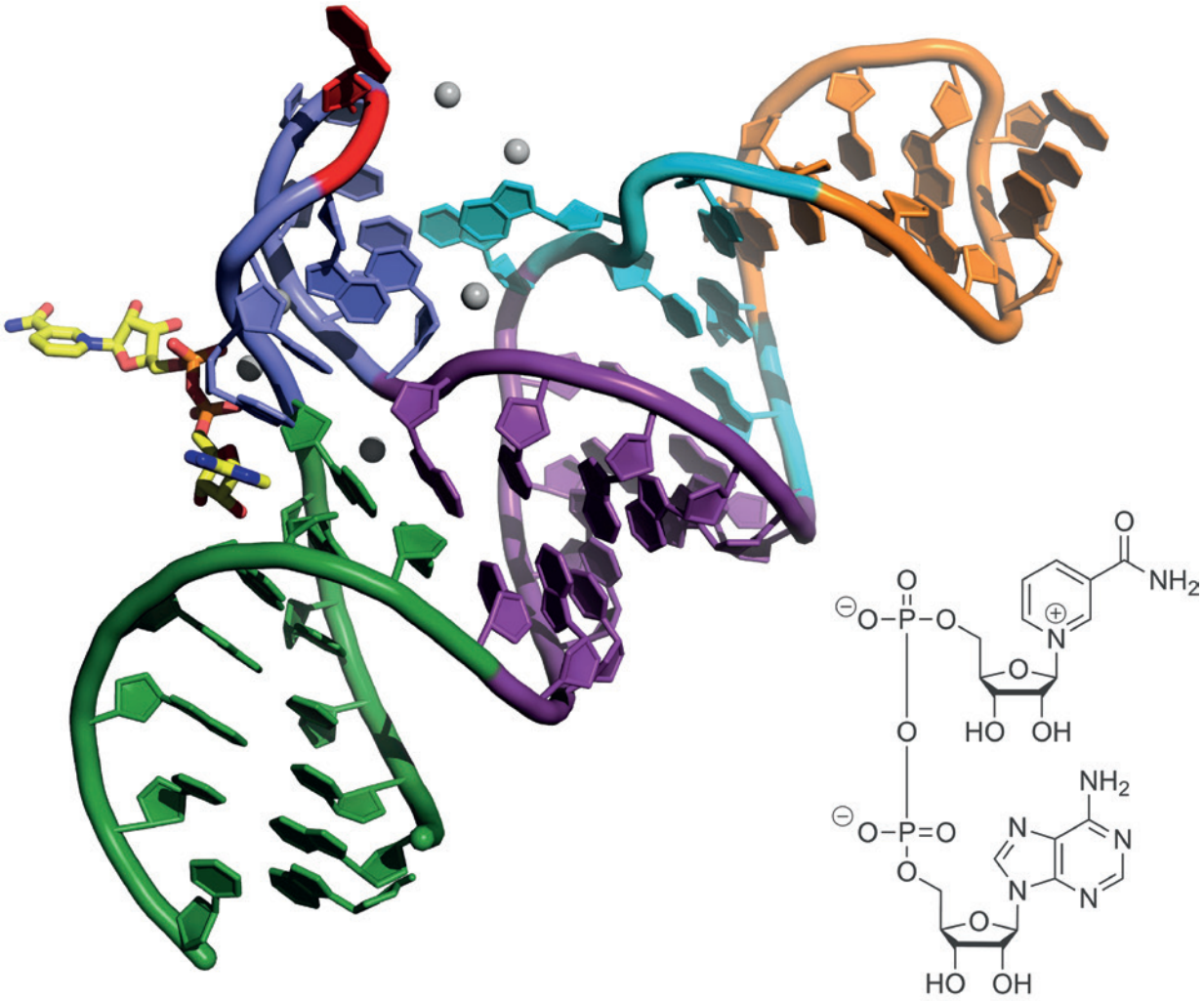
universität innsbruck

Research Area
Center for Molecular Biosciences (CMBI)

scientific report 2018–2021



Scientific Coordinators

Ronald Micura, Bert Hobmayer, Alexandra Koschak

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Content: Ronald Micura, Professor of Organic Chemistry
Bert Hobmayer, Professor of Zoology
Alexandra Koschak, Professor of Pharmacology

Layout: Stephanie Brejla, Gabi Reiter

Contact: Research Area Center for
Molecular Biosciences (CMBI)

University of Innsbruck
Innrain 80-82
A-6020 Innsbruck
Tel: +43 512 507-57501
Fax: +43 512 507-57599
cmbi@uibk.ac.at
www.uibk.ac.at/cmbi

Cover figure:
The cover shows the three-dimensional structure of the NAD^+ riboswitch from *Acidobacterium capsulatum* bound to NAD^+. The chemical structure of the cofactor NAD^+ is depicted at the bottom right (adapted from Chen, H. *et al.*, Structural distinctions between NAD^+ riboswitch domains 1 and 2 determine differential folding and ligand binding. *Nucleic Acids Research* **2020**, **48**, 12394–12406).

The „Center for Molecular Biosciences Innsbruck (CMBI)“ – a life science network in western Austria

The present report for the years 2018 to 2021 highlights recent scientific breakthroughs, the latest developments in ongoing research projects, and outstanding achievements of members of the Center for Molecular Biosciences of Innsbruck University (CMBI). As one of the most dynamic and exciting fields in modern research, the molecular biosciences aim at a comprehensive understanding of cellular processes by bridging the gap between properties of isolated molecules and their various functions in living organisms. For example, even small changes in conformation or constitution of bioactive molecules such as DNA, RNA, and proteins can profoundly affect the state of cells, microorganisms, plants, animals, and humans, with implications for health and disease. Recent technological advances in microscopic imaging, new generation sequencing applications, and instrumentation for analyzing molecular structure provide multifaceted information critical to a detailed understanding of biological systems and human health. The CMBI aims to provide an interdisciplinary platform for addressing key research questions in the rapidly developing field of molecular biosciences, to promote collaborative projects with added value, and to increase the visibility of the CMBI and its members on an international level.

The CMBI currently consists of 28 internationally competitive research teams from three faculties (Chemistry and Pharmacy; Biology; Mathematics, Informatics and Physics) whose activities are focused on research and teaching. CMBI members head the EC Horizon–2020 programs MESI-STRAT, ARDRE, CRAFTMOL, and AGEMEC, and contribute to the FWF special research program SFB-F80 RNA-Deco. Notably, several members have initiated the CMBI-embedded University PhD programs “Ageing and Regeneration” and “CavX – Calcium channels in excitable cells”. Moreover, CMBI members were able to successfully compete in the 1st FFG call for university infrastructure and have established new facilities for Nuclear Magnetic Resonance (NMR) spectroscopy in 2018. These infrastructures will significantly advance biomolecular structural analysis and thus the life sciences in the Western-Austrian area. To further strengthen the life sciences community in Tyrol, and to enable new professional perspectives for young scientists, the CMBI is a co-organizer of the internationally visible Innsbruck Life Science meetings.

The CMBI coordinators:
Ronald Micura Bert Hobmayer Alexandra Koschak

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>> CMBI facts

The C*enter for Molecular Biosciences (CMBI)* at the University of Innsbruck is an integrative and multidisciplinary research and teaching institution. The mission of the CMBI is to advance studies on the structure, function, and interaction of biological macromolecules and low molecular weight compounds relevant for cellular growth, metabolism, and development. The research activities in the CMBI take advantage of existing research strength in different fields and have strongly promoted interdisciplinary research activities in five major fields of biomolecular sciences.

Basic and applied biomolecular research fields at the CMBI

- Structure, dynamics and interactions of biologically important molecules
- Molecular basis of physiological and pathophysiological processes
- Metabolites, natural and synthetic compounds that modulate important biological processes
- Cell-to-cell communication and cellular function
- Development, regeneration and aging of whole organisms

Twenty-eight research groups from the Faculty of Chemistry and Pharmacy, the Faculty of Biology, and the Faculty of Mathematics, Informatics & Physics are members of the CMBI.

members I

CMBI members	Areas of expertise
	Chemistry
G. Bonn, C. Huck	bioanalytics
K. Breuker	biomolecular mass spectrometry
B. Kräutler, T. Müller	organic and bioorganic chemistry
K. Liedl	theoretical chemistry, computer-aided molecular design
T. Magauer	synthetic organic chemistry
R. Micura	organic chemistry and chemical biology
R. Schneider	molecular biology, biotechnology
E. Stefan, M. Hartl	biochemistry, molecular genetics
K. Thedieck	biochemistry, cell biology
M. Tollinger, C. Kreutz	biomolecular NMR spectroscopy
	Pharmacy
R. Gust	medicinal chemistry
A. Koeberle	molecular pharmacology
A. Koschak	cell biology, molecular physiology
M. Spetea	pharmaceutical chemistry, drug design
J. Striessnig, N. Singewald	cell biology, neuropharmacology
H. Stuppner, M. Ganzera	pharmaceutical biology, phytochemistry
P. Tuluc	cell biology, molecular endocrinology
	Biology
R. Dallinger	cell physiology, ecotoxicology
F. Edenhofer	stem cell biology
B. Hobmayer, P. Ladurner	cell and developmental biology
M. Höckner	molecular biology, cell physiology
P. Jansen-Dürr	cell biology, molecular biology
I. Kranner	plant physiology, biochemistry
J. Mertens	neural aging
D. Meyer, R. Kimmel	developmental biology
B. Pelster, A. Sandbichler, T. Schwerte	cell biology, cell physiology
W. Zwerschke	molecular cell biology
	Physics
S. Denifl	biophysics, radiation physics

CMBI members received renowned scientific awards and prizes over the last four years thus documenting their successful research activities to the scientific community and general public. In 2018, Jörg Striessnig became Member of the Academia Europaea. Jerome Mertens received an ERC Starting Grant in 2019. Thomas Magauer received an ERC Consolidator Grant in 2020 and became Member of the Young Academy of the Austrian Academy of Science (ÖAW). Andreas Koeberle was awarded the EFMC prize 2019 in the category "Young Medicinal Chemist in Academia" and Christian Huck the Tomas Hirschfeld Award 2018. Several early-career scientists were awarded, among those were the Karl-Schlögl Award 2021 (ÖAW) to Monica Fernández-Quintero, the Award of Excellence (Austria Federal Ministry of Education, Science and Research) to Nadja Hofer (2020) and to Monica Fernández-Quintero (2021). Moreover, fourteen research projects to young CMBI researches were approved by the Tiroler Wissenschaftsförderung (TWF). Furthermore, several CMBI scientists are members of the Austrian Academy of Sciences (Bernhard Kräutler, Ronald Micura, Jörg Striessnig) and of the German Academy of Sciences, Leopoldina (Bernhard Kräutler, Jörg Striessnig). Ilse Kranner is Board Member of the Austrian Science Fund (FWF) for the discipline of biology. The activities of the CMBI are currently coordinated by Ronald Micura (head), Alexandra Koschak and Bert Hobmayer.

In the years 2018 - 2021 the CMBI member labs published 884 papers in peer reviewed journals. This includes 107 publications in the world leading journals *Nature, Science, Cell, Immunity, Nature Neuroscience, Cell Stem Cell, Physiological Reviews, Nature Chemistry, Gastroenterology, Nucleic Acids Research, Advanced Science, Nature Communications, Nature Metabolism, Proceedings of the National Academy of Sciences of the United States of America, EMBO Journal, and Autophagy*, and in top journals of chemistry and physics, including *Journal of the American Chemical Society, Angewandte Chemie International Edition, Chemical Science,* and *Chemical Society Reviews.* The total amount of third-party funding since 2018 amounts to more than 44 million EUR. Modern infrastructure obtained through special governmental funding for research equipment significantly strengthens research in structural chemistry and biology, bioanalytics, and biophysics at the CMBI.

The specific research topics of the 28 CMBI member labs are listed below.

topics

Research topics
• Metabolic signaling (Thedieck)
• Functional lipidomics, molecular phytopharmacology (Koeberle)
• Proteomics, metabolomics, phytomics (Bonn, Huck)
• Regulation of cell function by protein modification (Schneider)
• Oncogenic transcription factors and their cellular targets (Stefan, Hartl)
• Development of theoretical and computational methods describing molecular interactions in chemical and biological systems (Liedl)
• Biomolecular interactions in solution – NMR spectroscopy (Kreutz, Tollinger)
• Biomolecular interactions in the gas phase – mass spectrometry (Breuker)
• Synthesis, structure, function and interactions of RNA (Micura)
• Natural product synthesis, total synthesis, synthetic methods (Magauer)
• Natural products chemistry, pigments of life (Kräutler, Müller)
• Inelastic interaction of low energy electrons with molecules of biological relevance (Denifl)
• Bioactive natural products from the plant kingdom (Stuppner, Ganzera)
• Development of selectively acting antitumor drugs (Gust)
• Development of potential drugs interacting with opioid receptors (Spetea)
• Ion channels as new drug targets and the neuropathological basis of anxiety disorders (Striessnig, Singewald)
• Ion channels in retinal physiology, diseases and pharmacotherapy (Koschak)
• Ion channels structure-function and their role in hormone release (Tuluc)
• Molecular and genetic control of vertebrate development (Meyer, Kimmel)
• Stem cell differentiation, regeneration and bioadhesion in basal Metazoa (Hobmayer, Ladurner)
• Neural reprogramming to study brain aging and neurological disorders (Mertens)
• Stem cell biology, cellular reprogramming & regeneration (Edenhofer)
• Biology of aging, mitochondrial physiology (Jansen-Dürr)
• Stress metabolites and signaling pathways in plants (Kranner)
• Cell ion and volume homeostasis and metabolic activity (Pelster, Sandbichler, Schwerte)
• Stress response and immunity, epigenetics and gene regulation (Höcker)
• Trace element homeostasis in animal cells (Dallinger)
• Role of adipose tissue in obesity and ageing (Zwerschke)

CMBI SPECIALS – Infrastructure funding and research programs

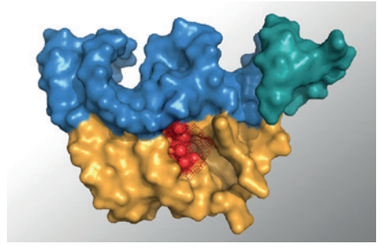

picture: Otto Peter

>> NEW NMR-SPECTROMETERS

With new laboratory infrastructure, the CMBI is being further strengthened. In 2018, two more nuclear magnetic resonance (NMR) spectrometers have become available to the research groups. The Austrian Research Promotion Agency FFG has funded the purchase as part of the 1st call of its new research infrastructure program with over 1.8 million euros.

Structure and structural dynamics of nucleic acids, and their interactions with proteins or small molecules have been successfully studied by CMBI research groups over the past years. With their application, the scientists around Ronald Micura, Christoph Kreutz, Martin Tollinger, Kathrin Breuker, Ronald Gust, and Hermann Stuppner prevailed in a tough Austria-wide competition. Out of a total of 81 applications submitted, only eight were approved. "The new devices expand the possibilities in the area of structural chemistry and they perfectly complement the existing NMR instrumentation, which have been working to capacity for the last years," says Micura. "We were able to prevail in this very competitive process thanks to the joint effort within the CMBI."

With the underlying research program, the international visibility of NMR-based RNA research in the CMBI is to be further expanded. The main goal is to achieve a thorough understanding of structure, structural dynamics, and folding of RNA, and of the interaction of RNA with low molecular weight compounds. Particular attention is paid to riboswitches, which control gene regulation and which are potential targets for new drugs. Complex dynamic folding mechanisms are involved, which can be clarified by means of nuclear magnetic resonance spectroscopy. In addition, new approaches for labeling RNA are to be developed with the aid of NMR. Another focus is laid on the investigation of RNA-modifying enzymes and proteins that can trigger allergies or are important for inflammatory signaling pathways. Additionally, the search for natural products with antibacterial effects by directly targeting RNA is an important aim.



NMR spectroscopy is particularly powerful for the study of dynamic interactions between biomolecules.

"The wealth of 'dynamic' information that can be made accessible using NMR spectroscopic methods is complementary to the 'static' images of biomolecular systems obtain by crystallography," says Micura. "Over the past sixty years, NMR spectroscopy has been an indispensable analytical method in the field of organic synthesis and is about to become the method of choice for studying dynamic interaction networks of biomolecules." Besides the Innsbruck scientists, the external research groups led by Robert Konrat from the Max F. Perutz Laboratories in Vienna, Fatima Ferreira-Briza at the University of Salzburg, and Michael Oberhuber at the Laimburg Research Center in South Tyrol, are involved as scientific collaborations of the NMR research program.

>> Start of the Marie Curie CoFund PhD program "ARDRE" – Ageing, Regeneration and Drug Research

In a new PhD program starting in 2020, twelve internationally recruited young researchers start their four-year projects. Coordinated by Pidder Jansen-Dürr and his deputies Kathrin Thedieck and Frank Edenhofer, the major aims of this program are to uncover cellular and molecular mechanisms acting in organismic ageing and regeneration, and to use the new findings in developing strategies for producing novel drugs. Building upon an earlier University of Innsbruck PhD program, AGEREG, which had been established within the frame of the CMBI, twelve research groups from across all of the major CMBI areas, biology, chemistry, and pharmaceutical sciences, participated in the competitive ARDRE application process. The European H2020 program granted the application and provided a total of 1.3 Million Euro. In addition, a corresponding amount of money is granted by the University of Innsbruck. Taking the PhD candidates from ARDRE and AGEREG together, currently more than 25 young researchers work on topics of stem cells, ageing, regeneration and drug design, making this research area one of the major educational strongholds among the Tyrolean life sciences.

Core element of the two programs is their interdisciplinary nature, strongly aiming at collaborations between the participating groups. This is supported by a specific educational schedule, in which ARDRE PhD students participate in research group seminars and special lectures, lab courses and regular retreats to discuss current progress. The program also offers and supports international mobility to mediate collaboration with defined academic and industrial partner institutions across the world. At the end of the four-year tenure, ARDRE should result in strongly trained PhDs with a unique knowledge about modern applications and trends in ageing and regeneration research, and with a basic understanding of drug discovery.

CMBI SPECIALS – Infrastructure funding and research programs

>> ERC Consolidator grant awarded in 2020 to Thomas Magauer

Ivana Stiperski and Thomas Magauer each received an ERC Consolidator Grant. (Credit: Jordan Mertes/University of Innsbruck).

Thomas Magauer (CMBI) is a "molecular architect" with a passion and enthusiasm for highly functionalized, bioactive molecules. Since his time as a doctoral student, he has been fascinated by the complexity and diversity of molecular architectures and their role as valuable lead structures for the development of novel drugs. For the systematic investigation of these molecular architectures, considerable amounts of substance must be available. "However, many of the architectures are currently not accessible from natural sources or require lengthy and expensive synthetic strategies. The CRAFTMOL project was developed to provide a solution to this problem. Together with a team of molecular architects, novel polyene cyclizations are being investigated in order to construct currently inaccessible natural substances with, for example, anticancer, antiviral or anti-inflammatory effects", explains Magauer. Chemists recognized the potential of this cyclization for organic synthesis early on and made great efforts to mimic it in the chemical laboratory. In the project CRAFTMOL, novel modes for polyene cyclizations and novel termination steps are developed. Based on the two complementary, synergistic work packages, the limitations of previous systems are circumvented and the synthesis of biologically active molecules is simplified.

>> ERC Starting grant awarded in 2019 to Jerome Mertens

Jerome Mertens received an ERC Starting Grant. (Credit: Jerome Mertens)

Jerome Mertens (CMBI) is a molecular biologist with a core interest in stem cell-based approaches to treat neuro-degenerative diseases, particularly Alzheimer's disease. He works on this topic since his PhD thesis finished in 2012 at the University of Bonn (Germany). He then stayed as a PostDoc at the Salk Institute in San Diego/California, where he still holding a position as Staff Scientist. In 2017, he joined the Department of Molecular Biology at Innsbruck University, and now he is head of the Neural Ageing Laboratory.

The cellular and molecular causes of ageing are in general not sufficiently clear. I.e., it is not well understood, why Alzheimer's disease affects only aged brains and not the young ones. Moreover, a mechanistic understanding of this progressing illness is primarily based on findings in animal models that have limits to explain similar processes in humans. Moreover, previous attempts to use reprogrammed neural stem cells partially failed, because these cells are rejuvenated and thus do not exactly represent the aged state of Alzheimer's neurons. Jerome Mertens recently succeeded to overcome some of these basic hurdles by developing a technique to produce aged neurons using reprogramming, but in a more direct differentiation pathway from adult human skin tissue. In the frame of his ERC grant, he is now using his breakthrough by applying a broad set of state-of-the-art bioinformatics and big data technologies to these cells. These studies will be supplemented by international co-operating partners at the University of Colorado, Denver, and the Universities of Würzburg and Freiburg, Germany.

>> Joint research in the neurosciences is encouraged

Scientific cooperation projects were supported with funds from the Jubilee Fund of the University of Innsbruck and the Medical University of Innsbruck in 2018. The two Vice-Rectors for Research from the Medical University of Innsbruck and the University of Innsbruck, Christine Bandtlow and Ulrike Tanzer, recently awarded these funds to a research project in the field of neuroscience. The project "Neuroanatomical characterization of a newly established trangenic mouse model of autism spectrum disorder" is a collaboration between the Pharmacology and Toxicology (Jörg Striessnig (CMBI), University of Innsbruck) and the Institute of Pharmacology of the Medical University of Innsbruck (Francesco Ferraguti). Two promising young researchers - Enrica Paradiso and Nadine Ortner - are investigating the molecular basis of autism. For the first time, a new disease model makes it possible to investigate the role of the calcium channel Cav1.3 in more detail. Six mutations of this calcium channel are already known to occur in patients with an autism spectrum disorder. This is an indication that these mutations could be a cause of the serious developmental disorder.

Expertise from both universities should bring new insights. "In our research work, we bring together the methodical knowledge and research tools from both universities in order to gain new insights", explain Paradiso and Ortner. In order to obtain new starting points for the development of new drugs, the function and impact of the mutated calcium channel must be known more precisely. "We both learn from each other", says Ortner about the collaboration with Paradiso. The two young scientists will use the funding for their project to continue their innovative research work.

With the funding of the work, the good interdisciplinary cooperation of both universities in the field of neurosciences should be emphasized. Promoting young talent and raising our profile in this area is therefore very important to us", explained Bandtlow. "The committed research work of the two young scientists shows that a good education is the basis for innovative research work", added Tanzer.

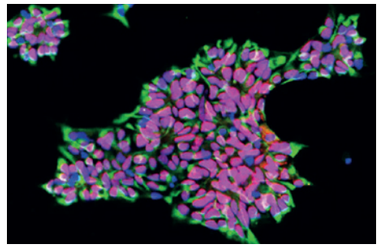
CMBI SPECIALS – Infrastructure funding and research programs

>> The Herbal Medicinal Products Platform Austria (HMPPA)

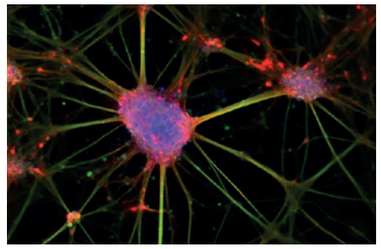
The Herbal Medicinal Products Platform Austria (HMPPA) – consisting of experts from Austrian universities, among them Hermann Stuppner (CMBI) – annually selects the medicinal plant of the year in Austria. The medicinal plant of the year 2022 is *Gentiana lutea L.*, a well-known alpine plant. Extracts of Yellow Gentian roots are used as traditional herbal medicines to treat digestive problems and to stimulate appetite. Bitter-tasting plant constituents stimulate secretion of saliva and gastric acid via activation of bitter taste sensing receptors. Recent studies show that Gentian extracts and their ingredients exhibit anti-inflammatory, lipid-lowering and anti-atherosclerotic effects, but also promote nerve regeneration. These effects have yet to be confirmed in human clinical trials, however, the experts see a high potential for future applications. On the skin, bitter substances from the Gentian promote the formation of protective proteins and lipids, and thus the formation of an intact skin barrier. This mechanism could explain the use of the Yellow Gentian for wound healing. But there are also new studies that show anti-inflammatory effects of externally applied Gentian extract on the skin and in neurodermatitis. The molecular structure of the bitter substance receptors was first elucidated in 2000. Today, more than 25 bitter substance receptors are known in humans, which can be found in almost all organs of the human body. In the respiratory system, stimulation of bitter substance receptors expressed in respiratory epithelia and smooth muscle has been implicated in protective airway reflexes, ciliary beating, and bronchodilation, positive effects that have already been tested on asthma patients and patients with *chronic obstructive pulmonary disease*. It can be assumed that the discovery of the bitter substance receptors throughout the body not only provides a rationale for the traditional use of Yellow Gentian, but also shows new uses for the Gentian.

CMBI SPECIALS – Publication highlights

>> Use of induced neural stem cells in chronic inflammatory and neurodegenerative diseases



Human induced neural stem cells can be derived from skin or blood cells and do proliferate indefinitely in the petri dish. (Credit: Frank Edenhofer)



Networking of reprogrammed neurons. (Credit: Frank Edenhofer)

Two studies carried out by stem cell biologists in Innsbruck, Cambridge, and Heidelberg show significant suppressive effects of transplanted induced neural stem cells on chronic neuro-inflammation and -degeneration in mice. These findings offer new strategies to approach diseases such as multiple sclerosis and Parkinson's disease. In the first study, Frank Edenhofer (CMBI) and colleagues used stem cells obtained by reprogramming of skin fibroblasts. Upon transplantation into the brain, these stem cells reduced the level of macrophage-derived succinate, one of the major drivers of inflammation in neuronal tissue. The stem cells use their succinate receptors SUCNR1/GPR91 to bind succinate and at the same time trigger the release of the anti-inflammatory factor Prostaglandin E2 to amplify the response.

In the second study, researchers at the German Cancer Research Center in Heidelberg and Frank Edenhofer's group at the Institute of Molecular Biology succeeded to identify a new sub-group of neural stem cells using single-cell sequencing techniques. They then pioneered to establish a method to generate induced stem cells of this new type using blood cells. These newly developed methods further improve the availability of induced neural stem cells, providing the platform to palliate symptoms of Parkinson's or Alzheimer's disease in transplantation assays. The studies were published in *Cell Stem Cell* in 2018 and 2019.

>> A new mechanism protects against cancer cell migration

The signaling protein mTOR (Mechanistic Target of Rapamycin) is a sensor for nutrients such as amino acids and sugars. When sufficient nutrients are available, mTOR boosts metabolism and ensures that sufficient energy and building blocks are available for the growth and function of all cells in the human body. "Because mTOR is such a central switch for metabolism, errors in its activation lead to serious diseases. These include cancers associated with excessive metabolic activity, cell growth and proliferation. Dysregulated mTOR also causes malformations of the nervous system, disturbing stimulus processing and eliciting behavioral disorders and epilepsy", explains Kathrin Thedieck (CMBI).

To prevent errors in mTOR-based signal processing, the cell controls its activity precisely. This is achieved through so-called suppressors,

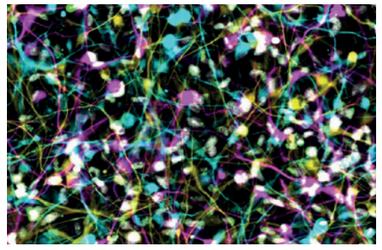
CMBI SPECIALS – Publication highlights

The graphic shows G3BP (G) binding the TSC complex to a lysosome, preventing the MTOR (aka Thor) signaling protein from becoming active. (Credit: Christoph Luchs)

molecules that inhibit a protein and help to regulate its activity. The TSC complex is such a suppressor for mTOR. It is named after the disease that is caused by its absence - tuberous sclerosis complex (TSC) disease. Together with mTOR, the TSC complex localizes to small cellular structures, the lysosomes, where it keeps mTOR in check. If the TSC complex - for example due to changes (mutations) in one of its components - no longer remains at the lysosome, this can lead to excessive mTOR activity with severe consequences for human health.

