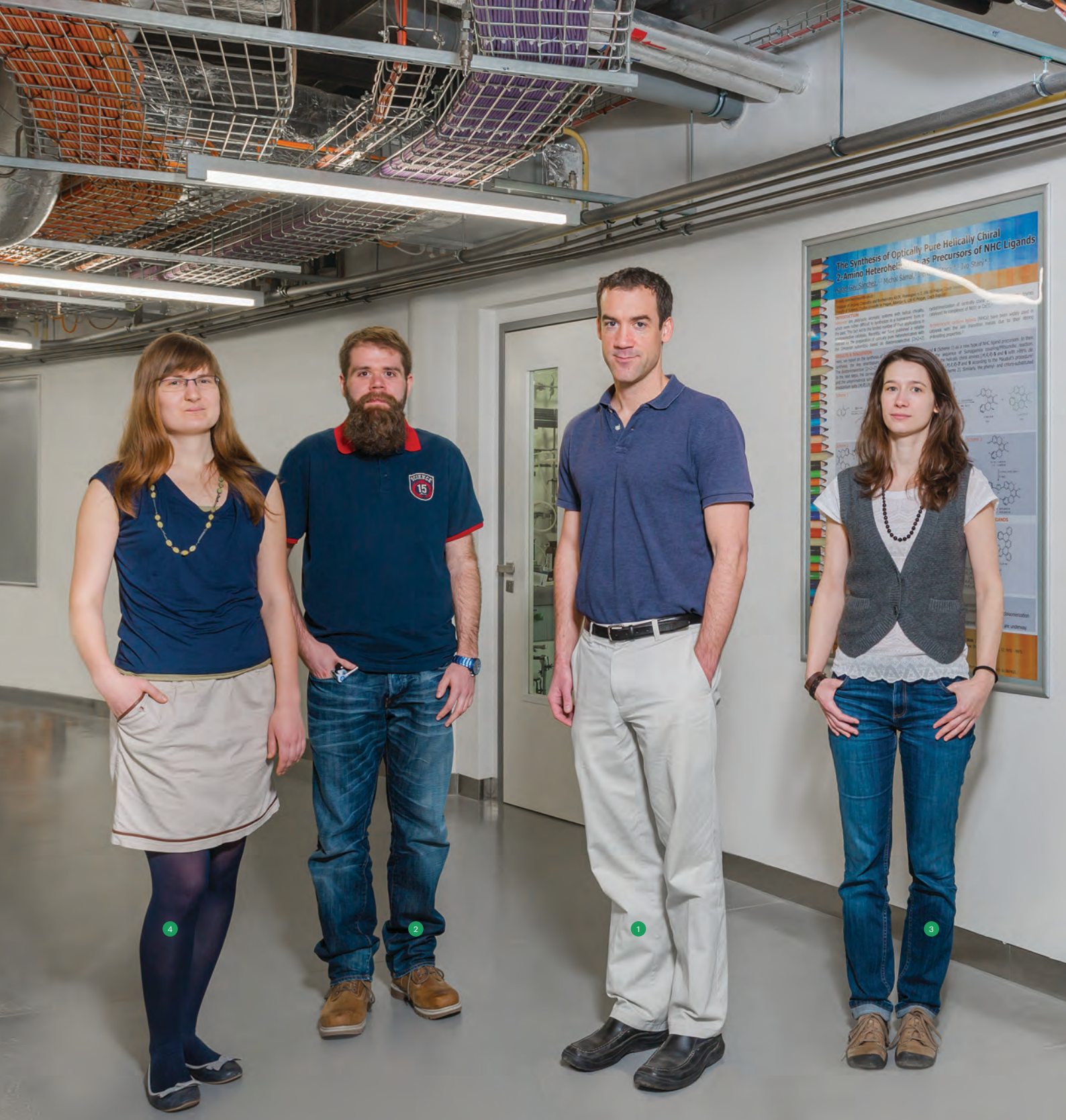
Cahová, H., Winz, M. L., Höfer, K., Nübel, G., and Jäschke, A. (2015) NAD captureSeq indicates NAD as a bacterial cap for a subset of regulatory RNAs. *Nature* **519**, 374-+

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

CURRENT GRANTS

Junior research grant, Project no. 16-16358Y, Czech Science Foundation (GA ČR), 2016–2018, Cahová, H.



Edward Curtis Group

BIOCHEMISTRY AND MOLECULAR BIOLOGY

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Head of the group: Edward Curtis[1] / Postdoc: Juan Alfonso Redondo Marin[2]
Ph.D. students: Kateřina Švehlová[3], Tereza Streckerová[4] / Student: Sofia Kolesnikova

KEYWORDS / ribozyme, deoxyribozyme, aptamer, *in vitro* selection, functional nucleic acid, biosensor

Following the discovery of catalytic RNA molecules (ribozymes) in the early 1980s, nucleic acids were shown to be capable of a variety of interesting functions, including the ability to bind chemically diverse ligands and to catalyze a wide range of chemical transformations. DNA and RNA motifs with increasingly sophisticated functions have also been identified, including sensors that only produce a signal in the presence of specific ligands, recombinases that insert themselves into specific target sequences, and even ribozyme polymerases that can synthesize smaller catalytic RNA molecules in the presence of the appropriate template.

Most of these examples were identified using the technique of *in vitro* selection, in which multiple cycles of *in vitro* transcription, selection, and RT-PCR are performed to isolate rare molecules with unusual and interesting properties from pools containing up to 10^{15} random sequences. Our group uses *in vitro* selection as well as complementary techniques to learn more about functional capabilities of both artificial and naturally occurring DNA and RNA molecules. The research group is interdisciplinary in character and we are especially interested in students with backgrounds in molecular biology, biochemistry, chemistry, and computer science.

SELECTED PAPERS

Švehlová, K., Lawrence, M.S., Bednárová, L., Curtis, E.A. (2016) Altered biochemical specificity of G-quadruplexes with mutated tetrads. *Nucleic Acids Res.*, in press.

McDonald, R. I., Guilinger, J. P., Mukherji, S., Curtis, E. A., Lee, W. I., and Liu, D. R. (2014) Electrophilic activity-based RNA probes reveal a self-alkylating RNA for RNA labeling. *Nat. Chem. Biol.* **10**, 1049-+

Curtis, E. A., and Liu, D. R. (2014) A naturally occurring, noncanonical GTP aptamer made of simple tandem repeats. *RNA Biol.* **11**, 682-692

Curtis, E. A., and Bartel, D. P. (2013) Synthetic shuffling and in vitro selection reveal the rugged adaptive fitness landscape of a kinase ribozyme. *RNA-Publ. RNA Soc.* **19**, 1116-1128

Curtis, E. A., and Liu, D. R. (2013) Discovery of Widespread GTP-Binding Motifs in Genomic DNA and RNA. *Chem. Biol.* **20**, 521-532

Robert Hanus Group

CHEMISTRY OF SOCIAL INSECTS

JUNIOR RESEARCH GROUP / robert.hanus@uochb.cas.cz

Head of the group: Robert Hanus[1] / Scientists: Pavel Jedlička[2], Anna Jirošová[3], Pavlína Kyjaková[4] / Postdocs: Ulrich Ernst[5]
Lucie Pompeiano Vaníčková[6] / Ph.D. student: Klára Dolejšová[7] / Students: Jan Křivánek[8], Marie Pangrácová

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

Social insects are among the most complex and most successful forms of life. One of the common characteristics of social insects is their ability to produce a rich variety of chemicals implicated in various aspects of social life, especially communication and defence against predators and pathogens. Our group is interested in the chemical diversity, biosynthesis and biological role of endocrine and exocrine chemicals used in social regulation, communication and defence in the societies of termites, with the ultimate goal to unravel the significance of these chemicals for social organization and ecological success of termites.

Our research aims in two directions. First, we study the chemical diversity of defensive chemicals produced by termite soldiers, search for new and original structures, their biosynthetic origin and underlying enzymes. We try to interpret our observations on diverse biosynthetic pathways and their defensive products in functional, phylogenetic and evolutionary contexts and in relation to defensive strategies of different lineages and taxa.

And second, we study the chemical communication, endocrine regulation and genetic mechanisms implicated in division of labour among the fertile individuals (kings and queens) and the majority of sterile colony members, with emphasis on how the genetic mechanisms and chemical stimuli shape the social organization and influence reproductive dominance, fertility and longevity of the kings and queens.

Our approaches include a spectrum of methods ranging from analytical chemistry and biochemistry through biological disciplines, such as ethology, electrophysiology and microscopy, to genetic tools allowing us to infer genetic structures of colonies and populations, characterize transcriptomic profiles of individuals and tissues and expression of target genes.

SELECTED PAPERS

Fougeyrollas, R., Dolejšová, K., Sillam-Dussès, D., Roy, V., Poteaux, C., Hanus, R., and Roisin, Y. (2015) Asexual queen succession in the higher termite *Embiratermes neotenicus*. *Proc. R. Soc. B-Biol. Sci.* **282**, 20150260

Bagnères, A.-G., and Hanus, R. Communication and social regulation in termites. in Aquiloni, L., and Tricarico, E. (2015) Social Recognition in Invertebrates. Springer, 193–248

Sillam-Dussès, D., Hanus, R., Poulsen, M., Roy, V., Favier, M., and Vasseur-Cognet, M. (2016) The role of the glucose-sensing transcription factor carbohydrate-response element-binding protein pathway in termite queen fertility. *Open Biology* **6**, 160080

Dolejšová, K., Krasulová, J., Kutalová, K., and Hanus, R. (2014) Chemical alarm in the termite *Termitogeton planus (Rhinotermitidae). J. Chem. Ecol.* **40**, 1269-1276

Jirošová, A., Majer, P., Jančařík, A., Dolejšová, K., Tykva, R., Sobotník, J., Jiroš, P., and Hanus, R. (2014) Sphinganine-Like Biogenesis of (E)-1-Nitropentadec-1-ene in Termite Soldiers of the Genus *Prorhinotermes*. *ChemBioChem* **15**, 533-536

CURRENT GRANTS

Regulation of reproduction in higher termites (Termitidae), Project no. 580413, Grant Agency of the Charles University in Prague (GA UK), 2013–2015, Dolejšová, K.

Biogenesis of (E)-1-nitropentadec-1-ene in soldiers of the termite genus Prorhinotermes, Project no. 13-25137P, Czech Science Foundation (GA ČR), 2013–2015, Jirošová, A.

Evolutionary trends in chemical and mechanical defence in the termite subfamily Termitinae, Project no. 13-25354P, Czech Science Foundation (GA ČR), 2013–2015, Kyjaková, P.

Reproductive regulation and fertility signalling in higher termites (Termitidae), Project no. 14-12774S, Czech Science Foundation (GA ČR), 2014–2016, Hanus, R.

Facultative parthenogenesis as a stable element of reproductive strategies in higher termites, Project no. 358815, Grant Agency of the Charles University in Prague (GA UK), 2015–2016, Křivánek, J.

Jiří Jiráček Group

CHEMISTRY AND BIOLOGY OF INSULIN AND INSULIN-LIKE GROWTH FACTORS

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Head of the group: Jiří Jiráček[1] / Scientists: Michaela Collinsová[2], Jan Hajduch, Irena Selicharová[3]
Lenka Žáková[4], Jan Pícha[5] / Research assistant: Václav Vaněk[6] / Postdocs: Benjamin Fabre[7], Jelena Radosavljević
Ph.D. students: Martina Chrudinová[8], Kateřina Macháčková[9], Emília Kletvíková-Antolíková, Květoslava Křížková, Jana Mládková
Pavlo Potalitsyn / Students: Petra Halušková[10], Kateřina Hanková, Tereza Halamová, Anna Povalová / Technician: Jitka Viková[11]

KEYWORDS / insulin, receptor, IGF, diabetes, growth, analog, peptidomimetics

Our research group is engaged in structure-activity studies of insulin and insulin-like growth factors 1 and 2 (IGFs). These important hormones and growth factors share similar 3-D structures and cell membrane receptors; two isoforms of an insulin receptor (IR-A and IR-B) and a receptor for IGFs (IGF-1R). 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.

We are interested in all aspects of insulin's and IGFs' physiology. Our general goal in insulin/IGF research is understanding of the structural basis for the different cellular responses, metabolic and mitogenic, generated by insulin and IGFs, respectively. We develop analogues of insulin and IGFs to study their interaction with cognate receptors (IR-A, IR-B and IGF-1R).

We are also involved in development of insulin and IGF mimetics. Our group comprises of biochemists and organic chemists and combines chemical synthesis with biochemical approaches. We have a close collaboration with structural biologists at the University of York in U.K.

SELECTED PAPERS

Viková, J., Collinsová, M., Kletvíková, E., Buděšínský, M., Kaplan, V., Žáková, L., Veverka, V., Hexnerová, R., Aviñó, R. J. T., Straková, J., Selicharová, I., Vaněk, V., Wright, D. W., Watson, C. J., Turkenburg, J. P., Brzozowski, A. M., and Jiráček, J. (2016) Rational steering of insulin binding specificity by intra-chain chemical crosslinking. *Sci. Rep.* **6**, 19431

Vaněk, V., Pícha, J., Fabre, B., Buděšínský, M., Lepšík, M., and Jiráček, J. (2015) The Development of a Versatile Trifunctional Scaffold for Biological Applications. *Eur. J. Org. Chem.*, 3689-3701

Kosinová, L., Veverka, V., Novotná, P., Collinsová, M., Urbanová, M., Moody, N. R., Turkenburg, J. P., Jiráček, J., Brzozowski, A. M., and Žáková, L. (2014) Insight into the Structural and Biological Relevance of the T/R Transition of the N-Terminus of the B-Chain in Human Insulin. *Biochemistry* **53**, 3392-3402

Menting, J. G., Whittaker, J., Margetts, M. B., Whittaker, L. J., Kong, G. K. W., Smith, B. J., Watson, C. J., Žáková, L., Kletvíková, E., Jiráček, J., Chan, S. J., Steiner, D. F., Dodson, G. G., Brzozowski, A. M., Weiss, M. A., Ward, C. W., and Lawrence, M. C. (2013) How insulin engages its primary binding site on the insulin receptor. *Nature* **493**, 241-U276

Žáková, L., Kletvíková, E., Veverka, V., Lepšík, M., Watson, C. J., Turkenburg, J. P., Jiráček, J., and Brzozowski, A. M. (2013) Structural Integrity of the B24 Site in Human Insulin Is Important for Hormone Functionality. *J. Biol. Chem.* **288**, 10230-10240

CURRENT GRANTS

The role of T- and R-conformations of insulin in binding to the insulin receptor, Project no. P207/11/P430, Czech Science Foundation (GA ČR), 2011–2013, Žáková, L.

A molecular dissection of the interplay between diabetes and cancer: an integrated, multidisciplinary approach, Project no. MR/K000179/1, Medical Research Council (MRC, U.K.), 2012–2017, Jiráček, J. (co-PI) and Brzozowski, A.M. (PI)

Preparation and characterization of selective analogues of insulin and IGF-1/2 and their hybrid analogues for both forms of insulin receptor and IGF-1 receptor, Project no. 638613, Grant Agency of the Charles University in Prague (GA UK), 2013–2014, Křížková, K.

Insulin mimetics, Project no. 14-17305S, Czech Science Foundation (GA ČR), 2014–2016, Jiráček, J.

Towards molecular separation of metabolic and mitogenic effects of insulin and IGF-2, Project no. 15-19018S, Czech Science Foundation (GA ČR), 2014–2017, Žáková, L.

Jan Konvalinka Group

PROTEASES OF HUMAN PATHOGENS

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Head of the group: Jan Konvalinka[1] / Scientists: Pavel Šácha[2] Milan Kožíšek[3], Klára Grantz Šašková[4] Taťána Majerová[5] / Postdocs: Klára Hlouchová[6], Jana Pokorná[7] / Ph.D. students: Michal Navrátil, Václav Navrátil[8] Tomáš Knedlík[9], František Sedlák, Michal Svoboda[10], Barbora Vorlová[11], Monika Sivá[12], Kristýna Blažková[13] Students: Petra Dvořáková[14], Jan Belza, Alžběta Baudyšová, Vojtěch Dolejš[15], Jakub Hejdánek[16], Jakub Staníček Iva Hrubá, Karolína Janoušková, Elena Karluková[17], Zuzana Kružíková, Anežka Písačková, Robin Kryštůfek[18] Jaroslav Kurfürst, Barbora Ptáčková, Vjačeslav Tretjačenko, Kristýna Šmilauerová / Assistants: Jitka Krčmářová[19] Technicians: Jana Starková[20], Iva Flaisigová[21], Karolína Šrámková[22]

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

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

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

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

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

SELECTED PAPERS

Šácha, P., Knedlík, T., Schimer, J., Tykvart, J., Parolek, J., Navrátil, V., Dvořáková, P., Sedlák, F., Ulbrich, K., Strohalm, J., Majer, P., Šubr, V., and Konvalinka, J. (2016) iBodies: Modular Synthetic Antibody Mimetics Based on Hydrophilic Polymers Decorated with Functional Moieties. *Angew. Chem.-Int. Edit.* **55**, 2356-2360

Machara, A., Lux, V., Kožíšek, M., Grantz Šašková, K., Štěpánek, O., Kotora, M., Parkan, K., Pávová, M., Glass, B., Sehr, P., Lewis, J., Müller, B., Kräusslich, H. G., and Konvalinka, J. (2016) Specific Inhibitors of HIV Capsid Assembly Binding to the C-Terminal Domain of the Capsid Protein: Evaluation of 2-Arylquinazolines as Potential Antiviral Compounds. *J. Med. Chem.* **59**, 545-558

Schimer, J., Pávová, M., Anders, M., Pachl, P., Šácha, P., Cígler, P., Weber, J., Majer, P., Řezáčová, P., Kräusslich, H. G., Müller, B., and Konvalinka, J. (2015) Triggering HIV polyprotein processing by light using rapid photodegradation of a tight-binding protease inhibitor. *Nat. Commun.* **6**, 8

Tykvart, J., Bařinka, C., Svoboda, M., Navrátil, V., Souček, R., Hubálek, M., Hradilek, M., Šácha, P., Lubkowski, J., and Konvalinka, J. (2015) Structural and Biochemical Characterization of a Novel Aminopeptidase from Human Intestine. *J. Biol. Chem.* **290**, 11321-11336

Sedlák, F., Šácha, P., Blechová, M., Březinová, A., Šafařík, M., Šebestík, J., and Konvalinka, J. (2013) Glutamate carboxypeptidase II does not process amyloid-beta peptide. *Faseb J.* **27**, 2626-2632

CURRENT GRANTS

Design, characterization, and mechanism of action of novel inhibitors of HIV assembly, Project no. 13-19561S, Czech Science Foundation (GA ČR), 2013–2015, Konvalinka, J.

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

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

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

Josef Lazar Group

ADVANCED OPTICAL MICROSCOPY

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Head of the group: Josef Lazar[1] / Postdocs: Alexey Bondar, Petro Khoroshyy[2], Paul Miclea, Ievgeniia Iermak[3]
Lab technician/manager: Olga Rybakova[4] / Students: Kristýna Sládková[5], Aneta Sládková[6], Karolína Svobodová[7]

KEYWORDS / two-photon polarization microscopy, linear dichroism, molecular probes, G-proteins, voltage sensors

The Laboratory of Advanced Optical Microscopy develops advanced techniques of optical microscopy and uses them to gain information about mechanisms of molecular processes taking place in living cells and organisms. The Laboratory has developed the technique of two-photon polarization microscopy (2PPM), which allows sensitive observations of changes in conformation of membrane proteins. Such conformational changes can occur, for example, in response to a therapeutic drug or to changes in cell membrane voltage.

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

The Laboratory's multidisciplinary expertise in biochemistry, molecular and cell biology, biophysics, optics, electronic engineering, computer programming and mathematical modeling allows tackling of a wide range of difficult scientific questions.

SELECTED PAPERS

Timr, Š., Brabec, J., Bondar, A., Ryba, T., Železný, M., Lazar, J., and Jungwirth, P. (2015) Nonlinear Optical Properties of Fluorescent Dyes Allow for Accurate Determination of Their Molecular Orientations in Phospholipid Membranes. *J. Phys. Chem. B* **119**, 9706-9716

Bondar, A., and Lazar, J. (2014) Dissociated G alpha(GTP) and G beta gamma Protein Subunits Are the Major Activated Form of Heterotrimeric Gi/o Proteins. *J. Biol. Chem.* **289**, 1271-1281

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

Han, Z., Jin, L., Chen, F. Y., Loturco, J. J., Cohen, L. B., Bondar, A., Lazar, J., and Pieribone, V. A. (2014) Mechanistic Studies of the Genetically Encoded Fluorescent Protein Voltage Probe ArcLight. *PLoS One* **9**, 21

Lazar, J., Bondar, A., Timr, S., and Firestein, S. J. (2011) Two-photon polarization microscopy reveals protein structure and function. *Nat. Methods* **8**, 684-690

CURRENT GRANTS

Insights into protein structure from polarization fluorescence microscopy, Project no. 13-10799S, Czech Science Foundation (GA ČR), 2012–2016, Lazar, J.

Systems biology center (C4Sys), center of excellence, Project no. LM2015055, Ministry of Education, Youth and Sports (MŠMT ČR), 2016–2022, Lazar, J.

Lenka Maletínská Group

PATHOPHYSIOLOGICAL MECHANISMS OF FOOD INTAKE REGULATION

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KEYWORDS / obesity, metabolic syndrome, Tau pathology, anorexigenic neuropeptide, prolactin releasing peptide, lipopeptide, CART peptide, ghrelin antagonist

The research of our group is focused on food intake regulation with the aim to develop new pharmacological interventions for obesity and related conditions. Our research has a multidisciplinary character, it involves peptide chemistry, biochemistry, physiology, and pharmacology.

Food intake regulating peptides not only affect hunger or satiety but also energy homeostasis. Recently discovered anorexigenic – food intake attenuating – neuropeptides, such as prolactin-releasing peptide (PrRP) and cocaine- and amphetamine-regulated transcript (CART) peptide, represent new trends in development of anti-obesity agents. They target directly the brain areas regulating food intake, rarely have unwanted side effects but generally do not cross the blood-brain barrier if administered peripherally. Recently, we designed stable lipidized analogs of PrRP with agonistic effect capable to cross the blood-brain barrier. Lipidized PrRP analogs had prolonged half-lives in blood and exerted anti-obesity effects after peripheral administration in mice and rats with diet induced obesity and insulin resistance. For CART peptide, known for two decades, 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.

Ghrelin is the only orexigenic peptide of gut origin. Ghrelin antagonists represent other potential anorexigenic substances. Ghrelin antagonists containing trisubstituted 1, 2, 4-triazoles accomplished an anorexigenic effect resulting in attenuated body – preferably adipose tissue – mass in mice with diet induced obesity.

Type 2 diabetes was shown to be a risk factor for Alzheimer disease. We found the connection between central insulin resistance and pathological phosphorylation of tau protein – the hallmark of Alzheimer disease – in mice with monosodium glutamate obesity, a model of prediabetes.

Head of the group: Lenka Maletínská[1] / Scientists: Jaroslav Kuneš[2], Blanka Železná[3], Martina Holubová[4] Andrea Popelová[5] / Postdoc: Zuzana Majerčíková[6] / Ph.D. students: Veronika Pražienková[7], Barbora Mikulášková[8] Jana Zemenová[9] / Research assistant: Lucie Hrubá[10] / Students: Barbora Judita Kasperová, Anna Kákonová[11] Lucie Šatrová[12], Barbora Kochmanová[13] / Technician: Hedvika Vysušilová[14]

SELECTED PAPERS

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

Špolcová, A., Mikulášková, B., Holubová, M., Nagelová, V., Pirník, Z., Zemenová, J., Haluzík, M., Železná, B., Galas, M. C., and Maletínská, L. (2015) Anorexigenic lipopeptides ameliorate central insulin signaling and attenuate Tau phosphorylation in hippocampi of mice with monosodium glutamate-induced obesity. *J. Alzheimers Dis.* **45**, 823-835

Maletínská, L., Nagelová, V., Tichá, A., Zemenová, J., Pirník, Z., Holubová, M., Špolcová, A., Mikulášková, B., Blechová, M., Sýkora, D., Lacinová, Z., Haluzík, M., Železná, B., and Kuneš, J. (2015) Novel lipidized analogs of prolactin-releasing peptide have prolonged half-lives and exert anti-obesity effects after peripheral administration. *Int. J. Obes.* **39**, 986-993

Nagelová, V., Pirník, Z., Železná, B., and Maletínská, L. (2014) CART (cocaine- and amphetamine-regulated transcript) peptide specific binding sites in PC12 cells have characteristics of CART peptide receptors. *Brain Res.* **1547**, 16-24

Holubová, M., Nagelová, V., Lacinová, Z., Haluzík, M., Sýkora, D., Moulin, A., Blayo, A. L., Fehrentz, J. A., Martinez, J., Stofkova, A., Jurčovičová, J., Železná, B., and Maletínská, L. (2014) Triazole GHS-R1a antagonists JMV4208 and JMV3002 attenuate food intake, body weight, and adipose tissue mass in mice. *Mol. Cell. Endocrinol.* **393**, 120-128

CURRENT GRANTS

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

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

The possible role of stable analogs of prolactin-releasing peptide in experimental models of obesity and hypertension, Project no. 15-08679S, Czech Science Foundation (GA ČR), 2015–2017, Maletínská, L.

Metabonomics of mouse models of obesity and lipoatrophy - studies of metabolic pathways perturbations, disease progression and therapy response, Project no. 13-14105S, Czech Science Foundation (GA ČR), 2013–2016, Železná, B. (co-PI)

Effect of different types of antidiabetic interventions on the development of neurodegenerative changes in brain of diabetic mice, Project no. P303-12-0576, Czech Science Foundation (GA ČR), 2012–2014, Maletínská, L.

Pavlína Maloy Řezáčová Group

STRUCTURAL BIOLOGY

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KEYWORDS / X-ray crystallography, biomolecular NMR spectroscopy, rational drug design, fragment-based drug discovery, transcription regulation, medicinal targets

The main interest of the laboratory lies in structural characterization of proteins and protein-protein complexes having biological or medicinal interest. We use structural knowledge for understanding and also modulation of biological roles and functions of proteins and protein-protein complexes. We are interested in the structure of transcription factors, both prokaryotic and eukaryotic. To understand the mechanism of carbon catabolite repression in *B. subtilis* on a molecular level, we combine X-ray structures with other techniques to study the binding of small molecules to selected repressors and their modulation. Structural studies of human transcription factors are focused on proteins interacting with LEDGF/p75, a prominent cellular cofactor for HIV integration.

In our structure-based drug discovery project, targeting enzymes from pathogenic organisms as well as human enzymes (e.g. carbonic anhydrases), the knowledge of protein structures provides a platform for the rational design of specific inhibitors. We also use fragment-based drug discovery techniques for targeting biomedicinally important protein-protein interactions.

The topic of structural biology of metabolic pathways focuses on structural characterization of components of important metabolic pathways which can contribute to development of perspective therapeutics for metabolic diseases.

Head of the group: Pavlína Řezáčová[1] / Scientists: Jiří Brynda[2], Václav Veverka[3] / Postdocs: Kateřina Čermáková[4] Aleš Hnízda[5], Petr Pachl[6], Pavel Srb[7], Jana Škerlová / Research assistants: Marcela Mádlíková[8], Blanka Klepetářová[9] Irena Sieglová[10] / Technicians: Jitka Kredbová, Kate Tratsiak[12] / Ph.D. students: Rozálie Hexnerová[13], Michael Kugler[14] Petr Těšina, Lukáš Vrzal[15] / Undergraduate students: Vítězslav Brinsa, Vojtěch Duchoslav[16], Markéta Nováková[17] Klára Pospíšilová[18], Anna Soldánová

SELECTED PAPERS

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

Čermáková, K., Tesina, P., Demeulemeester, J., El Ashkar, S., Mereau, H., Schwaller, J., Řezáčová, P., Veverka, V., and De Rijck, J. (2014) Validation and Structural Characterization of the LEDGF/p75-MLL Interface as a New Target for the Treatment of MLL-Dependent Leukemia. *Cancer Res.* **74,** 5139-5151

Škerlová, J., Fábry, M., Hubálek, M., Otwinowski, Z., and Řezáčová, P. (2014) Structure of the effector-binding domain of deoxyribonucleoside regulator DeoR from Bacillus subtilis. *Febs J.* **281**, 4280-4292

Pachl, P., Fábry, M., Rosenberg, I., Šimák, O., Řezáčová, P., and Brynda, J. (2014) Structures of human cytosolic and mitochondrial nucleotidases: implications for structure-based design of selective inhibitors. *Acta Crystallogr. Sect. D-Biol. Crystallogr.* **70**, 461-470

Brynda, J., Mader, P., Šícha, V., Fábry, M., Poncová, K., Bakardiev, M., Grüner, B., Cígler, P., and Řezáčová, P. (2013) Carborane-Based Carbonic Anhydrase Inhibitors. *Angew. Chem.-Int. Edit.* **52**, 13760-13763

CURRENT GRANTS

Rational drug design using NMR spectroscopy, Project no. LK11205-Navrat, Ministry of Education, Youth and Sports (MŠMT ČR), 2012–2016, Veverka, V.

Center for development of original drugs (CDOD), Technology Agency of the Czech Republic (TA ČR), 2012–2019, Maloy Řezáčová, P.

Molecular mechanisms of relapsed acute lymphoblastic leukemia: characterization of hyperactive mutants of cytosolic purine 5´-nucleotidase, Project no. GA15-06582S, Czech Science Foundation (GA ČR), 2015–2017, Hnízda, A.

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

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

Gilead Sciences Research Centre (GSRC-3), 2016-2021, Maloy Řezáčová, P., Veverka, V., Brynda, J.

Michael Mareš Group

CATHEPSIN PROTEASES IN PATHOLOGY

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KEYWORDS / protease, inhibitor, protein structure, parasite, cancer

Our research focuses on cathepsin proteases involved in parasitic diseases, cancer, and degenerative diseases. In blood-feeding parasites, cathepsins function as digestive enzymes responsible for the breakdown of host blood proteins and represent pharmacological targets.

The major project investigates the blood flukes causing schistosomiasis, which afflicts more than 250 million people worldwide. The research includes identification of schistosome cathepsins, mapping of their structure-function relationships, and rational designing of inhibitor drugs.

The second project is focused on *Ixodes* ticks that are vectors of tick-borne encephalitis and borreliosis in Europe and the US. We investigate digestive cathepsins and salivary cathepsin inhibitors from ticks as potential anti-tick vaccines.

Finally, we study human cathepsins associated with cancer and degenerative diseases. Here we focus on novel biochemical mechanisms of regulation of cathepsin activity and their exploitation for the development of therapeutic molecules and strategies.

Head of the group: Michael Mareš[1] / Scientists: Martin Horn[2], Jan Dvořák
Research assistants: Lucie Marešová[3], Jana Pytelková[4] / Postdocs: Adéla Jílková[5], Manasi Mishra
Ph.D. students: Jakub Benýšek[6], Michal Buša[7], Pavla Fajtová[8], Iva Hanová, Radka Hobizalová, Adrian Leontovyč[9]
Zuzana Matoušková, Jaroslav Srp[10], Lenka Ulrychová[11] / Students: Bagina Sreelatha, Marina Bakardijeva, Hana Illichová[12]
Irena Oupicová, Daniela Polatová[13], Petra Rubešová[14] / Technician: Irena Pražáková

SELECTED PAPERS

Srp, J., Nussbaumerová, M., Horn, M., and Mareš, M. (2016) Digestive Proteolysis in the Colorado Potato Beetle, *Leptinotarsa Decemlineata:* Activity-Based Profiling and Imaging of a Multipeptidase Network. *Insect Biochem. Mol. Biol.* **78**, 1-11

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Novel antiparasite drugs: from target proteins to inhibitor chemotherapeutics, Project no. LH12023, AMVIS / MŠMT ČR (Czech-US S&T Cooperation), 2012–2015, Mareš, M.

Centre of molecular interactions in biomedicine, Project no. LO1302, NPU / Ministry of Education, Youth and Sports (MŠMT ČR) , 2014–2019, Mareš, M.

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

New inhibition mechanisms for regulation of aspartic proteases in pathological processes, Project no. 15-189295, Czech Science Foundation (GA ČR), 2015–2017, Mareš, M.

Chemical and structural genomics of peptidase drug targets in human blood fluke, Project no. LD15101, COST / Ministry of Education, Youth and Sports (MŠMT ČR) – European S&T Cooperation, 2015–2017, Horn, M.

Iva Pichová Group

VIRAL AND MICROBIAL PROTEINS

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Head of the group: Iva Pichová[1] / Scientists: Olga Hrušková, Michaela Rumlová, Helena Zábranská[2], Aleš Zábranský[3]
Postdocs: Michal Doležal[4], Jiří Dostál[5], Jan Snášel[6] / Ph.D. students: Aleš Buček[7], Alena Keprová[8], Klára Herkommerová[9]
Hana Langerová, Iva Machová[10], Ondřej Žítek / Research assistants: Mária Čechová[11], Romana Hadravová[12]
Ivana Křížová[13] / Technicians: Romana Cubínková[14], Elena Dolejší[15], Dagmar Grundová[16]

KEYWORDS / retroviruses, hepatitis B virus, assembly, replication, *Mycobacterium tuberculosis*, metabolism, latent infection, pathogenic *Candida* yeasts, secreted proteases, desaturases

During this period the interdisciplinary research of our group was centered on understanding the role of proteins involved in different steps of a life cycle of several human pathogens and on host factors that modulate pathogenesis of diseases.

In a project focused on retroviruses we investigated the mechanism of assembly of HIV-1, Mason-Pfizer monkey virus, and mouse mammary tumor virus immature particles and identified structural motifs and interactions mediating formation of both immature as well as mature particles. We also identified the cellular protein which interacts with HIV-1 protease (PR) and enhances HIV-1PR induced apoptosis. Our new project is focused on the study of interactions of Hepatitis B virus X protein with cellular factors and on maturation of precore protein HBe during the HBV life cycle.

Another target of our group is *Mycobacterium tuberculosis* (Mtb). We explored the function of enzymes in regulation of non-replicating Mtb metabolism. We focused on phosphoenolpyruvate carboxykinase (Pck) that catalyzes reactions in anaplerotic node, distributing carbon flow in glycolysis, gluconeogenesis, and tricarboxylic cycle, and identified conditions and cellular interacting proteins that modulate its specificity and influence the carbon flow. Our new targets are phosphofructokinase A and B that are differently expressed during Mtb infection stages.

In our research of *Candida* pathogenic yeasts we investigated the role of secreted aspartic proteases (Sap) in regulation of metabolism under stress conditions and performed structure-function characterization of different Sap isoforms. We further characterized fatty acid desaturases (FAD) of *C. parapsilosis* and using insect model FADs we identified the structural motif that determines FAD specificities. Our new project is focused on identification of carbonic anhydrases in *C. parapsilosis* and development of its inhibitors and on the study of interaction of *C. albicans* with *Pseudomonas aeruginosa*.

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Systems biology of Mycobacterium tuberculosis, Project no. 7E11070, Ministry of Education, Youth and Sports (MŠMT ČR), 2010–2014, Pichová, I.

Immobilized yeasts in biotechnology: development of new applications for manufacturing, Project no. TA01011461, Technology Agency of the Czech Republic (TA ČR), 2011–2014, Pichová, I.

Study of structure and interactions critical for formation of immature retroviral particles for testing and rational design of HIV assembly inhibitors, Project no. GA14-15326S, Czech Science Foundation (GA ČR), 2014–2016, Rumlová, M.

Gilead Sciences Research Centre (GSRC-2, GSRC-3), 2011-2021, Pichová, I.

Kvido Stříšovský Group

INTRAMEMBRANE PROTEOLYSIS AND BIOLOGICAL REGULATION

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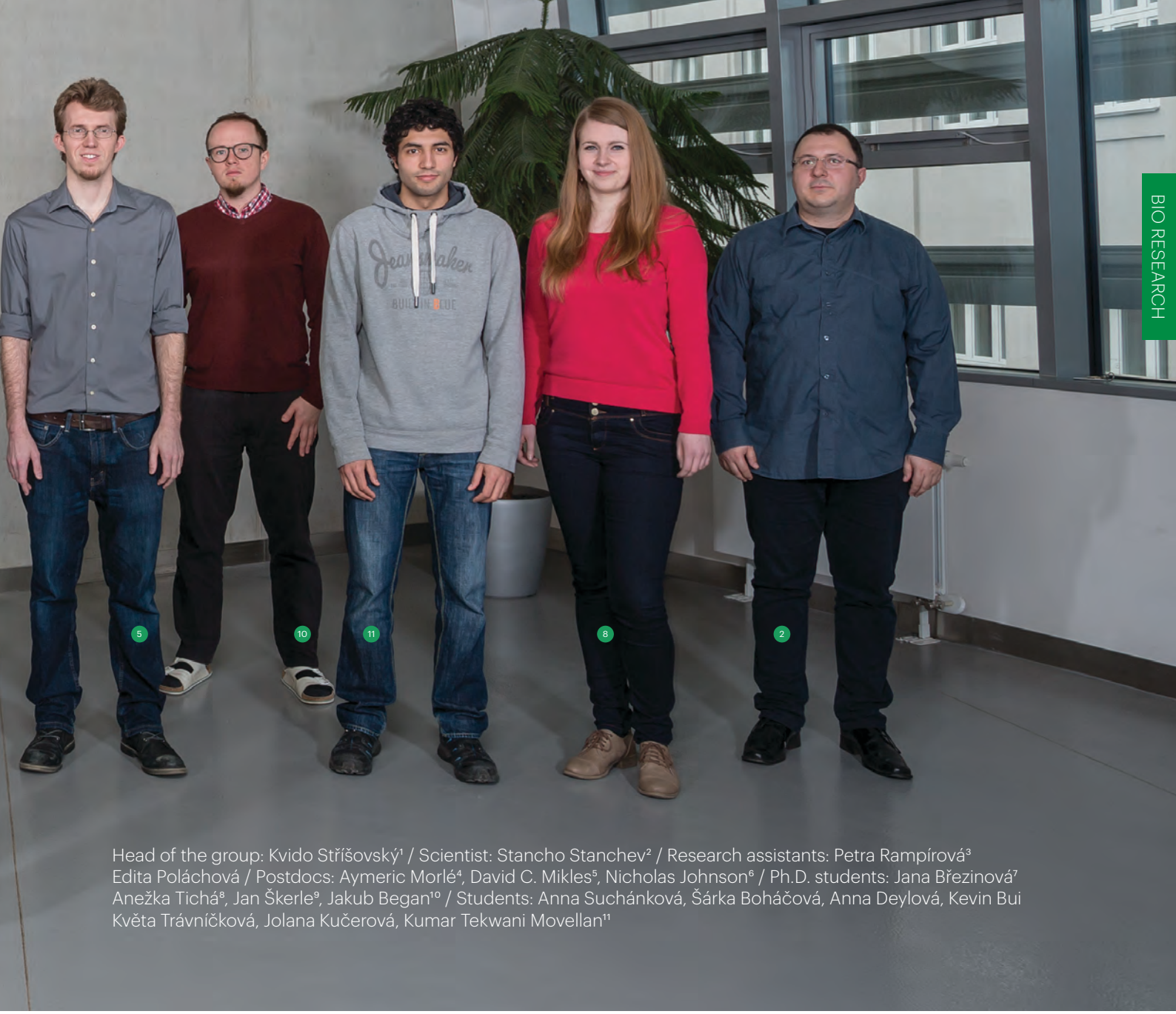
KEYWORDS / membrane protein, signaling, intramembrane proteolysis, protein structure, lipid membrane

The complexity of biological membranes and of chemical processes occurring in their context are fascinating and essential for life. Most of the functions of biological membranes are performed or catalysed by proteins integrated in or associated with membranes, and as much as 25 to 30 % 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 or 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 recognise and cleave transmembrane domains of other membrane proteins within the hydrophobic, lipid environment. They have been implicated in human diseases, including Alzheimer's, Parkinson's, immune disorders, cancer, and some infectious diseases. Understanding the mechanisms, structures, and regulation of these enzymes can open new ways to fight multiple pathological conditions. We focus on intramembrane proteases of the rhomboid family, which control growth factor signaling in flies, mitochondrial dynamics in yeast or pathogenicity of the malaria parasite, and on their proteolytically inactive cousins, iRhoms, which regulate membrane protein trafficking.

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



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Intramembránové proteasy rodiny rhomboidů v sekreční dráze savčích buněk: repertoár substrátů, specifita, biologické úlohy a jejich inhibice, Project no. LK11206, Reintegration grant, Ministry of Education, Youth and Sports (MŠMT ČR), 2012–2016, Stříšovský, K.

Intramembrane proteases of rhomboid family – specificity, mechanism, and substrate identification as a key to their biological roles, Project no. P305/11/1886, Czech Science Foundation (GA ČR), 2011–2013, Stříšovský, K.

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

Irena Valterová Group

INFOCHEMICALS

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Technicians: Pavlína Hovorková[7], Anna Nekolová[8], Jarmila Titzenthalerová[9]

KEYWORDS / chemical ecology, social insects, pheromones, biosynthesis, bumblebees, bumblebee parasites, fruit flies

The goal of the team is to deepen the understanding of chemical ecology of social insects, namely bumblebees as a representative of beneficial insects (important pollinators both in fields and in greenhouses), and of some economically important insect pests such as fruit flies.

Using multidisciplinary approaches, combining analytical chemistry (comprehensive two-dimensional gas chromatography/mass spectrometry) with biology (electroantennography, electron microscopy, bioassays), molecular biology, and transcriptomics, the group focuses on studying sex pheromones as well as biosynthetic pathways of pheromone formation and the enzymes involved. Furthermore, the group studies the role of lipids in biosynthesis. Transcriptomic approach enables us to identify candidate genes involved in pheromone biosynthesis. The aspects of molecular biology underlying our research are studied in collaboration with IOCB team of Iva Pichová.

Besides the general focus on basic research, we are aiming our projects at particular aspects of life history of insect species with a future prospect of pest control.

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CURRENT GRANTS

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Pollinators as a crucial factor in agriculture, Project no. TA01020969, Technology Agency of the Czech Republic (TA ČR), 2011–2014, Valterová, I.

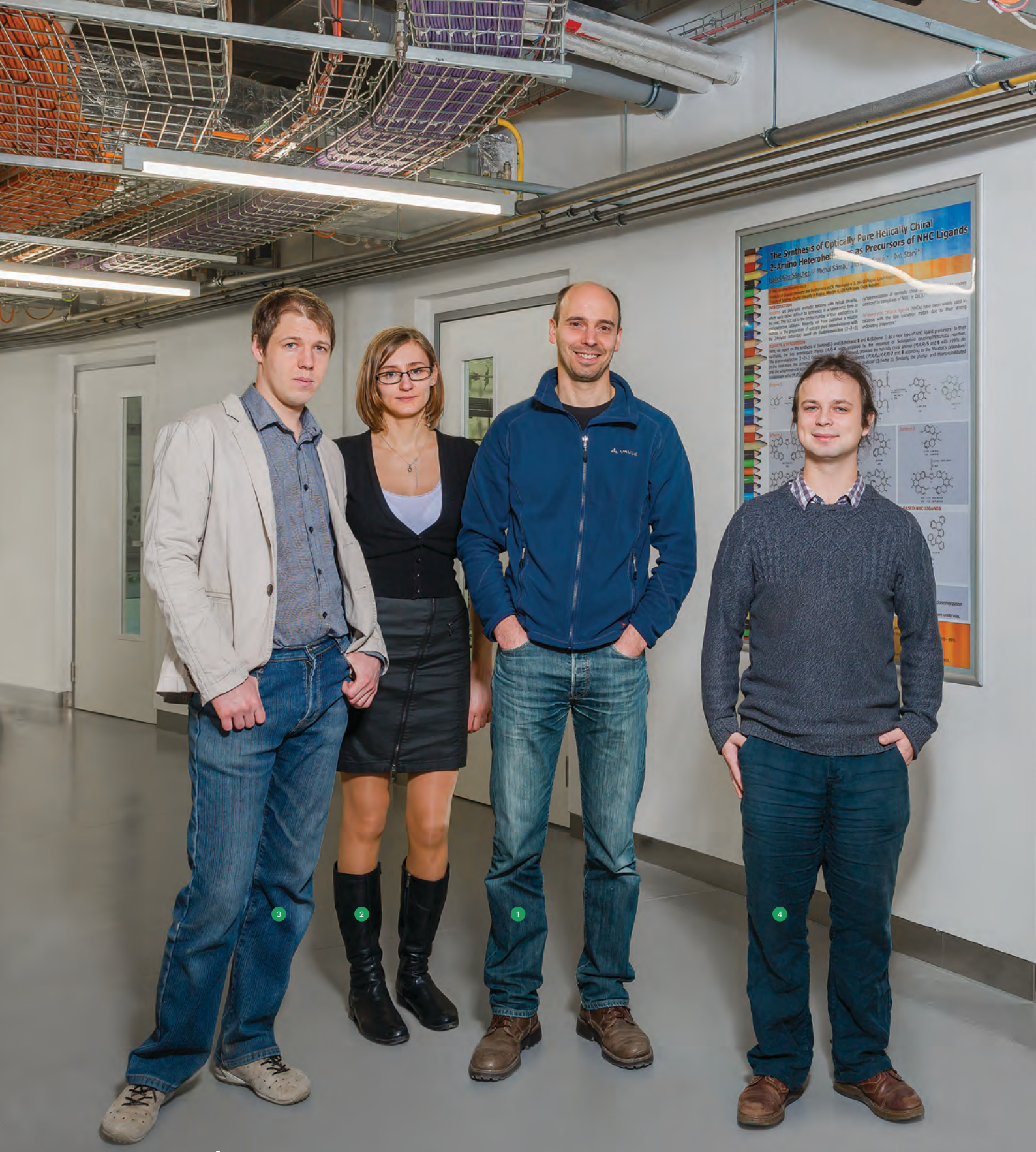
Chemical Ecology of African *Ceratitis* FAR Complex, Project no. 16965, IAEA, 2011–2016, Hoskovec, M.

Analysis of epicuticular composition in genera *Anastrepha and Ceratitis*, Project no. 16106, IAEA, 2010–2015, Kalinová, B.

Hibernation versus aestivation in bumblebees: A lipidomic study, Project no. 14-04291S, Czech Science Foundation (GA ČR), 2014–2016, Valterová, I.

Bumblebee pollinators: Pheromones can help to manage and protect bumblebee colonies, Project no. LD15102, COST Action FA1307, Ministry of Education, Youth and Sports (MŠMT ČR), 2015–2017, Valterová, I.

Enzyme-catalyzed reduction of fatty acids in the biosynthesis of the bumblebee pheromones and its regulation by neuropeptides, Project no. 15-0659S, Czech Science Foundation (GA ČR), 2015–2017, Valterová, I.



Norbert Weiss Group

ION CHANNELS AND DISEASES

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Head of the group: Norbert Weiss[1] / Postdocs: Joanna Lazniewska[2], Yuriy Rzhepetskyy[3], Paula Rivas Ramirez
Students: Amine Belaouad, Tomáš Pelant[4] / Visiting Student: Aisylu Gaifullina, Merve Acil

KEYWORDS / ion channels, calcium channels, channelopathies, neuron, neuroscience, pain, epilepsy, ALS

Research in the laboratory of Norbert Weiss is directed toward understanding molecular and cellular mechanisms underlying human diseases caused by dysfunction of ion channels, more specifically calcium channels. Calcium is the Mother Nature's "ion-of-choice" for orchestrating fundamental cellular functions, as it contributes to neuronal excitability, muscle contraction, gene transcription, and a plethora of other key processes conducing to normal physiology of the body. Calcium channels, which act as gated pathways for movement of calcium across cell membranes, play a central part in the initiation of calcium signals, and defects in calcium channel function have dramatic consequences resulting in severe human diseases, so-called channelopathies.