A molecular TSC anchor at lysosomes. The teams led by Kathrin Thedieck and Christiane Opitz investigated how the TSC complex binds to lysosomes. They discovered that the Ras GTPase-activating protein-binding proteins (G3BP) localize to lysosomes, together with the TSC complex. There, the G3BP proteins form an anchor that ensures that the TSC complex can bind to the lysosomes. This anchor function plays a crucial role in breast cancer. If the amount of G3BP decreases, not only mTOR activity but also cell motility is increased in cancer cell cultures. MTOR inhibitors suppress this hypermotility. In breast cancer patients, low G3BP correlates with a worse prognosis. "G3BP proteins could therefore be valuable markers to personalize therapies and improve the efficacy of drugs that inhibit mTOR", says Christiane Opitz. G3BP proteins also inhibit mTOR in the brain. In zebrafish, an important animal model for pharmaceutical research, the scientists observed disturbances in brain development when G3BP was missing. Loss of G3BP also resulted in neuronal hyperactivity and ensuing behavioral abnormalities reminiscent of epilepsy in humans. Compounds that target mTOR suppressed the neuronal hyperactivity. "We therefore anticipate that patients with neurological disorders and G3BP malfunction could benefit from mTOR inhibitors and we look forward to further exploring this together with our scientific network", says Kathrin Thedieck. Also Lukas A. Huber, Director of Cell Biology at the Medical University of Innsbruck, is pleased with the joint success: "Through this successful collaboration a strong research focus on mTOR and lysosomes is emerging at the two Innsbruck universities, and I am excited to embark on our next projects", states Lukas A. Huber. The interdisciplinary study was published in the year 2021 in *Cell*.

>> First molecular modelling of sporadic Alzheimer's disease



The figure shows induced neurons from Alzheimer's patients from an immunofluorescence image. The DNA damages in these nerve cells are visible as green dots. (Credit: Jerome Mertens)

The genetically inheritable form of Alzheimer's disease is well studied. However, there is a rare sporadic form associated with higher age that is much less well understood, because there are no genetic models for the sporadic version. Induced pluri-potent stem cells offer an alternative approach, and Jerome Mertens and his co-workers succeeded to set up a method for obtaining induced neurons from adult skin tissue, which maintain their age-dependent epigenetic modifications. Thus, induced neurons can be obtained from Alzheimer patients and can be compared to those from healthy control individuals of similar age. The results of these analyses confirmed the age-dependent induction of sporadic Alzheimer's, and now provide a platform for further studies.
An unexpected finding of this study was the loss of functionality of neurons from the patient group. These neurons corresponded to a pre-mature status of differentiation. They showed features normally found in developing neurons that had not reached full maturity, with some astounding similarities to cancer cells. Mertens and colleagues suggested that stress and DNA damage resulted in partial de-differentiation, particularly affecting the action of well-known signaling pathways. While cancer cells do in fact typically overgrow and do not degenerate, these similarities were surprising. But they demonstrate that it could be valuable to look for aspects of cancer treatments also useful in a broader context in neuronal degeneration. The study was published in *Cell Stem Cell* in 2021.

>> New ways to turnoff side effects

Successful collaboration with Phosphoproteomics, from left: Mariana Spetea from the Institute for Pharmacy at the University of Innsbruck, first author Jeffrey J. Liu from the Max Planck Institute for Biochemistry in Martinsried and Christoph Schwarzer from the Institute for Pharmacology at the Medical University Innsbruck. (Credit: MUI/D.Heidegger)

Opioids are effective analgesics, but they also have a range of harmful side effects, including addiction. The group of Mariana Spetea (CMBI) is part of an international team of researchers from the Max Planck Institute of Biochemistry in Martinsried, the Medical University of Innsbruck, the University of Innsbruck, and the Temple University in Philadelphia that developed a tool that gives deep insights into the brain's response to opioids. Using the κ opioid receptor as a G protein-coupled receptor (GPCR) model, high-throughput phosphoproteomics were effectively employed to investigate signaling induced by structurally diverse agonists in five mouse brain regions. Quantification of 50,000 different phosphosites provided a systems view of the κ opioid receptor in vivo signaling, revealing novel mechanisms of drug action. The enrichment of the mechanistic target of mTOR pathway by an agonist causing aversion was discovered. Strikingly, mTOR inhibition during κ opioid receptor activation eliminated aversion while preserving beneficial antinociceptive and anticonvulsant effects. This study established high-throughput phosphoproteomics as a general strategy to investigate GPCR in vivo signaling, enabling prediction and modulation of behavioral outcomes. The study was published in *Science* in 2018.

CMBI SPECIALS – Publication highlights

>> Searching for personalized cancer drugs

Illustration indicates how the KinCon biosensor works. (Credit: www.mertensdesignlab.com)

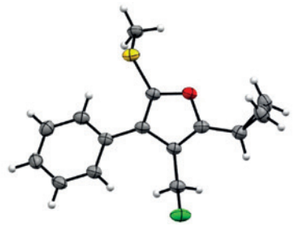
With new biosensors, researchers at the CMBI are able to determine the activity of kinases directly in intact cells. Now the basic researchers around Eduard Stefan have further developed this technology in order to be able to predict whether drugs inhibit certain kinases, the mutations of which can trigger cancer.

Signaling pathways in human cells can be disrupted by mutations in kinases that act as molecular switches. Serious illnesses such as cancer are often the result. For several years now, medicine has had the means to take targeted action against mutated kinases. In 2011, for example, vemurafenib was the first kinase drug to be approved that inhibits a mutated variant of the protein kinase BRAF, which contributes to the development of melanomas. Over 60 kinase inhibitors have now been approved for clinical applications, mainly in oncology. Scientists led by Eduard Stefan have now investigated whether BRAF inhibitors could also be effective in other tumor diseases. To do this, they use a patent-pending biosensor technology that was developed at the University of Innsbruck and is currently being further developed as part of the "KinCon biolabs" spin-off fellowship funded by the Research Promotion Agency FFG. In the process, the two ends of the kinase protein are fused with two reporter protein fragments and expressed in cells. "If the mutated kinase in the cell is inactivated by the inhibitor, the structure of the kinase changes. In the case of the BRAF kinase, the two ends of the enzyme and thus the two reporter protein fragments approach each other, interact and begin to glow in the cell," says Eduard Stefan, explaining how the KinCon biosensor works. In this way, the researchers can track the pathological function of various ONCO kinases directly in intact cell populations.

Personalized medicine with KinCon biosensors. In a work in the journal *Proceedings of the National Academy of Sciences* 2020 Stefan's group and Jakob Troppmair's team from the Medical University of Innsbruck show that drugs that are approved for the treatment of melanoma may also be involved specific BRAF kinase mutations that also occur in lung cancer could be effective. The three approved kinase inhibitors show differences in effectiveness in the biosensor studies. These predictions by the basic researchers were confirmed in analyses with lung carcinoma cell lines that have certain BRAF mutations. The same applies to an experimental active ingredient that is still in preclinical studies. These results are also confirmed retrospectively by translational studies by other research groups on the efficiency of these active ingredients in lung cancer.

"Today one can characterize the mutation spectrum of cancer cells very precisely through genetic examinations. We therefore hope that with our KinCon biosensor platform we can help predict the effectiveness of kinase inhibitors in relation to the patient-specific kinase mutation profile", explains Stefan. "Such biotechnological approaches pave the way for new concepts of personalized medicine, with which one hopes to find the right drug for patients." With his team, the biochemist Eduard Stefan now wants to expand the KinCon biosensor platform to other classes of kinases and thus make a decisive contribution to the search for personalized medicines.

>> New building blocks for organic synthesis



X-ray structure of a highly substituted furan. (Credit: Thomas Magauer)

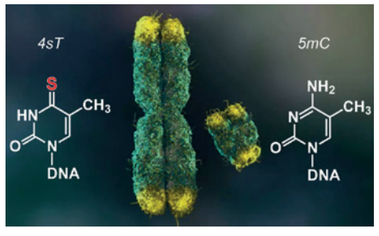
Furans belong to the class of five-membered heterocycles and play an important role in everyday life as fragrances and active ingredients. Thomas Magauer (CMBI) found new ways to enable the synthesis of highly functionalized products employing mild reaction conditions.

The Magauer team discovered a novel transformation to produce the five-membered aromatic heterocycle "furan". In general, five-membered heterocycles represent a very important class of molecukes that are part of biological processes and serve as key structural subunits of drugs. Modified furans are also present in food. When coffee is roasted, the so-called Maillard reaction creates the relatively simple compound furan-2-carboxylic acid, a furan with only one substituent. "Highly substituted furans with three to four substituents tend to undergo chemical degradation reactions very easily and are therefore more or less exotic in nature", explains Magauer.

The presence of oxygen, light and water promotes these degradation reactions and many natural substances therefore only show relics of the original furan. "In the work that has just been published, we have succeeded in developing a very mild reaction process. In this way, very unstable furans can also be produced and isolated as pure substances. The by-product formed during the reaction is a solid that can be recovered simply by filtering", explains the chemist. By applying a wide variety of post-modifications, an extensive library of novel building blocks could be generated and these could also be used in the field of natural product synthesis. "We have succeeded in synthesizing the unique natural substances pleurotin A and B as an example. Both representatives belong to the class of sesquiterpenes and feature a very rare, fully substituted furan. Previous methods did not allow access to this very demanding motif", said the scientist, who further noted, "Together with Maren Podewitz from the Institute for General, Inorganic and Theoretical Chemistry, we were also able to clarify the exact reaction mechanism of the transformation. In doing so, we discovered a very interesting and unusual rearrangement, which has not yet been documented in the literature." The results were published in *JACS - Journal of the American Chemical Society* in 2021.

CMBI SPECIALS – Publication highlights

>> Osmium is key to shed light on genome organization

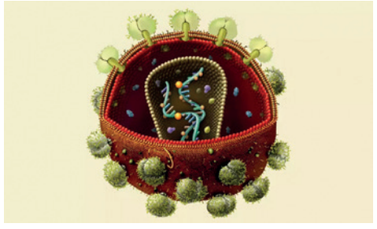


With 4sT-to-m5C conversion-based sequencing, new light is shed on the spatial organization of chromosomes. (Credit: University Innsbruck)

Chromosomes are the carriers of genetic information. In multiplying cell populations, chromosomes are constantly reorganized to ensure two fundamental functions: During cell division, a copy of the genetic information is mechanically transported to the daughter cells, while the genetic information is doubled and read between two cell divisions. The research groups of Ronald Micura (CMBI) and Daniel Gerlich from Vienna BioCenter have developed a new method that analyzes the spatial organization of chromatin in a cell. Their article in *Nature* in the year 2020 demonstrates how the two replicated sister DNA molecules can be mapped in each chromosome using chemical labeling and nucleoside conversion.

Chemistry to success. The new method is based on metabolic DNA labeling with 4-thiothymidine and high-throughput sequence analysis, which generates a genomic map of contact points between labeled and unlabeled sister DNA molecules. With this method, the function of key factors of the chromosome organization, such as cohesin, has been be elucidated. The new technology of 'Sister chromatid-sensitive chromosome conformation capture (scsHi-C)' will make it possible to address a broad range of fundamental biological questions in the future, e.g. the organization of the genome in DNA repair processes or in recombination events of meiosis. The work thus provides the basis for gaining important knowledge about cellular genome inheritance and establishes an innovative technology for the investigation of DNA folding structures. The key to success of the study lies in the osmium tetroxide-based conversion of thionucleosides. This chemistry was originally developed in the group of Micura for RNA sequencing applications (Thiouridine to Cytidine Conversion sequencing, TUC-seq) allowing mRNA life cycle determinations, published in *Angewandte Chemie International Edition* in 2020.

>> HIV: New Mechanism Discovered



A look inside the HI virus. (Credit: Illustration by Angie Fox / worldofviruses.unl.edu)

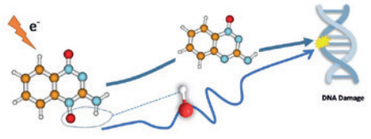
Even after years of research, the fight against the human immunodeficiency virus (HIV) has not been won. Millions of people worldwide are infected with HIV, and if its proliferation is not contained with the help of antivirals, an infection leads to AIDS after a while. Scientists are still striving to find new strategies to attack the virus and to develop more efficient therapies. An important step in developing better therapies is to gain a thorough understanding of how the virus replicates at the molecular level. A team led by Kathrin Breuker (CMBI) in collaboration with the group of Christoph Kreutz (CMBI) has now deciphered a previously unrecognized mechanism that is central to HIV replication and offers a new RNA target for therapy.

Break the destructive cycle. In order to multiply and spread, the HI virus penetrates human cells and builds its genetic information into the DNA in the cell nucleus. As a result, new virus mRNA is produced from the built-in viral DNA, which is transported from the cell nucleus into the cytosol, where it is transcribed into viral proteins that are used for virus replication. In order to accelerate the transport of viral mRNA into the cytosol, the viral DNA encodes for a specific protein called rev. It is known that around eight to ten such rev molecules bind to the viral RNA so that the mRNA can quickly leave the cell nucleus. Science has long been concerned with the question in which order and where exactly the rev molecules bind to the RNA as this process is a possible point of attack for targeted therapy to interrupt the destructive cycle of virus replication. So far, attempts have been made to solve this riddle with the help of nuclear magnetic resonance spectroscopy, crystallography and biochemical experiments. Experiments with wild-type RNA constructs were, however, unsuccessful because they are too dynamic and do not crystallize in the affected areas. "Using these methods and modified RNA, an important binding site was discovered already several years ago," explains Breuker. She and her team have now used a new method to take a closer look at the virus's replication mechanism.

New binding site discovered. The Innsbruck chemists have synthesized segments of the unmodified viral mRNA of different lengths in the laboratory and studied their interactions with a peptide that corresponds to the binding domain of the rev protein by native electrospray ionization mass spectrometry and collision-activated dissociation. "In addition to RNA with one peptide, we also found complexes with two peptides. With longer pieces of RNA, we also observed complexes with five peptides, but what was really surprising was that the occupation of RNA binding sites with rev peptide changed over the course of the association reaction" explains Breuker. The team then took a closer look at these constructs and discovered a new binding site that could not previously be detected. "This is a transient binding site that captures each of the rev molecules one at a time, and relays them to the previously known binding sites and is thus central to the formation of stable RNA-protein complexes", says Breuker, explaining the new insights that were published in *Nature Communications* in 2020.

CMBI SPECIALS – Publication highlights

>> Physics explains the medical effect



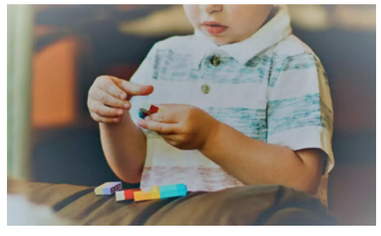
Tirapazamine molecule with dissociated radical damaging the DNA. (Credit: Eugene Arthur-Baidoo)

Tirapazamine (TZP) is a frequently used and effective substance in the fight against cancer. Its effectiveness has been tested and proven in clinical studies. However, it is still unclear how the antitumour drug works in detail. The group of Stefan Denifl (CMBI) has deciphered an important mechanism.

One strategy for the treatment of solid tumours is the combination of radiotherapy and chemotherapy, known as radio-chemotherapy. Chemical agents can be used to prevent the tumour cells from growing by damaging their DNA, thereby enhancing the effect of radiotherapy. In the cells of hypoxic tumours there is a lack of oxygen. Since tirapazamine is only activated under oxygen-deficient conditions, the substance is particularly well suited for targeted damage to the corresponding tumour tissue. The mechanism of the drug follows an enzymatic reduction of the TPZ and the subsequent formation of different radicals. These radicals are important because they contribute to the damage of the tumour cell DNA and thus to the killing of the cancer. Until now, it was unclear how the respective radicals individually contribute to the biological efficacy of the substance. Two different radicals are combined to damage tumour cells. Besides the hydroxyl radical (OH radical with a single, unpaired electron), the benzotriazinyl radical, i.e. the oxidized radical of TZP, might be involved.

On the track of radical formation.
The mode of action was investigated jointly by the group for computational photophysics of Milan Ončák and the group for inelastic electron scattering of Stephan Denifl. In their work, they dealt with the low-energy electron attachment to TZP and investigated the decomposition of the formed TPZ anion by mass spectrometry. Quantum chemical calculations then provided a detailed insight into the reaction dynamics. They observed that hydroxyl radical formation (HO.) is the main decomposition channel. In a special reaction pathway, the hydroxyl radical glides through the vicinity of the molecule and can attach itself to different parts of the molecule (“roaming mechanism”). In the most probable pathway, the hydroxyl radical leaves subsequently the anion. The complementary reaction channel with the emission of a benzotriazinyl radical is almost insignificant. The situation changes when the tirapazamine molecules are microsolvated, whereby the production of hydroxyl radicals is considerably suppressed. The results obtained provide a clear picture of the basic molecular properties of this important molecule and was published in *Angewandte Chemie International Edition* in 2020.

>> Jigsaw piece for the therapy of rare genetic diseases



Autism and epilepsy occur more frequently in early childhood. The causes of these developmental disorders are still largely in the dark. Researchers have now discovered important connections for the first time. (Credit: Caleb Woods/Unsplash)

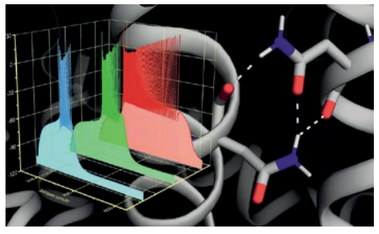
Many human cell types show precise calcium uptake mechanisms. One gene that encodes so-called calcium channels is also partly to blame for a rare human developmental disorder that triggers epilepsy and autism. The research group led by Joerg Striessnig (CMBI) is exploring these links and working on a potential form of therapy.

In the human body, calcium is a strictly regulated substance. Not only vital for bones and teeth, the mineral also plays an essential role in the function of muscles, in the cardiovascular system, the hormone balance or the nervous system. Many human cell types have a specific mechanism for admitting an exact amount of charged calcium ions when required. When these cells are electrically excited, so-called calcium channels, which are small pores that only permit ions of this element to slip through, open for fractions of a second. The Striessnig group has investigated how the gating of these channels actually works and in what way this mechanism is influenced by drugs. Thanks to advanced molecular biological research methods, the researchers have been able to relate certain problems in the regulation of the channels to rare genetic diseases that trigger developmental disorders in children, autism or epilepsy.

Spontaneous gene mutations trigger diseases. “Using powerful next generation sequencing, we can capture the genetic information of a person quickly and comparatively cheaply”, Striessnig explains. “This also facilitates characterization of genetic diseases that are not inherited but are a consequence of spontaneous mutations – we refer to them as ‘de novo mutations’.” The rapid sequencing methods and novel bioinformatic evaluation options enable researchers to identify more and more human genes that can trigger congenital developmental disorders when defective. In this way, a gene called *CACNA1D* has been identified as a risk factor for the development of autism. *CACNA1D* is also well known to Striessnig and his team from their calcium channel research, since the gene is responsible for the production of a specific type of calcium channel called Cav1.3. Using cell culture models, the scientists have now been investigating what functional change the gene defect that is responsible for the developmental disorder triggers in these calcium channels. “We have found that there is a change in the way the calcium channel opens and closes”, notes Striessnig, summarizing the result of this investigation. “The genetic defect activates these calcium channels and boosts their function.” The work was published in *Molecular Autism* in 2020. The team currently addresses the important question to which extent symptoms are responsive to therapy with Ca^{2+}-channel blockers.

CMBI SPECIALS – Publication highlights

>> Calcium channel: disease gene for neurodevelopmental disorder

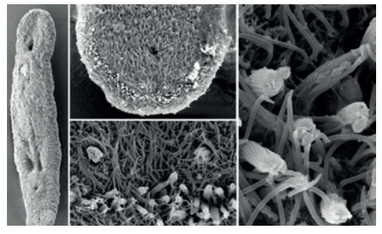


A team led by Petronel Tuluc from the Institute of Pharmacy and Bernhard Flucher from the Medical University, in cooperation with Kerstin Kutsche from the University of Hamburg-Eppendorf, published the results in the scientific journal *Brain*. (Credit: MUI)

Voltage-activated calcium channels recognize the electrical signals from nerve and muscle cells and translate them into cell functions such as the secretion of neurotransmitters and hormones, contraction of cardiac and skeletal muscle, or activity-dependent gene regulation. T-type channels (so-called Low-Voltage-Activated Calcium Channels; CaV3.1 – 3.3) already react to slight changes in the membrane voltage and are thus particularly involved in the development of neuronal action potentials and the control of rhythmic activity in the brain. It is not surprising that these channels are suspected to play a role in neuronal arrhythmias, such as in epilepsy, and that they are highly regarded as promising drug targets for the development of new drugs.

CaV3.3/CACNA1I identified as disease gene. When human geneticists from the University Hospital Hamburg Eppendorf found a strong genetic connection between variants of the CACNA1I gene and neurological diseases of different severity in several patients, the expertise of the Innsbruck calcium channel researchers (groups of Flucher (MUI) and Tuluc (CMBI)) was used to characterize the effect of the mutations functionally. The results of these investigations were clear and remarkable in several respects: First, the channel variants showed functional changes that could be classified as gain-of-function, i.e. as an increase in channel function, which fits well with the heterozygous dominant inheritance of the genetic changes. Second, the increased calcium influx damages or kills neurons, which explains the dramatic defects in the neuronal and intellectual development of the patients, or can lead to an increased excitability of neurons, which could explain the epileptic seizures in the more severely affected patients. Third, the extent of altered channel function in the different mutations correlated well with the severity of the disease in each patient. The results leave no doubt that the genetic changes in the CACNA1I gene are the cause of the diseases and were published in 2021 in *Brain*. Encouraged by the Innsbruck researchers' findings, clinicians began treatment with T-type calcium channel blockers, which actually resulted in noticeable relief from seizures.

>> Adhesive mechanism of the flatworm *Macrostomum lignano* resolved



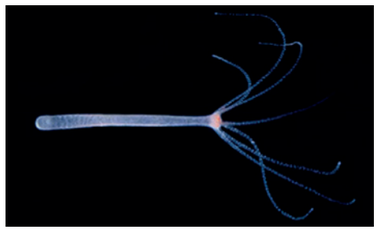
Researchers from the University of Innsbruck were able to disclose the gluing mechanism in the gluing organs of the 1.3 millimeter large flatworm Macrostomum lignano. (Credit: Scilog)

Naturally occurring bio-adhesives are regarded to represent prime candidates for the development of potent biomimetic and non-toxic glue substances used in biomedical and technical applications. In trying to characterize such glues, Peter Ladurner and his team at the Institute of Zoology selected a simple marine flatworm, *Macrostomum lignano*, as their model of choice. *Macrostomum* can be easily cultured in the lab, is accessible for most of the state-of-the-art molecular techniques, and its genome is fully sequenced. *Macrostomum* also exhibits a pronounced adhesive behavior by attaching to and detaching of the substrate several times per minute, using roughly 130 mini-organs in its tail plate. Based on the worm's biology, it might be possible to not only identify glue proteins, but also their natural solvents. In nature, this behavior is a response to mechanical forces created by braking waves at the upper layers of sandy beaches. Using a set of omics approaches, the Ladurner team succeeded to isolate the two core glue proteins, Ap-1 and Ap-2. Both proteins share enormous size, exhibit extensive repetitive units, and are heavily glycosylated.

Transmission electron and super-resolution light microscopy was applied to investigate the mechanisms of secretion from the specialized gland cells in the mini-organs. Furthermore, it was possible to study structure and composition of foot prints left behind after detachment. Based on this, Ladurner and his colleagues provided an interaction model for the glue mechanism. In perspective, the next challenge is to uncover the nature of the releasing factor. Furthermore, structural sub-units of the two glue proteins need to be tested for their adhesive strength in order to be able to develop synthetic analogs exhibiting comparative adhesive properties. The study was published in *Proceedings of the National Academy of Sciences of the United States of America* in 2019.

CMBI SPECIALS – Publication highlights

>> A pan-metazoan concept for adult stem cells



The freshwater polyp Hydra. (Credit: Wolfgang Dibiasi)

An international consortium of stem cell researchers proposed a model, the "Wobbling Penrose Landscape", conceptualizing the unexpected broad plasticity and life-long tissue dynamics observed in a number of invertebrate animal lineages. All members of the consortium belong to "MARISTEM", a European COST network on adult stem cells in invertebrates that will end in 2022. Starting point for this concept paper published in *Biological Reviews* in 2021 was a three-day workshop held in the Innsbruck University Center Obergurgl and organized by Bert Hobmayer from the Institute of Zoology. There, 14 group leaders from European countries and Israel and Russia gathered and developed the basic outline of the new model.

Members of various invertebrate phyla exhibit features lost in the vertebrates, including unlimited body growth, extensive capacities for the regeneration of entire body parts, and immortality. These fascinating features rely on large pools of adult stem cells readily available for the replacement of any ageing or damaged tissues. Actually, in some of the animals - sponges, cnidarian polyps and flatworms - adult stem cells make up for up to 30-40 % of all cells of their bodies. Furthermore, some of these adult stem cell lineages seem to have a capacity to replace most if not all cells of the body, a trait called toti-potency and usually found only in early embryonic stem cells. In some lineages, there are no borders between germ line or somatic differentiation, and some exhibit a capacity for unlimited proliferation without forming tumors. In several lineages, adult stem cells can form de novo by trans-differentiation from other stem cell types. The new concept aims at incorporating all these elements.

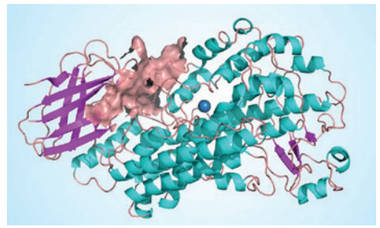
>> Cadmium and zinc – a competition in snails

The Spanish slug uses sophisticated mechanisms to protect itself from environmental stress.
(Credit: Dallinger)

Due to their close association with soil surfaces, snails are classic model animals to study mechanisms of detoxification, particularly dealing with heavy metals such as cadmium. While cadmium is severely toxic at even very low concentrations, the closely related zinc is an essential micronutrient acting in many enzymatic processes in animal cells. Snails evolved a family of metallothionein (MT) proteins to selectively inactivate cadmium without binding zinc. These proteins are modular units, usually composed of six domains. Due to changing environments, MTs were demonstrated to have dynamically adapted during evolution by duplication, loss, and *de novo* formation of domains driven by the specific requirements of metal binding.

A consortium of zoologists and physicists around Reinhard Dallinger and Armin Hansel applied newly developed methods for ion detection in order to unravel so far unknown physiological pathways processing low molecular zinc complexes. These mass spectrometry-based methods allowed the identification of compounds smaller than 2 kDa in liquid phases. Zinc was clearly confirmed in a fraction of about 900 Da, indicating that snails metabolize this metal using pathways that now need to be characterized in more detail. The studies were published in *Scientific Reports* in 2019 and *Molecular Biology and Evolution* in 2021.

>> Effects of vitamin E more diverse than expected



Structure of an enzyme that plays a key role in inflammatory processes. The binding pocket for vitamin E metabolites that has been identified is highlighted (top left). (Credit: Veronica Temml)

Together with an international research team, pharmacists from the CMBI deciphered the anti-inflammatory effects of vitamin E and its metabolic products. The study shows how diverse and complex vitamin E and its metabolites can be. A team in pharmacy has been researching natural substances for their anti-inflammatory effects for a long time. The studies are carried out together with an international consortium with the participation of researchers from Germany, France and Italy. In these studies, data came to light that indicated vitamin E and related structures as an actor in the inflammatory process: "Vitamin E is an antioxidant, it neutralizes cell-damaging free radicals", explains Andreas Koeberle (CMBI). But although this has been adequately proven in cell and animal models under laboratory conditions, vitamin E has so far not been convincing in clinical studies: "We find very different results here", says Koeberle. "Not only do the positive effects often not occur in the expected strength, sometimes the administration of vitamin E even shows negative effects", says the biochemist. The international research team has now found a possible cause for this in a broad, interdisciplinary study. Accordingly, the effect of vitamin E, which is taken as a tablet or capsule, is not based on the vitamin itself, but on its metabolic products. One metabolite called alpha-carboxychromanol has a promising anti-inflammatory effect.

The key enzyme in the inflammatory process is inhibited. In the study, the scientists examined in detail the anti-inflammatory potential of alpha-carboxychromanol and other vitamin E metabolites. The bioactive metabolite inhibits a key enzyme in inflammatory processes, 5-lipoxygenase. This is a very promising finding, say the scientists, because this enzyme plays a central role in inflammatory diseases such as asthma and arthritis. A team led by Veronika Temml from the Pharmacognosy Department at the Institute of Pharmacy at the University of Innsbruck has found out how alpha-carboxychromanol binds to the enzyme. The measurements of the colleagues in Jena had produced the surprising result that this metabolite does not bind where it was previously suspected. "That is why we examined the enzyme more closely in the computer model and identified other possible binding sites for the metabolite," says Temml. "It turned out that the active vitamin E metabolites fit ideally into one of these binding pockets." The study is published in the journal *Nature Communications* in 2018.