Channelopathies are a heterogeneous group of disorders resulting from dysfunction of ion channels located in the membranes of all cells and many cellular organelles. These include diseases of the nervous system, cardiovascular system, respiratory system, endocrine system, urinary system, and immune system. There are two types of channelopathies: congenital and acquired. Congenital conditions are genetic in nature and can be inherited or a result of spontaneous mutations. Acquired conditions occur usually later in life and are a result of alteration of ion channels functions caused by aging, drugs, toxins, and other cellular environment.

The laboratory uses a combination of electrophysiological recordings (patch-clamp), confocal imaging microscopy and molecular and biochemical assays to identify the underlying mechanisms of alteration of ion channels in neurological disorders including neuropathic pain, epilepsy, and amyotrophic lateral sclerosis (ALS) to provide a better understanding of the pathology and ultimately propose new therapeutic avenues.

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Proft, J., and Weiss, N. (2015) G Protein Regulation of Neuronal Calcium Channels: Back to the Future. *Mol. Pharmacol.* **87**, 890-906

Lazniewska, J., and Weiss, N. (2014) The "sweet" side of ion channels. *Rev. Physiol. Biochem. Pharmacol.* **167**, 67-114

CURRENT GRANTS

Pathophysiology of T-type calcium channels in diabetic neuropathy, Project no. 15-13556S, Czech Science Foundation (GA ČR), 2015–2017, Weiss, N.

Pathophysiology of T-type calcium channels in painful peripheral diabetic neuropathy. Project no. 7AMB15FR, Ministry of Education, Youth and Sports (MŠMT ČR), 2015–2016, Weiss, N.

Petr Beier Group

ORGANIC CHEMISTRY OF FLUORINE AND MAIN GROUP ELEMENTS

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

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

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

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

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

Other research projects under investigation include synthesis of butenolide germination promotors and inhibitors and determination of mechanism of their action and structure-activity relationship as well as investigation of properties and utilization of perfluorocarbons.

Head of the group: Petr Beier[1] / Scientists: Svatava Voltrová[2], Martin Pošta[3]
Postdoc: David Manley[4] / Ph.D. students: Jiří Václavík, Zsófia Blastik[5], Javier Ajenjo[6]
Viktor Khutoryanskiy[7], Iveta Klimánková[8] / Student: Alena Budinská[9]

SELECTED PAPERS

Matoušek, V., Václavík, J., Hájek, P., Charpentier, J., Blastik, Z. E., Pietrasiak, E., Budínská, A., Togni, A., Beier, P. (2016) Expanding the scope of hypervalent iodine reagents for perfluoroalkylation: From trifluoromethyl to functionalized perfluoroethyl. *Chem. Eur. J.* **22**, 417-424

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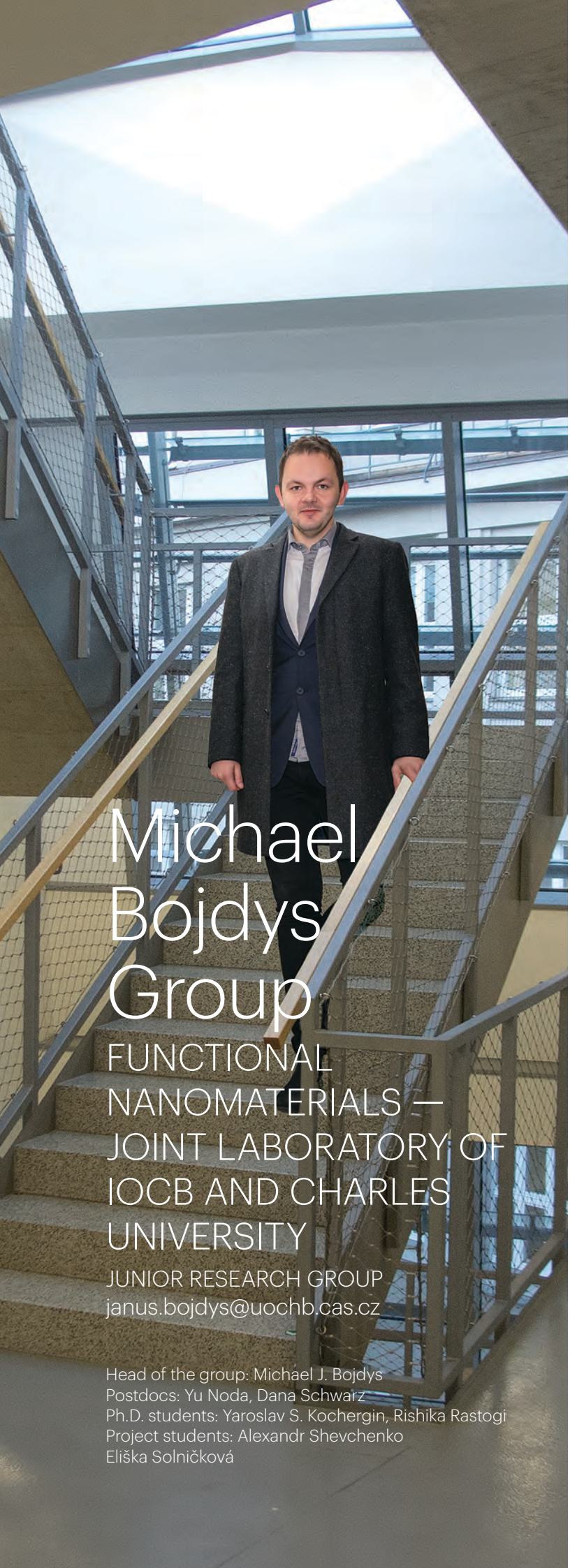
CURRENT GRANTS

Development of new methodologies towards (pentafuorosulfanyl) benzenes, Project no. P207/12/0072, Czech Science Foundation (GA ČR), 2012–2014, Beier, P.

Initiation and Enhancement of Cooperation Grant, Project no. RO 362/54-1, Deutsche Forschungsgemeinschaft (DFG), 2012–2013, Beier, P.

FLUOR21: Synthesis, structure and function of fluorinated systems, Project no. FP7-PEOPLE-2013-ITN, European Commission 7th Framework Programme, The People Programme, Initial Training Network, 2014–2017, Beier, P.



Michael Bojdys Group

FUNCTIONAL NANOMATERIALS — JOINT LABORATORY OF IOCB AND CHARLES UNIVERSITY

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Eliška Solničková

KEYWORDS / graphene, covalent organic frameworks, triazine-based frameworks, ionothermal synthesis, C3N4, semiconductors

As of 2016, the number of mobile phone subscriptions outstrips Earth's human population. Critical raw materials (CRMs) and silicon, won in energy intensive refinement, make up the electronics in all these devices. While graphene still has to deliver on its potential in electronic applications, we look to 2D polymer materials that go beyond silicon and graphene.

Since its recent rise, graphene has been considered as a candidate material for "post-silicon electronics" thanks to its advantageous combination of high electrical and thermal conductivity and stability. However, the (half-)metallic character of graphene and the resulting absence of an electronic band gap have frustrated the development of a graphene-based electronic switch so far. There is an apparent lack of non-metallic 2D materials for construction of electronic devices and only five materials of the "graphene family" are known: graphene, hBN, BCN, fluorographene and graphene oxide.

The potential to make 2D materials "beyond graphene" is a great challenge to chemical bond formation and material design. In 2014 we have demonstrated the feasibility of the concept to expand the "graphene family" with a triazine-based graphitic carbon, a compound highlighted as an "emerging competitor for the miracle material" graphene. Now, our group is building a full-scale research program on layered functional materials that offers unique insights into controlled, covalent linking chemistry and that addresses practicalities in device manufacturing and structure-properties relationships.

www.uochb.cz/bojdys web.natur.cuni.cz/orgchem/funanomat

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Cooper, A. I., and Bojdys, M. J. (2014) Carbon nitride vs. graphene–now in 2D! *Materials Today* **10**, 468-469

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CURRENT GRANTS

Functional Nanomaterials Beyond Graphene (BEGMAT), Project no. 678462, European Research Council (ERC Starting Grant), 2016–2021, Bojdys, M. J.

Crystalline fully-aromatic materials (CAMs), Project no. 16-21151Y, Czech Science Foundation (GA ČR), 2016–2019, Bojdys, M. J.


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Petr Cígler Group

SYNTHETIC NANOCHEMISTRY

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Head of the group: Petr Cígler[1] / Scientist: Hana Španielová / Postdoc: Goutam Pramanik[2]
Research assistant: Zuzana Chumová[3] / Ph.D. students: Jan Havlík[4], Jitka Neburková[5]
Helena Raabová[6], Jan Bartoň[7], Marek Kindermann / Students: Jan Vávra[8], Veronika Chadimová[9]
Jan Majer[10] / Technicians: Matěj Přibyl[11], Lucie Wohlrábová

KEYWORDS / nanoparticles, bioimaging, sensing, fluorescence, nanodiamond, virus-like capside, theranostics, plasmonics

In our laboratory we find new approaches for synthesis of nanoparticles for diagnostic and therapeutic medical applications. Currently, we work 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).

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

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

For all the projects we design and synthesize novel linkers, fluorescent dyes, ligands and (in collaboration) polymers and enzyme inhibitors.

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SELECTED PAPERS

Havlík, J., Raabová, H., Gulka, M., Petráková, V., Krečmarová, M., Mašek, V., Louša, V., Štursa, J., Boyen, H. G., Nesládek, M., Cígler, P. (2016) Benchtop Fluorination of Fluorescent Nanodiamonds on a Preparative Scale: Toward Unusually Hydrophilic Bright Particles. *Adv. Funct. Mater.* **26**, 4134-4142

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

Řehoř, I., Lee, K. L., Chen, K., Hájek, M., Havlík , J., Lokajová, J., Mašát, M., Šlegerová, J., Shukla, S., Heidari, H., Bals, S., Steinmetz, N. F., and Cígler, P. (2015) Plasmonic Nanodiamonds: Targeted Core-Shell Type Nanoparticles for Cancer Cell Thermoablation. *Adv. Healthc. Mater.* **4**, 460-468

Řehoř, I., Šlegerová, J., Kučka, J., Proks, V., Petráková , V., Adam, M. P., Treussart, F., Turner, S., Bals, S., Šácha, P., Ledvina, M., Wen, A. M., Steinmetz, N. F., and Cígler, P. (2014) Fluorescent Nanodiamonds Embedded in Biocompatible Translucent Shells. *Small* **10**, 1106-1115

Havlík, J., Petráková , V., Řehoř, I., Petrák, V., Gulka, M., Štursa, J., Kučka, J., Ralis, J., Rendler, T., Lee, S. Y., Reuter, R., Wrachtrup, J., Ledvina, M., Nesládek, M., and Cígler, P. (2013) Boosting nanodiamond fluorescence: towards development of brighter probes. *Nanoscale* **5**, 3208-3211

CURRENT GRANTS

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

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

Use of plasmonic nanoparticles for in vitro diagnostics, Project no. FV10755, Ministry of industry and trade (MPO ČR), 2016-2020, Cígler, P.

Biocompatible nanodiamond probes for in vivo multimodal bioimaging, Project no. P108/12/0640, The Czech Science Foundation (GA ČR), 2012–2014, Cígler, P.

Biocompatibilization and targeting of nanoparticles for diagnostic and therapeutic applications, Project no. LH11027, Ministry of Education, Youth and Sports (MŠMT ČR), 2011–2014, Cígler, P.

Michal Hocek Group

BIOORGANIC AND MEDICINAL CHEMISTRY OF NUCLEIC ACIDS — JOINT LABORATORY OF IOCB AND CHARLES UNIVERSITY

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Head of the group: Michal Hocek[1] / Scientist: Tomáš Kraus[2] / Postdocs: Ketaki Ghosh[3], Fabricia Nici[4], Pavla Perlíková Veronika Raindlová, Sabina Smoleń[5], Zbigniew Zawada[6] / Ph.D. students: Soňa Boháčová[7], Michael Downey[8] Marianne Fleuti[9], Pedro Güixens-Gallardo[10], Ivana Ivancová[11], Matouš Krömer[12], Miroslav Kuba[13], Ján Matyašovský[14] Nemanja Milisavljević[15], Agata Olszewska[16], Marek Ondruš[17], Alessandro Panattoni[18], Nazarii Sabat[19], Anna Simonova[20] Michaela Slavíčková[21], Anna Tokarenko[22], Zuzana Vaníková[23], Lucia Veselovská[24]

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

The group designs and prepares novel types of modified derivatives and analogues of nucleobases, nucleosides, nucleotides and nucleic acids for applications in all areas of biomedicinal sciences.

Developments of synthetic methodology rely on cross-coupling and C-H arylation reactions, as well as glycosylations and phosphorylations. In medicinal chemistry, rational design as well as systematic biological activity screening of libraries of modified nucleobases and nucleosides led to discovery of several new types of potent nucleoside antivirals and cytostatics. Selected aryl-7-deazapurine nucleosides undergo preclinical study of 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 major groove of DNA for switching of interactions with proteins or regulation of transcription).

SELECTED PAPERS

Balintová, J., Špaček, J., Pohl, R., Brázdová, M., Havran, L., Fojta, M., and Hocek, M. (2015) Azidophenyl as a click-transformable redox label of DNA suitable for electrochemical detection of DNA-protein interactions. *Chem. Sci.* **6**, 575-587

Nauš, P., Caletková, O., Konečný, P., Džubák, P., Bogdanová, K., Kolář, M., Vrbková, J., Slavětínská, L., Tloušťová, E., Perlíková, P., Hajdúch, M., and Hocek, M. (2014) Synthesis, Cytostatic, Antimicrobial, and Anti-HCV Activity of 6-Substituted 7-(Het)aryl-7-deazapurine Ribonucleosides. *J. Med. Chem.* **57**, 1097-1110

Vaníková, Z., and Hocek, M. (2014) Polymerase Synthesis of Photocaged DNA Resistant against Cleavage by Restriction Endonucleases. *Angew. Chem.-Int. Edit.* **53**, 6734-6737

Kielkowski, P., Fanfrlík, J., and Hocek, M. (2014) 7-Aryl-7-deazaadenine 2'-Deoxyribonucleoside Triphosphates (dNTPs): Better Substrates for DNA Polymerases than dATP in Competitive Incorporations. *Angew. Chem.-Int. Edit.* **53**, 7552-7555

Dadová, J., Orság, P., Pohl, R., Brázdová, M., Fojta, M., and Hocek, M. (2013) Vinylsulfonamide and Acrylamide Modification of DNA for Cross-linking with Proteins. *Angew. Chem.-Int. Edit.* **52**, 10515-10518

CURRENT GRANTS

Praemium Academiae, Czech Academy of Sciences (AV ČR), 2016-2021, Hocek, M.

Gilead Sciences Research Centre (GSRC-2, GSRC-3), 2011-2021, Hocek, M.

Click chemistry for future gene therapies to benefit citizens, researchers and industry (CLICKGENE), International Training Network, European Commission (Horizon 2020), 2015–2019, Hocek, M.

Modifications and bioorthogonal reactions in the major groove of DNA for regulation of protein binding and gene expression, Project no. 14-04289S, Czech Science Foundation (GA ČR), 2014–2016, Hocek, M.

Center of novel approaches to bioanalysis and molecular diagnostics, Project no. P206/12/G151, Czech Science Foundation (Center of Excellence) (GA ČR), 2012–2018, Hocek, M.

Combinatorial and rational approaches for the synthesis and evaluation of novel modified nucleosides with cytostatic and antimicrobial activity, Project no. 207/11/0344, Czech Science Foundation (GA ČR), 2011–2015, Hocek, M.

Construction of novel functional nucleic acids for applications in chemical biology, catalysis and self assembly, Project no. 203/09/0317, Czech Science Foundation (GA ČR), 2009–2013, Hocek, M.

DNA labeling with redox markers for electrochemical sensing. Applications in analysis of nucleotide sequences and molecular diagnostics, Project no. IAA400040901, Grant Agency of AS CR (GA AV ČR), 2009–2013, Hocek, M.

Ullrich Jahn Group

CHEMISTRY OF NATURAL PRODUCTS

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

The major research areas of this group are total synthesis of natural products and their analogs as well as their biological evaluation in collaboration with partner groups.

Current efforts are directed toward total syntheses of autoxidatively formed lipid metabolites, insect pheromones, antiviral compounds, biologically active fungal alkaloids, especially bridged diketopiperazine alkaloids, and *ent*-steroids as molecular tools to decipher neuroprotection exerted by steroids at the NMDA receptor.

This requires a strong methodology development component to enable unique and efficient total synthesis approaches. In this field the group is especially active in electron-transfer chemistry and the development of new tandem processes, which incorporate multiple intermediates of different redox state.

More recently also new approaches to metal catalysis, photocatalysis and the design of new organosuperbases became a focus of the group.

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Ph.D. students: Tynchtyk Amatov[4], Maria Bosi[5], Denisa Hidasová[6], Pratap Jagtap[7], David Just[8], Vojtěch Kapras
Mikhail Klychnikov[9], Shraddha Mahamulkar[10], Tomáš Mašek[11], Lucie Řehová, Michal Šimek[12], Jakub Smrček[13]
Research assistant: Meenakshi Singh[14] / Technician: Anna Hlavačková / Student: Václav Chmela[15]

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SELECTED PAPERS

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

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

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

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

Lagoutte, R., Šebesta, P., Jiroš, P., Kalinová, B., Jirošová, A., Straka, J., Černá, K., Šobotník, J., Cvačka, J., and Jahn, U. (2013) Isolated Sex Pheromone of Strepsiptera. *Chem. Eur. J.* **19**, 8515-8524

Zlatko Janeba Group

TARGETED ANALOGUES OF NUCLEIC ACID COMPONENTS

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KEYWORDS / organic synthesis, antivirals, antiparasitic agents,
antibacterial activity, antimetabolites, nucleoside phosphonates, enzyme inhibitors

Our research group is mainly engaged in design, development, and synthesis of biologically active antimetabolites, especially analogues of nucleic acids components. Such compounds are able to act as potent inhibitors of various enzymes of nucleoside and nucleotide metabolism. Acyclic nucleoside phosphonates (ANPs), nucleotide analogues developed at IOCB, represent a key class of antimetabolites for their antiviral, cytostatic, and antiparasitic properties.

Efficient methods for synthesis of novel types of ANPs are developed in our group and biological properties of prepared compounds are studied within numerous collaborations in the Czech Republic and abroad. A special attention has recently been devoted to bisphosphonate analogues, a special class of ANPs containing a second phosphonate moiety in the acyclic part of the molecule. These analogues were shown to be potent inhibitors of purine salvage pathway HG(X)PRTases, essential enzymes for many parasites and bacteria (e.g. *Plasmodium falciparum and Mycobacterium tuberculosis*). Efficient inhibitors of adenylate cyclases represent another type of ANPs with a potential to be used in treatment of diseases caused by pathogens like *Bordetella pertussis* (whooping cough) or *Bacillus anthracis* (anthrax).

Furthermore, we study biological as well as interesting physicochemical properties of polysubstituted pyrimidines (intramolecular charge transfer, intramolecular hydrogen bonding, planamerism). Substantial effort is continuously directed to design of non-nucleoside reverse transcriptase inhibitors with potent antiviral activity and to development of pyrimidines with significant anti-inflammatory properties. Such compounds have a promising potential in treatment of ulcerative colitis, rheumatoid arthritis, and colon cancer.

Head of the group: Zlatko Janeba[1] / Scientists: Michal Česnek[2], Dana Hocková[3] / Research assistant: Petra Břehová[4]
Postdocs: Ondřej Baszczyňski, Martin M. Kaiser[5], Viktor Kolman[6] / Ph.D. students: Lucie Čechová[7], Jan Frydrych[8]
Tomáš Klejch, Jan Skácel[9], Petr Špaček[10], Pavla Tomanová[11] / Student: Filip Kalčic[12]/ Secretary: Barbara Česneková[13]

SELECTED PAPERS

Keough, D. T., Hocková, D., Janeba, Z., Wang, T. H., Naesens, L., Edstein, M. D., Chavchich, M., and Guddat, L. W. (2015) Aza-acyclic Nucleoside Phosphonates Containing a Second Phosphonate Group As Inhibitors of the Human, *Plasmodium falciparum* and *vivax* 6-Oxopurine Phosphoribosyltransferases and Their Prodrugs As Antimalarial Agents. *J. Med. Chem.* **58**, 827-846

Česnek, M., Jansa, P., Šmídková, M., Mertlíková-Kaiserová, H., Dračínský, M., Brust, T. F., Pávek, P., Trejtnar, F., Watts, V. J., and Janeba, Z. (2015) Bisamidate Prodrugs of 2-Substituted 9- 2-(Phosphonomethoxy)ethyl adenine (PMEA, adefovir) as Selective Inhibitors of Adenylate Cyclase Toxin from *Bordetella pertussis*. *ChemMedChem* **10**, 1351-1364

Eng, W. S., Hocková, D., Špaček, P., Janeba, Z., West, N. P., Woods, K., Naesens, L. M. J., Keough, D. T., and Guddat, L. W. (2015) First Crystal Structures of *Mycobacterium tuberculosis* 6-Oxopurine Phosphoribosyltransferase: Complexes with GMP and Pyrophosphate and with Acyclic Nucleoside Phosphonates Whose Prodrugs Have Antituberculosis Activity. *J. Med. Chem.* **58**, 4822-4838

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

Keough, D. T., Špaček, P., Hocková, D., Tichý, T., Vrbková, S., Slavětínská, L., Janeba, Z., Naesens, L., Edstein, M. D., Chavchich, M., Wang, T. H., de Jersey, J., and Guddat, L. W. (2013) Acyclic Nucleoside Phosphonates Containing a Second Phosphonate Group Are Potent Inhibitors of 6-Oxopurine Phosphoribosyltransferases and Have Antimalarial Activity. *J. Med. Chem.* **56**, 2513-2526

CURRENT GRANTS

Targeted drug design for bioterrorism prevention. Development of effective inhibitors of the adenylate cyclase toxin of *Bordetella pertusis* and *Bacillus anthracis*, Project no. VG20102015046, Ministry of Interior of the Czech Republic (MV ČR), 2010–2015, Janeba, Z.

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

Inhibitors of 6-oxopurine phosphoribosyltransferases based on acyclic nucleoside phosphonates: potential novel antibacterial and antiparasitic agents, Project no. 16-06049S, Czech Science Foundation (GA ČR), 2016–2018, Hocková, D.

Novel types of acyclic nucleoside phosphonates with potential antimalarial activity: hypoxanthine-guanine-xanthine phosphoribosyltransferase inhibitors, Project no. P207/11/0108, Czech Science Foundation (GA ČR), 2011–2014, Hocková, D.

Structure-activity relationship (SAR) study of immunosuppressive effects of pyrimidine analogues, Project no. P303/12/0172, Czech Science Foundation (GA ČR), 2012–2016, Zídek, Z. & Janeba, Z.

An integrated study of acyclic nucleoside phosphonates as antimalarial drugs, Project No. 1030353, National Health and Medical Research Council, Australia, 2012–2014, Guddat, L & Hocková, D.

Gilead Sciences Research Centre (GSRC-2, GSRC-3), 2011-2021, Janeba, Z.