Natural product and molecular biological analysis applying novel separation and vibration spectroscopic tools

Günther Bonn and Christian Huck

>> Department of Analytical Chemistry and Radiochemistry

>> Goal: Development of new chromatographic and vibrational spectroscopic tools with enhanced efficiency, selectivity and sensitivity to get detailed analytical information upon the composition, origin and/or species of samples in the fields of phytomics, metabolomics, proteomics and foodomics.

>> Background: Advances in chromatography enable research into inaccessible areas of phytoanalysis, metabolomics, proteomics and foodomics. Novel enrichment and purification methods have been developed to reduce the complexity of multi-constituent samples. Significant progress has been made in developing new stationary phases that can be tailored to a specific application. A further coupling to high-resolution mass spectrometry facilitates the identification and quantification of target analytes. Additionally, separation science can assist as a potent reference method for developing vibrational spectroscopic analytical methodologies in phyto- as well as food analysis. Vibrational spectroscopy (MIR, NIR, Raman) enables a fast, simultaneous qualitative/quantitative analysis of chemical and physical parameters.

>> Research Highlights and Outlook: Major focus is placed on the synthesis and structure elucidation of novel stationary phases. Polymeric mixed-mode stationary phases are of high importance regarding their use as small SPE columns in analytical sample preparation approaches. In this context, analytes of interest can be isolated from complex matrices and enriched to enable reproducible quantifications with certain detection methods. Therefore, the development of efficient sample preparation methods is highly necessary to further improve analytical sample preparation procedures.
Although these methods enable detailed analysis they require expensive equipment and are not suitable for real fast analysis within seconds. In modern analytical chemistry these methods can assist spectroscopic analysis. Vibrational spectroscopy can overcome these drawbacks by offering the advantages of being fast, non-invasive, enabling simultaneous analysis of chemical and physical parameters. Attenuated total reflection (ATR) mid-infrared (MIR) spectroscopy can be potent for screening solid samples, near-infrared (NIR) spectroscopy offers the advantages of manifold information due to the high number of overtones and combination bands. Raman, which is based on scattering effects, offers a powerful alternative. On one hand, the miniaturization of especially NIR-spectrometers (Figure 1) is a fast-developing field offering advantages such as easy handling at any place. On the other hand, high resolution MIR, NIR, Raman imaging spectroscopy enables the investigation with a spatial resolution down to only a few micrometers, atomic force microscopy infrared spectroscopy (AFM-IR) even down to nanometers. Surface enhanced Raman spectroscopy (SERS) allows to enhance the spectroscopic signal by a factor of up to 10^6. New methods, including neural networks and artificial intelligence methods, improve the analytical performance. Quantum chemical simulation of spectra allows to get a deeper understanding of the spectral features. 2-dimensional correlation spectroscopy (2D-COS) gives additional information for perturbated systems.

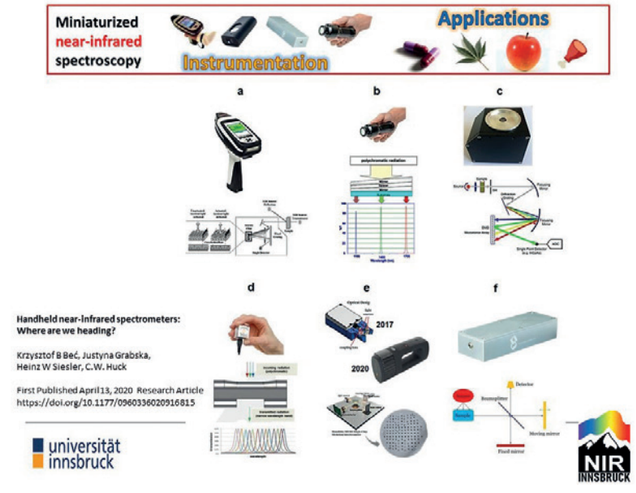


Figure 1: Portable NIR spectrometers working on different technical principles.

A combination of these techniques can be successfully applied for the determination of optimum harvest time for medicinal plants (phytomics), food quality, cancer diagnosis, etc. With this approach it is for the first time possible to detect within one measurement quality related chemical parameters such as the concentration of distinct ingredients and also physical parameters, e.g. anti-oxidative and or anti-bacterial activity, respectively. Another ongoing project is the analysis of micro- and nano-plastics in atherosclerotic plaques and different other biological samples.

>> Research Grants

Marie Curie; Cost Action Ca19145e Action 872602; Lise-Meitner M2729; FWF P32004; Euregio FWF IPN00118; Interreg AB116; Interreg ITAT1005

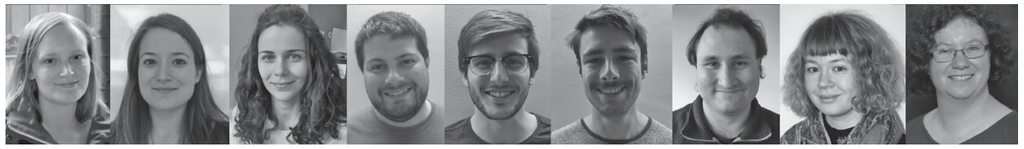
>> Coworkers

A.Univ.-Prof.Mag.Dr. Dagmar Obendorf; PD Dr. Rania Bakry; A.Univ.-Prof. Mag. Dr. Andreas Zemann; Assoc.-Prof.Mag.Dr. Matthias Rainer; Dr. Justyna Grabska; Dr. Nami Ueno; Dr. Krzysztof Bec; Jovan Badzoka MSc; Christoph Kappacher MSc; Susanne Huber Msc; Clemens Losso MSc; Matthias Harder MSc; Vanessa Moll; Louise Laube; Nicole Plewka; Sophia Mayr MSc; Michael Sasse MSc; Marco Kreidl MSc; Dr. Verena Wiedemair; Dr. Stefan Stuppner; Dr. Anel Beganovic; Alexandra Pucher; Sabine Ruech; Ines Glatz; Markus Gabl; Julius Thöni; Bernhard Märk; Peter Rutzinger

Characterization of RNA, proteins, and their noncovalent complexes by MS

Kathrin Breuker

>> Department of Organic Chemistry



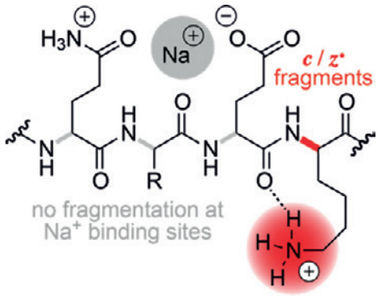


Figure 1: Protein backbone cleavage into *c*, *z*• fragments by ECD requires hydrogen bonding of protonated sites to backbone amide oxygen (Schneeberger EM, Breuker K. *Chem. Sci.* **9**, 7338-7353, 2018).

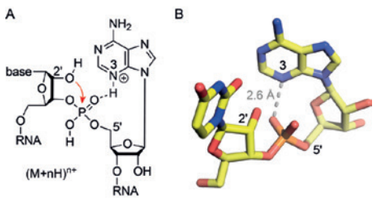


Figure 2: Proposed mechanism for phosphodiester backbone bond cleavage in CAD of RNA $(M+nH)^{n+}$ ions in which nucleophilic attack of the 2'-OH group on the phosphorus is facilitated by ionic hydrogen bonding between A protonated at N3 and the phosphodiester moiety (Fuchs E, Falschlunger C, Micura R, Breuker K. *Nucleic Acids Res.* **47**, 7223-7234, 2019).

>> Goal: A major focus of our research is to explore the determinants of biomolecular structure, stability, binding, and dissociation in the gas phase. Insights from fundamental and mechanistic studies allow us to develop new methodologies for protein and ribonucleic acid (RNA) characterization by mass spectrometry (MS), including the identification, localization, and relative quantitation of posttranslational and post-transcriptional modifications, and the determination of stoichiometry and binding sites of noncovalent complexes of RNA.

>> Background: Mass spectrometry is an evolving technique with unique potential for biomolecular characterization beyond mere sequencing. Current research in the field aims, for example, at developing MS approaches for studying different proteoforms, posttranscriptional modifications of non-coding RNA, and the higher order structure of functional biomolecular assemblies, all of which require a solid understanding of biomolecular gas phase ion structure, stability, binding, and dissociation.

>> Research Highlights and Outlook: Electron capture dissociation (ECD) and electron transfer dissociation (ETD) are routinely used in high-throughput studies of proteomes. However, the mechanism by which protein ions undergo N-Cα backbone cleavage into characteristic c and *z*• fragments while preserving labile posttranslational modifications such as phosphate groups is still hotly debated. We have studied peptide anions and cations by negative ion electron capture dissociation (niECD) and ECD, respectively, and successively replaced protons by alkali metal ions to test the hypothesis that a charge other than H^+ can effect N-Cα backbone bond cleavage. Our study revealed that dissociation into *c* and *z*• fragments requires electron capture at a protonated site, and that this protonated site must interact with backbone amide oxygen, which resolved a decades-old controversy about the previously proposed ‚Utah-Washington' and ‚Cornell' mechanisms.

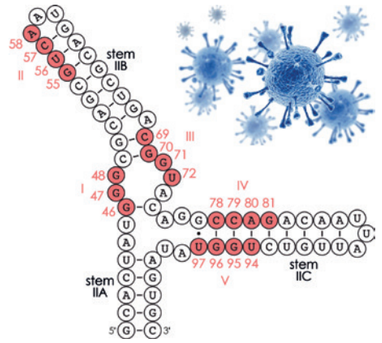


Figure 3: CAD MS revealed a new, transient binding site and a relay mechanism for the formation of HIV-1 RRE RNA and rev protein complexes central to virus replication (Schneeberger EM, Halper M, Palasser M, Heel SV, Vušurović J, Plangger R, Juen M, Kreutz C, Breuker K. Native mass spectrometry reveals the initial binding events of HIV-1 rev to RRE stem II RNA. *Nat. Commun.* **11**, 5750, 2020).

>> Research Grants

FWF P27347, FWF P30087, FWF M2757

>> Coworkers

Maria van Agthoven (postdoctoral researcher); Heidelinde Glasner, Eva-Maria Schneeberger, Jovana Vušurović, Matthias Halper, Giovanni Calderisi, Michael Palasser, Sarah Viola Heel (Ph.D. students); Simon Chwatal (master student)

In another project, we have studied the mechanism by which RNA undergoes phosphodiester backbone bond cleavage into *c* and *y* fragments in collisionally activated dissociation (CAD), and how this relates to catalytic strategies of small self-cleaving ribozymes. We found convincing evidence for a stepwise mechanism for RNA dissociation into *c* and *y* fragments in which a pentacoordinate oxyphosphorane intermediate is formed by nucleophilic attack of a ribose 2'-OH group on the adjacent phosphorus in the first step at low energy, which can be facilitated by ionic hydrogen bonding. In the next step at elevated ion internal energy, the breaking of hydrogen bonds leads to full extension of the RNA $(M+nH)^{n+}$ ion structure and subsequent intramolecular proton transfer according to simple Coulombic repulsion. In the last step at even higher ion internal energy, the intermediate dissociates into *c* and *y* fragments by phosphodiester backbone bond cleavage. Our study suggests that interactions between protonated adenine and phosphodiester moieties of the RNA may play a more important mechanistic role in biological processes than considered until now.

Noncovalent bonds are generally weaker than covalent bonds, but we recently found evidence that in the gas phase, electrostatic interactions between RNA and native ligands can be stronger than RNA phosphodiester backbone bonds. Based on this observation, we developed a new MS-based approach for probing of complex stoichiometry and binding site mapping in RNA-ligand complexes by CAD. For the RRE-rev ribonucleoprotein complex that is critical to HIV-1 replication, we found that rev protein initially binds to the upper stem of RRE IIB RNA, from where it is relayed to binding sites that allow for rev dimerization. This new and detailed understanding of the mechanism of RRE RNA and rev protein association has implications for the rational design of potential drugs against HIV-1 infection. We are currently extending our novel approach to other biologically relevant complexes of RNA, including studies of drug binding to RNA in competition experiments.

Cadmium has driven the evolution of metal-selective snail metallothioneins since 430 million years

Reinhard Dallinger

>> Department of Zoology

>> Goal: To track back and comprehend how the rare and toxic trace element Cadmium (Cd) has impacted on the evolutionary history and differentiation of snail metallothioneins, and how this metal has shaped and optimized their structural and metal-specific features.

>> Background: With an abundance of 0.00001%, Cd is one of the rarest metallic trace elements of the earth crust. An essential function for Cd has so far only been observed in some marine diatoms. For most other organisms, the metal is highly toxic at even low concentrations. Yet, Cd can be enriched up to several hundred times above environmental concentrations by some eukaryotes, such as certain plants acting as metal hyper-accumulators, or some invertebrates known as so-called macro-concentrators, including mollusks like many slugs and snails. These animals tolerate highly elevated Cd levels by accumulating and inactivating the metal in their digestive organs. An important role in Cd detoxification is attributed to the wide-spread gene / protein family of metallothioneins (MTs), although most MTs of modern vertebrates and many other animal species are devoted to multifunctional tasks, binding mainly Zn^{2+} and Cu^{+} ions, in addition to Cd^{2+}. However, many species of snails (Gastropoda) possess Cd-selective MT isoforms. Since the first snails can be dated back to the Cambrian era about 530 million years (my) ago, this suggests that the origin of Cd-selective MTs may go back to the evolutionary roots of mollusks, and has since been developed and preserved until today in snails and other ancient animal lineages, too.

>> Research Highlights and Outlook: By applying a metallomics approach including 74 MT sequences from 47 gastropod species, and combined with molecular, biochemical and phylogenomic methods, we were able to retrace the evolution of snail MTs back to the Silurian, 430 my ago (Dallinger *et al.* 2020). It appears that throughout the geological eras until today, fluctuating emissions of Cd through continental and super-volcanic metal emissions in combination with catastrophic extinction events may have shaped and optimized Cd-selectivity in snail MTs (Palacios *et al.* 2011). An extensive body of evidence for increased Cd emissions throughout the earth's history is provided by elevated Cd concentrations in worldwide bedrock formations of different geological origin, from Paleozoic through Mesozoic and Cenozoic (Grasby *et al.* 2015; Dallinger *et al.* 2020). We suggest that because of this persistent selective pressure, snail MTs have developed Cd-selectivity in order to increase their Cd detoxification efficiency. This has happened through convergent evolution towards Cd-selectivity of metal-binding domains that significantly differ in their primary structures and by their shaping and modification upon lineage-specific adaptation of gastropod lineages to different habitats. In particular, lineages of the two sister clades Caenogastropoda and Heterobranchia (with thousands of marine, freshwater and terrestrial snail species) have developed Cd-selective MTs through parallel evolution since 460 my (Figure 1). Cd-selective MTs have also evolved independently (and hence, convergently) in the clade of Patellogastropoda (marine limpets), about 430 my ago (Figure 1). Significantly, Cd-selectivity in MTs of Patellogastropoda was achieved with a primary structure of the C-terminal Cd-binding domain that differs fundamentally from that in the two sister clades of Caenogastropoda and Heterobranchia (Figure 1). As a consequence, the Cd-binding stoichiometry in MTs of limpets comes to seven 7 Cd^{2+} ions bound per protein molecule (4 Cd^{2+} ions in the N-terminal domain and 3 Cd^{2+} ions in the C-terminal domain), in contrast to 6 Cd^{2+} ions bound in CdMTs of Caenogastropoda and Heterobranchia snails (3 Cd^{2+} ions per each of the two domains). Overall, the Cd-selective binding features in snail MTs have gradually been optimized through evolution by stepwise replacement of amino acids in the protein chain that make Cd-binding clusters stiffer and more specific for allocation of Cd^{2+} ions (Baumann *et al.* 2017; Beil *et al.* 2019), and by repeated duplication of Cd-binding domains (Dallinger *et al.* 2020; Pedrini-Martha *et al.* Calatayud *et al.* 2021).

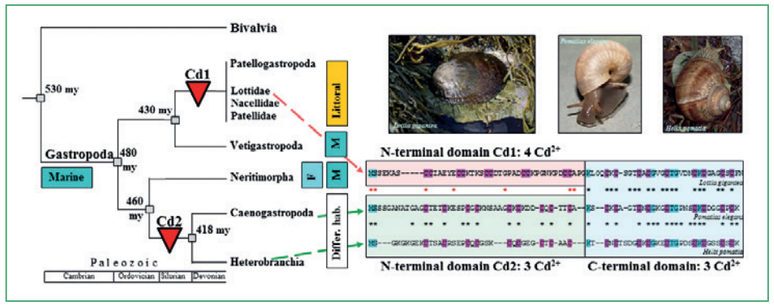


Figure 1: Chronogram of evolution of Cd-selective MTs in the mollusk class of Gastropoda (snails) through the Paleozoic (time scale on the bottom) with approximate divergence time in million years (my) at the respective branching nodes (grey squares), illustrated against its sister class of Bivalvia (mussels). Reported are the major gastropod subclasses (Patellogastropoda, Vetigastropoda, Neritimorpha, Caenogastropoda and Heterobranchia) on the left-hand site. Independent gain of Cd-selectivity in Patellogastropoda (7 Cd^{2+}) and the two sister clades Caenogastropoda and Heterobranchia (6 Cd^{2+}) is shown by red triangles. Also shown within colored boxes are the principal habitats of the respective clades (Marine, M; Freshwater, F; Different habitats, Differ.hab.; Littoral). Cd-selective MT sequences with their C (γ and β2) and N-terminal domains (β1) are shown within highlighted boxes (pink, green and blue) for *Lottia gigantea* (Patellogastropoda, see photograph), *Pomatias elegans* (Caenogastropoda, see photograph) and *Helix pomatia* (Heterobranchia, see photograph). Cys residues within the sequences are highlighted in pink, and identical amino acid positions between sequences are indicated by stars. The number of Cd^{2+} ions bound per domain (N- or C-terminal) are given above and below the sequence boxes.

>> Research Grants

FWF I1482-N28 (DACH, leading agency: FWF); FWF I3032-B21 (DACH, leading agency: FWF); recent FWF P 33973-B (joint project with Veronika Pedrini-Martha and Oliver Zerbe, Zürich University)

>> Coworkers

Veronika Pedrini-Martha (postdoc); Michael Niederwanger (postdoc), Reinhard Lackner (Ex-scientific assistance); Martin Dvorak, Raimund Schnegg (Ex-Ph.D. students)

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Radiation damage in biological compounds induced by low energy electrons

Stephan Denifl

>> Department of Ion Physics and Applied Physics

>> Goal: Exploring negative and positive ion formation by secondary electrons formed upon radiation of biological compounds.

>> Background: A large number of secondary particles are generated when energetic primary radiation (e.g. photons, ions or cosmic radiation) interacts with biological material like living cells. The most abundant secondary species formed are electrons which are released with an average kinetic energy of a few eV. These electrons subsequently interact with cell components before they become a chemically inactive species. The electron interaction may however be severe even leading to single and double strand breaks of DNA. Therefore it is crucial to investigate the interaction of low energy electrons with simple biomolecules representing building blocks of biological material (nucleobases, amino acids, etc.). Mass spectrometry of anions formed by electron attachment represents our experimental approach.

>> Research Highlights and Outlook: In recent experiments we carried out mass spectrometric studies with the nimorazole molecule. This compound is used as radiosensitizer for the treatment of head and neck cancers in Denmark. The exact mechanism of radiosensitization is not known yet. Radio-biologic studies suggested that efficient reduction of the compound may play an essential role. We investigated this hypothesis with studying reduction by free low-energy electrons. Figure 1 shows the resulting anion yield as function of the mass of the product ion and the initial electron energy. This graph shows that the intact parent radical anion is the most abundant anion formed by the interaction with an electron. The only competing reaction channel leads to the formation of NO_2^-, which is mainly formed in the electron energy region between 2 and 4 eV. It turned out that the cross sections (measure of the formation probability) are extraordinarily high and among the highest cross sections known for electron attachment to molecules. We also investigated electron attachment to nimorazole in water clusters and observed that the NO_2^- fragment anion becomes quenched upon solvation. Only the intact parent radical anion of nimorazole remains as abundant reaction product. These results fully support the previous suggestion that reduction processes play an important role in the activation of the radiosensitizer in tumor cells.

For future studies on the molecular level, we will investigate other classes of radiosensitizer compounds in order to evaluate, if efficient reduction processes occur or not.

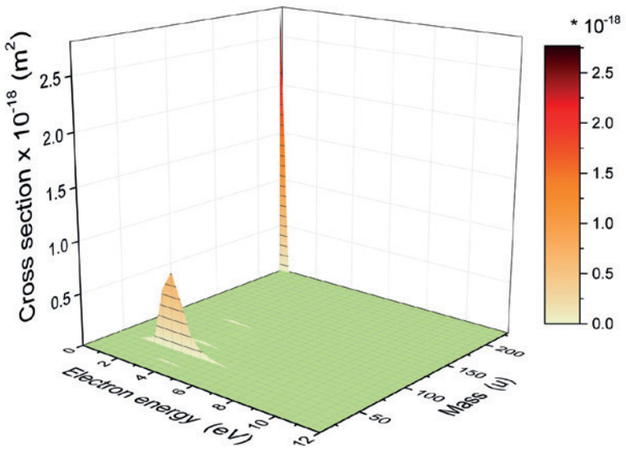


Figure 1: Intensity map of anions formed by attachment of a low-energy electron to nimorazole. The intensity is expressed as a cross section, which is a measure of the formation probability. Two anions are dominant, (i) the parent radical anion (mass 226 u) at about 0 eV and (ii) the NO_2^- anion (mass 46 u), which is mainly formed between 2 and 4 eV. Taken from Meissner *et al.*, *Nat. Comm.* **10** 2388 (2019), CC-BY 4.0 license.

>> Research Grants
FWF-P30332, I5390

>> Coworkers
Joao Ameixa, Eugene Arthur-Baidoo, Rebecca Meissner, Muhammad Saqib, Harvey Suarez (Ph.D. students); Patrick Ziegler (master student)

Reprogramming neural cells to understand disease and develop new therapeutic strategies

Frank Edenhofer

>> Department of Molecular Biology – Laboratory of Genomics, Stem Cell Biology & Regenerative Medicine

>> Goal: To obtain comprehensive understanding of disease and ageing of the nervous system by cellular reprogramming and genome-wide analysis.

>> Background: Our laboratory has a long-standing interest in the study of neurological disorders and ageing by cellular reprogramming. Cellular reprogramming enables the derivation of patient-specific induced pluripotent stem cells (iPSCs) from somatic cells such as skin or blood cells. We established direct conversion protocols to derive induced neural stem cells (iNSCs). Employing these cell models we aim at i) exploring the reprogramming process as a proxy for physiological regeneration pathways at molecular level, ii) exploiting patient-specific cells to model neurodegeneration such as Alzheimer's and Parkinson's Disease and other neurological disorders, and iii) harnessing the potential of patient-specific reprogrammed cells for cell therapy approaches. For phenotyping we employ multi-omics approaches including RNAseq and single cell RNAseq together with targeted metabolomics.

>> Research Highlights and Outlook: We identified the direct reprogramming of both adult human fibroblasts and blood cells into induced neural plate border stem cells (iNBSCs) by ectopic expression of four neural transcription factors. Self-renewing, clonal iNBSCs can be robustly expanded in defined media while retaining their differentiation potential. To model a human pain syndrome we generated *SCN9A*-mutated lines via CRISPR/Cas gene editing (Thier *et al.*, 2019). Reprogramming does not only facilitate insights into neural pathophysiology but provides an autologous stem cell source for applications in regenerative medicine. We demonstrated that transplanted neural stem cells ameliorate chronic inflammation in the central nervous system by reducing succinate levels in the cerebrospinal fluid. Our work reveals an unexpected role for the succinate-SUCNR1 axis in transplanted cells, which controls the response of stem cells to inflammatory metabolic signals released by type 1 macrophages in the chronically inflamed brain (Peruzzotti-Jametti *et al.*, 2018; Figure 1)

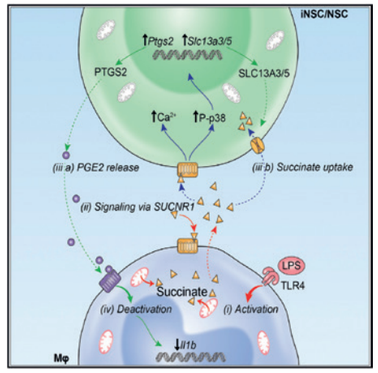


Figure 1: Induced neural stem cells (iNSCs) injected into the cerebrospinal fluid of mice with experimental multiple sclerosis ameliorate chronic neuroinflammation. Activated macrophages secrete the inflammatory metabolite succinate contributing to neuropathological lesions. Grafted stem cells use SUCNR1 to decrease the pro-inflammatory succinate, thus inducing a metabolic switch in endogenous macrophages and microglia toward an anti-inflammatory phenotype. SUCNR1-mediated signaling induces upregulation of PTGS2, a key enzyme for prostaglandin synthesis. This results in increased release of prostaglandin E2 (PGE2) that in turn deactivates inflammatory macrophages (Mphi). NSCs derived from *Sucnr1*-mutant mice show reduced anti-inflammatory activity after transplantation confirming the *Sucnr1*-dependent immunosuppression mechanism (Peruzzotti-Jametti *et al., Cell Stem Cell* 2018).

Together with the group of Jerome Mertens we aimed at analyzing mitochondrial features in iN cells from individuals of different ages to get better insight into the age-dependent deterioration of the human brain. Our analyses revealed that iNs from old donors display decreased oxidative phosphorylation-related gene expression and increased oxidized proteins levels. In contrast, the fibroblasts from which iNs were generated show only mild age-dependent changes, consistent with a metabolic shift from glycolysis-dependent fibroblasts to OXPHOS-dependent iNs. These data suggest that iNs are a valuable tool for studying mitochondrial ageing and support a bioenergetic explanation for the high susceptibility of the brain to ageing.

>> Research Grants

FWF I 3029-B30, FWF W 1206-B18, bmwfw 10.420-WF/V/3c/2016, DFG AOBJ 635622, EU H2020-MSCA-IF-2017; FFG: VascAge Comet-C Center; Wings for Life - Spinal Cord Research Foundation.

>> Coworkers

Katharina Günther, Angeliki Spathopoulou, Julianne Beirute-Herrera, Elisa Gabassi, Marcel Tisch, Ahmad Salti (postdoc); Angeliki Spathopoulou, Julianne Beirute-Herrera, Elisa Gabassi, Marcel Tisch, Anita Erharter, Gabriella Fenkart, Larissa Traxler (Ph.D. students); Alexander Eschlböck, Laura de Gaetano, Nina Grill, Miriam Lechner, Theresa Lindlbauer, Valentin Marteau, Martina Podlesnic, Lorenz Schwankler, Regina Gassler, Anna Hausruckinger, Felix Strasser (master students); Marta Suarez Cubero, Urban Tscheikner-Gratl, Johanna Vanacker (technicians); Caroline Baldemair, Marion Staudinger (secretary)

Development of selectively acting antitumor agents

Ronald Gust

>> Department of Pharmacy, Pharmaceutical Chemistry Section

>> Goal: Development of antitumor drugs to overcome intrinsic and acquired resistance of tumor cells.

>> Background: During the past years, many new strategies were established in the fight against cancer. However, the fundamental problem of such targeted therapies, the development of resistance, is not yet solved. Cancer is a disease of evolution and often adapts rapidly and ruthlessly to the used therapy. Therefore, medicinal chemists force the search for compounds with a new mode of action. In this context, established drugs with new indications come more and more into the focus. This applies for instance to telmisartan, which is approved as AT1 blocker, with potency to activate the nuclear receptor PPARγ as partial agonist. Furthermore, selective induction of ferroptosis and necroptosis in tumor cells is a hopeful strategy in anticancer therapy. Both pathways differ from apoptosis and can be alternatively induced by iron complexes.

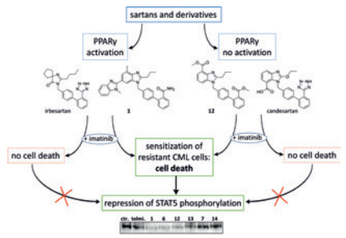


Figure 1: Investigation of sartans and related derivatives as cell death sensitizer.