Josef Michl Group

ORGANIC CHEMISTRY

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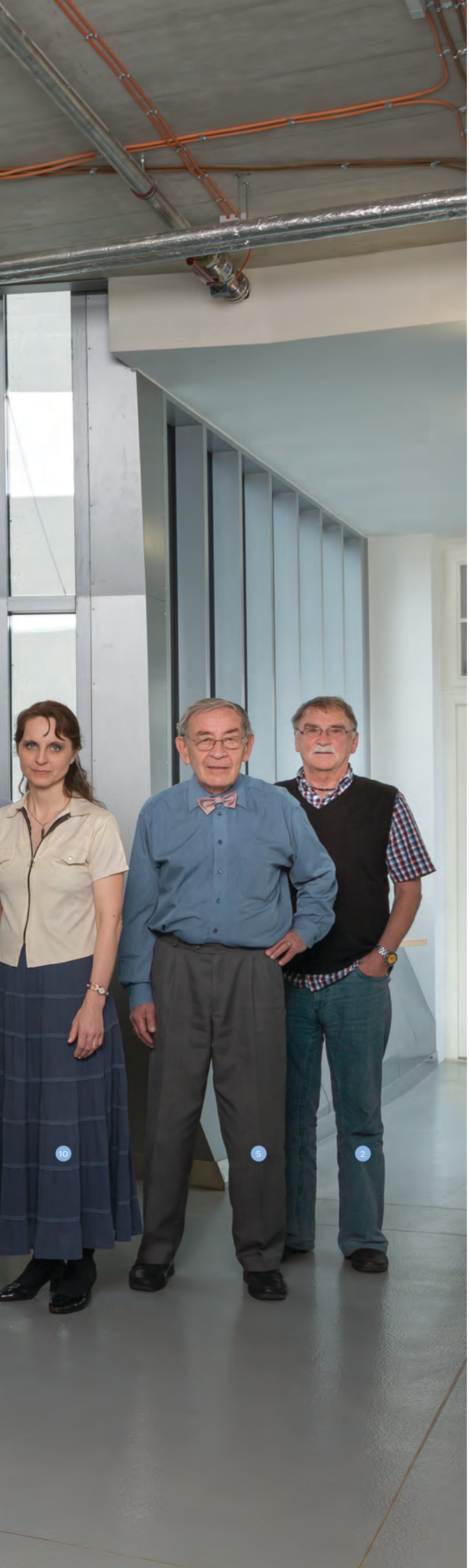
Anna Kohutová, Milan Mašát[8], Carina Santos Hurtado, Katarina Varga[9], Yenupuri Tej Varma
Secretaries: Dana Račková, Anna Kozáková[10], Kateřina Pokorná



KEYWORDS / alkylation of gold surfaces, singlet fission, molecular rotors, carboranes, fluorination

NEW TYPES OF FUNCTIONALITIES FOR MOLECULAR SELF-ASSEMBLY AND ATTACHMENT TO SURFACES
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 are attempting to find out whether direct attachment of carbon to gold can be achieved simply.

SINGLET FISSION SENSITIZERS FOR SOLAR CELLS
Singlet fission is a usually inefficient process in which a molecular chromophore excited into its singlet state shares energy with a nearby ground state chromophore, producing a pair of triplet excited chromophores, at first coupled into an overall singlet. We are working on syntheses of suitable candidate molecules based on computational results of Dr. Zdeněk Havlas's group.

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

FLUORINATION OF WEAKLY NUCLEOPHILIC ANIONS DERIVED FROM $CB_{11}H_{12}$- AND GRAPHENE BASED MATERIALS
Construction of a modular laboratory fluorine line in our laboratory gives a possibility for synthesis of weakly nucleophilic anions with a high oxidation potential like 1H-$CB_{11}F_{11}$-, 1H-$CF_6B_{11}(CF_3)_5$-, and 1H-$CF_5B_{11}(CF_3)_6$-. The line also enables fluorination of graphene based materials to produce a new class of graphenes with an industrial potential.

SELECTED PAPERS

Kaletová, E., Kohutová, A., Hajduch, J., Kaleta, J., Bastl, Z., Pospíšil, L., Stibor, I., Magnera, T. F., and Michl, J. (2015) The Scope of Direct Alkylation of Gold Surface with Solutions of C-1-C-4 n-Alkylstannanes. *J. Am. Chem. Soc.* **137**, 12086-12099

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

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

Givelet, C. C., New functionalization of gold surfaces, Project no. 14-2337S, Wen, J., Magnera, T. F., Zamadar, M., Čépe, K., Fujiwara, H., Shi, Y., Tuchband, M. R. K., Clark, N., Zbořil, R., Michl, J. (2016) Challenges in the Structure Determination of Self-Assembled Metallacages: What Do Cage Cavities Contain, Internal Vapor Bubbles or Solvent and/or Counterions? *J. Am. Chem. Soc.* **138**, 6676-6687

Urbanová, V., Karlický, F., Matěj, A., Šembera, F., Janoušek, Z., Perman, J. A., Ranc, V., Čépe, K., Michl, J., Otyepka, M., and Zbořil, R. (2016) Fluorinated graphenes as advanced biosensors – effect of fluorine coverage on electron transfer properties and adsorption of biomolecules. *Nanoscale* **8**, 12134-12142

CURRENT GRANTS

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

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

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

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

Radim Nencka Group

DRUG DESIGN AND MEDICINAL CHEMISTRY GROUP

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Head of the group: Radim Nencka[1] / Scientists: Hubert Hřebabecký[2], Michal Šála[3], Milan Dejmek[4]
Postdoc: Ján Kozic[5] / Ph.D. students: Ivana Mejdrová[6], Mbilo Misehe / Student: Tomáš Otava, Milan Štefek
Research assistant: Marcela Dvořáková[7] / Technician: Jaroslava Sklenářová[8] / Secretary: Barbara Česneková

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

Our group has been focused on medicinal chemistry and synthetic organic chemistry leading to drug-like molecules.

Originally, we were interested in the design and synthesis of conformationally constrained nucleoside and nucleotide derivatives. These efforts resulted in the discovery of a completely novel class of compounds, which exert significant activities against Coxsackie virus B3, an important member of *Picornaviridae* family that causes various human diseases ranging from mild flu-like symptoms to serious and life-threatening conditions such as severe myocarditis. Recently, we turned our attention to phosphatidylinositol 4-kinase (PI4K) inhibitors as potential broad-spectrum antiviral agents. Human cells contain four distinct subtypes of PI4K, but only PI4K IIIβ is hijacked by several viruses (mainly from *Picornaviridae* and *Flaviviridae* family) for modulation of plasmatic membranes inside the cell in order to build functional replication complex. We have discovered highly potent inhibitors of PI4K IIIβ with unprecedented selectivity in comparison with other protein and lipid kinases, which exert outstanding antiviral properties against various RNA viruses, e.g. human rhinovirus and hepatitis C virus.

Apart from medicinal chemistry, we are also interested in development of novel synthetic methodologies for fast synthesis of various heterocyclic compounds. We have invented a one-pot procedure for synthesis of purine derivatives from amine precursors, which was recently granted a patent.

SELECTED PAPERS

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

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CURRENT GRANTS

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

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

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

Towards cyclohexenyl and cyclohexyl locked nucleic acids, Project no. P207/12/P625, Czech Science Foundation (GA ČR), 2011–2014, Šála, M.

Ivan Rosenberg Group

NUCLEOTIDES & OLIGONUCLEOTIDES

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Head of the group: Ivan Rosenberg[1] / Deputy head: Dominik Rejman[2] / Senior Scientists: Radek Liboska[3] Magdalena Petrová[4], Ondřej Páv[5], Sárka Rosenbergová[6], Ondřej Šimák[7], Ivana Markusová Kóšiová Research Assistant: Ivana Dvořáková, Pavel Novák[8] / Postdoc: Marcel Ehn[9] / Ph.D. students: Ondřej Kostov Tomáš Jandušík[10] / Students: Gulmíra Munis, Jakub Zýka[11]

KEYWORDS / nucleotide and nucleoside analogs, phosphonates, phosphinates, antisense oligonucleotides, RNase H, solid phase synthesis

Scientific program of the group is directed toward basic research in the area of Nucleoside Phosphonic Acids (NPAs) as potential antimetabolites and Oligonucleotide Analogs as compounds capable of interfering with gene expression and those with a regulatory role (2′,5′-oligoadenylates and CpG oligonucleotides).

NUCLEOSIDE PHOSPHONIC ACIDS

Our investigation in the area of the chemistry of NPAs has provided an impressive number of novel structurally diverse compounds containing both classical (furanose) and modified (pyrrolidine, prolinol, piperidine, and phospholane) rings. Among them, several potent inhibitors of human thymidine and purine nucleoside phosphorylases, HXG phosphoribosyl transferase, and human pyrimidine specific mitochondrial and cytosolic 5′(3′)-deoxynucleotidases were found. The acquired knowledge obtained in the synthesis of NPAs is unique as such and will be fully utilized in new generation of nucleoside and nucleotide analogs.

OLIGONUCLEOTIDE ANALOGS

Modified oligonucleotides containing several types of nucleoside phosphonic acids exhibit significantly increased nuclease stability, enhanced hybridization, and stimulation of RNase H activity. These properties may classify phosphonate oligonucleotides for their potential use in biology as antisense compounds and siRNAs in regulation of gene expression. In this respect we developed a straightforward synthesis of novel monomers – nucleoside-O-methyl-(H)-phosphinates for the synthesis of chimeric phosphonate-phosphodiester oligonucleotides via H-phosphonate chemistry. The O-methyl-(¬H)-phosphinate internucleotide linkages can be oxidized, sulfurized, amidated, or borylated to give rise to new type phosphonate linkages. For construction of gapmers we developed nuclease stable phosphodiester C4′-alkoxyoligodeoxynucleotides adopting preferentially the C3′-endo conformation of the sugar rings which leads to preferential hybridization with RNA target.

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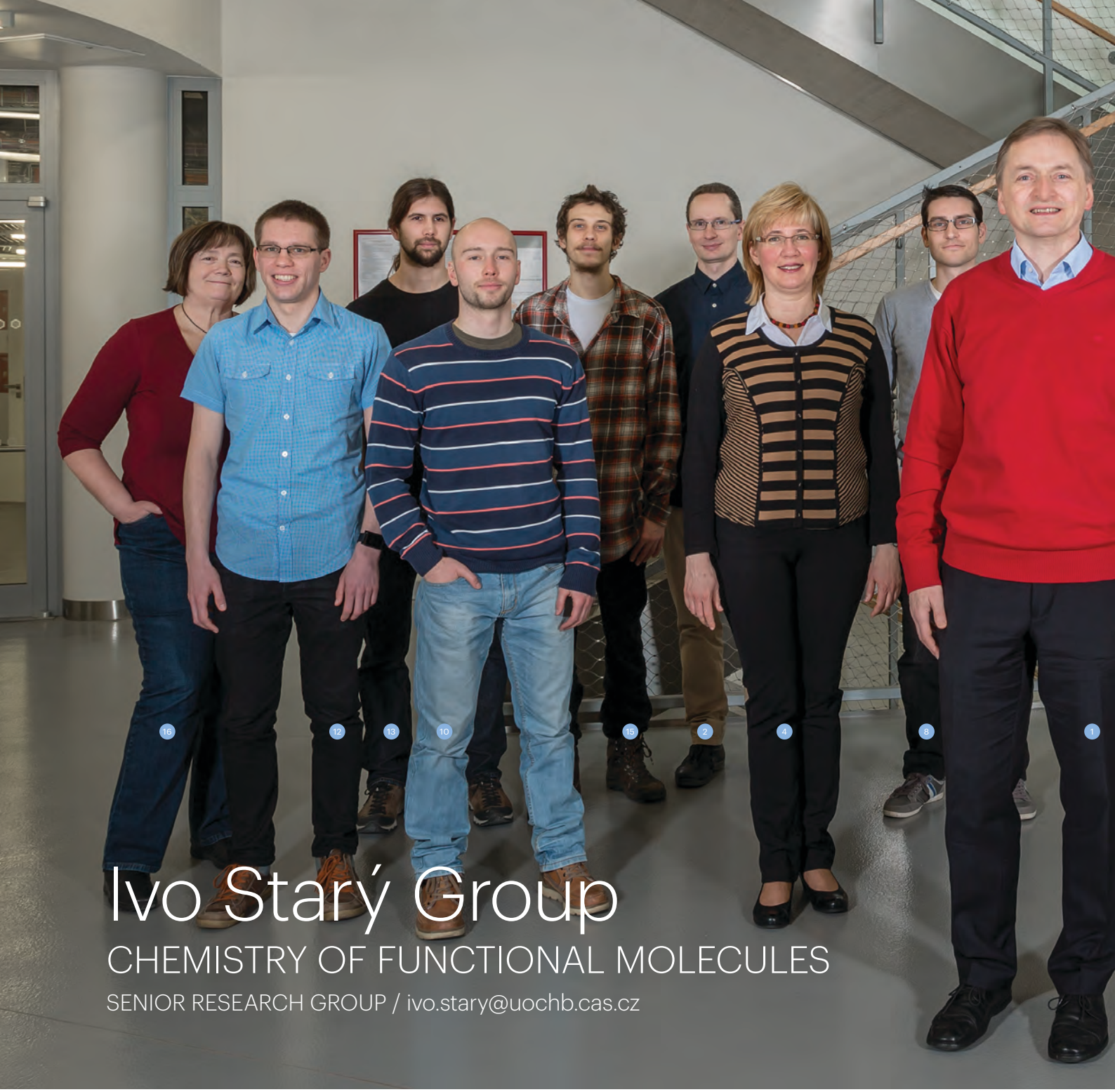
Košiová, I., Šimák, O., Panova, N., Buděšínský, M., Petrová, M., Rejman, D., Liboska, R., Páv, O., and Rosenberg, I. (2014) Inhibition of human thymidine phosphorylase by conformationally constrained pyrimidine nucleoside phosphonic acids and their "open-structure" isosteres. *Eur. J. Med. Chem.* **74**,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

Páv, O., Zborniková, E., Buděšínský, M., and Rosenberg, I. (2013) A new class of phosphanucleosides containing a 3-hydroxy-1-hydroxymethylphospholane 1-oxide ring. *Tetrahedron* **69**, 9120-9129

CURRENT GRANTS

Novel DNA and RNA oligonucleotides with Phosphonothioate and Phosphonoamidate Internucleotide Linkages, Project no. 13-26526S, Czech Science Foundation (GA ČR), 2013-2016, Rosenberg, I.

Targeted damage of the DNA repair mechanisms as a tool for cancer therapy, Project no. 15-31604A, Ministry of Health of the Czech Republic (MZ ČR), 2015-2018, Rosenberg, I.



Ivo Starý Group

CHEMISTRY OF FUNCTIONAL MOLECULES

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KEYWORDS / helical aromatics, functional π-electron systems, enantioselective catalysis, charge transport, 2D self-assembly, on-surface chemistry, functionalised nanoparticles

Our research is focused on development of new synthetic methodologies for preparation of non-trivial π-electron systems, which are attractive for applications in chemistry and physics. In particular, our attention focuses on helically chiral aromatics (helicenes) that are enantiopure and properly functionalised to be employed as chiral ligands in enantioselective catalysis. We systematically investigate physicochemical properties of new aromatics to describe their self-assembly at interfaces, on-surface reactivity at nanoscale, chiroptical and charge transport properties. Specifically, we utilise a mechanically controllable break junction method to study single molecule conductivity of helical aromatics, we explore properties of inorganic nanoparticles functionalised by chiral π-electron systems, and we strive for fabrication and characterisation of respective molecular devices. The experimental approaches go hand in hand with computational ones in order to obtain deep insights into 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.

Head of the group: Ivo Starý[1] / Scientists: Jiří Rybáček[2], Ladislav Sieger[3], Irena G. Stará[4], Michal Šámal[5]
Jaroslav Vacek[6], Jana Vacek Chocholoušová[7] / Ph.D. students: Michal Buchta[8], Isabel Gay Sanchez[9]
Jan Holec[10], Václav Houska[11], Jiří Janoušek[12], Jiří Klívar[13], Jindřich Nejedlý[14] / Student: Gaël Amans[15]
Technician: Jaroslava Perková[16] / Secretary: Kateřina Pokorná

SELECTED PAPERS

Stetsovych, O., Švec, M., Vacek, J., Vacek Chocholoušová, J., Jančařík, A., Rybáček, J., Stará, I. G., Jelínek, P., and Starý, I. (2016) From Helical to Planar Chirality by On-Surface Chemistry. *Nat. Chem.*, doi:10.1038/nchem.2662

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Chercheja, S., Klívar, J., Jančařík, A., Rybáček, J., Salzl, S., Tarábek, J., Pospíšil, L., Chocholoušová, J. V., Vacek, J., Pohl, R., Císařová, I., Starý, I., and Stará, I. G. (2014) The Use of Cobalt-Mediated Cycloisomerisation of Ynedinitriles in the Synthesis of Pyridazinohelicenes. *Chem. Eur. J.* **20**, 8477-8482

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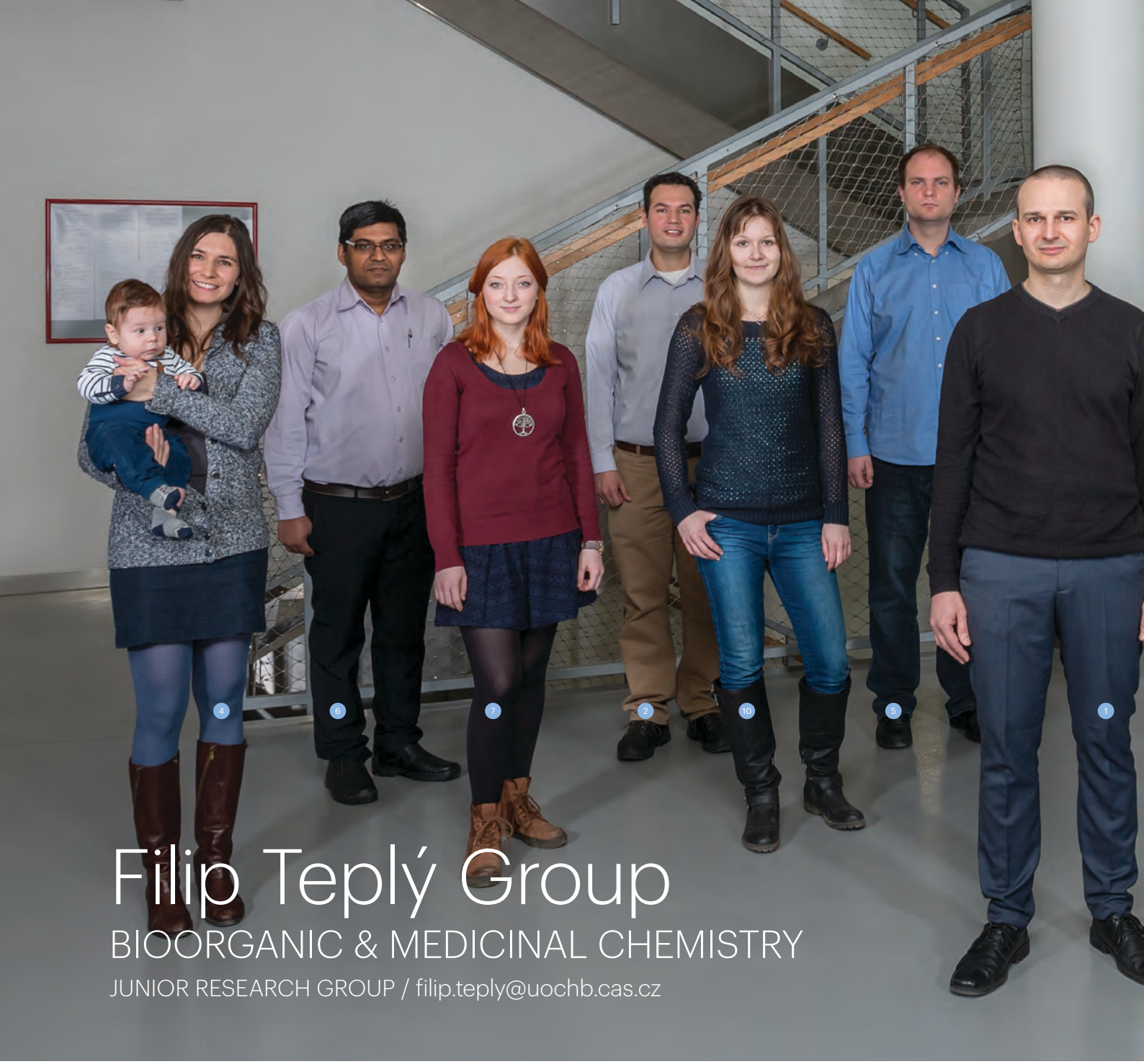
Exploring helically chiral ligands in enantioselective transition metal catalysis, Project no. 203/09/1766, Czech Science Foundation (GA ČR), 2009–2013, Stará, I. G.

New nonplanar polyaromatic systems of high complexity: their synthesis and properties, Project no. P207/10/2207, Czech Science Foundation (GA ČR), 2010–2014, Stará, I. G.

Donor-acceptor interactions in designing functional molecular arrays, Project no. P207/10/2214, Czech Science Foundation (GA ČR), 2010–2013, Starý, I.

The preparation of enantiopure helically chiral aromatics and their use in catalysis, Project no. 14-29667S, Czech Science Foundation (GA ČR), 2014–2016, Stará, I. G.



Filip Teplý Group

BIOORGANIC & MEDICINAL CHEMISTRY

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KEYWORDS / synthesis, ligands, c-myc downregulators, c-myc G-quadruplex, DNA, chiral small molecules, helquats

C-MYC DOWNREGULATORS

Binding of small molecules to promoter G-quadruplexes has been shown to modulate transcription of the associated genes. This project focuses on c-myc oncogene, overexpression of which is linked to a wide range of human cancers. Our work includes chemical synthesis, purification, and characterization of novel types of heterocyclic G-quadruplex ligands able to bind and to stabilize c-myc G-quadruplex DNA. Part of the work is accomplished in close collaboration with team of biologists conducting research of biological effects of the newly synthesized ligands including assessment of their ability to bind to G-quadruplex and inhibit expression of c-myc oncogene which is one of the key engines of cancer.

HELQUATS & RELATED COMPOUNDS

Further area of interest is centered around helquats and their applications. Our group has introduced these doubly positive helical systems as a novel structural class and has demonstrated that these helical dications are easily accessible and exhibit a range of interesting properties. Our efforts have been driven by a hypothesis that crossbreeding rich fields of viologens and helicenes leading to helquats opens a large and unexplored territory with attractive applications. In the broadest sense, our current work explores supramolecular chemistry of helquats. We pursue identification of biologically interesting molecules interacting with our helical dications, which is the key to cultivation of helquat chemistry for its future applications.