>> Research Highlights and Outlook:

Development of cell death modulators to circumvent imatinib resistance in CML cells

A new approach to eradicate cancer stem cells in chronic myeloid leukaemia (CML) represents the combination of imatinib with pioglitazone. Its feature as full peroxisome proliferator-activated receptor gamma (PPARγ) agonist was hold responsible to act as sensitizer for imatinib in resistant CML cells. We recently identified the partial PPARγ agonist telmisartan as a more effective cell death modulator in resistant K562 CML cells, with the 4′-((2-propyl-1*H*-benzo[*d*]imidazol-1-yl)methyl)-[1,1′-biphenyl]-2-carboxylic acid moiety as essential core. Related carbazoles as well as indoles were less active. In contrast, derivation of the 2-COOH group at the biphenyl moiety increased the sensitizing effect. It is noteworthy that all the tested compounds were *per se* not cytotoxic. Studies on the mode of action revealed that PPARγ activation is not necessary to sensitize CML cells for imatinib therapy. However, the repression of the STAT5 phosphorylation caused by the cell death modulators relates with their possibility to sensitize K562-resistant CML cells.

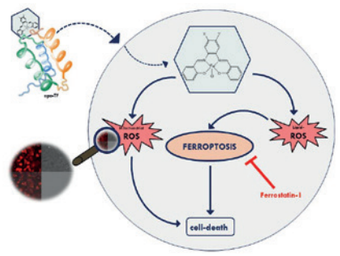


Figure 2: Iron salophene complexes as ferroptosis inducers.

Ferroptosis and necroptosis inducers as antitumor agents

Chlorido[*N,N′*-disalicylidene-1,2-phenylenediamine]iron(III) was identified as appropriate lead structure for the design of ferroptosis and necroptosis inducers. The substituents at the phenylenediamine moiety determined the cytotoxicity and the mode of action (ferroptosis and/or necroptosis). Within this project, we demonstrated that ferroptosis, which is yet defined as $Fe^{2+/3+}$-dependent programmed cell death, is also caused by iron complexes and not only by "free" iron ions. Especially NB1 neuroblastoma cells were sensitive to this mode of action. Interestingly, the iron salophene complexes showed also antimicrobial activity against *Staphylococcus aureus* and MRSA. This effect correlates with the ability to generate reactive oxygen species and to induce ferroptosis. Analogues with metals other than iron (Ni(II), Cu(II), Co(II), and Zn(II)) were inactive or marginally less active (Mn(II)).

Metal complexes as COX inhibitors

The acetylsalicylic acid derivatives [prop-2-ynyl-2-acetoxybenzoate] dicobalthexacarbonyl (Co-ASS) and potassium {trichlorido[η^2-(but-3-en-1-yl)-2-acetoxybenzoate]platinate(II)} (Pt-Butene-ASA) were synthesized as cytotoxic COX inhibitors. In both cases, a higher inactivation rate of COX-1 compared to COX-2 was observed. Introduction of substituents at the aromatic ring of Co-ASS decreased the binding to COX-1 and retained the inhibition of COX-2. To study the stability of Zeise´s salt derivatives of the Pt-Butene-ASA type under physiological conditions, we developed a capillary electrophoresis method. Elongation of the spacer between ASA and the platinum centre increased the stability and made the complex suitable for biological studies. We further investigated the binding of Pt-Butene-ASA to the model peptides angiotensin 1 (AT), substance P (Sub P) and ubiquitin (UB). Methionine in Sub P led to the formation of dimers, while the N-donors in AT caused stable adducts containing the intact Pt-Buten-ASA substructure. In contrast, the complex built two platinum adducts at UB and additionally acetylated Ser and Lys residues of the peptide. This is the first example of concomitant platination and acetylation of a peptide with an ASA metal complex.

>> Research Grants

FWF P 31166-B33, FFG (West-Austrian BioNMR), TWF UNI-0404/1982

>> Coworkers

CZIFERSZKY Monika (postdoc), BÄCKER Daniel (PhD student), CUCCHIARO Andrea (PhD student), DESCHER Hubert Aaron (PhD student), GÖTZFRIED Sina Katharina (PhD student), HONGNAK Siriwat (PhD student), HÖRMANN Nikolas (PhD student), HUPFAUF Andrea (PhD student), KALCHSCHMID Christina (PhD student), KNOX Alexandra (PhD student), LAROSA Grazia (PhD student), SAGASSER Jessica (PhD student), SCHÖPF Anna (PhD student), WENINGER Alexander (PhD student)

Stem cells, regeneration, and bioadhesion in basal animal model systems

Bert Hobmayer and Peter Ladurner

>> Department of Zoology

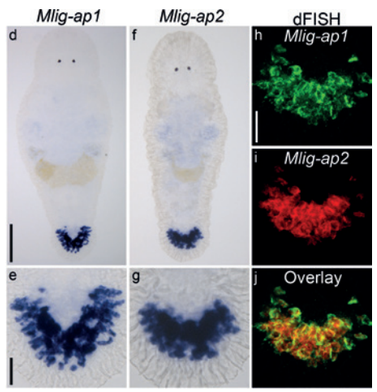


Figure 1: Expression of *M. lignano* adhesive proteins. From Wunderer *et al. PNAS*, 2019
https://doi.org/10.1073/pnas.1814230116

>> Goals: (1) We want to understand mechanisms of decision making in stem cell lineages during embryonic development and during tissue homeostasis and regeneration in adult animals. (2) We analyze bio-adhesion and characterize naturally occurring glue proteins in aquatic animals.

>> Background: We work on simple model organisms such as cnidarian polyps, flatworms, and embryos of sea squirts (tunicates). We study cellular decision-making, axial patterning, regeneration, and bio-adhesion. We analyze evolutionarily conserved signaling pathways and transcription factors and aim at a better understanding of principle molecular mechanisms. A transfer of our knowledge to higher organisms may point to potential targets for biomedical research. Furthermore, we use omics approaches and microscopic imaging to characterize bio-adhesive substances used for attaching to the substrate primarily in flatworms, but also in *Hydra* and tunicate larvae.

>> Research Highlights and Outlook: We have characterized the two major adhesive glyco-proteins of the the flatworm *Macrostomum lignano* using a transcriptomic and high throughput *in situ* screening approach combined with mass spectrometry, confocal and electron microscopy, RNA interference, specific antibodies and lectin staining. Flatworms evolved adhesives adapted to different environments such as freshwater, seawater and parasite attachment onto its host. We now expand our search for bio-adhesives to 20 different flatworm species. It is the goal to understand the mode of action of these molecules to enable the development of new synthetic counterparts.

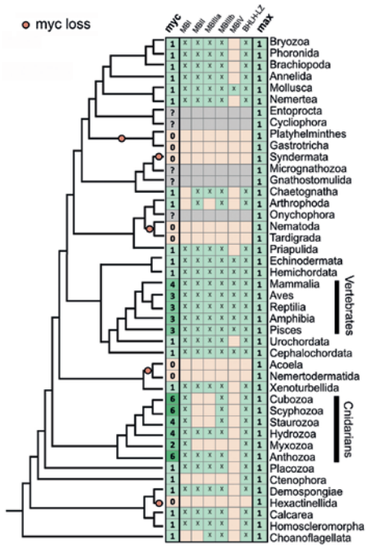


Figure 2: Unexpected and independent losses of Myc, dynamic modifications of protein domains during animal evolution, and diversification of the ancestral *c-myc*-like gene into several paralogs in the cnidarian and vertebrate phyla. From Lechable *et al.* (in preparation)

The cnidarian polyp *Hydra* is a classic model for stem cell and regeneration research. Up to one third of all cells of the polyp are adult stem cells building a platform for its unparalleled regeneration capacity and its longevity. These cells continuously proliferate producing a homeostatic state of permanent tissue growth. One of the three types of adult stem cells, the interstitial stem cell, shows multi-potency giving rise to somatic differentiation products such as nerve and stinging cells, as well as both types of gametes. We showed that Wnt/β-Catenin signalling regulates the action of Myc1, one of the two known *Hydra* Myc stem cell maintenance factors, and thereby likely contributes - together with Myc2 - to self-renewal. In contrast, Myc3, a third and rather derived member of the Myc protein family, acts in early nerve cell differentiation. Using approaches for genetic interference (siRNA and stable transgenesis), we have started to analyse the roles of Wnt/β-Catenin signalling and Myc transcriptional regulation in *Hydra* in a broader molecular network underlying decision-making in the interstitial stem cell lineage. Furthermore, we intend to define structure-function properties of oncogenic *Hydra* Myc proteins in collaboration with Markus Hartl and the Klaus Liedl group (Department of Biochemistry and Department of General, Inorganic and Theoretical Chemistry, respectively).

In order to complement our research with expertise for genetic regulation and promoter analysis, Ute Rothbächer works with sea squirts, model organisms for functional genomics. She studies the controlled exit of embryonic stem cells from pluripotency towards nervous or epidermal cell fate and takes advantage of efficient gene transfer techniques (electroporation, microinjection), *in silico* data bases, and sophisticated functional genomics tools.

>> Research Grants

FWF 25404; FWF 30347; FWF 31612; FWF 35402; FWF J4071; H2020 Marie Skłodowska-Curie ARDRE-COFUND DP847681; Doc Fonds National de la Recherche Luxembourg; ÖAW-DOC 24699; ÖAW-DOC 25629; ÖAW-DOC 25874; TWF F.18737; TWF F.33302; TWF F.33477

>> Coworkers

Ute Rothbächer (Assoc. Prof.); Bernhard Egger (Assis. Prof.); Robert Pjeta, Birgit Lengerer (PostDoc); Julia Wunderer, Fan Zeng, Philip Bertemes, Alexandra Grosbusch, Isabel Dittmann, Moses Kitilit Kibet, Alessandro Pennati, Marion Lechable (PhD students); Willi Salvenmoser, Thomas Ostermann (electron microscopy); Lena Seppi, Natalie Kolb, Dzenana Tufegzic (technician and animal culture)

Stress response to environmental stress in earthworms

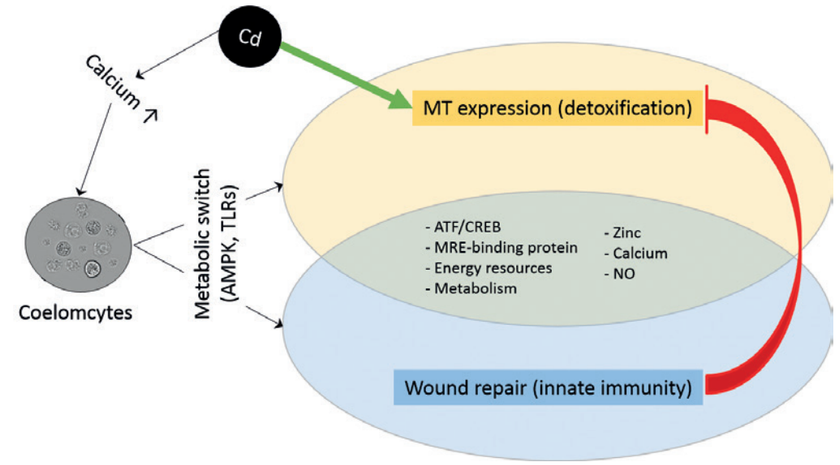
Martina Höckner

>> Department of Zoology

>> Goal: To understand the molecular stress response to changing environmental conditions with a special focus on regulation, epigenetics, and immunity in soil dwelling organisms like earthworms.

>> Background: How organisms respond and adapt to environmental changes is of special interest in times of rapidly changing environmental conditions. The stress response has been studied extensively in aquatic and terrestrial organisms to identify biomarkers. However, it has been neglected to study the mechanisms and regulation networks that are responsible for a coordinated response to stress in a broad range of invertebrate species. The latter lead to a scarce knowledgebase on evolutionary and functional aspects of cellular processes that are responsible for the development of coping and adaptation strategies. Important aspects of stress-induced effects are assigned to epigenetic factors like DNA methylation, little of which is known in invertebrates like earthworms.

>> Research Highlights and Outlook: We know already that even low levels of Cd lead to DNA hypermethylation in earthworms. Interestingly, these changes are persistent. The genes which are affected by these persistent Cd-induced methylation changes are determined in an ongoing project. Moreover, we investigate metallothionein (MT) gene body methylation and its effect on gene expression in control and Cd-exposed individuals. We were also able to determine details of the transcriptional regulation of MTs, which are highly important stress-induced proteins, in earthworms.



The DNA methylation machinery as well as methionine cycle intermediates (SAM, SAH) are characterized to reveal the mechanisms of maintaining, de novo, and removal of DNA methylation. These data will answer the question how Cd induces DNA hypermethylation while giving important general information on epigenetics in invertebrates. A project on Cd-related effects on the earthworm microbiome showed that the number of heavy metal resistant bacteria or bacteria that possess heavy metal binding capacities prevailed, which could serve as biomarkers for soil biomonitoring.

In addition, the link of stress response mechanisms to innate immunity and the involvement of metabolic and regulatory parameters will be analyzed in a recently funded FWF project.

>> Research Grants

FWF Einzelprojekt P33835-B; L'Oreal PostDoc grant; Nachwuchsförderung der Leopold-Franzens-Universität Innsbruck; Lise Meitner Projekt I 3136-B29

>> Coworkers

Maja Šrut, Veronika Pedrini-Martha, Victoria Drechsel, Claudio Piechnik (PostDocs); Gerhard Aigner (PhD student); Verena Pittl, Pamela Nenning, Veronika Peer, (master students); Birgit Fiechtner (Technician)

Molecular and cell biology of human ageing

Pidder Jansen-Dürr

>> Research Department for Biomedical Aging Research

>> Goal: To obtain an integrated understanding of molecular and cellular mechanisms underlying ageing and cellular senescence in mammals.

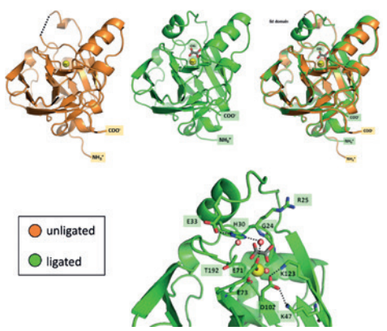


Figure 1: Structure of FAHD1 and its catalytic center.
Upper panel: Alignment of FAHD1 crystal structures. Structural comparison of human FAHD1 in its unligated (orange) and ligated (green) form. The catalytic center contains a magnesium ion (yellow sphere), and the bound ligand oxalate (OXL). Superposition of the free and the ligated form is shown in in the rightmost panel, demonstrating an N-terminal region referred to as "lid domain" which is essential for the catalytic activity.
Lower panel: Detailed view of the catalytic center. Upon oxalate binding, the coordination of the magnesium ion is altered: two water molecules of the inner coordination sphere are replaced by oxygens from the ligand. Subsequently, the dyad E33–H30 of the lid region is positioned close to the magnesium ion. Water molecule 6 is stabilized by H30–E33 and E71. Amino acid residues involved in OAA decarboxylation are highlighted.

>> Background: The ageing process is modulated by a complex network of interacting genetic pathways, which have been elucidated through studies on model organisms. Recent progress in biogerontology suggests that mitochondria, cellular organelles best known for their ability to generate energy in form of ATP from dietary nutrients, take center stage in many processes driving ageing.

>> Research Highlights and Outlook: We identified FAH domain containing protein 1 (FAHD1) as oxaloacetate decarboxylase (ODx) localized in mitochondria. We found that knocking down FAHD1 expression in human endothelial cells induced premature senescence in these cells, suggesting that FAHD1 is a novel regulator of mitochondrial function and cellular senescence. In the reporting period, the group has elucidated the structure of FAHD1 with particular emphasis on its catalytic center and established the catalytic mechanisms by which FAHD1 catalyzes the decarboxylation of OAA (Fig. 1).

Previous work established that the genetic inactivation of *fahd-1*, the nematode homolog of FAHD1, induces a complex phenotype, characterized by a loss of mitochondrial function and a significant locomotion defect; moreover, behavioral alterations were observed for such animals. In recent work, the deficiency in egg-laying behavior of FAHD1 mutant worms was traced back to changes in signal transduction in serotonergic neurons, combined with an altered serotonin metabolism. These findings suggest that lack of *fahd-1* affects serotonin metabolism, potentially caused by alterations in the flux through the TCA cycle which serves as a reservoir for the biosynthesis of various metabolites including serotonin.

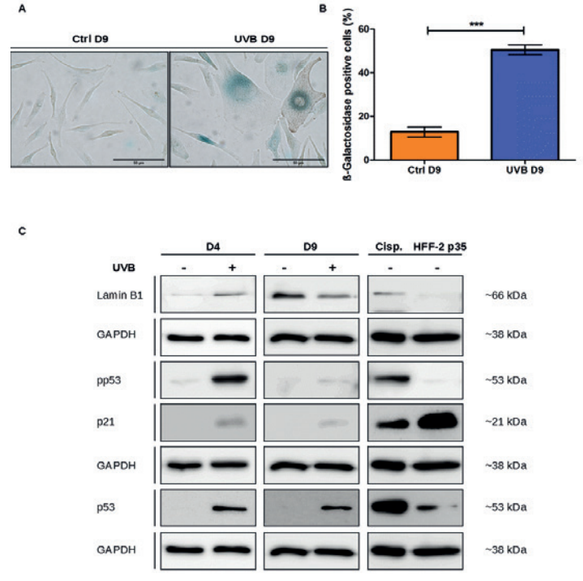


Figure 2: UVB induces senescence in human epidermal melanocytes.
(A) Representative pictures of control and UVB-irradiated melanocytes stained for SA-β-Gal on D9 of the experiment. (B) Percentage of SA-β-Gal positive melanocytes. For each group at least 300 cells were analyzed. (C) p21, pp53 (serin 15), p53 and Lamin B1 protein expression of UVB-irradiated and the respective control cells were analyzed by western blot on days 4 and 9 of the experiment. Representative pictures are shown. Lysates from HDFs passage 35 and HDFs treated with 33 µM Cisplatin were used as positive controls. GAPDH was used as a protein loading control.

In a second project, the group addresses molecular mechanisms of cellular senescence using model systems reflecting extrinsic ageing of the human skin. To this end we use exogenous stressors, such as UV irradiation or the exposure to environmental pollutants to drive human skin-derived cells into stress-induced premature senescence (SIPS), using both 2D and 3D cell culture systems. Previous results suggest a key role for autophagy in UVB-induced cellular senescence of human dermal fibroblasts, both in monolayer culture and in 3D organotypic culture. We have now extended the analysis to melanocytes, another important cell type in the epidermis and established an experimental system to study UVB-induced melanocyte senescence in vitro. Exposure to mild and repeated doses of UVB directly influenced melanocyte proliferation, morphology and ploidy. We confirmed UVB-induced senescence with increased senescence-associated β-galactosidase positivity and changed expression of several senescence markers, including p21, p53 and Lamin B1 (Fig. 2). UVB irradiation impaired proteasome and increased autophagic activity in melanocytes, while expanding intracellular melanin content. In addition, using a co-culture system, we could confirm that senescence-associated secretory phenotype components secreted by senescent fibroblasts modulated melanogenesis. This new model serves as an important tool to explore UVB-induced melanocyte senescence and its involvement in photoaging and skin pigmentation.

>> Research Grants
EU H2020 COFUND DP ARDRE 847681, FWF P315820, MSCA RISE 691158 MediHealth, FFG Bridge1 848474, COST Action MITOEAGLE, Tiroler Wissenschaftsfonds (Michele Petit, Maria Cavinato, Ines Martic), Swarovski grant (Sophia Wedel, Alexander Weiss), PhD position LFUI Nachwuchsförderung (Sophia Wedel, Max Holzknecht, Ines Martic), Sonderförderung VR Forschung der LFUI (Alexander Weiss)

>> Coworkers
Eva Albertini, Maria Cavinato, Solmaz Etemad, Athanasios Seretis, Alexander Weiss (postdocs); Giorgia Baraldo, Lena Guerrero Navarro, Max Holzknecht, Michele Petit, Sophia Wedel, Ines Martic (Ph.D. students); Elia Cappuccio, Franziska Nobis, Tiziano Paravicini, Lorena Petric, Anna Simonini (M.Sc. students); Ayse Öztürk, Paula Schmidt, Elisabeth Damisch, Konstanze Simbriger, Beata Szalka (technicians)

From functional lipidomics to biomedical innovations

Andreas Koeberle

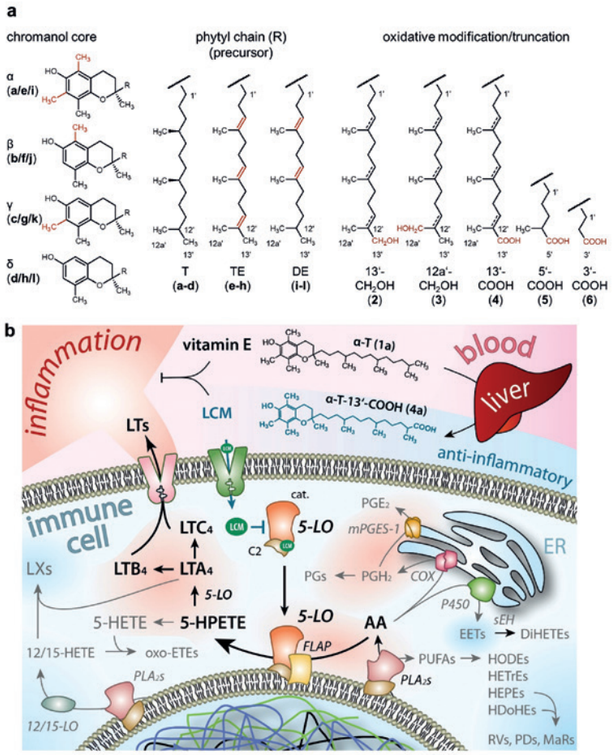
>> Research Institute Michael Popp

>> Goal: To explore the link between lipid metabolism, signal transduction, and homeostasis for the development of phytomedicine.

>> Background: Cells contain tens of thousands different lipids with pleiotropic functions that we are only beginning to understand. Lipids provide structure to the cell and serve as energy source, but they also act as signaling molecules with hormone-like character. To identify bioactive lipids and determine their role in cellular processes related to inflammation and cancer, we combine chemical biology with sensitive targeted lipidomics (UPLC-DMS-ESI/APCI-MS/MS). We elucidate the mode of action of natural products and address molecular targets and pharmacophores. In interdisciplinary collaboration, we perform structure-activity relationship studies, investigate binding modes and study (patho)physiological/pharmacological activities. Our findings give insight into mitogenic, stress-adaptive, and pro-inflammatory signal transduction (small molecules as tools), provide a molecular basis for their use in phytomedicine, and foster the discovery of novel phytopharmaceuticals and bio-inspired lead structures.

>> Research Highlights and Outlook: We explored biosynthetic lipid mediator networks in innate immune cells and during their interaction with cancer cells, identified promising drug candidates, and forwarded them to (pre)clinical studies in collaboration with laboratories experienced in phytoextraction, organic chemistry, bioinformatics, pharmaceutical technology, animal physiology, and clinical research. A recent highlight was our discovery that immunomodulatory functions of vitamin E are mediated by endogenous metabolites that limit inflammation (Figure 1). Motivated by this finding, we reoriented our search for anti-inflammatory drug candidates towards natural products that actively support the resolution of inflammation.

Figure 1: Endogenous metabolites of vitamin E inhibit 5-lipoxygenase (5-LO) to suppress inflammation. **a** Natural vitamin E forms and metabolites. **b** Schematic overview about eicosanoid and docosanoid biosynthesis. The biosynthesis of leukotrienes (LTs) in immune cells is initiated by phospholipases (PL)A_2, which release polyunsaturated fatty acids (PUFAs) such as arachidonic acid (AA) from membrane phospholipids. AA is transferred by 5-LO-activating protein (FLAP) to 5-LO at the nuclear membrane, dioxygenized to 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) and either reduced to 5-hydroxy-eicosatetraenoic acid (5-HETE) or rearranged to leukotriene (LT)A_4 by the LTA_4 synthase activity of 5-LO. Conversion of LTA_4 to LTB_4 and cysteinyl-LTs (*i.e.*, LTC_4) yields potent mediators of inflammation. Mode of action of LCMs: α-T (**1a**, vitamin E) is metabolized in the liver to α-T-13′-COOH (**4a**, LCM), which binds to 5-LO as high-affinity inhibitor at the interface of the catalytic (cat.) and regulatory C2-like domains. α-T-13′-COOH (**4a**) is released from the liver and present in plasma at concentrations that are sufficient to inhibit 5-LO, accumulates in immune cells at inflammatory sites and counteracts acute inflammation by suppressing LT formation.



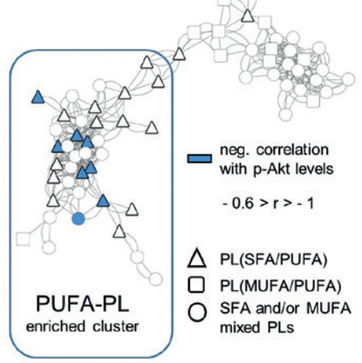


Figure 2: Polyunsaturated fatty acids (PUFAs) accumulate in membrane phosphatidylcholines (PC) during the onset of programmed cell death and decrease Akt activation at the (peri)nucleus. Cell death was induced in fibroblasts via ten different mechanisms. The network of co-regulated phospholipids (PLs) visualizes positive lipid-lipid correlations with a correlation factor (r) ≥ 0.7. Nodes represent individual lipid species. The network was calculated based on mean proportions of phospholipid species. Negative correlations (-0.6 > r > -1) between cellular p-Akt (Ser472) levels and the cellular proportion of phospholipid (PL) species are highlighted in blue.

Our functional lipidomics approach gives access to phospholipid profiles (Figure 2), which we specifically manipulate to explore the physiological and pharmacological functions of individual species. Among others, we studied the impact of lipid metabolism on programmed cell death, cell migration, stem cell differentiation, aneuploidy, sorafenib resistance, and health benefits by metformin therapy. We further addressed the delivery of natural products and phospholipids to target sites in collaboration with pharmaceutical technologists and investigated their potential for pharmacotherapy in context of stress-adaption and overcoming tumor resistance. Ongoing studies in our laboratory focus on ferroptosis, a newly identified non-apoptotic cell death pathway, which we consider as missing link that connects tumor plasticity with therapy resistance and chronic inflammation.

>> Research Grants

PRC AKO-2015-037/1-1, InfectoOptics SAS-2015-HKI-LWC, DFG KO 4589/7-1, FSU/SZU Joint PhD program, DAAD 57389523, FSU/DFG GRK1715 SP10, PRC AKO-2019-070/2-1, BNO P7490-012-013, FWF I 4968, ÖGKM Project Award, UIBK 2021-CHEM-10, TWF F.33467

>> Coworkers

Ehsan Bonyadirad, Zhigang Rao (postdocs); Minh Bui-Hoang, André Gollowitzer, Stephan Permann, Fengting Su, Lorenz Waltl, Finja Witt (PhD students); Felix Benscheidt, Julia Grander (technical assistant)

Pharmacotherapeutic potential of retinal L-type calcium channels

Alexandra Koschak

>> **Department of Pharmacy, Pharmacology and Toxicology Section**

>> Goal: Exploit the pharmaco-therapeutic potential of voltage-gated Cav1.4 L-type calcium channels for treatment of retinal diseases.

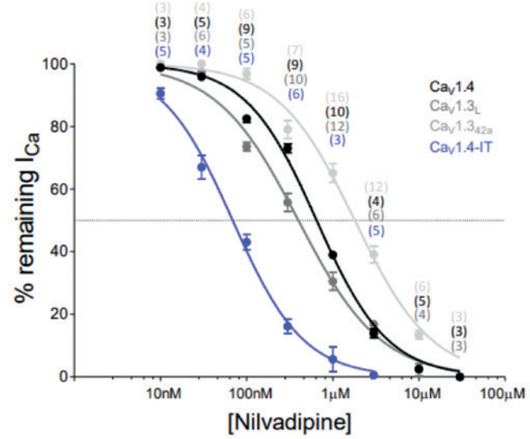
>> Background: Cav1.4 L-type calcium channels (LTCCs) serve as the predominant source for Ca^{2+} entry in photoreceptors and retinal bipolar cell because they allow sustained release of glutamate at their synaptic sites which are specialized ribbon synapses. Previous studies highlighted the importance of Cav1.4 channels for the assembly and maintenance of the retinal ribbon synapse. Importantly, mutations in the encoding *CACNA1F* gene have been associated with a number of retinal diseases, among those is congenital stationary night blindness type 2 (CSNB2).