Head of the group: Filip Teplý[1] / Postdocs: Paul E. Reyes-Gutiérrez[2], Harish R. Talele[3], Erika Kužmová[4]
Ph.D. students: Lukáš Severa[5], Vishwas D. Joshi[6], Pradeep Devadig, Alice Pomeislová / Students: Nikola Ďásková[7]
Michael Jirásek[8], Alena Karnošová[9], Markéta Koutová[10], Anna Neužilová[11], Alexandra Smorto[12]

SELECTED PAPERS

Reyes-Gutiérrez, P. E., Kapal, T., Klepetářová, B., Šaman, D., Pohl, R., Zawada, Z., Kužmová, E., Hájek, M., and Teplý, F. (2016) Structural revisions of small molecules reported to cross-link G-quadruplex DNA in vivo reveal a repetitive assignment error in the literature. *Sci. Rep.* **6**, Article number: 23499

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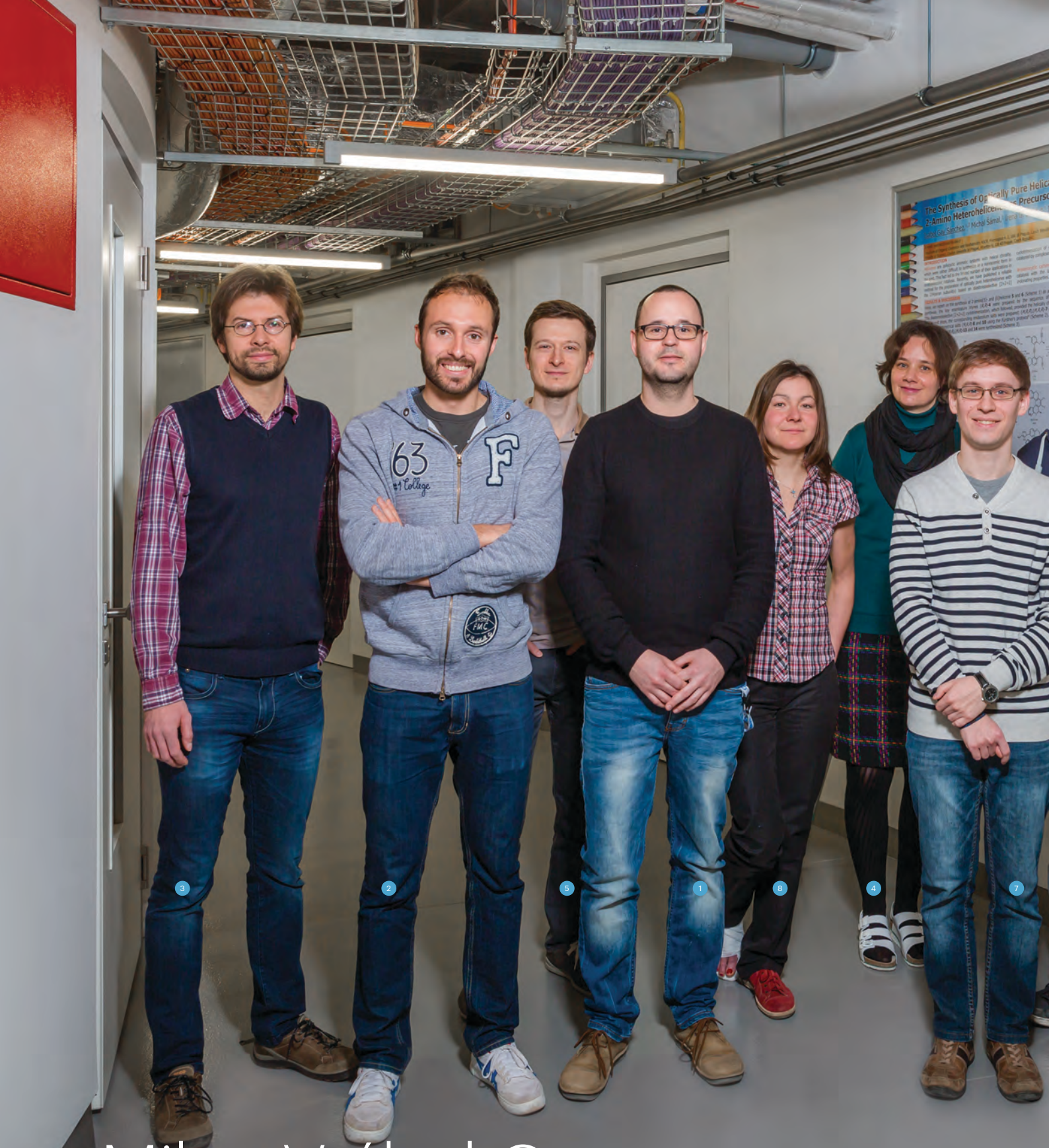
CURRENT GRANTS

Center for Development of Original Drugs (CDOD), Project no. TE01020028, Technology Agency of the Czech Republic (TA ČR), 2016–2019, Teplý, F.

Application of proteomics, immunohistochemistry, and new experimental approaches for amyloid typization, Project no. 16-31156A, Ministry of Health of the Czech Republic (MZ ČR), 2016-2019, Teplý, F.



Milan Vrábel Group

THE BIOORTHOGONAL CHEMISTRY

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KEYWORDS / bioorthogonal reactions, click chemistry, peptide libraries, glycoconjugates, sugar-processing enzymes

NEW BIOCONJUGATION REACTIONS

One of the goals of our laboratory is to develop chemical transformations that can be performed selectively on various biomolecules in their native environment. We aim to improve existing bioorthogonal reactions and to discover new reactions that will enable us to study biological processes under native, physiological conditions.

SYNTHESIS OF PEPTIDE LIBRARIES CONTAINING UNNATURAL AMINO ACIDS

This project deals with optimization of the synthesis of peptides containing unnatural amino acid building blocks. Peptide libraries containing these artificial functional groups are used to select peptide sequences able to selectively recognize various biological targets in complex samples. Our goal is to identify peptides that will serve as therapeutics and/or diagnostic tools with enhanced properties.

SELECTIVE INHIBITORS OF SUGAR PROCESSING ENZYMES

Our group aims to develop new methodology for construction of highly selective inhibitors of various sugar processing enzymes. By combination of the biological activity of small molecules with the specificity of biologics we want to prepare a new type of inhibitors of enzymes and proteins acting on carbohydrates. Our technology will equip us with a set of new tools that can be used for studying this important class of biomolecules.

SELECTED PAPERS

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

Vrábel, M., Kolle, P., Brunner, K. M., Gattner, M. J., Lopez-Carrillo, V., de Vivie-Riedle, R., and Carell, T. (2013) Norbornenes in Inverse Electron-Demand Diels-Alder Reactions. *Chemistry* **19**, 13309-13312

CURRENT GRANTS

Development of new bioorthogonal reactions, Project no. P207/15-06020Y, Czech Science Foundation (GA ČR), 2015–2018, Vrábel, M.

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

Dmytro Yushchenko Group

CHEMICAL BIOLOGY

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Head of the group: Dmytro Yushchenko[1] / Scientist: Volodymyr Shvadchak[2] / Postdoc: Oleksandr Kucherak[3]
Ph.D. students: Kseniia Afitska[4], Yevhenii Kyriukha[5] / Student: Andrii Kurochka

KEYWORDS / biology of α-synuclein, protein-lipid interactions, β-cell signaling, insulin secretion, lipid signaling, fluorescent biosensors, photoinducible molecules, environmentally sensitive dyes

Our current scientific interests are focused on two main areas: protein aggregation in neurodegenerations and lipid-mediated cell signaling.

In the area of aggregating proteins we are particularly interested in the mechanisms of aggregation and toxicity of protein α-synuclein (αSyn) and its role in the development of Parkinson's disease. We aim to examine a prevalent hypothesis in the field stating that αSyn toxicity comes from oligomeric spices which disrupt lipid membranes causing neuronal death. To address the question of reproducible oligomer preparation we synthesize small-molecule oligomerizers and apply them to prepare synthetic αSyn oligomers with a defined number of monomers and configurations. We investigate the affinities of these oligomers to membranes of different lipid compositions and their propensity to disrupt membranes in vitro. In later stages of the project we will develop inducible oligomerizers to study the mechanisms of oligomer toxicity in living cells.

In the area of lipid-mediated signaling we are particularly interested in understanding the roles of lipids, such as diacylglycerols, phosphatidic acids, and phosphatidyl inositols, in the regulation of insulin secretion from β-cells. To address these questions we develop chemical biology tools that enable manipulation of signaling lipids with subcellular resolution and investigation of the functions of the lipids at different sites of cellular membranes. These tools include e.g. caged and photoswitchable lipids as well as inducible enzymes controlling lipid metabolism. When used together with lipid sensors, calcium indicators, and sensors of insulin secretion, these tools will help to determine the role of distinct lipids in regulation of insulin secretion. To get more insight into the mechanisms of lipid signaling we will develop sophisticated molecules that will enable identification of lipid interacting proteins at different subcellular sites.

www.uochb.cz/yushchenko

SELECTED PAPERS

Frank, J. A., Yushchenko, D. A., Hodson, D. J., Lipstein, N., Nagpal, J., Rutter, G. A., Rhee, J. S., Gottschalk, A., Brose, N., Schultz, C., and Trauner, D. (2016) Photoswitchable diacylglycerols enable optical control of protein kinase C. *Nat. Chem. Biol.* **12**, 755-762

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Petr Bouř Group

BIOMOLECULAR SPECTROSCOPY

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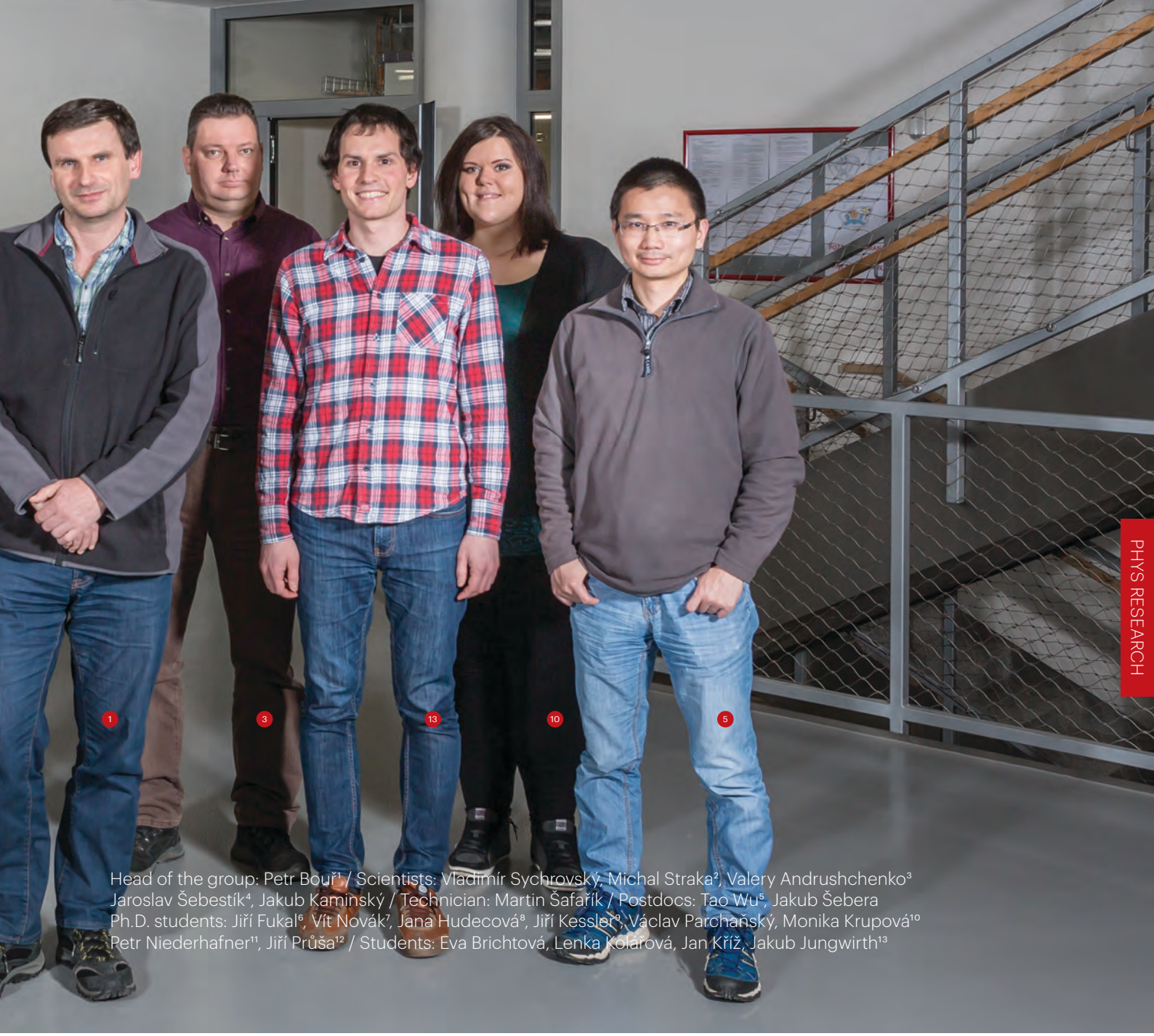
KEYWORDS / optical spectroscopy, molecular modeling, organic synthesis, optical activity, method development

Spectroscopy helps to understand structure and interactions of molecules, and their functions in living cells. Our group is, therefore, devoted to fundamental development of theoretical and experimental methods revealing molecular properties using spectroscopy techniques. We believe this is useful for new functional compounds including drugs and in the long term computational modeling can, for example, reduce chemical testing on animals.

As a typical long-term project, we develop chiral spectroscopic methods. The name comes from Greek *chiros*, hand, because they are sensitive to the "left and right hand" symmetry. Such techniques use circularly-polarized light and are very sensitive to variations in molecular structure. In particular, vibrational optical activity exploiting molecular vibrations brings about valuable information, especially if accompanied with thorough modeling and computations of studied systems. Within 2013–2016 we expanded the combined computational and spectroscopic approach to large proteins with thousands of atoms and developed new experimental and computational procedures. We developed a sensitive measurement of circular polarized luminescence, sum over state method for efficient calculation of magnetic circular dichroism spectra and explored using nuclear magnetic resonance in chiral solvents.

Also, advanced methods of organic synthesis are used to prepare model systems interesting for spectroscopy or biological activity, such as functionalized proteins with modified folding properties appearing in Alzheimer and other neurodegenerative diseases. New materials based on fullerenes or modified nucleic acids were proposed and studied by the combined experimental and theoretical approach as well.



Head of the group: Petr Bouř[1] / Scientists: Vladimír Sychrovský, Michal Straka[2], Valery Andrushchenko[3] Jaroslav Šebestík[4], Jakub Kaminský / Technician: Martin Šafařík / Postdocs: Tao Wu[5], Jakub Šebera Ph.D. students: Jiří Fukal[6], Vít Novák[7], Jana Hudecová[8], Jiří Kessler[9], Václav Parchaňský, Monika Krupová[10] Petr Niederhafner[11], Jiří Průša[12] / Students: Eva Brichtová, Lenka Kolářová, Jan Kříž, Jakub Jungwirth[13]

SELECTED PAPERS

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

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

Parchaňský, V., Kapitán, J., and Bouř, P. (2014) Inspecting chiral molecules by Raman optical activity spectroscopy. *RSC Adv.* **4**, 57125-57136

Šebestík, J., and Bouř, P. (2014) Observation of Paramagnetic Raman Optical Activity of Nitrogen Dioxide. *Angew. Chem.-Int. Edit.* **53**, 9236-9239

Kaminský, J., Budešínský, M., Taubert, S., Bouř, P., and Straka, M. (2013) Fullerene C-70 characterization by C-13 NMR and the importance of the solvent and dynamics in spectral simulations. *Phys. Chem. Chem. Phys.* **15**, 9223-9230

CURRENT GRANTS

3-Nitro-L-tyrosine in structures of neurodegenerative proteins, Project no. 14-00431S, Czech Science Foundation (GA ČR), 2014–2016, Šebestík, J.

Endohedral Actinide Fullerenes. From Spectroscopy to Molecular Devices, Project no. 14-03564S, Czech Science Foundation (GA ČR), 2014–2016, Straka, M.

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

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

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

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

Zdeněk Havlas Group

COMPUTATIONAL CHEMISTRY

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Head of the group: Zdeněk Havlas[1] / Scientist: Mojmír Kývala[2] / Postdocs: Jakub Chalupský[3]
Jin Wen[4] / IT specialist: Pavel Dvořák / Student: Alexandr Zaykov[5] / Assistant: Anna Kozáková[6]

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

The group is mainly focused on theoretical studies of the properties and chemistry of organic and bioinorganic compounds with complex electronic structure, 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 represent for example 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.

Due 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.

SELECTED PAPERS

Wen, J., Havlas, Z., and Michl, J. (2015) Captodatively Stabilized Biradicaloids as Chromophores for Singlet Fission. *J. Am. Chem. Soc.* **137**, 165-172

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

Chalupský, J., Rokob, T. A., Kurashige, Y., Yanai, T., Soomon, E. I., Rulíšek, L., and Srnec, M. (2014) 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.* **136**, 15977-15991

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

Havlas, Z., and Michl, J. (2016) Guidance for Mutual Disposition of Chromophores for Singlet Fission. *Isr. J. Chem.* **56**, 96-106

SIGNIFICANT 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

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Pavel Hobza Group

COMPUTATIONAL CHEMISTRY

DISTINGUISHED CHAIR / pavel.hobza@uochb.cas.cz

Head of the group: Pavel Hobza[1] / Scientists: Ota Bludský, Filip Lankaš, Martin Lepšík[2], Dana Nachtigallová[3] Jan Řezáč[4], Jindřich Fanfrlík[5] / Postdocs: Miroslav Rubeš, Vijay Madhav Miriyala[6], Olga Stasyuk[7], Adam Pecina[8] Róbert Sedlák[9], Rabindranath Lo[10], Susanta Haldar, Pathik S. Brahmkshatriya / Ph.D. students: Haresh Ajani[11] Tomáš Dršata, Saltuk Mustafa Eyrilmez[12], Junjie He, Jiří Hostaš[13], Cemal Köprülüoğlu[14], Michaela Nekardová[15] Students: Michal Trachta[16], Jakub Trnka / Secretary: Helena Černá[17]

KEYWORDS / noncovalent interaction, quantum chemistry, drug design, protein-ligand binding, molecular dynamics

Our ultimate goal is to find new drugs against devastating diseases, such as cancer. To this aim, we use the available in silico methods – docking/virtual screening – and develop our own quantum mechanics–based scoring function. This was enabled by our decade-long experience in computational description of noncovalent interactions in biomacromolecules using quantum chemical and molecular dynamics methods. We have applied our methodology to discover and optimize new ligands of cyclin-dependent kinases and understand the binding of HIV-1, aldose reductase or parasitic cysteine peptidase inhibitors.

The generality of the newly developed quantum mechanics-based scoring functions was tested on extended dataset of diverse protein – ligand complexes and their performance was compared to that of widely used scoring functions from academia and industry. We found that our scoring functions clearly outperform the standard functions. We propose this method for general use in computer-aided drug design.

SELECTED PAPERS

Pecina, A., Meier, R., Fanfrlík, J., Lepšík, M., Řezáč, J., Hobza, P., Baldauf, C. (2016) The SQM/COSMO filter: reliable native pose identification based on the quantum-mechanical description of protein–ligand interactions and implicit COSMO solvation. *Chem. Commun.* **52**, 3312-3315

Fanfrlík, J., Ruiz, F. X., Kadlčíková, A., Řezáč , J., Cousido-Siah, A., Mitschler, A., Haldar, S., Lepšík , M., Kolář, M. H., Majer, P., Podjarny, A. D., and Hobza, P. (2015) The Effect of Halogen-to-Hydrogen Bond Substitution on Human Aldose Reductase Inhibition. *ACS Chem. Biol.* **10**, 1637-1642

Kolař, M., Hobza, P., and Bronowska, A. K. (2013) Plugging the explicit sigma-holes in molecular docking. *Chem. Commun.* **49**, 981-983

Řezáč, J., and Hobza, P. (2013) Describing Noncovalent Interactions beyond the Common Approximations: How Accurate Is the "Gold Standard," CCSD(T) at the Complete Basis Set Limit? *J. Chem. Theory Comput.* **9**, 2151-2155

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

CURRENT GRANTS

Controlling structure and function of biomolecules at the molecular scale: theory meets experiment, Project no. P208/12/G016, Czech Science Foundation (GA ČR), Projects supporting excellence in basic research, 2012–2018, Hobza, P.

Intelligent design of nanoporous adsorbents and catalysts, Project no. P106/12/G015, Czech Science Foundation (GA ČR), Projects supporting excellence in basic research, 2012–2018, Bludský, O. (co-PI)

Combined experimental and theoretical investigation of catalytic properties of metal organic frameworks, Project no. 14-07101S, Czech Science Foundation (GA ČR), 2014–2016, Bludský, O.

Nanomechanics of RNA and DNA structural motifs, Project no. 14-21893S, Czech Science Foundation (GA ČR), 2014–2016, Lankaš, F.

Molecular dynamics of essential building blocks of biomolecules: experiments in molecular beams and theory, Project no. 14-14082S, Czech Science Foundation (GA ČR), 2014–2016, Nachtigallová, D.

Dynamics and (photo)chemistry of pollutants at the ice/air and water/air interfaces by experiment and theory, Project no. 15-12386S, Czech Science Foundation (GA ČR), 2015–2017, Nachtigallová, D.

Theoretical description of the excited states of covalently and noncovalently functionalized graphenes, Project no. 15-12386S, Czech Science Foundation (GA ČR), 2016–2018, Nachtigallová, D.

Efficient quantum-mechanical model for noncovalent interactions in large molecular systems, Project no. 16-11321Y, Czech Science Foundation (GA ČR), 2016–2018, Řezáč, J.

Protein adsorption on molecular sieves: ab initio modeling, Project no. 14-18521P, Czech Science Foundation (GA ČR), 2014–2016, Rubeš, M.

Pavel Jungwirth Group

MOLECULAR MODELING

DISTINGUISHED CHAIR / pavel.jungwirth@uochb.cas.cz

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

We aim at gaining 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 include 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. And in our free time we entertain ourselves by "balcony experiments" involving, for example, explosions of alkali metals in water, which also allows us to connect to general public and popularize science.

Head of the group: Pavel Jungwirth[1] / Scientists: Lukasz Cwiklik, Hector Martinez-Seara Monne[2]
Phil Mason / Postdocs: Daniel Bonhenry, Elise Duboue-Dijon[3], Aniket Magarkar[4], Roman Pleskot[5], Pauline Delcroix[6]
Ph.D. students: Tomáš Martinek[7], Josef Melcr[8], Vladimír Palivec[9], Štěpán Timr[10] / Research Assistant: Barbara Jagoda-Cwiklik[11]
Students: Katarína Baxová, Kryštof Březina, Jan Kadlec, Tereza Perlácová, Ondřej Ticháček[12] / Secretary: Helena Černá

SELECTED PAPERS

Mason, P. E., Uhlig, F., Vaněk, V., Buttersack, T., Bauerecker, S., and Jungwirth, P. (2015) Coulomb explosion during the early stages of the reaction of alkali metals with water. *Nat. Chem.* **7**, 250-254

Schroeder, C. A., Pluhařová, E., Seidel, R., Schroeder, W. P., Faubel, M., Slavíček, P., Winter, B., Jungwirth, P., and Bradforth, S. E. (2015) Oxidation Half-Reaction of Aqueous Nucleosides and Nucleotides via Photoelectron Spectroscopy Augmented by ab Initio Calculations. *J. Am. Chem. Soc.* **137**, 201-209

Savolainen, J., Uhlig, F., Ahmed, S., Hamm, P., and Jungwirth, P. (2014) Direct observation of the collapse of the delocalized excess electron in water. *Nat. Chem.* **6**, 697-701

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

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

CURRENT GRANTS

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

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

Interaction of ions with biomolecules in solutions: computer simulations and experiments, Praemium Academiae, Czech Academy of Sciences (AV ČR), 2010–2016, Jungwirth, P.

Václav Kašička Group

ELECTROMIGRATION METHODS

SENIOR RESEARCH GROUP / vaclav.kasicka@uochb.cas.cz

Head of the group: Václav Kašička[1] / Scientists: Dušan Koval[2], Petra Sázelová[3], Veronika Šolínová[4], Sille Štěpánová[5]
Ph.D. students: Renáta Konášová[6], Sachinkumar Pangavhane[7], Martin Růžička[8], Tereza Tůmová[9] / Student: Jan Bílek[10]

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

The group is engaged in research and development of methodology and instrumentation of capillary electromigration (CE) methods and their application to separation, analysis, micropreparation, and physico-chemical and biochemical characterization of (bio)molecules.

METHODOLOGY

Methodology developments include all major CE techniques: zone electrophoresis in a free solution or in sieving media, affinity electrophoresis, isotachophoresis, isoelectric focusing, electrokinetic chromatography, and electrochromatography. New background electrolytes (strongly acidic, basic or isoelectric buffers) and (pseudo)stationary phases (chiral selectors, free or immobilized affinity ligands) are being developed to increase 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 magnitude and direction of electroosmotic flow.

INSTRUMENTATION

New devices for one- and two-dimensional CE methods with a multidimensional detection system are under development. 2 D separation is implemented by on-line combination of orthogonal CE methods in two in-series connected capillaries with a cross-shaped interface for independent filling of the capillaries by different separation media. 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, high sensitive qualitative and quantitative ultramicroanalysis, microscale isolation and physico-chemical and biochemical characterization of amino acids, peptides, proteins, nucleosides, nucleotides, and other biomolecules as well as functional organic molecules, such as helquats and azahelicenes.

SELECTED PAPERS

Konášová, R., Dytrtová, J. J., and Kašička, V. (2015) Determination of acid dissociation constants of triazole fungicides by pressure assisted capillary electrophoresis. *J. Chromatogr. A* **1408**, 243-249

Šolínová, V., Kaiser, M. M., Lukáč, M., Janeba, Z., and Kašička, V. (2014) Enantiopurity analysis of new types of acyclic nucleoside phosphonates by capillary electrophoresis with cyclodextrins as chiral selectors. *J. Sep. Sci.* **37**, 295-303

Růžička, M., Čížková, M., Jirásek, M., Teplý, F., Koval, D., and Kašička, V. (2014) Study of deoxyribonucleic acid-ligand interactions by partial filling affinity capillary electrophoresis. *J. Chromatogr. A* **1349**, 116-121

Kašička, V. (2014) Recent developments in capillary and microchip electroseparations of peptides (2011-2013). *Electrophoresis* **35**, 69-95

Ibrahim, A., Koval, D., Kašička, V., Faye, C., and Cottet, H. (2013) Effective charge determination of dendrigraft poly-L-lysine by capillary isotachophoresis. *Macromolecules* **46**, 533-540

CURRENT GRANTS

Design, synthesis, and characterization of new biomaterials as specific carriers of therapeutic agents, common project within cooperation between the Bulgarian Academy of Sciences and the Czech Academy of Sciences, Project no. 14, 2011–2013, Kašička, V.

New methods for determination of effective charge of polyelectrolytes based on electromigration techniques, Czech-French scientific and technical cooperation, Program Barrande, Project no. 7AMB12FR012, 2012–2013, Kašička, V.

Affinity capillary electromigration methods for selective nanoanalysis of biomolecules and investigation of their interactions, Czech Science Foundation (GA ČR), Project no. P206/12/0453, 2012–2014, Kašička, V.

Advanced polymer materials for high-efficient and selective electromigration and chromatographic separations, Czech Academy of Sciences (AV ČR), Project no. M200551207, 2012–2014, Koval, D.

Study of biomolecular interactions by capillary electrophoresis, Grant Agency of Charles University in Prague (GA UK), Project no. 629412; 2012–2014, Růžička, M.

Two-dimensional capillary electromigration methods for separation, analysis, and characterization of biomolecules, Czech Science Foundation (GA ČR), Project no. 13-17224S, 2013–2015, Kašička, V.

Enantioseparation of important analytes: helical dications as new chiral selectors, Czech Science Foundation (GA ČR), Project no. 13-32974S, 2013–2015, Koval, D.

Design, synthesis, and characterization of a new class of cationic antimicrobial peptides and peptide mimetics, common project within cooperation between the Bulgarian Academy of Sciences and the Czech Academy of Sciences, Project no. 34, 2014–2016, Kašička, V.

Correlation study of stability of metal ion complexes with neutral ligands in liquid and gas phases, Grant Agency of Charles University in Prague (GA UK), Project no. 134215, 2015–2016, Konášová, R.

Capillary electromigration techniques using affinity selectors and smart polymers for analysis and properties and interactions studies of biomolecules, Czech Science Foundation (GA ČR), Project no. 15-01948S, 2015–2017, Kašička, V.

Lubomír Rulíšek Group

THEORETICAL BIOINORGANIC CHEMISTRY

SENIOR RESEARCH GROUP / lubomir.rulisek@uochb.cas.cz

Head of the group: Lubomír Rulíšek[1] / Scientist: Martin Srnec[2] / Postdocs: Propokis Andrikopoulos[3]
Zahra Aliakbar Tehrani[4] / Ph.D. students: Ondrej Gutten[5], Daniel Bím[6]

KEYWORDS / metalloenzymes, computer modelling, catalysis, metal ions, molecular design

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

Notably, the key observation made in recent theoretical studies is that lowering of activation barriers to their 'enzymatic values' is already achieved in active site models of less than 200 atoms. This finding naturally invokes the question of what is the minimum size of a metalloprotein required for the catalysis.

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

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, and theoretical spectroscopy.

SELECTED PAPERS

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

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

Trujillo, C., Sanchez-Sanz, G., Karpaviciene, I., Jahn, U., Cikotiene, I., and Rulíšek, L. (2014) Divergent Pathways and Competitive Mechanisms of Metathesis Reactions between 3-Arylprop-2-ynyl Esters and Aldehydes: An Experimental and Theoretical Study. *Chem. Eur. J.* **20**, 10360-10370

Rulíšek, L., and Ryde, U. (2013) Theoretical studies of the active-site structure, spectroscopic and thermodynamic properties, and reaction mechanism of multicopper oxidases. *Coord. Chem. Rev.* **257**, 445-458

Gutten, O., and Rulíšek, L. (2013) Predicting the Stability Constants of Metal-Ion Complexes from First Principles. *Inorg. Chem.* **52**, 10347-10355

CURRENT GRANTS

Computational Design of Minimalistic Metallopeptides: 'En Route' to Disentangling the Catalytic Power of Metalloproteins, Project no. 14-31419S, Czech Science Foundation (GA ČR), 2014–2016, Rulíšek, L.

Gilead Sciences Research Centre (GSRC-2), 2011-2016, Rulíšek, L.

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Josef Cvačka Group

MASS SPECTROMETRY

RESEARCH-SERVICE GROUP / josef.cvacka@uochb.cas.cz

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

The group uses mass spectrometry (MS) to answer various biological questions. The MS technology is mostly applied for structure elucidation, identification and quantification of organic substances, ranging from small molecules to large biomacromolecules. The standard MS-based approaches are sometimes inappropriate for particular tasks, which require new methods, applications and devices to be developed.

New methods for structure elucidation and characterization of lipids have been created. The approaches based on chromatography, atmospheric pressure chemical ionization and matrix-assisted laser desorption/ionization (MALDI) provided a deep insight into lipids of vernix caseosa, a biofilm which covers developing human fetus. New lipid classes have been discovered and structures of many lipids were disclosed. New HPLC/MS methods have been developed for long-chain aliphatic hydrocarbons acting as semiochemicals in social insects. A significant progress was achieved in the area of ambient ionization techniques. A device for detecting defense compounds on insect bodies has been assembled and the instrument made it possible to map spatial distribution of various compounds from exocrine glands. MALDI MS imaging was used for tracing drugs and their metabolites in tissue sections. A new device for coupling electrochemistry to MS has been fabricated and patented. It made it possible to detected organic compounds in the form of their metal ion (e.g., silver or copper) adducts, which is useful for samples with strong matrix effects and for detecting non-polar compounds by electrospray MS. The group members have also been involved in numerous projects focused on proteins, their characterization, identification, and quantification.

The group also performs routine MS analyzes for the IOCB scientific community, maintains open-access instruments and provides a collaborative support.

Head of the group: Josef Cvačka[1] / Scientists: Zuzana Demianová, Martin Hubálek[2], Jana Jaklová Dytrtová[3] Vladimír Vrkoslav[4] / Ph.D. students: Jana Březinová[5], Eva Háková, Aneta Kalužíková, Petra Macháčková Radka Míková, Jan Rejšek[6], Marie Zábranská / Research assistants: Anna Březinová, Kvetoslava Kertisová[7] Kateřina Nováková[8], Eva Slabá[9], Martin Svoboda[10] / Students: Pavlína Nekvasilová[11], Barbora Rumlová[12] Timotej Strmeň[13], Štěpán Strnad[14], Lenka Šubčíková, Martin Vít / Technician: Karel Rücker[15]

SELECTED PAPERS

Šubčíková, L., Hoskovec, M., Vrkoslav, V., Čmelíková, T., Háková, E., Míková, R., Coufal, P., Doležal, A., Plavka, R., and Cvačka, J. (2015) Analysis of 1,2-diol diesters in vernix caseosa by high-performance liquid chromatography – atmospheric pressure chemical ionization mass spectrometry. *J. Chromatogr. A* **1378**, 8-18

Háková, E., Vrkoslav, V., Míková, R., Schwarzová-Pecková, K., Bosáková, Z., and Cvačka, J. (2015) Localization of double bonds in triacylglycerols using high-performance liquid chromatography/atmospheric pressure chemical ionization ion-trap mass spectrometry. *Anal. Bioanal. Chem.* **407**, 5175-5188

Rejšek, J., Vrkoslav, V., Hanus, R., Vaikkinen, A., Haapala, M., Kauppila, T. J., Kostiainen, R., and Cvačka, J. (2015) The detection and mapping of the spatial distribution of insect defense compounds by desorption atmospheric pressure photoionization Orbitrap mass spectrometry. *Anal. Chim. Acta* **886**, 91-97

Míková, R., Vrkoslav, V., Hanus, R., Háková, E., Hábová, Z., Doležal, A., Plavka, R., Coufal, P., and Cvačka, J. (2014) Newborn Boys and Girls Differ in the Lipid Composition of Vernix Caseosa. *PLoS One* **9**, 8

Vrkoslav, V., Urbanová, K., Háková, M., and Cvačka, J. (2013) Analysis of wax esters by silver-ion high-performance liquid chromatography-tandem mass spectrometry. *J. Chromatogr. A* **1302**, 105-110

CURRENT GRANTS

Micro- and nanoflow atmospheric pressure ionizations for bioanalytical mass spectrometry, Project no. 16-01639S, Czech Science Foundation (GA ČR), 2016–2018, Cvačka, J.

Interactions of metal and nutrient ions with high priority pesticides in soil and on biomembranes, Project no. 13-21409P, Czech Science Foundation (GA ČR), 2013–2016, Jaklová Dytrtová, J.

Lipidome of vernix caseosa: comprehensive analysis and biological variability, Project no. P206/12/0750, Czech Science Foundation (GA ČR), 2012–2015, Cvačka, J.

Ambient ionization mass spectrometry: structure elucidation and spatial distribution of organic molecules, Project no. M200551204, Czech Academy of Sciences (AV ČR), 2012–2015, Cvačka, J.

Development of the new analytical methods for analysis of extremely long-chain aliphatic hydrocarbons, Project no. P206/12/1093, Czech Science Foundation (GA ČR), 2012–2014, Vrkoslav, V.

Complex lipidomic characterization of plant and animal tissues, Project no. 203/09/0139, Czech Science Foundation (GA ČR), 2009–2013, Cvačka, J. (co-applicant)

Pavel Majer Group

MEDICINAL CHEMISTRY

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KEYWORDS / custom synthesis of peptides and small molecules, protein sequencing, amino acid analysis, LC-MS analysis of metabolites, drug discovery, prodrug development, cell targeting

The mission of the service part of the group consists of several activities, mainly:

— Solid phase synthesis of peptides up to about 50 amino acid residues
— Synthesis of peptide derivatives
— Synthesis of small molecules, mainly enzyme inhibitors with various warheads
— Qualitative and quantitative amino acid analysis of peptides and proteins
— Protein and peptide sequencing using Edman's method (standard and micro scale)
— Metabolic stability assays and metabolite analysis by LC-MS-TOF
— Quantitative amino acid analysis by fluorescent derivatization and HPLC

The main mission of the scientific part of the group is to collaborate with other groups at the Institute and provide them with design and synthesis of biologically active small molecules and chemical probes for their research. These collaborations include for example the following projects:

— iBodies: Modular Synthetic Antibody Mimetics Based on Hydrophilic Polymers Decorated with Functional Moieties (together with Jan Konvalinka group)
— DNA-linked Inhibitor Antibody Assay (DIANA): for sensitive and selective enzyme detection and inhibitor screening (together with Jan Konvalinka group)
— Controlling Structure and Function of Biomolecules at the Molecular Scale: Theory Meets Experiment (participation in a Center of Excellence, PI: Pavel Hobza)
— Inter-membrane Proteases of the Rhomboid Family in Secretionary Pathways of Mamalian Cells (together with Kvido Stříšovský group)

Head of the group: Pavel Majer[1] / Scientist: Marcela Krečmerová[2] / Postdocs: Andrej Jančařík[3], Lenka Monincová[4] Karel Pomeisl[5], Lukáš Tenora[6], Tomáš Tichý[7], Jan Vávra[8], Stancho Stanchev (guest)[9], Petr Šimon (guest)[10] Ph.D. students: Lenka Pallová[11] / Research assistants: Miroslava Blechová[12], Martin Hradílek, Zdeněk Voburka[13] Jitka Bařinková[14] / Technicians: Radko Souček[15], Aleksandrina Prichodko[16] / Student: Kateřina Novotná[17]

We are also collaborating with the Drug Discovery Group at Johns Hopkins University in Baltimore, U.S.A., to develop prodrugs of glutamine antimetabolite 6-Diazo-5-oxo-l-norleucine (DON) and inhibitors of Glutamate Carboxy Peptidase II, which may find use in treatment of cancer and neurodegenerative and autoimmune diseases. Our prodrugs target lymphoid cells, brain or cancer cells, they deliver the active compound selectively, thus lowering their toxicity. These prodrugs were patented and currently undergo pre-clinical testing in large mammals.

SELECTED PAPERS

Rais, R., Jančařík, A., Tenora, L., Nedelcovych, M., Alt, J., Englert, J., Rojas, C., Le, A., Elgogary, A., Tan, J., Monincová, L., Pate, K., Adams, R., Ferraris, D., Powell, J., Majer, P., and Slusher, B. S. (2016) Discovery of 6-Diazo-5-oxo-l-norleucine (DON) Prodrugs with Enhanced CSF Delivery in Monkeys: A Potential Treatment for Glioblastoma. *J. Med. Chem.* **59** (18), 8621-8633

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

Tykvart, J., Schimer, J., Jančařík, A., Bařinková, J., Navrátil, V., Starková, J., Šrámková, K., Konvalinka, J., Majer, P., and Šácha, P. (2015) Design of highly potent urea-based, exosite-binding inhibitors selective for glutamate carboxypeptidase II. *J. Med. Chem.* **58**, 4357-4363

Schimer, J., Pávová, M., Anders, M., Pachl, P., Šácha, P., Cígler, P., Weber, J., Majer, P., Řezáčová, P., Kräusslich, H. G., Müller, B., and Konvalinka, J. (2015) Triggering HIV polyprotein processing by light using rapid photodegradation of a tight-binding protease inhibitor. *Nat. Commun.* **6**, 6461

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

CURRENT GRANTS

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

Controlling Structure and Function of Biomolecules at the Molecular Scale: Theory Meets Experiment, Project No. P208/12/G016, Ministry of Education, Youth and Sports (MŠMT ČR), 2012–2018, Hobza, P.

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

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

Helena Mertlíková-Kaiserová Group

BIOCHEMICAL PHARMACOLOGY

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KEYWORDS / drug discovery, cell culture, screening, biotransformation, cancer, inflammation, nucleic acids, method development

Primary role of the group within IOCB is to bridge the chemistry and the biology aiming to promote drug discovery process. For this reason, our research projects are multidisciplinary and typically based on collaboration with medicinal chemistry, structural biology and biochemistry groups from IOCB (to minimize the need for outsourcing). Our essential research tools are cell-based and other *in vitro* assays. Traditionally, we focus on the analogues of nucleic acid components, i.e. variously modified nucleos(t)ides and purine or pyrimidine bases. However, we are open to all interesting (i.e. pharmacologically relevant) molecules coming from the synthetic laboratories. Our expertise is particularly strong in the field of anticancer, antiviral, and anti-inflammatory drugs. Generally, we evaluate the pharmacological potential at several stages, such as cellular uptake, biotransformation, and specific cellular targets, e.g. receptors, kinases, polymerases, telomeres, cytokines and others. Currently we are engaged in the following projects:

1. Anti-inflammatory effects of the substituted dichloropyrimidines
2. Helquats as novel anticancer drugs based on stabilization of G-quadruplexes in oncogene promoters
3. Identification and characterization of novel inhibitors of bacterial adenylate cyclase
4. Interactions of 9-norbornyl-6-chloropurines with GSH-related pathways: implications for their cytotoxicity
5. Novel amide-based steroidal inhibitors of NMDA receptors

Head of the group: Helena Mertlíková-Kaiserová[1] / Scientists: Miroslav Hájek[2] Markéta Šmídková[3], Marika Matoušová[4] / Postdocs: Jaroslav Kozák, Erika Kužmová[5] Martin Zavřel[6] / Ph.D. students: Alexandra Dvořáková, Pavla Plačková[7], Lenka Barchánková[8] Research assistants: Jana Günterová[9], Eva Tloušťová[10] / Students: Tadeáš Bílek[11] Lenka Vaněková[12], Jan Voldřich[13], Nikola Đásková[14], Alena Karnošová[15], Markéta Koutová[16] Anna Neužilová[17] / Technician: Karolína Müllerová[18]

Besides research activities, the group provides routine cytotoxicity screening and cell cycle analysis services. In addition to these, we are gradually increasing the number of "qualified services", which are more demanding in terms of both personnel qualification and time. They present the most dynamic component of our work standing at the border of research and services. Examples of these are primary cell culture isolation, dual luciferase reporter assay or kinase assays.

SELECTED PAPERS

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

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

Mejdrová, I., Chalupská, D., Kögler, M., Šála, M., Plačková, P., Baumlova, A., Hřebabecký, H., Procházková, E., Dejmek, M., Guillon, R., Strunin, D., Weber, J., Lee, G., Birkus, G., Mertlíková-Kaiserová, H., Bouřa, E., and Nencka, R. (2015) Highly Selective Phosphatidylinositol 4-Kinase III beta Inhibitors and Structural Insight into Their Mode of Action. *J. Med. Chem.* **58**, 3767-3793

Reyes-Gutierrez, P. E., Jirásek, M., Severa, L., Novotná, P., Koval, D., Sázelová, P., Vávra, J., Meyer, A., Císařová, I., Šaman, D., Pohl, R., Štěpánek, P., Slavíček, P., Coe, B. J., Hájek, M., Kašička, V., Urbanová, M., and Teplý, F. (2015) Functional helquats: helical cationic dyes with marked, switchable chiroptical properties in the visible region. *Chem. Commun.* **51**, 1583-1586

Šmídková, M., Dvořáková, A., Tloušťová, E., Česnek, M., Janeba, Z., and Mertlíková-Kaiserová, H. (2014) Amidate Prodrugs of 9- 2-(Phosphonomethoxy)Ethyl Adenine as Inhibitors of Adenylate Cyclase Toxin from Bordetella pertussis. Antimicrob. *Agents Chemother.* **58**, 664-671

CURRENT GRANTS

Targeted drug design for bioterrorism prevention. Development of effective inhibitors of the adenylate cyclase toxin of *Bordetella pertusis and Bacillus anthracis*, Project no. VG20102015046, Ministry of the Interior of the Czech Republic (MV ČR), 2011–2015, Janeba, Z.

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

InterBioMed, NPU I, LO1302, Ministry of Education, Youth and Sports (MŠMT ČR), 2014–2019, Pichová, I.

David Šaman Group

NMR AND MOLECULAR SPECTROSCOPY

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KEYWORDS / NMR, EPR, IR, Raman, circular dichroism, structural analysis, theoretical calculation

Our research is focused on structural studies of both synthetic compounds originating in the IOCB laboratories and compounds isolated from natural sources.

We utilize modern one- and multidimensional NMR techniques for structure elucidation of nucleosides, nucleotides, peptides, steroids, saccharides, pheromones, helicenes, and other classes of compounds. We develop new methods for determination of configuration on chiral centers. Our research is also focused on intra- and intermolecular hydrogen bonds and other non-covalent interactions, mechanism and kinetics of chemical reactions, determination of conformational dynamics in flexible five-membered rings.

Quantum-chemical calculations of NMR parameters are another important research area pursued in our group. The computational data are useful for prediction and interpretation of experimental NMR spectra. We develop new methods for accurate theoretical predictions that include nuclear quantum effects, vibrational and solvation effects, and molecular dynamics.

To be able to determine the presence and structure of paramagnetic species, our lab is equipped with electron paramagnetic resonance (EPR) spectrometer. Together with quantum chemical calculations, the method is applied in order to solve structures of paramagnetic molecules/intermediates in chemistry and biochemistry. We have, for example, studied redox reactions, such as reduction of viologen-like structures, nitroimidazole derivatives or phthalocyanines on graphite, or oxidation of flavonoid compounds and cobalt complexes used as mediators in synthetic chemistry.

Molecular spectroscopy, namely UV-vis and IR absorption spectroscopy, their chiral variants (electronic and vibrational circular dichroism, Raman optical activity), and fluorescence

Head of the group: David Šaman[1] / Scientists: Lucie Bednárová[2], Miloš Buděšínský[3], Martin Dračínský[4], Radek Pohl[5] Lenka Poštová Slavětínská[6], Eliška Procházková[7], Ján Tarábek[8] / Research assistants: Pavel Fiedler[9], Jana Hanzlíková Markéta Pazderková, Beáta Seidlerová / Students: Jakub Kovács, Martin Palušák / Technicians: Michal Doleček[10] Miroslava Otrubová[11], Marie Snopková[12]

spectroscopy are used for structural characterization of different molecular systems and/or their dynamic studies. Particular attention is given to the study of secondary and tertiary structure of other peptides and proteins and structural studies of other biopolymers (DNA, RNA etc.).

Our own research is oriented towards studies of molecular conformation and investigation of molecular dynamics of biopolymers and on assignment of absolute conformation of peptides or their analogs (combining chiral spectroscopy and quantum chemical calculations).

SELECTED PAPERS

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

Paluch, P., Pawlak, T., Jeziorna, A., Trébosc, J., Hou, G. J., Vega, A. J., Amoureux, J. P., Dracinsky, M., Polenova, T., and Potrzebowski, M. J. (2015) Analysis of local molecular motions of aromatic sidechains in proteins by 2D and 3D fast MAS NMR spectroscopy and quantum mechanical calculations. *Phys. Chem. Chem. Phys.* **17**, 28789-28801

Buděšínský, M., Vaněk, V., Dračínský, M., Pohl, R., Poštová-Slavětínská, L., Sychrovský, V., Pícha, J., and Císařová, I. (2014) Determination of the configuration in six-membered saturated heterocycles (N, P, S, Se) and their oxidation products using experimental and calculated NMR chemical shifts. *Tetrahedron* **70**, 3871-3886

Pospíšil, L., Bednárová, L., Štěpánek, P., Slavíček, P., Vávra, J., Hromadová, M., Dlouhá, H., Tarábek, J., and Teplý, F. (2014) Intense Chiroptical Switching in a Dicationic Helicene-Like Derivative: Exploration of a Viologen-Type Redox Manifold of a Non-Racemic Helquat. *J. Am. Chem. Soc.* **136**, 10826-10829

Procházková, E., Čechová, L., Janeba, Z., and Dračínský, M. (2013) A Switchable Intramolecular Hydrogen Bond in Polysubstituted 5-Nitrosopyrimidines. *J. Org. Chem.* **78**, 10121-10133

CURRENT GRANTS

Structure and properties of modified components of nucleic acids, Project no. 13-24880S, Czech Science Foundation (GA ČR), 2013–2015, Pohl, R.

Hydrogen bonds and nuclear quantum delocalisation studied by NMR spectroscopy and theoretical calculations, Project no. 15-11223S, Czech Science Foundation (GA ČR), 2015–2017, Dračínský, M.

Jiří Vondrášek Group

BIOINFORMATICS

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

Primary subject of studies in the group of Bioinformatics are proteins, their structures, architectures, interactions, stabilities, processes of their folding/unfolding, and evolutional pathways in which a function emerged and was further optimized. We are specifically interested in problems of local structure preferences along proteins main chain which are strongly dependent on a character of a side chain and define not only the character of the folding process but more importantly they determine proteins behavior in different environments. Most of the methods we used are combinations of molecular modeling, molecular simulations, computational chemistry, bioinformatics analysis, and mathematical statistics to establish a robust methodological background suitable to provide a solution of various structural biology and life science related problems. We also offer professional support for institutional users in modeling of protein structures, prediction of protein-protein interactions, and standard bioinformatics analysis and tools. One of the current topics we are working on is an Integrated Database of Small Molecules for chemical and medicinal biology, which should serve as a national contribution to the pan-European ESFRI project ELIXIR.