>> Research Highlights and Outlook: Besides rod-driven scotopic vision also cone-driven photopic responses are severely affected in CSNB2 patients. We recently examined functional and morphological changes in cones and cone-related pathways in mice carrying the Cav1.4 gain-of function mutation I756T ($Ca_V1.4$-IT) using multielectrode array, patch-clamp and immunohistochemical analyses. Cav1.4-IT ganglion cell responses to photopic stimuli were seen only in a small fraction of cells indicative of a major impairment in the cone pathway. Though cone photoreceptors underwent morphological rearrangements, they retained their ability to release glutamate. Our functional data suggested a postsynaptic cone bipolar cell defect, supported by the fact that the majority of cone bipolar cells showed sprouting. Horizontal cells maintained their contacts with cones and cone-to-horizontal cell input was preserved. Of note, a reduction of basal Ca^{2+} influx by the calcium channel blocker nilvadipine was not sufficient to rescue synaptic transmission deficits caused by the Cav1.4-IT mutation. However, long term treatments with low-dose Ca^{2+} channel blockers might be beneficial reducing Ca^{2+} toxicity without major effects on ganglion cells responses. In a joint project together with Hartwig Seitter we explore the expression of Cav1.4 and other LTCC subunits in rod bipolar cells (RBC) of the mouse retina. We catalogue the expression of calcium channel subunits in RBCs to determine their contribution to RBC calcium channel activity, with a particular focus on Cav1.4. Expression profiling and functional analyses indicate that Cav1.4 is not the only LTCC essential in rod bipolar cells.

To further validate these findings, we successfully generated Cav1.4 conditional knock-out mice and RBC specific Cav1.4 knock out mice are already available. The future investigation of both mouse strains generated in this project offer the opportunity to ask research questions that go beyond to the physiological importance of single LTCCs in the retina.

The fact that we have to consider more than only one type of LTCCs in RBCs is particularly important for gene-therapeutic approaches in Cav1.4-related retinal diseases which are currently developed in our group.

Figure 1: **Concentration-response curves for calcium current inhibition by nilvadipine.** In the nilvadipine dose-response curve the percentage of the remaining calcium current in the presence of different nilvadipine concentrations is indicated for human $Ca_V1.4$-WT (black), $Ca_V1.4$-IT (blue), $Ca_V1.3_L$ (dark grey) and $Ca_V1.3_{42a}$ (light grey) channels. The grey line indicates the IC_{50}. All data points represent mean ± SEM; the number of cells recorded is indicated in the graphs.



>> Research Grants

To Alexandra Koschak: FWF 29359, FWF 32747, DOC30 Doc funds (PhD program CavX). To Hartwig Seitter: P33566

>> Coworkers

Hartwig Seitter and Lucia Zanetti (postdocs); Irem Kilicarslan, Thomas Heigl and Matthias Ganglberger (PhD students); Michael Netzer (research assistant), Patricia Grabher, Marion Huber, Jana Obkircher (master students); Bettina Tschugg (technician)

Plant biochemistry and metabolism

Ilse Kranner

>> Department of Botany

>> Goal: To deepen our understanding of the regulation of plant metabolism with the aim to identify key molecular switchboards that determine plant stress response.

>> Background: Photosynthetic organisms are the basis of virtually all life on Earth. Every organic carbon molecule is derived from CO_2 fixed by photosynthesis, a process that has also led to the production of atmospheric O_2 needed for respiration. Although global agricultural productivity has increased over the past decades, the rate of gain has been hampered by climate change, and the forecast is bleak. Stress factors caused by climate change, such as increasing warming and more erratic precipitation are partly to blame. Our research group is dedicated to making significant contributions to unravelling the molecular basis of plant stress response. Parts of our work focus on the seeds of higher plants, aiming at understanding the impacts of climate change on seed quality and performance, but we are also interested in the mechanisms of plant adaptation to the alpine environment. Other foci are placed on understanding the chemical crosstalk between plants and their microbiota, such as in the lichen symbioses, and seeds and their microbiota, as well as chloroplast-to-nucleus signalling during acclimation to high light stress. We use mainly hyphenated techniques (UHPLC-MS/MS, GC-MS/MS) for untargeted metabolite profiling in combination with targeted assays of antioxidants, photosynthetic pigments, flavonoids, oxidised lipids and phytohormones, in combination with spectrophotometric methods to identify metabolic checkpoints that shape plant growth and development, and stress tolerance. We use a combination of standard model species (i.e. *Arabidopsis thaliana* and *Chlamydomonas reinhardtii* for accessing genetic tools and mutants), important crop plants (e.g. sunflower, cabbage, wheat and barley), and diverse genotypes of native alpine species.

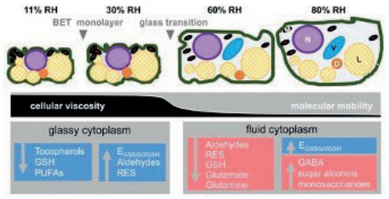


Figure 1: **Schematic overview of the cellular physicochemical changes occurring during seed ageing in response to relative humidity (RH) and O_2.** During seed maturation drying, the cytoplasm shrinks, reducing the area occupied by the cytosol and forcing organelles [nucleus (N), vacuole (V), mitochondria (M)], dry matter (D), including protein storage bodies and starch granules, the endomembrane system, and liquid lipid bodies (L), into close proximity. Cell walls and membranes are folded. Below a certain moisture content, the cytoplasm and organelles solidify, forming an intracellular glass. Therefore, at temperatures used for seed ageing (45°C) the cytoplasm is mostly glassy at 11 and 30% RH (left side), and cellular viscosity is high, with molecular mobility restricted to vibration, bending, and rotation of macromolecular side chains. At 60 and 80% RH (right side), the cytoplasm is fluid, and the carbon backbone of macromolecules can move. The biochemical changes indicated in blue were enhanced by O_2, and those in red occurred independently of O_2 availability. GSH, glutathione; PUFAs, (poly)unsaturated fatty acids; $E_{GSSG/2GSH}$, glutathione half-cell reduction; RES, reactive electrophile species; GABA, γ-aminobutyric acid. See details in Gerna *et al. Journal of Experimental Botany*, DOI:10.1093/jxb/erac024, in press.

>> Research Grants

FWF grants P 31027, P 32092 and P 32599, Korea University Research and Business Foundation grant "The redox chemistry of seeds under different ageing regimes"; EU - Horizon 2020, COFUND "ARDRE", FFG 891093

>> Coworkers

Thomas Roach (Associate Professor); Erwann Arc (Senior Scientist); Wolfgang Stöggl (Assistant Professor); Clara Bertel, Davide Gerna, Gregor Pichler (Postdocs); Dominik Kaplenig, Nicki Marami-Zonouz (PhD students); Birgit Stenzel, Christine Rossetti, Bettina Lehr, Otto Dämon (Technicians)

>> Research Highlights and Outlook: To investigate biochemical mechanisms leading to seed deterioration during storage, we studied molecular mechanisms contributing to seed deterioration in relation to seed water contents (Fig. 1). During seed maturation drying, the cytoplasm solidifies into an intracellular glass with highly restricted diffusion and molecular mobility. Seed ageing is governed by temperature and water content, whereby oxygen (O_2) can promote deteriorative reactions. However, the interaction between the physical state of the cytoplasm and O_2 in seed ageing remained unresolved. We aged *Pinus densiflora* seeds by controlled deterioration (CD) at 45 °C under distinct relative humidity (RH), resulting in cells with a glassy (11 and 30% RH) or fluid (60 and 80% RH) cytoplasm. Hypoxic conditions (0.4% O_2) during CD delayed seed deterioration, lipid peroxidation, and the decline of antioxidants (glutathione, α- and γ-tocopherol), but only when the cytoplasm was glassy. In contrast, when the cytoplasm was fluid, seeds deteriorated at the same rate regardless of O_2 availability, associated with limited lipid peroxidation, detoxification of lipid peroxide products, substantial loss of glutathione, and resumption of glutathione synthesis. Changes in metabolite profiles provided evidence of other O_2-independent enzymatic reactions in a fluid cytoplasm, including aldo-keto reductase and glutamate decarboxylase activities.

Together with Filip Kolář and Guillaume Wos, Charles University, Prague, we work on *Arabidopsis arenosa*, a wild relative of the model plant *Arabidopsis thaliana*, to further increase our understanding of plant response to environmental stress factors. We also collaborate with microbiologist Birgit Mitter, and bioinformatician Livio Antonielli, Austrian institute of Technology, for investigating the potential role of native endophytic bacteria in seed germination, and Oroboros GmbH for developing novel non-invasive technologies that provide deeper insights into photosynthesis.

Another project is dedicated to studying lichens, in collaboration with lichenologists from the University of Trieste, Fabio Candotto-Carniel, Lucia Muggia and Mauro Tretiach. The aim of this project is to unravel the molecular cross-talk required for the transition of free-living fungi and green micro-algae to the symbiotic state. Using UHPLC-MS/MS, we identified phytohormones in three lichen-forming and three free-living algae. Phytohormones are pivotal signalling compounds in higher plants, in which they exert their roles intracellularly, but are also released for cell-to-cell communication. We showed that indole-3-acetic acid, indole-3-butyric acid, abscisic acid, jasmonic acid, gibberellin A_3 and gibberellin A_4 are released extracellularly, and IAA was the most abundant. Phytohormone release was affected by light and water availability. In unicellular organisms, extracellularly released phytohormones can be involved in chemical crosstalk with other organisms, and further work is intended to see whether these phytohormones are recognized by lichenising fungi. The results are also expected to support biotechnological applications using micro-algae, for example algal bioreactors for wastewater treatment or CO_2 fixation.

Chemistry, chemical and structural biology of the pigments of life

Bernhard Kräutler and Thomas Müller

>> Department of Organic Chemistry

>> Goal: To gain knowledge on the chemistry, biological roles and bio-molecular interactions of critical porphyrinoid and other metabolites, and to apply this in biology and medicine.

>> Background: A large part of our research concerns the porphyrinoid 'pigments of life', which have crucial and diverse roles in cells, e.g. as cofactors in enzymes, in biological processes driven by solar light and as exceptional metabolites. They comprise heme, chlorophyll, corrinoids and linear tetrapyrroles, which result from breakdown of heme and of chlorophyll. Porphyrinoids owe their important roles in nature to their unique molecular properties and some of their basic structures are assumed to have pre-biotic origin. Frequently they are functional complements as coenzymes to proteins, or (less well known) as structuring and regulating ligands of proteins and noncoding RNA, e.g. in B_{12}-riboswitches. Our approach is dedicated to gaining chemistry-based insights into the biological roles of essential porphyrinoid and other metabolites, as well as at exploring their effects in important cellular processes.

>> Research Highlights and Outlook: We have continued to contribute to the chemistry of vitamin B_{12}-derivatives, in particular as part of our recent program on 'antivitamins B_{12}', metabolically inert B_{12}-derivatives. This research will help us learn more about mechanisms of B_{12}-dependent metabolic processes in microorganisms, animals and humans, as well as in looking at still enigmatic effects of B_{12}-deficiency by B_{12}-chemical biological approaches. In this context, we have developed a synthetic approach towards a group of B_{12}-mimics that contain transition metals other than cobalt, the specific metal center of the natural B_{12}-derivatives (Figure 1). A combination of biological and chemical total synthesis was developed for this purpose, furnishing the 'mother' ligand of vitamin B_{12}, hydrogenobyric acid, as key component. This 'contracted' helical corrin macrocycle appears to have an intriguing capacity for binding transition metals in activated, or 'entatic' states. As examples luminescent zinc and diamagnetic nickel analogues of the natural B_{12}-derivatives were synthesized and their structures scrutinized by X-ray analysis.

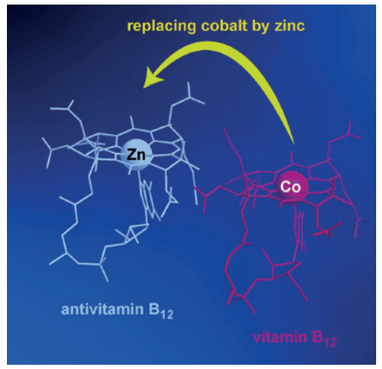


Figure 1. 'Antivitamins B_{12}' from B_{12}-vitamins by replacement of cobalt with specific other metals, as found for the case for zinc.

Figure 2. Chlorophyll breakdown products in fern, a plant that played a role even in early phases of plant evolution, were revealed to be novel phyllobilin isomers with a rearranged carbon skeleton.

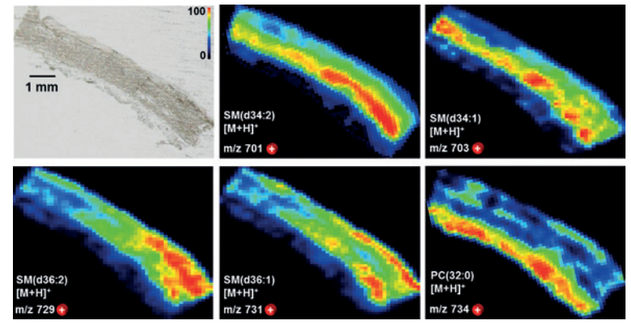


Figure 3. 2D Localization of lipids in human aortic tissue using MALDI-TOF mass spectrometry imaging.

Our labs have also pioneered studies on the structure and chemistry of chlorophyll catabolites from higher plants, named 'phyllobilins'. In the context of such studies we have become interested in studying evolutionary aspects of chlorophyll breakdown and were able to elucidate a so far unknown structure of a chlorophyll degradation product found in senescent ferns (Figure 2). Furthermore, we developed MALDI-TOF and DESI mass spectrometry imaging methodology for the 2D localization and identification of biologically relevant molecules, e.g. phyllobilins or lipids, in diverse biological tissue (Figure 3).

>> Research Grants

FWF P-28522, FWF P-28892, FWF P-33059, Sparkling Science project SPA/04-140/INDIAN SUMMER IN TYROL

>> Coworkers

T. Erhart, C. Kieninger, M. Wiedemair, A.K. Pandey (postdoctoral coworkers); T. Erhart, C. Kieninger, C. Meisenbichler, M. Scherl, C. Nadegger (Ph.D. students); M. Schäfer (master student)

Antibody dynamics and biomolecular recognition

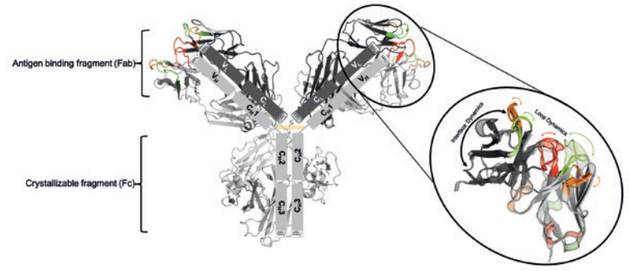
Klaus R. Liedl

>> Department of General, Inorganic and Theoretical Chemistry

>> Goal: The focus of our work lies in characterizing key features of biomolecular recognition by employing and developing a wide range of computational methods to profile key traits of biomolecular recognition and facilitate the design and optimization of biopharmaceuticals.

>> Background: Molecular recognition is a vital aspect of nearly all biological processes, however, understanding them on a microscopical level is not trivial. It is well established that proteins are inherently flexible. Meaning that, a protein in solution fluctuates between diverse conformational states of varying probability. Studying single static crystal structures is thus often not enough to understand the biological mechanisms of a molecule. Reliable information on the dynamics of a protein is essential for understanding its physico-chemical characteristics and biological functions. Theoretical methods such as molecular modelling and molecular dynamics have become more and more important in the past. State-of-the-art techniques not only enable a better understanding of experimental findings, but also create insights in macromolecular properties inaccessible to experiments.

>> Research Highlights and Outlook: Antibodies have emerged as a major class of biopharmaceuticals, with indications ranging from autoimmune diseases to cancer. A majority of antibody-related



research is currently based on sequence information or stationary structures alone without allowing to fully understand the molecular origins of the physico-chemical features of an antibody. We applied simulation-based techniques to link structural and dynamic information to pharmaceutically relevant properties such as specificity, stability, hydrophobicity and developability. Studying a broad range of model systems we have shown that molecular dynamics simulations allow an accurate representation of antibodies as conformational ensembles and that reliable models of interface dynamics are vital for the design of biopharmaceuticals.

Thus, in contrast to this prevalent static view of the binding interface we demonstrate a dynamic perspective not only of the paratope but of whole Fvs and Fabs. We show that antibodies exist as ensembles of paratope states. These paratope states are defined by a characteristic combination of complementarity determining region (CDR) loop conformations and interdomain orientations and interconvert into each other in the micro-to-millisecond timescale by correlated loop and interdomain rearrangements. Additionally, we demonstrate that crystal packing effects can distort the paratope state and thus result in misleading X-ray structures.
By extending the repertoire of cutting-edge simulations techniques, for the first time we achieve a complete description of conformations, thermodynamics and kinetics of the whole binding paratope in solution. These findings have broad implications in the field of antibody design and in the development of biotherapeutics as they provide a new paradigm in the understanding of CDR binding loop states, antibody-antigen recognition, relative V_H and V_L interface angles and elbow-angles distributions and their respective dynamics.

>> Research Grants

FWF P30565, FWF P30737, ITN H2020 Marie Sklodowska-Curie Actions, EU Horizon 2020 COFUND, EU Horizon 2020 Marie Skłodowska-Curie No. 847476, Boehringer Ingelheim, Roche, Lise-Meitner grant

>> Coworkers

Maren Podewitz, Philip Handle (postdocs) Dennis Dinu, Barbara Math, Franz Waibl, Patrick K. Quoika, Yin Wang, Anna S. Kamenik, Johannes R. Löffler, Ursula Kahler, Monica L. Fernández Quintero, Johannes Kraml, Florian Hofer, Radu A. Talmazan, Xuechen Tang, Nancy D. Pomarici (Ph.D. students) Martin C. Heiss, Lisa Bacher, Clarissa A. Seidler, Valentin J. Hörschinger, Leonida Lamp

Chemical synthesis of natural products

Thomas Magauer

>> Department of Organic Chemistry

>> Goal: To develop expedient synthetic access to biologically active natural products.

>> Background: Natural products constitute a vast and largely unexplored library of complex molecular architectures, and are a fundamental source for novel pharmaceutical and agricultural agents. However, the complex architecture of these molecules often prevented their application in medicinal chemistry. For us, this is an inspiration to think about new retrosynthetic bond disconnections which are not possible with current methods. The goal is to discover, design and develop novel, highly selective and efficient reactions for synthetic chemists. Mechanistic studies to better understand reactivity and selectivity will be performed when appropriate. These strategies will be applied in the synthesis of biologically relevant complex natural products and simplified analogs thereof. These projects should ultimately provide new lead compounds for the treatment of human diseases, shed light on proposed biosynthetic processes, and help to identify new molecular targets.

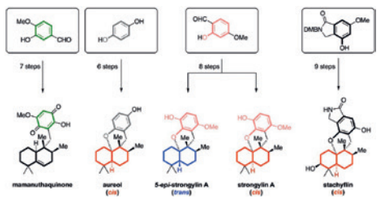


Figure 1

>> Research Highlights and Outlook: We recently described a highly convergent and modular "Lego-type" platform that enables rapid access to five natural antibiotics (stachyflin, aureol, smenosqualone, strongylin A, cyclosmenospongine), and 15 previously inaccessible synthetic analogs. The developed strategy allowed us to efficiently introduce deep-seated structural modifications and conduct first structure-activity relationship studies. The biological profiling revealed potent antibiotic activities for strongylin A and a non-natural analog against methicillin-resistant *Staphylococcus aureus*. The route described permits the synthesis of any candidate in amounts necessary for further biological evaluation together with Prof. Mark Brönstrup (Helmholtz Centre for Infection Research), both early- and late stage.

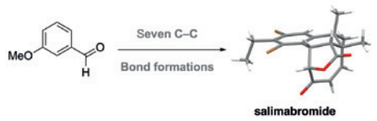


Figure 2

Figure 3

>> Research Grants

ERC Consolidator Grant "CRAFTMOL" 101000060, ERC Starting Grant „HALODRUGSYN" 714049, FWF P31023-NBL, FWF P 33894-N

>> Coworkers

Aldo Tancredi (PhD), Nicholas Tappin (Postdoc), Ondrej Kovac (Postdoc), Feilner Julian (PhD), Habiger Christoph (PhD), Haut Franz-Lucas (PhD), Höfler Denis (Postdoc), Rode Alexander (PhD), Röder Liesa (MSc), Sokol Kevin (Postdoc), Steinborn Christian (PhD), Plangger Immanuel (MSc), Feichtinger Niklas (MSc), Clemens Dietrich (MSc), Torres Venegas Sofia (PhD), Wein Lukas (PhD), Zamarija Ivica (PhD), Gerhard Scherzer (Technician)

We were also able to realize a practical synthesis of salimabromide, a unique antibiotic polyketide of marine origin. The target structure has been isolated once in minute quantitates (0.5 mg from 64 L medium) and has eluded its synthesis as well as re-isolation since then. Inspired by the logic of two-phase (bio)synthesis, the unprecedented tetracyclic carbon skeleton was created by several powerful C–C bond formations (tandem Wagner–Meerwein/Friedel–Crafts; ketiminium mediated (2+2)-cycloaddition) and finally subjected to a series of selective C–C and C–H oxidations. The overall sequence is robust enough to be conducted on multi-gram scale which is evident from the fact that more than 500 mg of the natural product were synthesized in our laboratory. In addition, it has enabled deep-seated structural modifications and has set the foundation for structure-activity-relationship studies together with Prof. Werz (Universität Jena).

In our most recent project, we accomplished the first synthesis of the complex *ent*-trachylobane natural product Mitrephorone B and disclosed its selective C–H oxidation to the oxetane containing congener Mitrephorone A. The presented C–H oxidation, which was unprecedented in the chemical literature, was accomplished by either iron-mediated or electrochemical oxidation. This enabled access to the fully substituted oxetane in one step, thereby circumventing the limited substrate scope observed for conventional oxetane formation methods such as ring-expansion, [2+2]-cycloaddition or nucleophilic displacement reactions. The selective formation of the oxetane also shed light on the putative biosynthesis of Mitrephorone C, which was believed to originate from Mitrephorone B. Based on the results obtained in this study, we conclude that the biosynthesis diverges at an earlier stage.

Neural cell reprogramming to study neurological disorders in cell type- and patient-specific models

Jerome Mertens

>> Department of Molecular Biology

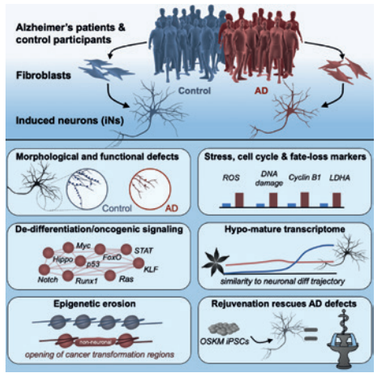


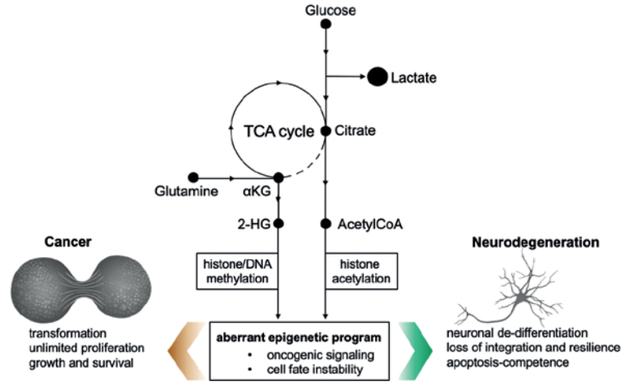
Figure 1: Schematic overview illustrating the generation of fibroblasts and iN cultures from a cohort of clinically characterized AD patients, and age-matched non-demented control donors (top panel). Compared to control iNs, AD iNs show morphological, functional, and epigenetic defects, which are driven by a cancer-like de-differentiation process towards a hypo-mature neuronal fate, which can be rescued via iPSC rejuvenation (lower panel). Figure adopted from Mertens *et al. Cell Stem Cell*, 2021.

>> Goal: To harness human patient-specific reprogramming models, integrative multi-omics tools, and functional cell biology to understand age-related neurological disorders.

>> Background: The human brain is a prime target for cellular aging. Our neurons are mainly born during embryogenesis and early life, and then survive as postmitotic cells throughout life with limited capacity for renewal. Old age is a stringently prerequisite for the development of neurodegenerative disease such as Alzheimer's Disease (AD), of which the vast majority of AD cases are sporadic, meaning that they lack a direct link between genetics and symptom manifestation. Studying the molecular interface between human biological aging and disease in patient-specific models will help to better understand neurodegeneration and may lead to therapeutic strategies for these yet uncurable diseases. Our approach involves the combination of iPSC differentiation and direct neuronal conversion (iN) with next-generation sequencing and other omics technologies and functional neuroscience to model diseases such as sporadic AD. In contrast to the more widely used iPSC approach, direct iN conversion preserves signatures of cellular aging.

>> Research Highlights and Outlook: We recently generated iNs from a cohort of AD patients and control donors, and found that AD iNs exhibit strong neuronal transcriptome signatures characterized by down-regulation of mature neuronal properties and up-regulation of immature and progenitor-like signaling pathways. Mapping iNs to longitudinal neuronal differentiation trajectory data demonstrated that AD iNs reflect a hypo-mature neuronal identity characterized by markers of stress, cell cycle, and de-differentiation. Epigenetic landscape profiling revealed an underlying aberrant neuronal state that shares similarities with malignant transformation and age-dependent epigenetic erosion (Fig.1). To probe for the involvement of aging, we also generated rejuvenated iPSC-derived neurons that showed no significant disease-related transcriptome signatures, a feature that is consistent with epigenetic clock and brain ontogenesis mapping, which indicate that fibroblast-derived iNs more closely reflect old adult brain stages. These new data further hint at neuron-specific metabolic changes that regulate cell fate impair neuronal identity in old human AD iNs. Mature somatic cell fate is markedly controlled by metabolic states and individual metabolites. Fate instability is a major hallmark of age-dependent diseases such as cancer or AD, and this marks an important new research direction in the field and in our lab.

Figure 2: Schematic drawing comparing metabolic state shifts in cancer and neurodegeneration.
Increased Warburg-effect-like glycolysis and glutamine uptake leads to alterations in the tricarboxylic acid (TCA) cycle metabolites citrate and αKG, which ultimately alters the epigenetic molecules acetylCoA (histone and transcription factor acetylation), and 2-HG (regulates histone and DNA methylation). The rewiring of metabolism in diseased cells is often dramatic, and may result in fate shifts, which further promote oncogenic signaling and cell fate instability. However, the effect of aberrant gene varies depending on the situation and cell type: in cancers, it leads to proliferation and growth, while in neurons it instead leads to neuronal hypo-maturity, loss of network integration and resilience. Figure adopted from Traxler *et al. Disease Models and Mechanisms*, 2021.



>> Research Grants

European Commission MSCA-RI 797205; BrightFocus Foundation A2019562S; European Commission ERC-StG 852086; CLENE/NAM/MJFF CNM-Au8-AD-PD-iN; FWF/NKFIH I5057

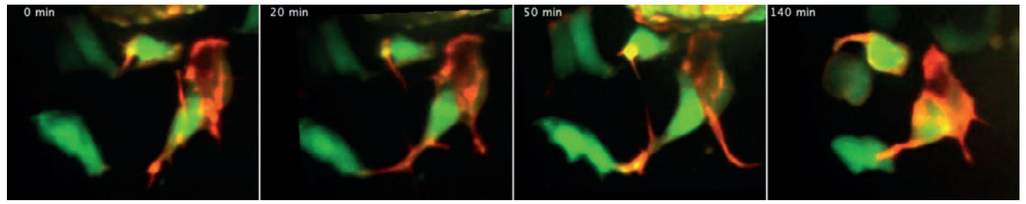
>> Coworkers

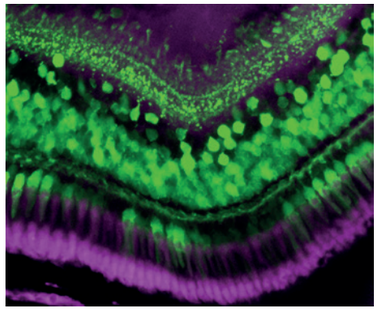
Eichhorner Sophie, Frantal Daniela (technicians); Borgogno Oliver, Karbacher Lukas, Iraci Matilde, Wagner Anna, Schön Florian, Lagerström Stina (MSc students); Böhnke Lena, Lagerwall Jessica, Zhou-Yang Lucia (PhD students); Pelucchi Silvia, Traxler Larissa (postdocs)

Developmental biology

Dirk Meyer and Robin Kimmel

>> Department of Molecular Biology





>> Goal: To understand molecular mechanisms underlying fate specification, differentiation, migration and maturation, with a focus on vertebrate gastrulation and the formation of pancreatic islet cells. We further aim to elucidate endocrine islet function and related disease mechanisms.

>> Background: Establishment and functionality of endodermal organs such as the pancreas requires a still poorly understood coordination between proliferation, migration, differentiation and maturation. In our research we apply genetics, molecular and *in vivo* imaging approaches in zebrafish and human stem cells to study (1) the transcription network of early embryonic germlayer induction, (2) the genetic and molecular programs regulating beta-cell and islet formation during embryonic development and regeneration and (3) to understand the underlying molecular and physiological defects of Diabetes associated risk factors.

>> Research Highlights and Outlook: Zygotic gene regulation: Using ChIP and overexpression approaches in zebrafish we identified a novel mode of early embryonic gene regulation that is independent of TGF-beta signaling and that connects the conserved transcription factors FoxH1 with chromatin remodeling and super-enhancer formation during zygotic gene activation.

Islet development: We have demonstrated that endocrine cells are highly motile during islet assembly, which is dependent on PI3K and G-protein coupled-receptor activity. Novel tools for single cell analysis of endocrine cell dynamics and physiology have been established, which are being applied to further interrogate molecular regulators of islet morphogenesis.

Diabetes-related studies: Together with international collaborators, we characterized novel requirements of Diabetes-associated ion-channels in glucose induced beta-cell excitability. Furthermore, using our diabetic zebrafish models to investigate the long term impact of disrupted glucose homeostasis, we show that zebrafish retinae develop vascular and neural pathologies resembling human diabetic retinopathy. Unlike in mammals, lost retinal photoreceptors are restored through a unique regenerative response. In the EU-funded project SWIMMOT, advanced nanoparticle-based contrast agents are being developed for high resolution *in vivo* imaging, which will be validated for biomedical relevance using our zebrafish disease models.

>> Research Grants

FWF P27338, FWF P30038, FWF P31883, EU H2020 Research and Innovation Programme, No. 899612 (SWIMMOT Project), EU H2020 Doctoral Programme “ARDRE - Ageing, Regeneration, and Drug Research”

>> Coworkers

Robin Kimmel, Pia Aanstad (Assistant Prof.); Patrick Fischer, Nicole Schmitner (Postdoc); Julia Freudenblum, Réka Lorincz, Dominik Regele, Philipp Tschaikner, Marc Sathianathan, Onur Temocin, Melanie Zott, Rosalie Dittrich (Ph.D. Students); Bernhard Röhrs, Nicole Kranebitter, Andrea Walcher, Sarah Berger, Fabian Rabensteiner (Master Students); Sonja Töchterle, Thomas Walder, Dzenana Tufegdzic (Technician)

Synthesis, structure, and function of non-coding RNAs

Ronald Micura

>> Department of Organic Chemistry

>> Goal: To obtain an integrated understanding of RNA modification and RNA mediated regulation and catalysis.

>> Background: For many years it was believed that there were only a small number of non-protein-coding RNAs (ncRNAs) and that they (tRNAs, rRNAs, spliceosomal RNAs) were involved primarily in assembling the predominant protein macromolecules. Even large RNA classes, such as snoRNAs and microRNAs, remained undetected. In recent years, it became apparent that ncRNAs are numerous and that their cellular functions – on their own or in complex with proteins – are diverse and important. Our lab aims at a comprehensive molecular understanding of cellular processes involving ncRNAs, in particular of gene regulation by riboswitches but also of traditional ncRNAs such as encountered during ribosomal translation. Our lab has a major focus on the *chemical synthesis of RNA* allowing the introduction of site-specific modifications, naturally occurring and artificial ones. This enables us to evaluate their structure and function by a great diversity of chemical and biophysical methods, with a focus on chemical and biochemical probing techniques, fluorescence spectroscopy (including single molecule imaging), NMR spectroscopy, and X-ray crystallography.

>> Research Highlights and Outlook: Methylation is a prevalent post-transcriptional modification encountered in coding and non-coding RNA. For RNA methylation, cells use methyltransferases and small organic substances as methyl-group donors, such as *S*-adenosylmethionine (SAM). SAM and other nucleotide-derived cofactors are viewed as evolutionary leftovers from an RNA world, in which riboswitches have regulated, and ribozymes have catalyzed essential metabolic reactions. To this end, we have disclosed the thus far unrecognized direct link between a present-day riboswitch and its inherent reactivity for site-specific methylation. The key is O^6-methyl pre-queuosine (m^6preQ_1), a potentially prebiotic nucleobase which is recognized by the native aptamer of a $preQ_1$ class I riboswitch. Upon binding, the transfer of the ligand's methyl group to a specific cytidine occurs, installing 3-methylcytidine (m^3C) in the RNA pocket under release of pre-queuosine ($preQ_1$). Our finding suggests that nucleic acid-mediated methylation is an ancient mechanism that has offered an early path for RNA epigenetics prior to the evolution of protein methyltransferases. Furthermore, our findings may pave the way for the development of riboswitch-descending methylation tools based on rational design as a powerful alternative to in vitro selection approaches.

Figure 1: RNA-catalyzed methylation – a direct link between riboswitches and ribozymes (Flemmich *et al., Nat. Commun.* 2021, 3877)

Another aim of our lab is to understand the functional roles of RNA in the cell. Consequently, it is essential to elucidate the dynamics of their production, processing and decay. A recent method for assessing mRNA dynamics is metabolic labeling with 4-thiouridine (4sU), followed by thio-selective attachment of affinity tags. Detection of labeled transcripts by affinity purification and hybridization to microarrays or by deep sequencing then reveals RNA expression levels. Our own efforts focused on the development of a novel sequencing method (TUC-seq, TUC-seq DUAL) that eliminates affinity purification and allows for direct assessment of 4sU-labeled RNA. It employs an OsO_4-mediated transformation to convert 4sU into cytosine. We exemplified the utility of the new method for verification of endogenous 4sU in tRNAs and for the detection of pulse-labeled mRNA of seven selected genes in mammalian cells to determine the relative abundance of the new transcripts. The results prove TUC-seq as a straight-forward and highly versatile method for studies of cellular RNA dynamics.

Finally, the continuous development of synthetic methods for efficient access to chemically modified RNA with novel functional properties is in the center of our research interests.

>> Research Grants

FWF (P27947, P31691, SFB RNA-Deco F8011, M2519), FFG (858017 – West-Austrian BioNMR), WWTF (LS17-003)

>> Coworkers

Karolina Bartosik, Olga Krasheninina, Jennifer Gebetsberger (postdoc); Catherina Gasser, Elisabeth Fuchs, Elisabeth Mairhofer, Christoph Falschlunger, Eva Neuner, Josef Leiter, Maximilian Himmelstoß, Sarah Moreno (née Klotz), Stefan Mair, Laurin Flemmich, Michaela Egger, Raphael Bereiter, Julia Thaler (Ph.D.); Daniel Fellner (technician)

Cell physiology and gene regulation

Bernd Pelster, Adolf Sandbichler, and Thorsten Schwerte

>> Department of Zoology

>> Goal: Our research aims at the analysis of molecular and structural mechanisms as well as genetic control pathways of physiological phenomena.

>> Background: The adaptation of animals to changing environmental conditions includes adaptations at the cellular and molecular level in order to maintain homeostasis of energy metabolism, ion regulation and acid base balance. Changing oxygen partial pressures, variable light regimes or temperatures, for example, are readily perceived by animals of different developmental stage. In our work we focus on the large-scale changes in the overall gene expression patterns induced by these environmental perturbations, typically resulting in characteristic modifications in metabolic defense reactions, activity patterns, oxygen transport capacities and overall metabolic or ion regulatory activity. Of particular interest are the control mechanisms guiding these expression changes at the transcriptional and translational level. The sophisticated interconnection and interaction between the different regulatory pathways is addressed using appropriate invertebrate and vertebrate model animals. The data, obtained at the molecular, cellular and organismic level, are discussed with respect to the possible adaptational benefit for the whole organism.

>> Research Highlights and Outlook: Half of the world's population is currently at risk of infection with mosquito-borne diseases. The spread of diseases is becoming a more important issue due to the invasion of tropical mosquitoes caused by climate change. Nevertheless, not only invasive species of mosquitoes pose a threat to human health, but also native mosquitoes become more harmful due to their ability to spread introduced pathogens. In order to gain a better understanding of the physiology of the native, widespread mosquito species of the *Culex pipiens* complex, we focus on *Culex pipiens pipiens*, one of the most common mosquito species in Tyrol, and their highly specialized biotype *molestus* adapted to our lifestyle. Hybrids of these two biotypes, which are spreading in Austria, are dangerous bridge vectors which transmit. In 2020 *Aedes albopicus* was shown to be surprisingly early present in Tyrol.

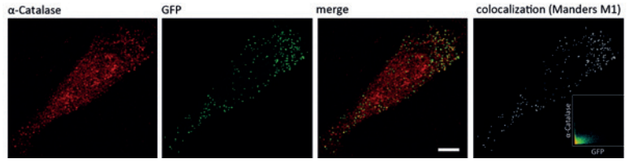


Figure 1: Immunohistochemistry of α-catalase and PTS1-tagged GFP sensors colocalizes in peroxisomes according to the Manders M1 correlation coefficient (Huygens software suite, SVI Imaging BV). The histogram insert shows exclusive α-catalase reactivity as well as reactivity colocalized with PTS1-tagged GFP signal (scale bar: 5 µm).

Figure 2: Aedes albopictus (Stegomyia albopicta), Asian tiger mosquito, native to the tropical and subtropical forest area of Southern east Asia, spread to many countries, including Austria, through the transport of goods and international travel, characterized by black-and-white-striped legs and body.

In our research focusing on cellular redox balance and hypoxia stress response we established the use of new and improved organelle-specific fluorescent protein sensors. These sensors in combination with state-of-the-art microfluidic live-cell imaging setups with full environmental control and semi-automated image acquisition enable us to measure the redox balance in different cellular organelles (e.g. peroxisomes) and their contribution to whole cell redox equilibrium. The cell physiological consequences of redox alterations and their effect on cellular oxygen consumption and glycolytic metabolism are being addressed.

We incorporate advanced image analysis with machine learning algorithms into our data extraction routines. With these new tools we can address changes in cellular and organellar morphology at high temporal and spatial resolution in long-term time-lapse live cell imagery.

An UPLC/MS system at the Institute of Zoology allows analysis of metabolite consumption and fate in cell culture and tissue samples exposed to diverse physiological drivers. This type of measurement expands and complements our expertise in the field of metabolic analysis in the Metabolic Analysis Cluster Innsbruck (MACI) in partnership with the Institute of Aging Research (IBA) and other CMBI partners.

Using the swimbladder as an air-breathing organ is connected to a whole set of physiological adaptations, including a shift of ion uptake from the gills to other organs including the gut. An extraordinary capacity to remove ions from the urine as detected in *Arapaima gigas* may also support ion homeostasis. The ROS defense capacity of tissues exposed to air is significantly improved. A swimbladder used as an air-breathing organ cannot be used as an efficient organ for buoyancy control.

During the spawning migration the European eel is exposed to extreme hydrostatic pressures. Continuous exercise in a swim tunnel revealed that oxygen consumption is not only temperature dependent, but also affected by hydrostatic pressure. An elevated gas impermeability of the swimbladder wall is achieved by guanine incrustation and elevated cholesterol concentrations, while CO_2 permeability and CO_2 diffusion into the bladder is supported by the presence of aquaporin 1, known to act as a CO_2 channel.

>> Research Grants

FWF I2984-B25; §27 Projekt DB-Nr: 215529; Interreg Projekt ALFFA ITAT 1041; INCT ADAPTA – CNPq (465540/2014-7)/FAPEAM (062.1187/2017)/CAPES (finance code 001) (Brasilien); TWF F.16954/5-2019; Förderung des Vizerektorats für Forschung Nr.: 235916)

>> Coworkers

Birgit Fiechtner, Bettina Peer (Technicians); Gabriel Schneebauer, Sigrid Zobl (PostDocs); Victoria Drechsel (PhD Student, PostDoc); Stefanie Jäger (PhD student)

Targeted proteolysis: from molecular mechanisms in human diseases to biotechnological applications

Rainer Schneider

>> Department of Biochemistry, Biotech-group

>> Goal: We are studying targeted proteolysis in a wide range of aspects from the human ubiquitin system to specific directed evolution of proteases for the development and production of drugs to treat human diseases.

>> Background: One of our main research fields covers the structure and functions of the MID1 protein complex, an important player in the regulation of phosphorylation and translational control. The ubiquitin ligase MID1 targets the catalytic subunit of Protein Phosphatase 2A (PP2A) for proteolytic degradation via the proteasome complex. Lack of human MID1 causes Opitz syndrome (midline defect with cognitive impairment). Furthermore, with PP2A as a target, the ubiquitin ligase MID1 has an impact on kinase signaling, alterations of which are involved in cancer as well as several intellectual disability and epilepsy syndromes with disturbances in the local protein homeostasis in hippocampal synapses (1). However, specific cleavages by proteolytic enzymes also play important roles as tools in biotechnology to improve the industrial production of biogenic drugs and especially proteases from viruses are drug targets themselves for which potent therapeutic inhibitors are developed (HIV or SARS-CoV-2).

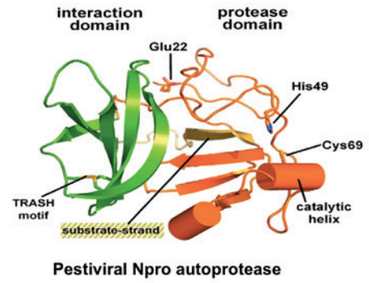


Figure 1: Structure of a pestiviral autoprotease that was developed as a self-cleaving fusion tag.

>> Research Grants

FWF-AKUT: I 5406, FFG-ACIB(K2) P94.081 (Company Project), FFG-ACIB P91.121 and COVISID (Strategic Projects), PRICE and UIBK-funding

>> Staff

Rainer Schneider (Project leader), Christina Kröß (PostDoc), Kamil Rolski, Alexander Mödlhammer, Kevin Vincze, Michael Schäfer, Bernhard Sprenger (PhD students), Magdalena Baier (diploma student)

>> Research Highlights and Outlook: With our research on human disease- and drug-mechanisms as well as on biotechnological innovations we achieved several major goals:

a) We found a potential anti prostate cancer drug that ablates the translation enhancing effect of MID1 on the CAG-repeat containing androgen-receptor mRNA, namely Metformin. In a follow-up study together with S. Krauss at the DZNE in Bonn and S. Schweiger in Mainz, we recently also identified resveratrol and EGCG as potential modulators. During studies on another polyphenol, namely Curcumin, we discovered specific crosslinking as a novel mechanism, how this ancient drug can exert its known pleiotropic functions against diseases like inflammation and cancer (6).

b) Together with an EU-consortium (ERANET NEURON) including groups from Milan, Berlin and Mainz we are studying several syndromes that are associated with altered MID1/mTOR signaling and present with epilepsy and/or intellectual disabilities. Presently, we use proteomics and RNomics to elucidate alterations in hippocampal synaptosomes from a TSC2 mouse model.

c) Under the framework of the Austrian Center of Industrial Biotechnology (ACIB) we are working successfully on several projects (strategic projects and company projects) in which we are developing novel biotechnological tools for up/downstream processing in biopharmaceutical productions (3 patents pending) and diagnostic as well as therapeutic approaches against SARS-CoV-2 (patent pending). Based on structure-function studies and sophisticated in-vivo bioengineering using bacterial selection systems we, together with partners from acib and BOKU in Vienna, develop novel protease-tools (Fig. 1) tailored for industrial platform processes (4,5,7,8,9). Novel in-silico supported designs of related selection systems pave the way to develop and monitor drugs to combat cancer and viral diseases as well as to profile respective drug resistances (2,3).

Development of opioid ligands with target-oriented activities

Mariana Spetea

>> Department of Pharmacy, Pharmaceutical Chemistry Section

>> Goal: To perform basic and applied research in medicinal chemistry and pharmacology of the opioid system with innovative ligands targeting the opioid receptors and new mechanism-based treatment strategies for human diseases.

>> Background: Around 20-30% of all people worldwide suffer from chronic pain, and pain is more prevalent than either heart diseases or cancer. Opioids are the mainstay in the management of moderate to severe acute and chronic pain, and remain the most efficacious analgesics currently available. Opioid receptors, mu (MOR), delta (DOR), kappa (KOR) and nociceptin (NOP), as G protein-coupled receptors (GPCRs), are molecular targets for opioid ligands, and modulate pain pathways in the central and peripheral nervous systems (CNS and PNS). Besides the beneficial analgesia, opioids also produce unwanted side effects. Medical use and misuse of opioids have significantly increased in the last decades, leading to an opioid epidemic worldwide. Development of effective and safer analgesics represents a key research goal for the 21st century analgesic drug discovery and pain medicine. Diverse strategies are evaluated to mitigate the deleterious effects of opioids, including G protein-biased opioid agonists, multifunctional drugs with mixed opioid and non-opioid activities and peripherally restricted opioid agonists.

>> Research Highlights and Outlook: Central directions of our projects include modulation of ligand/opioid receptor interactions, structure-activity relationships (SAR), understanding the mechanism of opioid actions and the link between therapeutic effects (i.e. analgesia), side effects and molecular mode of action. The specific research goals include drug design and synthesis, pharmacological characterization and SAR studies of ligands with distinct functional activities (agonism/partial agonism/antagonism, biased agonism), multifunctional ligands (acting at opioid/opioid and opioid/non-opioid receptors), and ligands with a selective site of action (central/peripheral). Our drug development strategies address structurally-diverse ligands (natural, naturally-derived and synthetic compounds; small molecules and peptides), and comprise screening of binding and signaling profiles at the opioid receptors together with mechanistic studies.
Highlights of our recent projects include: (a) discovery that the introduction of a 14-*O*-phenylpropyl group in 14-*O*-methyloxymorphone turns a selective MOR ligand into a mixed MOR/DOR/KOR agonist (POMO), having an extraordinary antinociceptive potency and reduced propensity for constipation in mice (Figure 1A) - (b) an extensive SAR study on a library of differently substituted *N*-methyl-14-*O*-methylmorphinans with natural and unnatural amino acids and dipeptides at C6 position, which emerged as potent MOR/DOR agonists producing effective antinociception via activation of peripheral opioid receptors. It is expected that such opioid agonists that are not able to enter the CNS would have a favorable side effect profile by lacking the centrally-mediated side effects (Figure 1A) - (c) multitarget peptidomimetic ligands: (c1) combination of a potent MOR agonist activity with an antagonist activity at the neuropeptide FF receptors (NPFF1R and NPFF2R); KGFF09 was identified a G protein-biased MOR agonist with a NPFFRs antagonist profile, merging the beneficial effects of biased MOR agonists on acute side effects (respiratory depression) and those of NPFFRs antagonists on chronic side effects (opioid-induced hyperalgesia, tolerance, withdrawal syndrome) (Figure 1B), and (c2) optimized opioid-neurotensin hybrid peptides showing the highest affinity and excellent selectivity to the neurotensin 2 (NTS2) receptor described to date, together with a significant and prolonged antinociception in mice - (d) development of peptide-based hydrogels as extended release delivery carriers of opioid peptides in view of the central goal in chronic pain control to provide analgesia of adequate efficacy and duration; strategies with drug-hydrogelator coformulation or a conjugate showed sustained antinociception up to 72 hours in mice; such systems have several advantages including protection of the drug against enzymatic degradation by encapsulation in the hydrogel network, lower dosage and frequency of administration with improvement of the drug efficacy, while reducing the risk of side effects (Figure 1B) - (e) high-throughput phosphoproteomics effectively employed to investigate signaling induced *in vivo* by the KOR as a GPCR model, and structurally-diverse agonists in the mouse brain; HS666, as a non-aversive KOR agonist, elicited differential dynamic phosphorylation of synaptic proteins as compared to aversive agonists; a new mechanism of drug action was discovered with inhibition of the mechanistic target of the mTOR (mechanistic target of rapamycin) pathway during the KOR activation eliminating aversion while preserving beneficial antinociceptive effects (Figure 1C). Overall, the new scientific solutions and knowledge with recognizable innovative potential were generated through strong alliances of our research group and other scientists, where multidisciplinary, synergistic approaches ranging from molecular *in silico* and *in vitro* levels to *in vivo* systems, were combined by linking bioinformatics with biochemical, pharmacological and disease animal models.

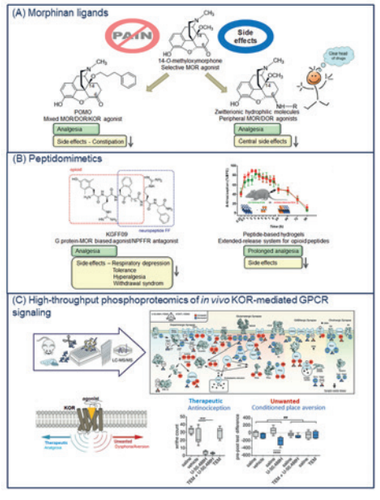


Figure1: Strategies for discovery of effective and safer analgesics with target-directed activities. (A) Development of morphinan opioid ligands with mixed MOR/DOR/KOR agonism and reduced side effects, and peripherally restricted MOR/DOR agonists; (B) Development of peptide-based analgesics combining MOR agonism and NPFFR antagonism, and peptide-based hydrogels as extended release delivery carriers of opioid peptides; (C) High-throughput phosphoproteomics of *in vivo* KOR-mediated GPCR signaling and a new mechanism of opioid drug action via inhibition of the mTOR pathway.

>> Research Grants

FWF I2463 (with FWO, lead agency: FWF), FWF I2697 (with DFG, lead agency: FWF), FWF P30430, FWF P30592; LFUI Nachwuchsförderung

>> Coworkers

Helmut Schmidhammer (Prof.); Sandro Neuner (postdoc); Maria Dumitrascuta, Filippo Erli, Aina-Leonor Olive Marti, Maria Guastadisegni (Ph.D. students); Annalisa Blasiol, Barbara Brunner, Roman Kainhofer, Linda Kunze, Stevany Louis, Dominic Jawer Pirchner, Elisabeth Pramstaller, Nevin Sertkaya (Diploma/Master students)

Signal transduction in cellular growth control and carcinogenesis

Eduard Stefan and Markus Hartl

>> Department of Biochemistry

>> Goal: We are interested in deciphering and perturbing cellular signaling nodes and networks which emanate from oncogenic kinases (=oncokinase) and critically controlled transcription units.

>> Background: Our research teams seek to decode basic principles of decontrolled signal transmission which emanate from signaling hubs such as receptors, kinases, and transcription factors. At the systems levels, we explore the relay of the oncogenic input signal (i) by rewiring metabolic fluxes, (ii) by characterization of pivotal molecular interactions, and (iii) by deciphering compartmentalized kinase complexes. This requires the implementation and development of OMICs technologies and the advancement of protein-centred biotechnology approaches to decipher the *modus operandi* of oncoprotein functions.

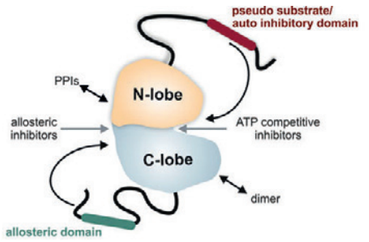


Figure 1. **Kinase dynamics.** Shown is a hypothetical full-length kinase with cis regulatory motifs. The N and C lobes of the kinase core are centered. Different types of intra- and intermolecular interactions affect kinase activities and/or conformations (Enzler *et al.* 2020).

>> Research Highlights and Outlook: The discovery that carcinogenesis depends on kinase mutations have promoted the targeted inhibition of critical players of this enzyme class. Thus, a collection of protein kinases have become major drug targets for oncology. One of the best studied oncogenic signaling cascade is the RAS-RAF-MEK-ERK (=MAP kinase) pathway. Oncogenic BRAF mutations unleash the auto-inhibited kinase conformation and promote RAS-independent proliferative and oncogenic MAP kinase signaling. We have recently implemented a cell-based technology to determine the effects of clinically approved BRAF and MEK inhibitors (BRAFi, MEKi) or lead molecules on full-length RAF/MEK conformations and interactions *in vivo* (EU and US patent). In systematic analyses of drug:kinase interactions we unveiled that FDA-approved BRAFi (Vemurafenib, Dabrafenib) engagements with the catalytic pocket of V600E-mutated BRAF stabilized an inactive and intermediate kinase conformation. This previously unappreciated allosteric effect of drug-driven intramolecular communication between the RAS-binding and mutated kinase domains of BRAF provokes the enhancement of binary RAS:RAF interactions, which happens also independently of RAF dimerization. We assume that this allosteric drug-effect on mutated BRAF interactions may further promote paradoxical downstream activation and drug resistance mechanisms (*Sci. Adv.* 2019, *PNAS* 2020*, Biomolecules* 2021). Besides deciphering orphan receptor functions (*Development* 2021) we participated in additional kinase projects (*EMBO J* 2021, *Sci. Signal.* 2021). Further, we contributed to discoveries how the ubiquitin proteasome complexes functionally interact with distinct kinase complexes and pathways (*Nat. Commun.* 2018, *Nat. Commun.* 2019).

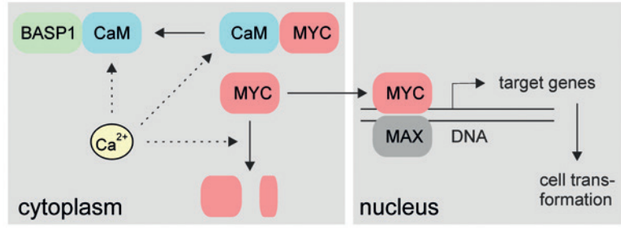


Figure 2. **MYC interactions.** Diagram showing the proposed mechanism of MYC inhibition by BASP1 competing for binding to calmodulin (CaM). CaM binding to BASP1 or to MYC is Ca^{2+}-dependent. Mitogenic signaling, amplification, translocation, or retroviral transduction lead to *MYC* hyperactivation and deregulation of transcriptional targets including downregulation of the tumor suppressor *BASP1*.

The *MYC* gene encodes the oncogenic transcription factor MYC, an evolutionarily conserved cancer driver whose overexpression represents a hallmark of most human tumors. We have shown that the presence of excess BASP1 protein leads to displacement of viral MYC (v-Myc) from calmodulin (CaM). BASP1 is a small signalling protein downregulated in MYC-dependent tumor cells. Disrupting the MYC:CaM interaction leads to decreased MYC stability accounting for the observed MYC inhibition. This suppression of MYC-induced transcriptional activation and cell transformation is compensated by ectopic CaM, suggesting that BASP1-mediated sequestration of CaM from MYC is a crucial event. In view of the tumor-suppressive role of BASP1, small compounds or peptides based on the BASP1 effector domain could be used in drug development strategies aimed at tumors with high MYC expression (*Mol. Oncol.* 2020, *FEBS J.* 2019). Concerning other interference possibilities with oncogenic MYC functions, we further found that the diarylheptanoid curcumin inhibits MYC-dependent cell transformation and transcriptional activation. Thereby the endogenous human MYC protein is specifically cross-linked to the transformation/transcription domain associated protein (TRRAP), a transcriptional coactivator. With regard to the broad impact of MYC in cancer, our findings contribute to explain the pleiotropic functions of curcumin, and suggest that this natural spice may constitute a useful adjuvant in the therapy of MYC-dependent human tumors (*Front. Oncol*. 2021).