Head of the group: Jiří Vondrášek[1] / Scientists: Jan Pačes[2], Robert Pergl[3]
Postdocs: Jakub Galgonek[4], Kirubakaran Palani[5], Jiří Vymětal / Ph.D. students: Dávid Jakubec[6]
Kristýna Boušová[7] / Students: Veronika Jurásková[8], Lucie Pfeiferová[9], Martin Sarker[10]
Project manager: Hana Pergl-Šustková / IT specialist: Pavel Dvořák[12] / Assistant: Tereza Votrubová

SELECTED PAPERS

Vymetal, J., Bednarova, L., and Vondrasek, J. (2016) 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* **120**, 1048-1059

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

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

Jilkova, A., Horn, M., Rezacova, P., Maresova, L., Fajtova, P., Brynda, J., Vondrasek, J., McKerrow, J. H., Caffrey, C. R., and Mares, M. (2014) Activation Route of the Schistosoma mansoni Cathepsin B1 Drug Target: Structural Map with a Glycosaminoglycan Switch. *Structure* **22**, 1786-1798

Vymetal, J., Bathula, S. R., Cerny, J., Chaloupkova, R., Zidek, L., Sklenar, V., and Vondrasek, J. (2014) Retro operation on the Trp-cage miniprotein sequence produces an unstructured molecule capable of folding similar to the original only upon 2,2,2-trifluoroethanol addition. *Protein Eng. Des. Sel.* **27**, 463-472

CURRENT GRANTS

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

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

Jan Weber Group

BIOSCIENCES (VIROLOGY, MOLECULAR BIOLOGY)

RESEARCH-SERVICE GROUP / jan.weber@uochb.cas.cz

Head of the group: Jan Weber[1] / Scientist: Barbora Lubyová[2] / Postdocs: Marcela Pávová[3], Jan Hodek[4]
Research assistants: Dmytro Strunin[5], Eva Mašínová[6] / Ph.D. student: Lenka Sácká[7] / Technicians: Hana Prouzová[8]
Jitka Weberová[9] / Students: Tomáš Suchý, Vratislav Eliáš

3

KEYWORDS / antiviral screening, drug discovery, human immunodeficiency virus, hepatitis B virus, replication, latency, reactivation

Virology research-service team assists in the IOCB drug discovery program by providing in-house facility for screening of antiviral compounds against variety of viruses and collaborates with other IOCB groups in projects involving viruses. Antiviral screening is currently performed against human immunodeficiency virus, influenza virus, dengue virus, herpes simplex virus, and coxsackie virus. In addition, we collaborate with other groups to improve entry of active compounds into cells using liposomal and macrocyclic delivery systems.

In our research we are particularly interested in new strategies for HIV inhibition, HIV drug resistance, HIV tropism, HIV reactivation and latency, viral fitness and its implication for HIV pathogenesis, and disease progression. HIV capsid plays two important roles: the first one early in the infection during virus core uncoating and the second one late in the infection during assembly of new virus. We investigate the timing and mechanisms of uncoating and search for compounds interfering with both of these roles. Disease progression varies significantly in HIV-infected patients and is dependent on a number of host genetic, immune, and virological factors. We investigate the role of HIV fitness in disease progression in the absence of antiretroviral treatment.

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

SELECTED PAPERS

Hodek, J., Zajícová, V., Lovětinská-Šlamborová, I., Stibor, I., Müllerová, J., and Weber J. (2016) Protective hybrid coating containing silver, copper and zinc cations effective against human immunodeficiency virus and other enveloped viruses. *BMC Microbiol.* **16** Suppl 1:56

Schimer, J., Pávová , M., Anders, M., Pachl, P., Šácha, P., Cígler, P., Weber, J., Majer, P., Řezáčová, P., Kräusslich, H. G., Müller, B., and Konvalinka, J. (2015) Triggering HIV polyprotein processing by light using rapid photodegradation of a tight-binding protease inhibitor. *Nat. Commun.* **6**, 8

Mejdrová, I., Chalupská, D., Kögler, M., Šála, M., Plačková, P., Baumlová, A., Hřebabecký, H., Procházková, E., Dejmek, M., Guillon, R., Strunin, D., Weber, J., Lee, G., Birkus, G., Mertlíková-Kaiserová, H., Bouřa, E., and Nencka, R. (2015) Highly Selective Phosphatidylinositol 4-Kinase III beta Inhibitors and Structural Insight into Their Mode of Action. *J. Med. Chem.* **58**, 3767-3793

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

Weber, J., Rose, J. D., Vazquez, A. C., Winner, D., Margot, N., McColl, D. J., Miller, M. D., and Quiñones-Mateu, M. E. (2013) Resistance Mutations outside the Integrase Coding Region Have an Effect on Human Immunodeficiency Virus Replicative Fitness but Do Not Affect Its Susceptibility to Integrase Strand Transfer Inhibitors. *PLoS One* **8**, 14

CURRENT GRANTS

The Role of HIV Fitness on Disease Progression in the Absence of Antiretroviral Treatment, Project no. LK11207, Ministry of Education, Youth and Sports (MŠMT ČR), 2012–2016, Weber, J.

Václav Čeřovský Group

ANTIMICROBIAL PEPTIDES

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Head of the group: Václav Čeřovský[1] / Postdocs: Vlasta Dudková[2], Jitka Nováková[3]
Ph.D. student: Ondřej Nešuta[4] / Research assistant: Lenka Borovičková[5], Andrea Volejníková[6]

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

ANTIMICROBIAL PEPTIDES FOR TREATMENT OF BONE INFECTIONS

Infections of bones (osteomyelitis) represent serious complications in orthopedics and traumatology, which may lead to limb amputation or even death. Bone infection is caused by microbes such as *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis, Enterococcus faecalis,* and *Streptococcus species*. These are resistant to majority of conventional antibiotics.

Currently, osteomyelitis is treated after surgical debridement with high dose of traditional antibiotics mixed with local carriers used in orthopedics. In our project we propose to fill the cavity in an infected bone with local carriers mixed with antimicrobial peptides (AMPs). The significant advantage of AMPs resides in their mechanism of action, which is different from that of conventional antibiotics and is assumed not to develop microbial resistance.

In our laboratory we have identified numerous new AMPs composed of 12–18 amino acid residues which show significant antibacterial and antifungal activities, accompanied by varying levels of toxicity to eukaryotic cells. We work with their chemically synthesized analogs which possess high efficacy against resistant pathogens including MRSA, *S. epidermidis, P. aeruginosa*, and the species of *Candida*, while their toxicity is low. We are testing these analogs in a model of osteomyelitis using samples of human bones obtained from a bone collection of Motol hospital in Prague.

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

SELECTED PAPERS

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

Monincová, L., Veverka, V., Slaninová, J., Buděšínský, M., Fučík, V., Bednárová, L., Straka J., and Čeřovský, V. (2014) Structure-activity study of macropin, a novel antimicrobial peptide from the venom of solitary bee *Macropis fulvipes* (Hymenoptera: Melittidae). *J. Pept. Sci.* **20**, 375-384

Čujová, S., Bednárová, L., Slaninová, J., Straka, J., and Čeřovský, V. (2014) Interaction of a novel antimicrobial peptide isolated from the venom of solitary bee *Colletes daviesanus* with phospholipid vesicles and *Escherichia coli* cells. *J. Pept. Sci.* **20**, 885-895

Čeřovský, V. (2014) Antimikrobiální peptidy izolované z hmyzu. *Chem. Listy* **108**, 344-353

Nešuta, O., Hexnerová, R., Buděšínský, M., Slaninová, J., Bednárová, L., Hadravová, R., Straka, J., Veverka, V., and Čeřovský, V. (2016) Antimicrobial peptide from wild bee *Hylaeus signatus* venom and its analogues: Structure-activity study and synergistic effect with antibiotics. *J. Nat. Prod.* **79**, 1073-1083

CURRENT GRANTS

New antifungal peptides for treatment of diseases caused by yeast pathogens, Project no. TA04010638, Technology Agency of the Czech Republic (TA ČR), 2014–2016, Čeřovský, V.

Novel antimicrobial peptides for topical treatment of osteomyelitis and prevention of implant-related infections in orthopedics, Project no. 16-27726A, Czech Health Research Council (AZV ČR), 2016–2020, Čeřovský, V.

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Martin Kotora Group

STEROIDAL INHIBITORS

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Head of the group: Martin Kotora[1] / Scientists: Eva Kudová[2], Hana Chodounská[3]
Research assistant: Barbora Slavíková[4] / Postdocs: Kumar Adla Santosh[5], Ondřej Štěpánek[6]
Ph.D. student: Eva Prchalová[7] / Students: Kateřina Kouřilová[8], Miroslav Kašpar

KEYWORDS / steroids, estrone, 17βHSD, inhibitor, breast cancer, prostate cancer, NMDA receptor, neuroprotectives

Research in the "Steroidal Inhibitors" group is focused on development and synthesis of new compounds with selective biological properties targeting drug-like compounds with expected therapeutical effect.

NEW BREAST AND PROSTATE CANCER THERAPEUTICS
This project targets synthesis of estrone derivatives which are able to inhibit the action of 17β-hydroxysteroid dehydrogenase (17βHSD). Various isoforms of this enzyme in various tissues are responsible for conversion of estrone to estradiol and can contribute to development and progression of estrone dependent diseases. Our derivatives of estrone are selective inhibitors of 17βHSD1 and 17βHSD5 isoforms. These isoenzymes are mainly present in breast and prostate cancer tissue. In collaboration with other research facilities we are trying to establish our compounds as possible new breast and prostate cancer therapeutics.

S.M.A.R.T. STEROIDS
The fundamental goal of this project is a design and synthesis of S.M.A.R.T. Steroids – Steroidal Molecules As Rapid-acting Therapeutics. S.M.A.R.T. Steroids are neuroactive molecules targeting primarily NMDA receptors. These receptors play a significant role in the process of learning and memory; however, overactivation of NMDA receptors under pathological conditions is connected with various neurodegenerative diseases. Our results show that S.M.A.R.T. Steroids: (i) are potent modulators of NMDA receptors, (ii) do cross blood-brain-barrier; (iii) are stable against fast metabolic degradation while maintaining their biological activity; (iv) show neuroprotective effects in animal models; (v) do not show side effects of NMDA antagonism in animal models; (vi) have therapeutic effects in animal models (mice and rats).

SELECTED PAPERS

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

Vyklicky, V., Krausova, B., Cerny, J., Balik, A., Zapotocky, M., Novotny, M., Lichnerova, K., Smejkalova, T., Kaniakova, M., Korinek, M., Petrovic, M., Kacer, P., Horak, M., Chodounska, H., and Vyklicky, L. (2015) Block of NMDA receptor channels by endogenous neurosteroids: implications for the agonist induced conformational states of the channel vestibule. *Sci. Rep.* **5**, 15

Sedlák, D., Eignerová, B., Dračínský, M., Janoušek, Z., Bartůněk, P., and Kotora, M. (2013) Synthesis and evaluation of 17 alpha-(carboranylalkyl) estradiols as ligands for estrogen receptors alpha and beta. *J. Organomet. Chem.* **747**, 178-183

Adamusová, E., Cais, O., Vyklický, V., Kudová, E., Chodounská, H., Horák, M., Vyklický, L. Jr. (2013) Pregnenolone Sulfate Activates NMDA Receptor Channels. *Physiol. Res.* **62**, 731-736

CURRENT GRANTS

Neurosteroid modulation of NMDA receptors. Project no. 303/12/1464, Czech Science Foundation (GA ČR), 2012–2017, Chodounská, H.

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

Genetic and functional studies of NMDA receptors targeted on the prospective diagnosis and treatment of schizophrenia. Project no. NV15-29370A, Ministry of Health (MZ ČR), 2015–2018, Kudová, E.

TARGETED RESEARCH

Gabriel Birkuš Group

HBV CURE

TARGETED RESEARCH GROUP
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KEYWORDS / chronic hepatitis B, nuclear receptor transcription factors, STING/TMEM173, hepatitis B virus, drug discovery

Chronic Hepatitis B (CHB) is a major global health problem with treatment options limited to pegylated-interferon-alpha or nucleos(t)ide analogues. While infection can be controlled with these antivirals, the development of efficient strategies to eliminate Hepatitis B virus (HBV) and thus to cure infection remains a key unmet medical need.

HBV transcription is controlled by a number of ubiquitous and liver enriched host transcription factors (TFs), including nuclear receptors (NRs). Interfering with the function of some NRs, such as chicken ovalbumin upstream promotor TFs, small heterodimer partner or hepatocyte nuclear factor 4α was reported to inhibit HBV transcription. NRs are ligand-dependent, hence their activities can be modulated with small molecules. Our group studies the role of NRs in HBV transcription using HBV infected cells with an ultimate objective to assess whether some of them could serve as a target for CHB drug discovery. We employ RNA interference, Chip-Seq, over-expression, CRISPR-Cas 9, and commercially available small molecule ligands to achieve this objective.

Besides nuclear receptor transcription factors, our group is also involved in biological characterization of novel STING/TMEM173 agonists prepared by our Medicinal Chemistry Department. Activation of this pattern recognition receptor results in the stimulation of host innate responses and it is believed that STING represents a good target for drug discovery efforts aiming to treat chronic hepatitis B or cancer.

SELECTED PAPERS

Rebbapragada, I., Birkus, G., Perry, J., Xing, W., Kwon, H., and Pflanz, S. (2016) Molecular Determinants of GS-9620-Dependent TLR7 Activation. *PLoS One* **11**, e0146835

Birkus, G., Bam, R. A., Willkom, M., Frey, C. R., Tsai, L., Stray, K. M., Yant, S. R., and Cihlar, T. (2016) Intracellular Activation of Tenofovir Alafenamide and the Effect of Viral and Host Protease Inhibitors. *Antimicrob. Agents Chemother.* **60**, 316-322

Mello, C., Aguayo, E., Rodriguez, M., Lee, G., Jordan, R., Cihlar, T., and Birkus, G. (2014) Multiple Classes of Antiviral Agents Exhibit In Vitro Activity against Human Rhinovirus Type C. *Antimicrob. Agents Chemother.* **58**, 1546-1555

Bam, R. A., Birkus, G., Babusis, D., Cihlar, T., and Yant, S. R. (2014) Metabolism and antiretroviral activity of tenofovir alafenamide in CD4+ T-cells and macrophages from demographically diverse donors. *Antivir. Ther.* **19**, 669-677

Stray, K. M., Bam, R. A., Birkus, G., Hao, J., Lepist, E.-I., Yant, S. R., Ray, A. S., and Cihlar, T. (2013) Evaluation of the Effect of Cobicistat on the In Vitro Renal Transport and Cytotoxicity Potential of Tenofovir. *Antimicrob. Agents Chemother.* **57**, 4982-4989

CURRENT GRANTS

Targeting STING for Treatment of CHB and Cancer, Gilead Sciences Research Center (GSRC-3), 2016–2021, Birkus, G.

Stanislava Matějková Group

ANALYTICAL LABORATORY

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

For complete characterization of organic substances, detailed elemental analysis is an indispensable tool. Recently, new methodologies and instrumental techniques have been introduced in our laboratory to supplement or to replace traditional chemical methods of analysis. The implementation of instrumental methods is aimed at improvement of detection limit, sensitivity, and other performance characteristics of analytical methods. The amount of sample required for analysis should be reduced and non-destructive techniques could be applied. The range of elements determined has been expanded significantly.

Currently, C, H, N determination is performed using an automatic analyser in the CHN mode. Fluorine is determined potentiometrically by ion-selective electrode. Energy dispersive X-ray fluorescence (ED-XRF) spectrometry is used mainly for "routine" determination of elements in newly synthesized organic compounds. The developed quantitative analytical method is based on measurements of solutions of studied samples, the element range being Al to U. Semiquantitative analyses in the range of Na to U are feasible for diverse materials without calibration; the method is non-destructive. Inductively coupled plasma-optical emission spectroscopy (ICP-OES) is used for determination of the lightest elements, such as Li and B, analyses of nanoparticle systems, and macro to trace analysis, e.g. in biochemical and/or biological samples. Sophisticated combination with electrothermal vaporization (ETV-ICP-OES) allows trace analysis from minimal sample amounts (about 1 mg).

Optical activity measurement of organic compounds is a standard type of our services. Precise weighing of low amounts of samples for experiments carried out by scientific teams is performed on our precise analytical balance and microbalances.

The staff of Analytical Laboratory is involved in a project aimed at creation of a repository of all relevant samples synthetized in the IOCB.

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Věra Bártová[3], Jaroslava Hniličková[4]
Technicians: Štefan Štanga[5]
Magdalena Hošková[6]
Student: Luisa Šerá[7]

SELECTED PAPERS

Eng, A. Y. S., Poh, H. L., Šaněk, F., Maryško, M., Matějková, S., Sofer, Z., and Pumera, M. (2013) Searching for Magnetism in Hydrogenated Graphene: Using Highly Hydrogenated Graphene Prepared via Birch Reduction of Graphite Oxides. *ACS Nano* **7**, 5930-5939

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

Jankovský, O., Šimek, P., Klímová, K., Sedmidubský, D., Matějková, S., Pumera, M., and Sofer, Z. (2014) Towards graphene bromide: bromination of graphite oxide. *Nanoscale* **6**, 6065-6074

Wong, C. H. A., Sofer, Z., Kubešová, M., Kučera, J., Matějková, S., and Pumera, M. (2014) Synthetic routes contaminate graphene materials with a whole spectrum of unanticipated metallic elements. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 13774-13779

Jankovský, O., Libánská, A., Bouša, D., Sedmidubský, D., Matějková, S., and Sofer, Z. (2016) Partially Hydrogenated Graphene Materials Exhibit High Electrocatalytic Activities Related to Unintentional Doping with Metallic Impurities. *Chemistry* **22**, 8627-8634

Tomáš Elbert Group

LABORATORY OF RADIOISOTOPES

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KEYWORDS / labelled compounds, custom synthesis, tritium, tritium NMR, radio-HPLC

The tasks of the Laboratory of Radioisotopes are multiple: supply of commercially non-available radioactively labelled compounds to biochemical research teams of the institute, provision of radiometric services, management of radioactive waste, and management of radiation safety within the institute.

The problems concerning synthesis of compounds labelled by radionuclides are very specific for each of the radionuclide.

LABELLING OF PEPTIDES BY RADIONUCLIDE ^{125}I
We have optimized the labelling procedure of peptides with 5 to 35 amino acid residues with IODO–GENE™–Na[^{125}I]. The resulting mixture of the starting peptide and its mono-iodinated and di-iodinated derivatives is separated using radio-HPLC and thus the peptides with specific activities over 2 000 Ci/mmol are obtained. Lyophilized ^{125}I-labelled peptides can be stored at -20 °C for a period of two months.

LABELLING OF BIOLOGICALLY ACTIVE COMPOUNDS BY RADIONUCLIDE ^{3}H
An assortment of methods is used for introduction of tritium to biologically active molecules – from simple catalytic exchange methods through reduction of carbon-carbon multiple bonds, catalytic reductive dehalogenations to reductions with carrier-free complex metallic tritides. We are evaluating feasibility of Frustrated Lewis Pairs (FLP) as catalysts for tritiations in the quest for new and orthogonal tritiation methods.

We have experience in synthesizing tritiated compounds with high specific activities of tens of Ci per millimole. The tritiated compounds are fully characterised by their ^{3}H and ^{1}H NMR spectra. Their radiochemical purity is checked by radio-HPLC and radio-TLC. A selection of nucleosides and nucleotides analogues developed in IOCB was labelled as well as brassinosteroids exhibiting cytostatic activity against several human cancer cell lines, seed germination promoters and insect peptide hormones.

SYNTHESES OF ^{14}C-LABELED COMPOUNDS
Recently we have prepared S-[methyl-^{14}C]methyl-L-methionine, 6-amino-5-nitroso-[6-^{14}C]uracil and 5-acetyl-6-amino-1,3-dimethyl-[6-^{14}C]uracil. We have also developed and verified a new simple and rapid specific activity assay of these ^{14}C-labelled compounds using standard ^{13}C NMR spectra. This new method circumvents the time consuming inverse gated ^{13}C NMR experiments used before.

SELECTED PAPERS

Patil, M. R., Elbert, T., and Keri, R. S. (2015) Labelling of brassinosteroids by isotopes of hydrogen and carbon. *RSC Adv.* **5**, 39726-39745

Marek, A., Patil, M. R., and Elbert, T. (2015) The labeling of brassinosteroids by tritium. *RSC Adv.* **5**, 65214-65220

Marek, A., Klepetářová, B., and Elbert, T. (2015) A facile method for steroid labeling by heavy isotopes of hydrogen. *Tetrahedron* **71**, 4874-4882

Plačková, P., Rozumová, N., Hřebabecký, H., Šála, M., Nencka, R., Elbert, T., Dvořáková, A., Votruba, I., and Mertlíková-Kaiserová, H. (2013) 9-Norbornyl-6-chloropurine Is a Novel Antileukemic Compound Interacting with Cellular GSH. *Anticancer Res.* **33**, 3163-3168

Vogensen, S. B., Marek, A., Bay, T., Wellendorph, P., Kehler, J., Bundgaard, C., Frølund, B., Pedersen, M. H. F., and Clausen, R. P. (2013) New Synthesis and Tritium Labeling of a Selective Ligand for Studying High-Affinity gamma-Hydroxybutyrate (GHB) Binding Sites. *J. Med. Chem.* **56**, 8201-8205

CURRENT GRANTS

Subvention for the development of research organizations, Project no. RVO 61388963, Czech Academy of Sciences (AV ČR), 2012–2020, IOCB Prague

Membership in the scientific committee of Central European Division of International Isotope Society (IIS-CED) (INGO II), Project no. LG15033, Ministry of Education, Youth and Sports of the Czech Republic (MŠMT ČR), 2016–2017, Elbert, T.

Petr Mudra Group

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František Vávra[12], Jan Všetečka[13]
Secretary: Miroslava Bartáková[14]

Development Workshops came into being jointly with the Institute of Organic Chemistry and Biochemistry in 1950 as its integral part. Topics of Development Workshops include implementation of test equipment according to requirements of the researchers, unique maintenance of scientific instruments, development and construction of simple apparatuses and development and construction of unique scientific equipment which is commercially unavailable.

In 1990–1999, in cooperation with American and Czech companies the group developed and implemented a number of peptide synthesizers, a solid phase of economic multiple manual synthesizer type MPS1 through fully automated multiple synthesizer type COMPAS to fully automatic multiple peptide synthesizer with a possibility of producing the type of peptide libraries for Illumina Inc., US. An in vitro model of an in vivo human digestive tract type GOLEM was developed and realized in cooperation with Zentiva a.s. in 2008.

In the last year, for example, were completed devices for a two-dimensional capillary electrophoresis, as well as a unique weighting system for monitoring and measuring food consumption for a set of up to 24 laboratory mice to determine the effect of drugs on food intake. We also developed even smaller devices or products, often as unique supplements to products available on the market. These are in frequent use both in the Institute laboratories as well as by external customers. They include e.g. an UV monitor for preparative chromatography or electronic reflux. Simple applications are thermoblocks for heating or cooling files of vials that are made for customers tailored to their needs.

The number of the IOCB service orders exceeds 1 100 per year including complex editing equipment which would otherwise need to be sent abroad for expensive repairs or summon foreign services.

Lukáš Rynda Group

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The Waste Management Department mainly deals with disposal of hazardous wastes. The wastes are prepared for transport and disposal with respect to current legislation, in particular the Waste Act and the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR). The department further performs statutory duties of an administrative nature, such as evidence of waste, sending reports required by state institutions, granting permissions for hazardous waste handling, monitoring of legislative changes.

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IOCB TTO, s.r.o. is a subsidiary company of the Institute providing services in the area of technology transfer. The responsibilities include analyzing the commercial value of novel IP, protection of IP, management of internal targeted projects, attracting the investors and presenting the novel IP at international meetings. The company was incorporated in 2009 and it is 100 % owned by the Institute. During the last years there were over 70 new patent applications submitted, many of them have been awarded. Several projects led to successful licensing.

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Michaela Záluská[13]

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ITS department takes care of the information technology networks, hardware, software and services including library services, electronic information sources administration and reprography services.

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MOST SIGNIFICANT IOCB PAPERS

Most significant articles in 4 different categories are selected each year both by external (international) and internal panels of reviewers. Each group can nominate one or two papers to the prestigious contest. Winning papers are awarded with prizes.