>> Research Grants

Austrian Science Fund: P35159 (2021-2024), P33662 (2020-2024), P32960 (2020-2023), P30441 (2018-2021), P27606 (2015-2018), I5406 (2021-2024, UIBK co-applicant)

FFG: FFG Bridge 'MitoKin' (2020-2023), FFG Spin-off Fellowship (2019-2021), **H2020** - RISE (2020-2024)

>> Coworkers

O. Torres-Quesada, P. Tschaikner (Postdoc); F. Enzler, A. Feichtner, P. Tschaikner, J. Mayrhofer, R. Röck, S. Schwaighofer, V. Kugler, S. Lechner, J. Fleischmann, G. Zegg, P. Schöpf, D. Demmel, N. Ayhan, A. Geng, F. Eichner, T. Nuener, S. Atzl, A. Fritz, S. Strich (Master and Ph.D. students)

Cell signaling in chronic CNS disorders

Nicolas Singewald and Jörg Striessnig

>> Department of Pharmacy, Pharmacology and Toxicology Section

The pathophysiological processes underlying neuropsychiatric and neurological diseases are not well understood. The major research areas of our research groups within the CMBI are to study signaling events altered in common disorders (in particular anxiety and stress/trauma-related) as well as rare congenital disorders (neurodevelopmental syndromes including autism and epilepsy). Most of this work was embedded in the FWF-funded Spezialforschungsbereich SFB F44 "Cell signaling in chronic CNS disorders" which has been extended for a second four year funding period until September 2019. Moreover our groups were also participating in the FWF-funded doctoral programs Molecular Cell Biology and Oncology (MCBO, 2005-2018), Signal Processing in Neurons (SPIN, 2007-2021) and CavX (doc.funds: Calcium Channels in Excitable Cells) as well as the EU-cofunded interdisciplinary PhD training programme ARDRE.

Neuropharmacology group (N. Singewald)

>> Goal: A considerable part of anxiety and PTSD patients remains treatment-resistant to current therapeutic strategies and drugs, which are mainly antidepressants and benzodiazepines. Our main aim is therefore exploring novel drug targets to effectively attenuate pathological anxiety and to boost and normalize impaired fear-inhibitory learning (extinction learning), which is a common deficit observed in human anxiety disorders and attenuates treatment success.

>> Background: We study such potential mechanisms in clinically relevant animal models of pathological anxiety (hyperanxiety HAB mice) showing signs of treatment resistance and the S1 mouse model of impaired fear extinction by using a range of behavioral, neurochemical and neurobiological methods. Translation of findings to humans is a particular important recent aim, which we pursue in collaborative efforts.

>> Research Highlights and Outlook: In the S1 model of impaired fear extinction we have successfully identified underlying key neurobiological mechanisms and affected neurocircuitries, currently also by applying optogenetics and in-vivo electrophysiology, which we established in the last two years. The select manipulation of the identified systems by using for example histone deacetylation inhibitors (HDACi), microRNA down-regulation, or enhancing dopaminergic signaling (with drugs such as L-DOPA, DAT inhibitors or indirectly via the ghrelin system), revealed new ways of facilitating impaired fear extinction learning and improving protection from fear relapse. The dopaminergic effect of boosting extinction learning could be confirmed in a collaborative human study. In our HAB mouse model of pathological anxiety, we revealed new therapeutically successful interventions targeting systems different to those of established medications, including anti-neuroinflammatory or epigenetic (HDACi) drugs. Respective biomarker studies involving histone-acetylation patterns and inflammation signatures in anxiety patients are under way to identify individuals likely benefitting most from such approaches. We also identified a strong attenuation of hyperanxiety in HABs by beneficial environmental influences, which was correlated with reduced neuroinflammation in the brain. Finally, in collaborative human studies with the Neuroradiology Department of the Medical University Innsbruck, we could show anxiolytic effects, as well as evidence of changes in brain neuroplasticity and metabolism/energy consumption following (already only 7 weeks of) meditation training of the participants.

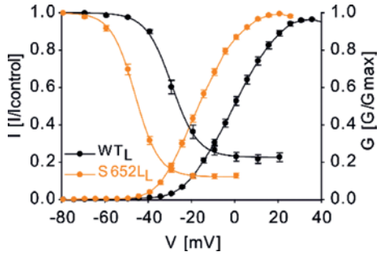


Figure: Characteristic changes of Cav1.3 channel function induced by disease-causing Cav1.3 (CACNA1D missense mutations: S652L has been identified in two patients with a severe neurodevelopmental syndrome. Electrophysiological analysis demonstrates both pronounced shifts of both the voltage-range for activation (normalized conductance, G) and inactivation (as normalized current, I). Depending on neuronal firing patterns this enables more Ca^{2+} ion entry through the channel (Hofer *et al.* 2019).

Molecular Pharmacology group (J. Striessnig)

>> Goal: Understand the function, regulation and disease potential of voltage gated Ca^{2+} channels (Cavs) in human disease.

>> Background: VGCCs are key regulators of activity-dependent Ca^{2+} influx into all electrically excitable cells. The fine tuning of these signals is essential for normal cell function. In neurons both reduced and excessive Cav signalling can cause human disease. A major focus of our work is on the Cav1.3-subtype (*CACNA1D* gene), because rare de novo missense mutations in humans provide exciting new insight into the function and pathophysiology of these channels.

>> Research Highlights and Outlook: Our major recent focus is on the Cav1.3-subtype (*CACNA1D* gene), because rare *de novo* missense mutations in humans provide exciting new insight into the function and pathophysiology of these channels. Systematic analysis of a number of these mutations now provides compelling evidence that they introduce unique functional changes of the channel, which induces a hyperactive state. Moreover, the clinical history of eight affected individuals (7 different mutations) revealed a clinical disease spectrum with most of the patients being affected by a severe neurodevelopmental disorder, including autism, intellectual disability, hyperactivity and in some cases also congenital seizures and endocrine dysfunctions. Since these mutations typically cause a gain of channel function this provides us with the unique opportunity to test if already existing drugs in clinical use (as antihypertensives) can improve disease symptoms (e.g. reduce abnormal behaviors or seizures) in these patients. For this purpose we have meanwhile successfully introduced one of these mutations into a mouse model which can be used to address this question and to identify aberrant signaling pathways induced by these variants. In addition we described a novel regulatory mechanism of these channels and identified another subtype (Cav2.3) as a potential central player in the pathophysiology of Parkinsons' disease.

>> Research Grants

FWF SFB-F4401, FWF SFB-F4402, FWF SFB-F4410, FWF DOC30 doc.fund, FWF W1101, FWF W1206, FWF P27809, FWF I2433, Tiroler Wissenschaftsförderung (TWF) 740036, 740044,
Univ. of Innsbruck (FLD #242170, #194449, #217264, #214976), County of Tyrol (FLD #225100, #152787), FWF P27852, FWF P28146, FWF I02215, FWF DACH: I3875-B26, FWF I2433-B26

>> Coworkers

Petronel Tuluc, Nadja Hofer, Nadine J. Ortner, Karl Ebner, Maria Kharitonova, Simone B. Sartori, Anupam Sah, Conor Murphy, Thomas Keil, Veronica Fontebasso, Sinead Rooney, Anita Siller, Eva Maria Fritz, Yuliia Nikonishyna, Ferenc Török, Ludovica Filippini

Pharmacognosy – unveiling some of nature's treasures

Markus Ganzera and Hermann Stuppner

>> Department of Pharmacy, Pharmacognosy Section

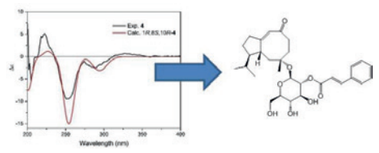


Figure 1: Determination of absolute configuration of polyanthoside D based on ECD calculations. Nguyen Ngoc, H., Alilou, A., Stonig, M., Nghiem, D.C., Kim, L.T., Gostner, J.M., Stuppner, H., Ganzera, M., *J. Nat. Prod.* 2019, **82**, 2941-2952, *doi:* 10.1021/acs.jnatprod.9b00208

>> Goal: To better understand the traditional use of (mainly) medicinal plants based on the occurrence of particular metabolites and their bioactivity, as well as to search for overall new natural compounds, which could serve as lead structures for the development of pharmaceuticals.

>> Background: Working with natural products is challenging because of their enormous chemical diversity and usually low abundance, at the same time it is also promising as they represent a largely untapped source for new drugs and leads. In its modern form Pharmacognosy covers several interdisciplinary aspects, including the isolation and structural elucidation of natural products (new structures), their analysis in diverse matrices like crude drugs, commercial products or biological samples (quality control and metabolism), as well as the search for bioactivity (pharmacological properties). The influence of environmental factors on their production is another interesting topic. Thanks to the state-of-the-art infrastructure available (LC-MS, GC-MS, CE-MS, LC-NMR, SFC-MS, 3D-databases for *in-silico* screening, etc.) and a well-balanced mixture of experienced staff scientists and motivated PhD students, the Institute of Pharmacy / Pharmacognosy has established an internationally recognized and leading position in all the fields mentioned above.

>> Research Highlights and Outlook: The work on *Fissistigma polyanthoides*, a medicinal plant from Vietnam, resulted in the isolation of sixteen new terpenoids. Besides using NMR and MS, their structure and stereochemistry were confirmed by innovative approaches like ECD- (Fig. 1) and NMR-calculations. Further phytochemical studies focused on the isolation of novel natural products from plants from Iran (*Ferula hezarlalehzarica*, *Rydingia persica*, *Dionysia diapensifolia*) and Angola (*Thonningia sanguinea)*.

An FWF funded project studied bioactive constituents in marine algae, and particularly for the group of MAAs (mycosporine like amino acids) several new findings were published (novel MAAs from *Bostrychia scorpioides*, their anti-aging / wound healing effects, etc.). In another FWF project the ecological function and pharmacological potential of mushroom pigments are studied in respect to their photocytotoxicity. One photosensitizer isolated from the fruiting bodies of *Dermocyboid cortinarii* is highly interesting as it is not active against a lung cancer cell line in the dark, but highly active under blue light irradiation (EC_{50} = 50 nM). A systematic screening of approx. 50 mushroom species covering all major biosynthetic pigment-pathways is in process.

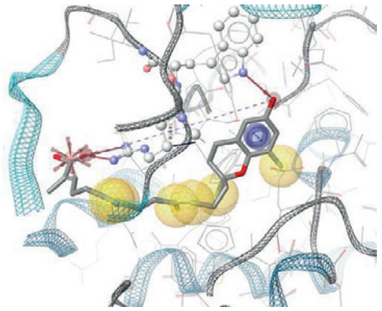


Figure 2: Binding mode of natural vitamin E metabolite garcinoic acid in 5-lipoxygenase.

Several Euregio-projects were conducted. "ExPoApple 2", investigating the pharmacological potential of apple dihydrochalcones, resulted in interesting insights in the interaction of tyrosinase and plant metabolites, as well as the discovery of a plant-derived dihydrochalcone as potential prostate cancer lead. "Vitisana" aimed to improve acceptance of mildew resistant *Vitis vinifera* varieties by decoupling negative quality traits from resistance traits. Dozens of novel breeds were fully characterized by LC-, GC-MS and NMR based profiling approaches in the harvests of two consecutive years. "HERBAL" focusses on the potential of alpine herbs as alternative anthelmintic treatment of livestock (chickens). To support our collaboration partners a *Caenorhabditis elegans* assay was established within the CMBI network. This model is very promising because the target of anthelmintics, ß-tubulin, is nearly identical to that of *Ascaridia galli*, the main parasite in chickens.

Within the project "New ways to counter inflammation - Computer aided discovery of multi-target anti-inflammatory natural products" ligands of natural and synthetic origin were investigated with computational methods for their effect on the arachidonic acid cascade. Main focus were natural vitamin E derivatives targeting 5-lipoxygenase (Fig. 2) and microsomal prostaglandine E synthase (mPGES) 1, as well as synthetic derivatives of diflapolin, a dual inhibitor of the 5-lipoxygenase activating protein and soluble epoxide hydrolase.

It is well known that diet strongly affects our health. Within the FFG funded K-project "VASCage" numerous fermented dairy products were successfully studied for their content of antihypertensive acting peptides by LC-MS/MS.

>> Research Grants

FWF P269170, FWF P293050, FWF P296710, FWF FP319150, FWF ZFT009420, FFG Alpine Kosmezeutika P7400-012-048, FFG VASCage P7400-012-047, BMWF P7400-012-052, EU H2020-MSCA-RISE - MediHealth P7400-012-049, EU-Horizon 2020 P1972-013-012, EUREGIO ZFIPN000550, EUREGIO ZFIPN000310, EUREGIO ZFIPN001190, TWF ZAP740041

>> Coworkers

Stefan Schwaiger, Sonja Sturm, Birgit Waltenberger (research associates); Mostafa Alilou, Anja Francois, Solveigh Koeberle, Caroline Linhart, Javad Mottaghipisheh, Bianka Siewert, Veronika Temml (postdocs); Ana Drmic, Nora Engels, Johannes Fiala, Nora Gibitz-Eisath, Verena Gratl, Fabian Hammerle, Stefanie Hofer, Mark Horgan, Tanja Kittelt, Stefan Loos, Fabian Mayr, Domenic Mittas, Simon Moosmang, Maria Orfanoudaki, Luca Pompermaier, Eduardo Villicana Gonzalez, Michael Zwerger (Ph.D. students)

Metabolic Signaling

Kathrin Thedieck

>> Department of Biochemistry

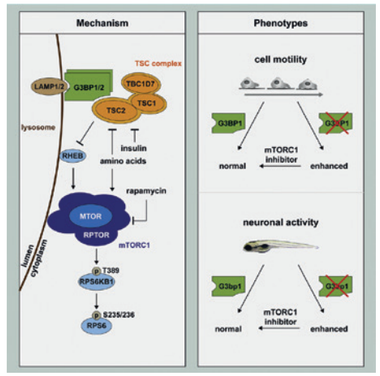


Figure 1: **G3BPs tether the TSC complex to lysosomes and suppress mTORC1 signaling.** Taken from Prentzell *et al.*, *Cell* 2021 PMID: 33497611

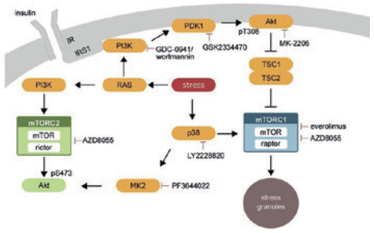


Figure 2: **The stress response of the mTOR network.** Stress activates the RAS-PI3K-PDK1-Akt axis, which in turn activates mTORC1. p38 activates mTORC1, independently of PI3K. Stress signaling to mTORC1 is required for stress granule assembly. Adapted from Heberle and Razquin *et al., LSA* 2019, PMID 30923191.

>> Goal: The Lab for Metabolic Signaling studies the control of metabolic homeostasis through kinase signaling networks converging on the metabolic master regulator mTOR (mammalian / mechanistic target of rapamycin) in health and disease. We adopt biochemistry, cell biology, proteomics, metabolomics and systems modelling approaches.

>> Background: The kinase mTOR is a central controller of metabolism and ageing that resides at the center of a complex signaling and metabolic network. mTOR is dysregulated in most cancers as well as in metabolic, neurodegenerative and congenital disorders, and is therefore of major biomedical interest as a drug target and biomarker. mTOR exists in two structurally and functionally distinct multiprotein complexes, mTOR complex 1 (mTORC1) and mTORC2. In response to growth factors, nutrients, energy and stress, mTORC1 enhances anabolic processes such as translation, and represses catabolic processes such as autophagy. mTORC2 is a central metabolic regulator as well which is for instance involved in lipid and glucose homeostasis.

mTOR controls virtually all metabolic processes at the cellular and organismal level. But how are specific metabolic responses to distinct metabolic inputs achieved? Our lab aims to identify novel mTOR network components and to delineate their interconnection in relation to mTOR's metabolic inputs and outputs. To this end, we analyze the mTOR interactome and ancillary signaling networks including their post-translational modifications (e.g. phosphorylation, methylation, acetylation) and metabolic outcomes. For this purpose, the newly funded mass spectrometry unit at our institute includes targeted, shotgun and fluxomic proteomic and metabolomic methods. To deal with mTOR network complexity, we adopt systems approaches to unravel novel regulatory connections governing mTOR's activity and outputs. We functionally characterize novel regulators and effectors by means of biochemistry and cell biology in *in vitro* and *in vivo* models as well as in human samples. Our *in vitro* models comprise 2D and 3D cultures of non-cancer and cancer cell lines as well as primary cultures and organoid models. *In vivo* analyses are conducted in rodent models and human samples.

Within the frame of the H2020 MESI-STRAT consortium, which we coordinate, our systems studies focus on the interplay of metabolism and signaling to predict relapse of estrogen receptor positive breast cancer patients on endocrine therapy, and to stratify the patients to second line targeted therapies. We also investigate mTOR driven metabolism and signaling in genetic syndromes including tuberous sclerosis complex (TSC), glycogen storage disease (GSD), and ciliopathies, as well as in metabolic diseases and liver cancer. We identify and functionally characterize novel metabolic cues that control mTOR signaling in response to the essential amino acids methionine and tryptophan and energy rich metabolites and consequences on epigenetic, transcription, and translation dynamics; and we dissect the interplay of mTOR with RNA binding proteins in healthy cells and cancer.

K. Thedieck joined the LFUI in January 2019 and became a CMBI member in May 2019. The first year at LFUI was mainly dedicated to establishing our lab at the Institute of Biochemistry, including the setup of a *High Resolution Mass Spectrometry Unit for Proteo-Metabolomics (Head: Ass.-Prof. Dr. M. Kwiatkowski)*, an *Organoid Systems Unit (Head: Dr. J. Ramos Pittol)*, a *Genome Editing Unit (Head. A.o. Prof. M. Hartl)*, a *Life Cell Imaging Unit* (*Head PD Dr. E. Stefan, Dep. Head Dr A. Heberle)* and a *Data Sciences Unit* (*Dr. M. Prugger*). Next to the CMBI colleagues from the Department of Biochemistry (R. Schneider, E. Stefan, M. Hartl), several CMBI groups including the labs of A. Koschak, F. Edenhofer, P. Tuluc, H. Stuppner, T. Müller and A. Koeberle collaborate with our researchers and tech units, and we kindly invite all colleagues to explore possible collaborations.

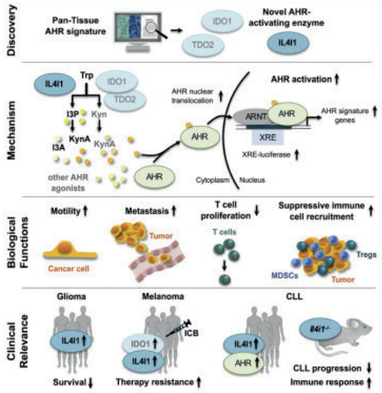


Figure 3: **IL4I1 Is a Metabolic Immune Checkpoint that Activates the AHR and Promotes Tumor Progression.** Taken from Sadik *et al.*, 2020, *Cell*, PMID: 32818467

>> Research Grants

SC1-PM-02-2017 H2020 MESI-STRAT (coordinator), H2020-MSCA-COFUND-2018 ARDRE, EU H2020 ITN PoLiMeR, DFG (TH 1358/3-1), Deutsche TS Stiftung, Stichting TSC Fonds NL, H2020 SwafS-08-2019-2020 VERSA

>> Coworkers

Alexander Heberle (postdoc), Jose Ramos Pittol (senior scientist), Martina Prugger (senior scientist), Marcel Kwiatkowski (assistant professor); technicians: Lea Timpen, Tobias Kipura; PhD students: Ulrike Rehbein (defended. now postdoc), Yang Zhang (defended. now postdoc), Patricia Razquin Navas (defended), Marti Cadena Sandoval, Alienke van Pijkeren, Cecilia Barile, Maria Rodriguez Peiris, Lucas Hensen, Anna-Sophia Egger, Paul Atigbire (joint supervision with John Neidhard, Oldenburg University, DE), Luc-Alban Veuillemot (joint supervision with Andreas Milias, Groningen University, NL), Petra Engele (project manager).

LFUI Guest Professor

Dr. Christiane Opitz (DKFZ, Heidelberg)

>> Research Highlights and Outlook: A major focus of our research was initiated by our discovery that mTOR complex 1 (mTORC1) is regulated by RNA-protein granules (stress granules, SGs) which are built in response to stressors that inhibit translation (Thedieck *et al., Cell* 2013). We recently discovered that the importance of SG proteins in mTOR signaling reaches beyond classical stress conditions. G3BP proteins, widely recognized as SG core components, reside at lysosomes in the absence of stress (Prentzell *et al., Cell* 2021). They anchor the TSC complex – a key mTORC1 suppressor – to lysosomes and suppress activation of mTORC1 by amino acids and insulin. Like the TSC complex, G3BP1 deficiency elicits phenotypes related to mTORC1 hyperactivity.

Not only do SG proteins control mTORC1 acitivity, mTORC1 also controls SG assembly. In a systems approach, we identified PI3K and MAPK/p38 as pro-SG-kinases (Heberle *et al.* 2019). They act in a hierarchical manner to drive mTORC1 activity and SG assembly. This signaling hierarchy is present in human breast cancer tissue, suggesting that PI3K readouts predict sensitivity to p38 inhibitors.

Tryptophan (Trp) metabolism represents a powerful immunosuppressive mechanism hijacked by tumors. Yet, it remains unclear how tumor cells can proliferate while degrading the essential amino acid Trp. With LFUI Guest Professor Dr. Christiane Opitz (DKFZ, Heidelberg) we discovered that levels of the Trp-degrading enzymes IDO1 and TDO2 are associated with the tryptophanyl-tRNA synthestase WARS, likely protecting cancer cells from excessive intracellular Trp depletion. (*Oncoimmunology* 2018). We also contributed to the investigation of Aryl hydrocarbon receptor (AHR) activation by Trp catabolites and helped identify IL4I1 as a new Trp catabolizing enzyme in cancer (*Cell* 2020).

Biomolecular NMR spectroscopy

Martin Tollinger and Christoph Kreutz

>> Department of Organic Chemistry

>> Goal: The experimental characterization of structures, dynamics and function of proteins and (ribo)nucleic acids.

>> Background: Three-dimensional structures of proteins and (ribo) nucleic acids are inherently flexible. These biomolecules adapt a well-defined distribution of states that can include a highly populated "ground state", *i.e.* the single structure that is obtained by standard structure determination protocols such as X-ray crystallography. However, the presence of different and lower populated structures is of key importance for the biological function of these molecules, including ligand recognition and binding, protein and RNA folding and stability, and enzymatic catalysis. In our group we analyze the structural heterogeneity of proteins and (ribo)nucleic acids at atomic resolution using multidimensional NMR spectroscopy. We determine solution structures and complement these data by flexibility measurements in order to provide a genuine description of how these molecules function.

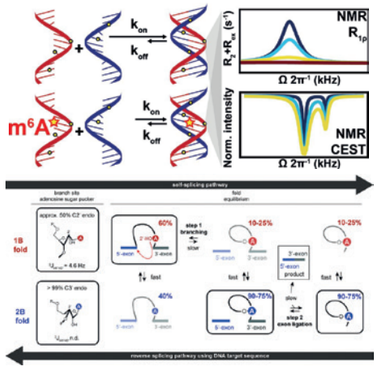


Figure 1. Upper panel: Influence of m^6A on hybridization kinetics. The naturally occurring modification leads to a slower annealing of RNA duplexes (*JACS* 2019, **141**, 19988-19993). Lower panel: A revised catalytic mechanism of the group II Intron: a linked secondary structure and sugar pucker equilibrium is used for the selection of catalytically relevant states (*NAR* 2019, **47**, 11430-11440).

>> Research Highlights and Outlook: Work in the Kreutz group is focused on advancing stable isotope labeling protocols for DNA and RNA. The main research interest lies on the synthesis of $^{13}C/^{15}N/^{2}H$ labeled RNA phosphoramidites and triphosphates that can be used to introduce stable isotope labels into nucleic acids. To this end, chemo-enzymatic syntheses are developed to give high yield, robust and efficient synthetic access to the desired $^{13}C/^{15}N/^{2}H$-labeled compounds. This labeling protocol can be used to apply state-of-the-art NMR experiments, including chemical exchange saturation transfer (CEST), relaxation dispersion (RD) or paramagnetic relaxation enhancement (PRE) measurements. Of special interest are experiments addressing the structure and function of only transiently populated (excited) states. One research focus of our group lies on the determination of high-resolution excited state structures using advanced stable isotope labeling. Another main topic includes the influence of naturally occurring RNA modifications on the folding landscape.

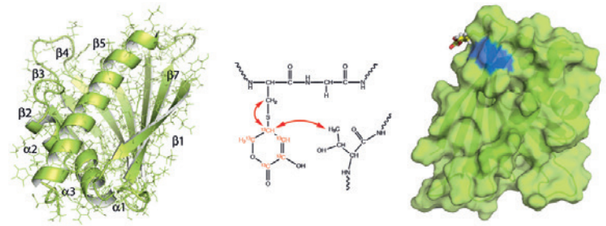


Figure 2. Left: NMR structure of the major apple allergen Mal d 1 from Golden Delicious and Granny Smith apples (*J. Agricult. Food. Chem.* 2017, **65**, 1606-1612). Center: ^{13}C-labeled vitamin C was used to study ascorboylation of Mal d 1 by NMR spectroscopy. Right: In ascorboylated Mal d 1 an IgE epitope (blue) is partially masked.

>> Research Grants

FWF-P26849 (MT), FWF-P28725 (CK), FWF-P30370 (CK), FWF-P30963 (MT), FWF-P32773 (CK), FWF-P31054 (MT), FWF-33953 (MT), FWF-P34370 (CK), FFG-858017 (MT, CK), ERDF-ITAT1013 (MT)

>> Coworkers

L. Ahammer, V. Dietrich, R. Eidelpes, K. Erharter, S. Führer, D. Glänzer, S. Hilber, F. Juen, M. Juen, D. Klingler, J. Kremser, J. Ludescher, F. Nußbaumer, R. Plangger, M. Röck, E. Strebitzer, J. Unterhauser, R. Zeindl, M. Huber (Ph.D. students); A. Marotto, M. Otter, L. Ruetz, M. Knapp (master students)

In the scientific focus of the Tollinger laboratory are allergenic proteins such as Mal d 1, which represents the main cause for allergies to apples. We determined the three-dimensional structure of the apple allergen Mal d 1 and identified various modifications of this protein by NMR and MS. These modifications are caused by naturally occurring constituents of apples such as vitamin C and polyphenols. They affect the immunological behavior of Mal d 1 by reducing its affinity to antibodies (IgE). For the NMR analysis of these modifications, NMR-active spin labels or paramagnetic labels are inserted. Our NMR data also show that the apple allergen Mal d 1 is unfolded apple juice, explaining its low allergenicity. We are currently extending these studies to allergenic proteins from other natural sources, including hazelnuts, kiwis and peaches.

Role of voltage gated calcium channels in endocrine cells

Petronel Tuluc

>> Department of Pharmacy, Pharmacology and Toxicology Section

>> Goal: Our main research goals are to identify the physiological roles of voltage-gated calcium channels (Ca_V) in endocrine cells hormone synthesis and release. Additionally, we work to understand how the Ca_V channel biophysical properties are determined by specific intramolecular interactions or disease-causing mutations.

>> Background: Calcium influx through Ca_V channels is critical for many cell functions like cellular excitability, synaptic neurotransmitter release, muscle contraction, as well as hormone synthesis and release. Additionally, calcium influx is an important regulator of gene transcription, cell differentiation and survival. Therefore, even small alterations in ion channel function or expression lead to severe physiological dysregulation and disease. Ca_V channels are transmembrane protein complexes formed by the pore-forming α_1 subunit and the auxiliary intracellular β, extracellular/transmembrane $\alpha_2\delta$ and the transmembrane γ subunits. Over the years, we and others have shown that the auxiliary subunits determine the Ca_V channel biophysical properties and localisation in many cell types. We have shown that deletion of $\alpha_2\delta$-1 Ca_V channel subunit alters pancreatic β-cell hormone release and induces diabetes in mice in a sex-specific manner.

>> Research Highlights and Outlook: Following on that observation, one project in our lab is to identify the molecular mechanisms leading to sex-specific pancreatic β-cell function and insulin release. We can show that pancreatic β-cells of female mice have a higher glucose-induced electrical activity. The different glucose-induced electrical activity in females compared to males is caused by changes in voltage gated potassium channel currents as well as altered functional coupling between Ca_V channels and calcium-activated SK potassium channels. The different β-cell potassium influx leads to a higher resting membrane potential in females causing a reduced Ca_V channel availability.