2013

Brynda, J., et al. (2013) Carborane-Based Carbonic Anhydrase Inhibitors. *Angew. Chem.-Int. Edit.* **52**, 13760-13763

Dadová, J., et al. (2013) Vinylsulfonamide and Acrylamide Modification of DNA for Cross-linking with Proteins. *Angew. Chem.-Int. Edit.* **52**, 10515-10518

Fanfrlík, J., et al. (2013) Quantum Mechanics-Based Scoring Rationalizes the Irreversible Inactivation of Parasitic *Schistosoma mansoni* Cysteine Peptidase by Vinyl Sulfone Inhibitors. *J. Phys. Chem.* B **117**, 14973-14982

Gutten, O., et al. (2013) Predicting the Stability Constants of Metal-Ion Complexes from First Principles. *Inorg. Chem.* **52**, 10347-10355

Jančařík, A., et al. (2013) Rapid Access to Dibenzohelicenes and their Functionalized Derivatives. *Angew. Chem.-Int. Ed.* **52**, 9970-9975

Keough, D. T., et al. (2013) Acyclic Nucleoside Phosphonates Containing a Second Phosphonate Group Are Potent Inhibitors of 6-Oxopurine Phosphoribosyltransferases and Have Antimalarial Activity. *J. Med. Chem.* **56**, 2513-2526

Kessler, J., et al. (2013) Parallel Variable Selection of Molecular Dynamics Clusters as a Tool for Calculation of Spectroscopic Properties. *J. Comput. Chem.* **34**, 366-371

Kolář, M., et al. (2013) Plugging the explicit sigma-holes in molecular docking. *Chem. Commun.* **49**, 981-983

Lagoutte, R., et al. (2013) Isolated Sex Pheromone of Strepsiptera. *Chem. Eur. J.* **19**, 8515-8524

Mucha, M., et al. (2013) Alkylation of gold surface by treatment with C18H37HgOTs and anodic Hg stripping. *J. Am. Chem. Soc.* **135**, 5669-5677

Sedlák, F., et al. (2013) Glutamate carboxypeptidase II does not process amyloid-beta peptide. *Faseb J.* **27**, 2626-2632

Selicharová, I., et al. (2013) Effects of hyperhomocysteinemia and betaine-homocysteine S-methyltransferase inhibition on hepatocyte metabolites and the proteome. *Biochim. Biophys. Acta* **1834**, 1596-1606

Stirnemann, G., et al. (2013) Mechanisms of acceleration and retardation of water dynamics by ions. *J. Am. Chem. Soc.* **135**, 11824-11831

Vávra, J., et al. (2013) Search for Conglomerate in Set of 7 Helquat Salts: Multigram Resolution of Helicene-Viologen Hybrid by Preferential Crystallization. *J. Org. Chem.* **78**, 1329-1342

Žáková, L., et al. (2013) Structural Integrity of the B24 Site in Human Insulin Is Important for Hormone Functionality. *J. Biol. Chem.* **288**, 10230-10240

2014

Baumlova, A., et al. (2014) The crystal structure of the phosphatidylinositol 4-kinase II alpha. *EMBO Rep.* **15**, 1085-1092

Buděšínský, M., et al. (2014) Determination of the configuration in six-membered saturated heterocycles (N, P, S, Se) and their oxidation products using experimental and calculated NMR chemical shifts. *Tetrahedron* **70**, 3871-3886

Čermáková, K., et al. (2014) Validation and Structural Characterization of the LEDGF/p75-MLL Interface as a New Target for the Treatment of MLL-Dependent Leukemia. *Cancer Res.* **74**, 5139-5151

Chalupský, J., et al. (2014) Reactivity of the Binuclear Non-Heme Iron Active Site of D9 Desaturase Studied by Large-Scale Multireference Ab Initio Calculations. *J. Am. Chem. Soc.* **136**, 15977-15991

Jílková, A., et al. (2014) Activation Route of the Schistosoma mansoni Cathepsin B1 Drug Target: Structural Map with a Glycosaminoglycan Switch. *Structure* **22**, 1786-1798

Kafka, F., et al. (2014) Oxidative Catalysis Using the Stoichiometric Oxidant as a Reagent: An Efficient Strategy for Single-Electron-Transfer-Induced Tandem Anion-Radical Reactions. *Angew. Chem.-Int. Edit.* **53**, 9944-9948

Kožíšek, M., et al. (2014) Thermodynamic and structural analysis of HIV protease resistance to darunavir – analysis of heavily mutated patient-derived HIV-1 proteases. *FEBS J.* **281**, 1834-1847

Krečmerová, M., et al. (2014) N(4)-Acyl derivatives as lipophilic prodrugs of cidofovir and its 5-azacytosine analogue, (S)-HPMP-5-azaC: chemistry and antiviral activity. *Bioorg. Med. Chem.* **22**, 2896-2906

Opekar, S., et al. (2014) Diethyl Fluoronitromethylphosphonate: Synthesis and Application in Nucleophilic Fluoroalkyl Additions. *Chemistry* **20**, 1453-1458

Pospíšil, L., et al. (2014) Intense Chiroptical Switching in a Dicationic Helicene-Like Derivative: Exploration of a Viologen-Type Redox Manifold of a Non-Racemic Helquat. *J. Am. Chem. Soc.* **136**, 10826-10829

Rehor, I., et al. (2014) Fluorescent Nanodiamonds with Bioorthogonally Reactive Protein-Resistant Polymeric Coatings. *ChemPlusChem* **79**, 21-24

Růžička, M., et al. (2014) Study of deoxyribonucleic acid-ligand interactions by partial filling affinity capillary electrophoresis. *J. Chromatogr. A* **1349**, 116-121

Savolainen, J., et al. (2014) Direct observation of the collapse of the delocalized excess electron in water. *Nat. Chem.* **6**, 697-701

Snášel, J., et al. (2014) Structural Basis for Inhibition of Mycobacterial and Human Adenosine Kinase by 7-Substituted 7-(Het)aryl-deazaadenine Ribonucleosides. *J. Med. Chem.* **57**, 8268-8279

Šebestík, J., et al. (2014) Observation of Paramagnetic Raman Optical Activity of Nitrogen Dioxide. *Angew. Chem.-Int. Edit.* **53**, 9236-9239

Šimák, O., et al. (2014) Conformationally constrained nucleoside phosphonic acids--potent inhibitors of human mitochondrial and cytosolic 5′(3′)-nucleotidases. *Org. Biomol. Chem.* **12**, 7971-7982

Vaníková, Z., et al. (2014) Polymerase Synthesis of Photocaged DNA Resistant against Cleavage by Restriction Endonucleases. *Angew. Chem.-Int. Edit.* **53**, 6734-6737

Vazdar, K., et al. (2014) Very Strong Organosuperbases Formed by Combining Imidazole and Guanidine Bases: Synthesis, Structure, and Basicity. *Angew. Chem.-Int. Edit.* **53**, 1435-1438

Zoll, S., et al. (2014) Substrate binding and specificity of rhomboid intramembrane protease revealed by substrate-peptide complex structures. *EMBO J.* **33**, 2408-2421

2015

Amatov, T., et al. (2015) Synthesis of Bridged Diketopiperazines by Using the Persistent Radical Effect and a Formal Synthesis of Bicyclomycin. *Angew. Chem.-Int. Edit.* **54**, 12153-12157

Buček, A., et al. (2015) Evolution of moth sex pheromone composition by a single amino acid substitution in a fatty acid desaturase. *Proc. Natl. Acad. Sci. U. S. A.* **112**, 12586-12591

Kaletová, E., et al. (2015) The Scope of Direct Alkylation of Gold Surface with Solutions of C-1-C-4 n-Alkylstannanes. *J. Am. Chem. Soc.* **137**, 12086-12099

Mason, P. E., et al. (2015) Coulomb explosion during the early stages of the reaction of alkali metals with water. *Nat. Chem.* **7**, 250-254

Mejdrová, I., et al. (2015) Highly Selective Phosphatidylinositol 4-Kinase III beta Inhibitors and Structural Insight into Their Mode of Action. *J. Med. Chem.* **58**, 3767-3793

Petrová, M., et al. (2015) Straightforward Synthesis of Purine 4 ′-Alkoxy-2 ′-deoxynucleosides: First Report of Mixed Purine-Pyrimidine 4 ′-Alkoxyoligodeoxynucleotides as New RNA Mimics. *Org. Lett.* **17**, 3426-3429

Schimer, J., et al. (2015) Triggering HIV polyprotein processing by light using rapid photodegradation of a tight-binding protease inhibitor. *Nat. Commun.* **6**, 8

Šámal, M., et al. (2015) An Ultimate Stereocontrol in Asymmetric Synthesis of Optically Pure Fully Aromatic Helicenes. *J. Am. Chem. Soc.* **137**, 8469-8474

Tesina, P., et al. (2015) Multiple cellular proteins interact with LEDGF/p75 through a conserved unstructured consensus motif. *Nat. Commun.* **6**, 14

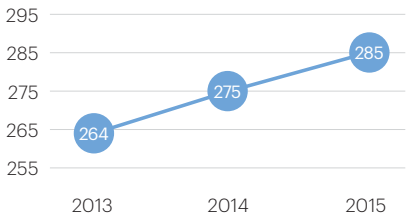
Tykvart, J., et al. (2015) Structural and Biochemical Characterization of a Novel Aminopeptidase from Human Intestine. *J. Biol. Chem.* **290**, 11321-11336

Wen, J., et al. (2015) Captodatively Stabilized Biradicaloids as Chromophores for Singlet Fission. *J. Am. Chem. Soc.* **137**, 165-172

Wu, T., et al. (2015) Detection of Circularly Polarized Luminescence of a Cs-Eu(III) Complex in Raman Optical Activity Experiments. *Angew. Chem.-Int. Edit* **54**, 14933-14936

PUBLICATIONS OVERVIEW

Publications in Impact Factor Journals in ASEP Database



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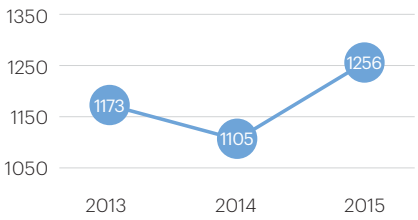

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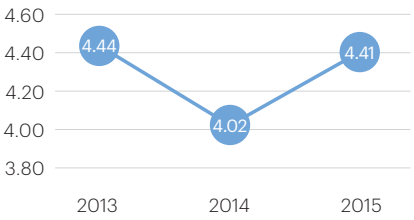
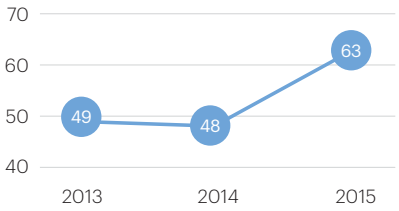


Average IF per publication

Publications by Impact Factor



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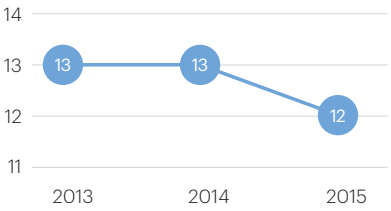

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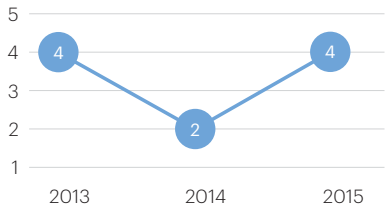
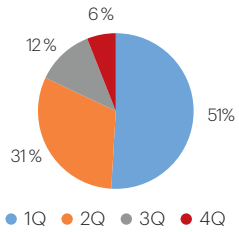
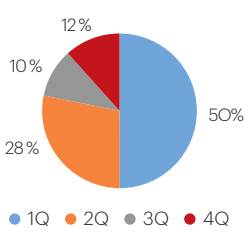


IF >20

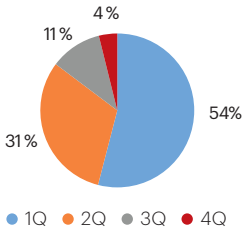
Publications by Quartile Ranking



2013



2014



2015

SELECTED GRANTS

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

New Horizons for Mass Spectrometry, Project no. AdG 226373, European Research Council (ERC), 2009–2013 (terminated prematurely), Schroeder, D.

Smart biologics: developing new tools in glycobiology, Project no. StG 677465, European Research Council (ERC), 2016–2021, Vrábel, M.

Viral RNA modifications – The essential steps in protein cofactors chemical evolution, Project no. LL1603, Ministry of Education, Youth and Sports of the CR – ERC CZ (LL), 2016-2019, Cahová, H.

Development of Diamond Intracellular Nanoprobes for Oncogene Transformation Dynamics Monitoring in Living cells, Project no. 245122, European Commission (EC FP7), 2010-2013, Ledvina, M.

Collaborative Project: Systems biology of Mycobacterium tuberculosis, Project no. 241587, European Commission (EC FP7), 2010–2014, Pichová, I.

Rhomboid substrates, Project no. 2329, European Commission (FP7-PEOPLE-2012-CIG — Marie-Curie Action: "Career Integration Grants"), 2012–2016, Stříšovský, K.

Structural targeting of PI4 kinases, Project no. 333916, European Commission (FP7-PEOPLE-2012-CIG — Marie-Curie Action: "Career Integration Grants"), 2013–2016, Bouřa, E.

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

Biological roles of rhomboid intramembrane proteases, their substrates and specificity, Project no. 2329, EMBO Installation Grant, European Molecular Biology Organisation (EMBO), 2012–2017, Stříšovský, K.

A molecular dissection of the interplay between diabetes and cancer: an integrated, multidisciplinary approach, Project no. MR/K000179/1, Medical Research Council (MRC, UK), 2012–2017, Jiráček, J. (co-PI)

GILEAD SCIENCES RESEARCH CENTRE

Gilead Sciences Research Centre at IOCB Prague (GSRC) is a partnership program between US-based biopharma company Gilead Sciences, Inc. and IOCB Prague. It was established originally in 2006 for an initial period of five years with an annual donation of $1.1 million to expand IOCB research efforts in the field of human diseases. The program has been renewed in 2011 and in 2016 again with an increased donation of $1.35 million annually.

PARTICIPATING PRINCIPAL INVESTIGATORS IN 2013-2016

GSRC-2 (2011—2016)

Zdeněk Havlas
Pavel Hobza
Michal Hocek
Ullrich Jahn
Zlatko Janeba
Jan Konvalinka
Radim Nencka
Iva Pichová
Lubomír Rulíšek

GSRC-3 (2016—2021)

Michal Hocek
Ullrich Jahn
Zlatko Janeba
Jan Konvalinka
Pavlína Maloy Řezáčová
Radim Nencka
Iva Pichová
Filip Teplý
Radek Pohl

INVITED LECTURES

IOCB invites dozens of outstanding scientists and rising stars to present
their lectures and to discuss scientific topics within the frame of Invited Lecture Series.

2013

Prof. Robert Crabtree (Yale University, USA): Organometallic Precatalysts for Oxidation of Water and Alkyl C-H Bonds

Prof. Steven M. Reppert (University of Massachusetts Medical School, USA): Monarch Butterfly Migration:
From Behavior to Neurons to Genes

Prof. Harry L. Anderson (Oxford University, UK):
New Approaches to the Design and Synthesis of Molecular Wires for Biomedical and Nanotechnology Applications

Prof. David Avnir (The Hebrew University of Jerusalem, Israel): Organic Molecules within Metals: Principles and Applications

Prof. Frank Glorius (Westfälische Wilhelms-Universität Münster, Germany):
Stories on Design & Surprise: C-H Activation, Asymmetric Arene Hydrogenation and NHC Organocatalysis

Prof. Thomas R. Cech (University of Colorado, USA): Crawling out of the RNA World: From Ribozymes to Telomerase

Prof. Tom L. Blundell (University of Cambridge, UK): Genomes, Structural Biology and Drug Discovery:
Exploring Chemical and Biological Space

Prof. Lawrence T. Scott (Boston College, USA):
Can Organic Chemists Deliver Structurally Uniform Fullerenes and Carbon Nanotubes by Custom Synthesis?

Prof. Charles S. Craik (University of California San Francisco, USA): Profiling and Detecting Unregulated Proteolytic Activity

Prof. Ronald Breslow (Columbia University, USA): The Origin of Homochirality in Amino Acids and Sugars on Prebiotic Earth

Prof. Thomas Carell (Ludwig-Maximilians-Universität and Charité Universitätsklinikum, Germany):
DNA Bases Beyond Watson and Crick

2014

Prof. Gary A. Molander (University of Pennsylvania, USA): Novel Organoboron Reagents and Reactivities

Prof. C. Dale Poulter (University of Utah, USA): From Genes to Enzymes to Compounds. A Chemical Basis for Evolution of Function

Prof. Wilfred A. Van Der Donk (University of Illinois, USA): Biosynthesis of Cyclic Peptide Antibiotics

Prof. Tom W. MUIR (Princeton University, USA): 'Houdini' Proteins: Discovery and Applications of Ultrafast Inteins

Prof. Benjamin G. DAVIS (University of Oxford, UK): Sugars & Proteins: Towards a Synthetic Biology

2015

Prof. Barbara S. Slusher (Johns Hopkins School of Medicine, USA):
Development of Glutamate Carboxypeptidase and System xc- Inhibitors for the Treatment of Neurodegenerative Disorders

Prof. Michael Groll (Technische Universität München, Germany):
Exploiting Nature's Rich Source of Proteasome Inhibitors as Starting Points in Drug Development

Prof. Peter Chen (ETH Zürich, Switzerland): Catalytic Electrophilic Cyclopropanation without Diazo Compounds:
De Novo Mechanistic Design and a Historical Twist

Prof. Gerald W. Zamponi (Cumming School of Medicine,University of Calgary, Canada):
Molecular Approaches towards New Pain Therapeutics

Prof. David O'Hagan (University of St. Andrews, UK):
Fluorination with an Enzyme and Applications towards Positron Emission Tomography for Clinical Imaging

Prof. K. Peter C. Vollhardt (University of California at Berkeley, USA):
Saving the Planet: Toward a Sun-charged Thermal Molecular Battery

2016

Prof. Wolfgang Graier (Medical University of Graz, Austria): Mitochondrial Calcium Uptake in Health and Disease

Prof. Michael J. Krische (University of Texas at Austin, USA):
Formation of C-C Bonds via Catalytic Hydrogenation and Transfer Hydrogenation

Prof. David Eisenberg (University of California Los Angeles, USA): The Amyloid State of Proteins

Prof. Vincent M. Rotello (University of Massachusetts, USA): Interfacing Nanomaterials with Biology:
Applications in Therapeutics and Diagnostics

Prof. James H. Hurley (University of California, USA): How HIV Hijacks Membrane Traffic

Prof. Tamas Balla (National Institute of Child Health and Human Development, USA):
Discovering the Secrets of Inositol Lipid Signals. A Quest that still Holds Many Surprises

SELECTED AWARDS

IOCB scientists are frequently nominated for prestigious national and international awards and accolades. We are proud of outstanding scientific achievements of our senior, junior and student colleagues.

2013

Petr Beier – Alfred Bader Prize in organic chemistry, Czech Chemical Society, 2013
Petr Cígler – Otto Wichterle Award, Czech Academy of Sciences, 2013
Martin Dračínský – Otto Wichterle Award, Czech Academy of Sciences, 2013
Jana Jaklová Dytrtová – excellent presentation of significant innovative analytical research on the occasion of the Euroanalysis XVII 2013, Springer, 2013
Robin Kryštůfek – Česká hlavička Award, 2013
Jiří Václavík – Česká hlava Award, 2013

2014

Pavel Hobza – Highly Cited Researchers, world-class research, ISI Thomson Reuters, 2014, 2015
Jana Jaklová Dytrtová (R. Norková, V. Kašička) – Karel Preis Award for 2013, Czech Chemical Society, 2014
Jiří Kaleta – The Coris award for the best oral presentation (Czech Republic), 2014
Jakub Kaminský – Otto Wichterle Award, Czech Academy of Sciences, 2014
Milan Kožíšek – Otto Wichterle Award, Czech Academy of Sciences, 2014
Josef Michl – Boron in the Americas Award, 2014
Jan Řezáč – Otto Wichterle Award, Czech Academy of Sciences, 2014

2015

Evžen Bouřa – Otto Wichterle Award, Czech Academy of Sciences, 2015
Hana Cahová – Otto Wichterle Award, Czech Academy of Sciences, 2015
Michal Hocek – Praemium Academiae, scientific excellence, Czech Academy of Sciences, 2015
Josef Michl – Hammond Award, I-APS, 2015
Jan Šilhán – Fellowship J. E. Purkyně of the Czech Academy of Sciences, 2015
Filip Teplý – Rudolf Lukeš Prize, Czech Chemical Society, 2015
Irena Valterová – Prize of the Future & Award for usefulness of the solution for project "Pollinators as a crucial factor in agriculture", Technology Agency of the Czech Republic, 2015
Lenka Žáková and Jiří Jiráček – Karel Preis Award for 2014, Czech Chemical Society, 2015

2016

Hana Cahová – Alfred Bader Prize in bioorganic chemistry, Czech Chemical Society, 2016
Pavel Jungwirth – Jaroslav Heyrovský Medal, Czech Academy of Sciences, 2016

FOR IOCB EMPLOYEES

Major event is a bi-annual scientific retreat, where research groups present their current projects. Both young and senior scientists attend and share promising results, new discoveries and successful publications.

Interacting with international science community is crucial for IOCB. The Institute invites experts in different fields from all over the world for IOCB Invited Lectures series which is held approximately once a month. In addition, there are numerous lectures, seminars, workshops and journal clubs organized regularly by different research groups.

IOCB regularly organizes Happy Hours – popular and informal get-together for employees with exhibitions and music.

STUDENTS AND POSTDOCS

IOCB is constantly searching for new student talents and there are dozens of new Ph.D. projects available annually at the Institute. Currently we host 140 Czech and international Ph.D. students from number of universities who contribute substantially to the Institute's achievements and gain priceless experience with research work in the international environment of the cutting-edge institute in return.

There are 80 postdocs working across IOCB research groups. The Institute announces application call for postdoctoral stipends (IOCB Fellowships) twice a year to allow young scientists from abroad joining IOCB.

IOCB organizes multiple events and activities for young scientists throughout the year:

- Weekend Bootcamp — informal retreat for new coming Ph.D. students
- Ph.D. Science Club series — monthly event with presentations by advanced Ph.D. students
- Prague Summer School: Advances in Drug Discovery — five-day school organized jointly by IOCB and UCT with experts from academia and international biotech and pharmaceutical industry
- Summer Student Program for students with completed BSc. studies
- Soft skills workshops — trainings on scientific writing and similar topics organized for the students roughly twice a year

SOCIAL RESPONSIBILITY

In addition to its primary goals, which is excellent science and education, IOCB applies targeted support for parents in science and backs contribution to the community life.

IOCB appreciates all moms in the Institute who try to harmonize childcare with their research career. In order to ease their challenging situation, IOCB offers a special financial subsidy designated to cover childcare expenses during working hours since June 2016.

Martina Roeselová Memorial Fellowship is dedicated to Ph.D. students or postdocs who are conducting competitive research at local universities or research institutes and are at the same time primary care givers of a pre-school age child. The grant provides a monthly salary support to selected applicants for a period of one year.

Since June 2015, IOCB is part of Kampus Dejvice initiative, which links universities (University of Chemistry and Technology Prague, Charles University in Prague and Czech Technical University in Prague), research institute (IOCB Prague) and National Library of Technology present in the Prague's district Dejvice. With the support of the municipality, Kampus Dejvice organizes activities and events for students and public and brings academic ground closer to the local community (Cross-campus run, concerts, etc.).

PUBLIC OUTREACH

IOCB presented its discoveries by artistic projection of healthy and pathological cell from the studio of Jakub Nepraš at Expo 2015 in Milan. The display called "The Cell" was awarded as the most impressive exhibit by the Czech Commissioner General. Over two millions people visited the Czech pavilion during Expo 2015.

IOCB opens its premises to public every year during Week of Science and Technology festival. Two days are reserved for school excursions and on the last day IOCB welcomes anybody to visit and find out more about the research at the Institute.

IOCB takes part in the Science Festival held annually for public in Prague. The Institute contributes with educative and fun activities related to organic chemistry and biochemistry. Over 15 000 visitors attended this event in 2016.

Scientists from IOCB participate in the Prague Museum Night and prepare program for both kids and adults.

IOCB also helps to organize educative lectures during Life Sciences Film Festival, covering topics from food to metabolic diseases.

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IOCB PRAGUE

IOCB 2013—2016
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