Additionally, as a consequence of higher membrane potential, the stimulatory incretin effect on β-cell insulin release works via a different pathway in females compared to males. Our data fully supports the observation that the incidence of type 2 diabetes mellitus (T2DM) in humans has a clear sexual dimorphism with diabetes and impaired fasting glycaemia being more common in men compared to women.

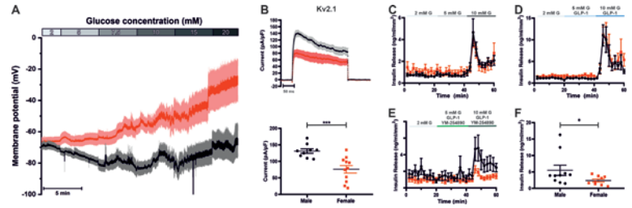


Figure 1: Sex differences of pancreatic β-cell function. (A) Average traces of glucose-induced electrical activity showing a more depolarised potential in females (red) compared to males (black). (B) Average traces and statistics of Kv2.1 currents showing a reduced amplitude in females compared to males. (C) Dynamic insulin release from pancreatic islets of male and females in 2, 5, and 10 mM glucose and (D) in the presence of GLP-1. (E,F) The application of 100nM YM-254890, a G_q pathway inhibitor shows that the peak of insulin release is significantly higher in males demonstrating that GLP-1 in females acts mainly through G_q pathway whereas in males via G_q and G_s.

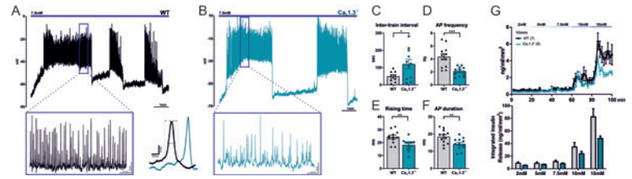


Figure 2: $Ca_V1.3$ deletion alters the glucose-induced β-cell electrical activity. Sample traces from a WT (A) and a $Ca_V1.3^{-/-}$ β-cell (B) recorded in 7.5mM extracellular glucose. Insets showing the typical electrical activity during an AP-train and direct comparison of single APs. (C) In 7.5mM glucose $Ca_V1.3$ deletion significantly increases the time between AP-trains and reduces the AP frequency in a train (D). The reduced electrical activity is caused by a slower membrane depolarization (E). In $Ca_V1.3^{-/-}$ β-cells the AP half-maximal duration (F) is smaller compared to WT. (G) $Ca_V1.3$ deletion seems to reduce the insulin release stimulated by all glucose concentrations.

Another project in the lab is to identify the functional relevance of $Ca_V1.3$ L-type calcium channels in pancreatic β-cell function and mass. Previously it has been shown that loss-of-function genetic polymorphism in *CACNA1D* gene encoding for $Ca_V1.3$ channel correlate with a higher incidence of T2DM in humans. Additionally, $Ca_V1.3$ gain-of-function mutations lead to hyperinsulinemia and life-threatening hypoglycemic events. We can demonstrate that $Ca_V1.3$ deletion reduces pancreatic β-cell mass by increasing apoptosis and decreasing β-cell proliferation. Additionally, we can show that $Ca_V1.3$ deletion alters β-cell calcium influx and glucose-induced electrical activity as well as gene transcription regulation. Recently, the groups of Dr. J. Striessnig and Dr. N. Ortner have generated the first mouse model ($Ca_V1.3^{AG}$) carrying a *CACNA1D* gain-of-function variant. In collaboration we can show that $Ca_V1.3^{AG/AG}$ mice faithfully recapitulate the metabolic abnormalities reported in patients with mice showing a significantly lower fasting plasma glucose levels and enhanced glucose tolerance.

Additional to the pancreatic β-cells we also characterize the role of Ca_V channel subunits in catecholamine release from adrenal chromaffin cells. Consistent with the known role of $\alpha_2\delta$-1 subunit on Ca_V channel function, we can demonstrate that $\alpha_2\delta$-1 deletion reduces chromaffin cell calcium influx. Surprisingly, this leads to a paradoxical increase in chromaffin cell electrical activity as well as a higher frequency of induced catecholamine release. Additionally, we can show that mouse chromaffin cells intracellular calcium concentration and vesicle exocytosis are not affected by $\alpha_2\delta$-1 deletion and the reduced calcium influx.

>> Research Grants

FWF P31434, DOC30-B30 to PT, TWF F.18863, NFB LSC19-017, and LFU 2021-CHEM-8 to SMG

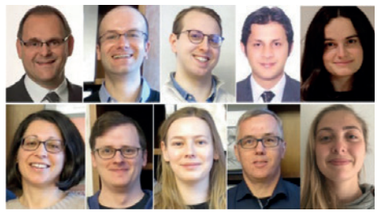
>> Coworkers

Stefanie M. Geisler (postdoc); Noelia Jacobo-Piqueras, Tamara Theiner (Ph.D. students); Christoph Dallago, Andrea Isser, Katharina Holzer, Chiara Schett, Maria Bogensberger, Nathalie Pinder, Sabina Mujovic, Isabell Gonella (diploma/master students)

Cell metabolism and differentiation research

Werner Zwerschke

>> Research Department for Biomedical Aging Research



>> Goal: The Zwerschke lab studies the biology of the adipose organ with main emphasis on molecular mechanisms underlying proliferation, differentiation and senescence of adipose stem/progenitor cells (ASCs). Moreover, the group investigates the role of ASCs and adipocytes in obesity and works on weight-loss mimetics.

>> Background: Age-related changes in the adipose organ play a major role in organismal aging and are detrimental for health. Major changes beginning already in midlifers are a decrease of the subcutaneous adipose tissue (sWAT) and rearrangements to more visceral and ectopic fat depots. This leads to reduced triglyceride storage capacity of the adipose organ, impaired metabolic performance and a low chronic inflammatory state. Similarly, obese people frequently show a phenotype of premature aging. In both scenarios, aging and obesity, a functional decline in ASCs and adipocytes plays an important part. The group studies genes in ASCs and adipocytes that are involved in aging, obesity and weight-loss. We investigate also ectopic adipose tissues that increase during aging. In addition, we work on the role of major reactive oxygen species (ROS) defense systems, especially carbonic anhydrase III, for the protection of highly metabolically active tissues against oxidative stress. Finally, the group fosters the development of weight-loss mimetics. To address our research goals, we work with primary human cells in cell culture and genetic animal models. Moreover, we use genomics, transcriptomics and proteomics technologies, modern techniques of molecular and cell biology including RNA interference, CRISPR-mediated genome editing, flow cytometry and imaging technologies.

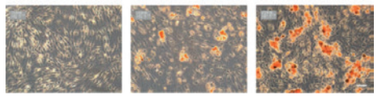


Figure 1: Adipogenesis in human ASCs: Staining of triglycerides by Oil Red O is shown prior the induction of differentiation (d0), on d9 and d14 of adipogenesis. Scale bar 100 µm (Mandl *et al.*, 2019 *Cell Death & Diff*).

>> Research Highlights and Outlook: A major aim of our group is to better understand the impact of weight-loss interventions on ASCs. We made substantial progress in this research area by the identification of Sprouty1, a negative regulator of Ras-MAPK signaling, as a novel weight-loss target gene in human ASCs. We demonstrate that Sprouty1 prevents cellular senescence maintaining proliferation and differentiation capacity of the ASCs and contributing to the maintenance of stemness in ASCs.

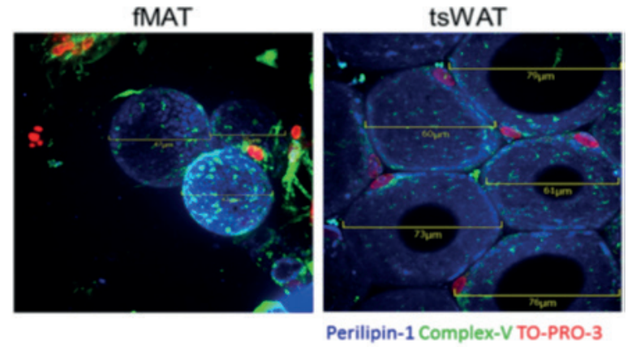


Figure 2: Comparison of human femur MAT (fMAT) and subcutaneous WAT of the thigh (tsWAT) shows that adipocyte size is smaller in MAT than in WAT. Representative merged IF images of whole mount stainings are shown. Adipocytes are labelled with the adipocyte marker perilipin-1 (blue). Nuclei were stained with To-Pro3 (red). Green fluorescence shows active mitochondria stained with ATP synthase β (ComplexV). (Miggitsch *et al.*, 2019, *EBioMedicine*).

In another research project, we studied bone marrow adipose tissue (MAT). The accumulation of this ectopic fat depot in the bone marrow of elderly people is thought to cause detrimental health effects; however, its importance is not precisely understood. Our recent study indicates that MAT is a unique type of adipose tissue containing considerably smaller adipocytes than sWAT (Fig. 2) and possessing high secretory activity. MAT adipocytes secrete high levels of pro-inflammatory cytokines, contributing to inflammation, elevated ROS levels and impairment of plasma cell function in the bone marrow. However, MAT adipocytes possessed also beneficial effects. They secrete high levels of adiponectin, a adipokine with insulin-sensitizing activity, that supports glucose and lipid metabolism. Together our findings suggest that human MAT displays distinct immune regulatory properties contributing to increased inflammation but possess also beneficial health effects mitigating insulin resistance in old people.

Finally, in a recent study addressing adipose stem cell functions, we showed that human ASCs of sWAT defined by the stem cell marker combination DLK1^{-}/CD34^{+}/CD24^{+} exist in a quiescent state and express high levels of somatic stemness genes but no pluripotency factors.

In the future, the group will continue the work on the importance of aging- and obesity-related genes in ASCs and adipocytes and on the development of weight-loss mimetics.

>> Research Grants

EU-Horizon 2020 - Research and Innovation Framework Programme (Proposal/Contract no.: 847681). EUREGIO Environment Food and Health project (http://e uregio-efh.eu/).

European Union (Doctoral program), Horizon 2020 - Research and Innovation Framework Programme (Proposal/Contract no.: 847681). Projekttitel: Ageing, Regeneration, and Drug Research (ARDRE). Fördersumme: 108480 Euro

>> Coworkers

Markus Mandl, Claudia Krautgasser, Asim Ejaz (postdocs); Florian Hatzmann, Camille Brucker (Ph.D. students); Saphira Baumgarten, Sonja Wagner, Valerie Schiller, Jochen Springer, Anna Ennemoser (diploma students); Rebecca Baumgartner, Katharina Rühlmann, Maria Zopoglou, Juliane Gasser (bachelor students); Hans-Peter Viertler, Petra Waldegger (Technicians)

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G. Bonn, C. Huck

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CMBI - Awards & Honors for CMBI Scientists

awards

Mostafa Alilou, Department of Pharmacy, Pharmacognosy Section: Hypo-Tirol-Bank Dissertationspreis, 2021

Giorgia Baraldo, Research Institute for Biomedical Aging Research: Tiroler Wissenschaftsfonds Projekt 2018

Philip Bertemes, Department of Zoology: Best Poster Award at the Meeting "International Conference on Adhesion in Aqueous Media: From Biology to Synthetic Materials" AAM2019, September 2019, Dresden, Germany

Ehsan Bonyadirad, Research Institute Michael Popp: Project Award of the Austrian Society for Bone and Mineral Research 2021

Giovanni Calderisi, Department of Organic Chemistry: "LFUI Best Student Paper Award 2020" for the research article "Radical transfer dissociation for de novo characterization of modified ribonucleic acids by mass spectrometry" published in in Angewandte Chemie as a 'Very Important Paper'

Maria Cavinato, Research Institute for Biomedical Aging Research: Tiroler Wissenschaftsfonds 2018

Maria Dumitrascuta, Department of Pharmacy, Pharmaceutical Chemistry Section: Oral Presentation Prize, 16th ANA - 25th APHAR Meeting, Innsbruck, 2019

Christoph Falschlunger, Department of Organic Chemistry: Hypo Tirol Bank Dissertationspreis 2020

Julian Feilner, Department of Organic Chemistry: Tiroler Wissenschaftsfonds Projekt 2019

Monica L. Fernández-Quintero, Department of General, Inorganic and Theoretical Chemistry: Antibody Society Writing Competition – Postdoctoral Winner, 2021; Prof. Brandl Preis, Dissertationspreis, 2021; Sosnovsky Preis – Dissertationspreis, 2021; Award of Excellence, Bundesministerium Österreich, 2021; Wissenschaftspreis 2021 der Wirtschaftskammer Tirol; Karl-Schlögl Award, Österreichische Akademie der Wissenschaften, 2021

Veronica Fontebasso, Department of Pharmacy, Pharmacology and Toxicology Section: Tiroler Wissenschaftsfonds Projekt 2020

Eva Maria Fritz, Department of Pharmacy, Pharmacology and Toxicology Section: OEGMBT/YLSA Best Poster Award at Life Science PhD Meeting, 2019; FENS IBRO-PERC Travel Grant for 11th FENS Forum of Neuroscience, 2018

Sebastian Führer, Department of Organic Chemistry: PhD Thesis Award 2021, Austrian Chemical Society

Stefanie Geisler, Department of Pharmacy, Pharmacology and Toxicology Section : Krems Cooperation Research Award - Best thesis award

Maria Dumitrascuta

Eva Maria Fritz

Davide Gerna

Christian Huck

Christina Kalchschmid

Ilse Kranner

Davide Gerna, Department of Botany: Travel grant by the Federation of European Societies of Plant Biology (FESPB) for the best student paper, to deliver an invited lecture at the Plant Biology Europe Congress, Copenhagen, Denmark 2018

Heidelinde Glasner, Department of Organic Chemistry: "LFUI Best Student Paper Award 2018" for the research article "Label-free, direct localization and relative quantitation of the RNA nucleobase methylations m^6A, m^5C, m^3U, and m^5U by top-down mass spectrometry" published in Nucleic Acids Research

André Gollowitzer, Research Institute Michael Popp: Poster award, 8. Berliner LC-MS/MS Symposium 2019

Franz-Lucas Haut, Department of Organic Chemistry: Tiroler Wissenschaftsfonds Projekt 2018

Nadja Hofer, Department of Pharmacy, Pharmacology and Toxicology Section: Award of Excellence 2020, Austria Federal Ministry of Education, Science and Research, State Prize awarded to the best doctorate graduates; Hypo Tirol Bank Dissertationspreis 2020

Denis Höfler, Department of Organic Chemistry: Marie Skłodowska-Curie Individual Fellowships 2020

Christian Huck, Department of Analytical Chemistry and Radiochemistry: Tomas Hirschfeld Award 2018; BID Chair of ICNIRS2023 conference

Matilde Iraci, Department of Molecular Biology: ERASMUS fellowship 2020

Stefanie Jäger, Department of Zoology: Tiroler Wissenschaftsfonds Projekt 2020

Pidder Jansen-Dürr, Research Institute for Biomedical Aging Research: Organizer of the 1st FEBS Workshop "Aging and Regeneration", Innsbruck, Austria, Sept 2019 (2nd Workshop scheduled for April 2022 in Obergurgl, Austria)

Michael Juen, Department of Organic Chemistry: Georg & Christine Sosnovsky PhD award 2019, University of Innsbruck

Lukas Karbacher, Department of Molecular Biology: Austrian Marshall Plan Foundation fellowship for US research stay 2021

Christina Kalchschmid, Department of Pharmacy, Pharmaceutical Chemistry Section: Poster Prize, **CMBI Meeting 2018**

Andreas Koeberle, Research Institute Michael Popp: EFMC prize 2019 in the category "Young Medicinal Chemist in Academia" 2019; Habilitation award of the Friedrich-Schiller-University Jena 2018

Ilse Kranner, Department of Botany: President of the ATSPB (Austrian Society of Plant Biology) and national delegate on the FESPB (Federation of European Societies of Plant Biology) Council.; Board member of the FWF for the discipline "Biology".

CMBI - Awards & Honors for CMBI Scientists

Thomas Magauer

Sandro Neuner

Nadine Ortner

Michael Palasser

Olga Krasheninina, Department of Organic Chemistry: FWF Meitner Program 2018; Tiroler Wissenschaftsfonds Projekt 2020

Johannes Kremser, Department of Organic Chemistry: Marietta Blau-Grant, OeAD, 2019

Stina Lagerström, Department of Molecular Biology: ERASMUS fellowship 2021

Elisabeth Mairhofer, Department of Organic Chemistry: IRT Travel Award, 2018, 23rd International Roundtable of Nucleosides, Nucleotides and Nucleic Acids, La Jolla, 26.-30.08.2018; Hypo Tirol Bank Dissertationspreis 2021

Ines Martic, Research Institute for Biomedical Aging Research: Tiroler Wissenschaftsfondsprojekt 2021

Thomas Magauer, Department of Organic Chemistry: ERC-Consolidator Grant, 2020; Scientific Research Award of the Innsbruck Municipal Council, 2019; Member of the Young Academy of the ÖAW, 2018

Jerome Mertens, Department of Molecular Biology: Preis für wissenschaftliche Forschung der Stadt Innsbruck 2019

Christina Meisenbichler, Department of Organic Chemistry: Tiroler Wissenschaftsfonds Projekt 2020

Simon Moosmang, Department of Pharmacy, Pharmacognosy Section: Young Talent Poster Award, First Place - Best Poster, VASCage Meeting, 2018

Eva Neuner, Department of Organic Chemistry: RNA Society Travel Fellowship 2019, The 24th Annual Meeting of the RNA Society (RNA 2019), Krakau, 2019; Monatshefte für Chemie/ Chemical Monthly – Young Scientists Best Paper Award 2021

Sandro Neuner, Department of Organic Chemistry: Sosnovsky Award 2018, University of Innsbruck

Nadine Ortner, Department of Pharmacy, Pharmacology and Toxicology Section: Erika Cremer Stipendium (Research award from the University of Innsbruck), 2019; Tiroler Wissenschaftsfonds Projekt 2019

Michael Palasser, Department of Organic Chemistry: Poster award, 7th Annual CMBI Meeting 2018, Vill, Austria; Outstanding short oral presentation award, EU FT-ICR MS 2nd Advanced User School 2021, Prague, Czech Republic

Alienke van Pijkeren

Sophia Wedel

Michele Petit, Research Institute for Biomedical Aging Research: Tiroler Wissenschaftsfonds Projekt 2019

Simone B. Sartori, Department of Pharmacy, Pharmacology and Toxicology Section: ECNP Poster Award, 32nd ECNP Congress, 2019

Florian Schön, Department of Molecular Biology: Leistungsstipendium of the University of Innsbruck 2021

Bianka Siewert, Department of Pharmacy, Pharmacognosy Section: Tiroler Wissenschaftsfonds Projekt 2019

Anita Siller, Department of Pharmacy, Pharmacology and Toxicology Section: Rotary Award for Excellence 2018 "Höchstbegabtenstipendium des Rotary Clubs 2018"; award for outstanding academic achievements together with social commitment and cultural engagement of the candidate (awarded to only one person in the whole country per year)

Jörg Striessnig, Department of Pharmacy, Pharmacology and Toxicology Section: Member of the Academia Europaea, 2018

Hermann Stuppner, Department of Pharmacy, Pharmacognosy Section: Outstanding Contribution in Natural Product Research - ICSB Waters, 2019

Nicholas Tappin, Department of Organic Chemistry: SNF Postdoctoral Fellowship

Sofia Torres Venegas, Department of Organic Chemistry: Tiroler Wissenschaftsfonds Projekt 2018

Larissa Traxler, Department of Molecular Biology: ISSCR 2020 Merit Abstract Award and Travel Award 2020; Austrian Marshall Plan Foundation fellowship for US research stay 2020

Sofia Torres Venegas, Department of Organic Chemistry: Tiroler Wissenschaftsfonds Projekt 2018

Anna Wagner, Department of Molecular Biology: ERASMUS fellowship 2021

Sophia Wedel, Research Institute for Biomedical Aging Research: Swarovski grant "2D goes 3D: tBHP-induced senescence in fibroblasts potentially drives structural rearrangement of Skin and extrinsic Skin aging"

Lukas Wein, Department of Organic Chemistry: Tiroler Wissenschaftsfonds Projekt 2019; Poster Prize at the 2nd Alpine Winter Conference on Medicinal and Synthetic Chemistry

Ricarda Zeindl, Department of Organic Chemistry: Master Thesis Award 2020, Austrian Chemical Society

CMBI - meetings

meetings

7TH CMBI MEETING INNSBRUCK 2018

The 7th CMBI Meeting of the Innsbruck University took place on September 19 to 20 2018 in the Grillhof/Vill. The high attendance confirmed the importance of exchange of experiences for the young scientists. It was an excellent opportunity to stimulate new collaboration between the research groups of the CMBI. Thematically, the meeting was focused on signaling mechanisms, methods and applications, RNA and protein structure dynamics and neuron disorder and disease. The success of the meeting was also reflected in the lively discussions during the oral presentations and poster sessions. As in the years before the best talks and posters were awarded. The winners of the CMBI Award are:
Belinda Artes, Department of Zoology; Michael Palasser, Department of Organic Chemistry; Kevin Erharter, Department of Organic Chemistry; Christina Kalchschmid, Department of Pharmaceutical Chemistry; Philipp Tschaikner, Department of Biochemistry; Larissa Traxler, Department of Molecular Biology.

CMBI Award ceremony

LIFE SCIENCE PHD MEETING

April 08/09, 2021 – The Life Science PhD Meeting Innsbruck 2021 took place in online format. The ARDRE ESR Marion LECHABLE was actively engaged as a member of the organizing committee, while Lucas HENSEN and Camille BRUCKER were acting as session chairs. From the 40 student talks, 4 speakers where selected by a jury of students, postdocs and PIs. The winners of the 2021 Short Talk Award are Gerlinde Karbon, Katharina Hutter, Katharina Klee and Elena Brunner. The prices of 150 euro each, were sponsored by the PhD programs ARDRE, CMBI, CBD, CaVX, SPIN, HOROS and the MUI clinical PhD program.

CMBI - meetings

Meetings

External speakers at previous CMBI meetings

In addition to the many exciting short talks and poster presentations from members of the CMBI and the Biocenter, guest lectures from invited top scientists contributed to the lively discussions. Like in previous meetings, the speakers also served as advisory experts for our research activities and as referees for the poster awards for young scientists.

7th CMBI Meeting Innsbruck, Innsbruck, Tyrol, September 19th - 20th, 2018
>> Zlatko Trajanoski
Division of Bioinformatics, Medical University of Innsbruck
>> Martina Höckner, Department of Zoology, University of Innsbruck
>> Hashim M Al-Hashimi
Department of Biochemistry, Duke, University Medical Center, Durham North Carolina, US

6th CMBI Meeting Innsbruck, Innsbruck, Tyrol, March 3th - 4th, 2016
>> Christian Griesinger
Max Planck Institute for Biophysical Chemistry Göttingen, Germany
>> Frank Edenhofer, University of Innsbruck, Austria
>> Remco Sprangers, Max Planck Campus Tübingen, Germany
>> Almut Schulze, University of Wuerzburg, Germany

7th Life Science Meeting Innsbruck, Innsbruck, Tyrol, Feb. 27th, 2015
>> Peter Hinterdorfer, University of Linz, Austria
>> Eduard Stefan, University of Innsbruck, Austria
>> Peter Ladurner, University of Innsbruck, Austria
>> Gunter Meister, University of Regensburg, Germany
>> Gerald Obermair, Medical University of Innsbruck, Austria
>> Natascha Kleiter, Medical University of Innsbruck, Austria
>> Pascal Meier, ICR London, UK
>> Marlies Meisl, University of Chicago, USA
>> Martin Puhr, Medical University of Innsbruck, Austria
>> Bill Earnshaw, University of Edinburgh, UK

6th Life Science Meeting Innsbruck, Innsbruck, Tyrol, Sept. 24th - 25th, 2014
>> Robert T. Batey, University of Colorado Boulder, USA
>> Veronika Sexl, University of Veterinary Medicine, Vienna, Austria
>> Florian Kronenberg, Medical University of Innsbruck, Austria

5th Life Science Meeting Innsbruck, Innsbruck, Tyrol, Sept. 25th - 27th, 2013
>> Asifa Akhtar
Max Planck Institute of Immunobiology and Epigenetics, Germany
>> Michel Desjardins, Universite de Montreal, Canada
>> Carl-Philipp Heisenberg, IST Austria
>> Karolin Luger, Colorado State University, USA
>> Frauke Melchior, ZMBH Heidelberg University, Germany
>> Nikolaus Pfanner, University of Freiburg, Germany
>> Britta Qualmann, Friedrich-Schiller-University Jena, Germany
>> Elena Rugarli, University of Cologne, Germany
>> Susan S. Taylor, University of California San Diego, USA

4th Life Science Meeting Innsbruck, Igls, Tyrol, Sept. 27th - 28th, 2012
>> Christine Foyer
Centre for Plant Sciences, University of Leeds, United Kingdom
>> Ari Helenius, Institute of Biochemistry, ETH Zürich, Switzerland
>> Anne-Claude Gavin
Structural and Computational Biology, EMBL Heidelberg, Germany

3rd Life Science Meeting Innsbruck, Igls, Tyrol, Sept. 23th - 24th, 2011
>> Ilme Schlichting
Department of Biomolecular Mechanisms, Max Planck Institute for Medical Research, Heidelberg, Germany
>> Adrian R. Ferré-D'Amaré
Laboratory of RNA Biophysics and Cellular Physiology, Biochemistry and Biophysics Center, National Heart, Lung and Blood Institute, Bethesda, USA
>> Daniel Minor
Cardiovascular Research Institute, Departments of Biochemistry & Biophysics, and Cellular & Molecular Pharmacology California Institute for Quantitative Biomedical Research, University of California, San Francisco, USA

2nd Life Science Meeting Innsbruck, Igls, Tyrol, Sept. 24th - 25th, 2010
>> Maria Sibilia
Institute for Cancer Research, Medical University of Vienna, Austria
>> Adriano Aguzzi
Institute of Neuropathology, University Hospital of Zürich, Switzerland
>> Rik Korswagen
Hubrecht Institute, Utrecht, Netherlands

1st Life Science Meeting Innsbruck, Igls, Tyrol, Sept. 18th - 19th, 2009
>> Dirk Trauner
Department of Chemistry and Biochemistry, LMU Munich, Germany
>> Didier Stainier, University of California, San Francisco, USA
>> Wolfgang Baumeister
Max-Planck-Institute of Biochemistry, Martinsried, Germany

CMBI - meetings

meetings

5th Annual CMBI-Meeting Igls, Tyrol, Sept. 26th - 27th, 2008
>> Peter Hegemann
Institute for Biology, Experimental Biophysics, Humboldt University Berlin, Germany
>> Stefan Schulte-Merker
Hubrecht Laboratory, Netherlands Institute for Developmental Biology Utrecht, Netherlands

4th Annual CMBI-Meeting Igls, Tyrol, Sept. 28th - 29th, 2007
>> Ulf R. Rapp
Medical Radiation & Cell Research, Univ. of Würzburg, Germany
>> Gregory J. Kaczorowski
Merck Research Laboratories, Rahway, New Jersey, USA
>> Thomas W. Holstein
Institute of Zoology, University of Heidelberg, Germany

3rd Annual CMBI-Meeting Vill, Tyrol, Sept. 29th - 30th, 2006
>> Naweed I. Syed, Anatomy and Physiology, University of Calgary, Canada
>> Erwin F. Wagner
Research Institute of Molecular Pathology, Vienna, Austria
>> Walter Schaffner
Institute of Molecular Biology, University of Zurich, Switzerland

2nd Annual CMBI-Meeting Vill, Tyrol, Sept. 30th - Oct. 1st, 2005
>> Wolfram Saenger
Inst. of Chemistry & Crystallography, Free University Berlin, D
>> Peter Herrlich, Institute of Molecular Biotechnology, Jena, Germany
>> Elisabeth Knust, Institute of Genetics, University of Düsseldorf, Germany

1st Annual CMBI-Meeting Vill, Tyrol, Oct. 1st - 2nd, 2004
>> Robert Huber
Nobel Laureate in Chemistry, MPI of Biochemistry, Martinsried, D
>> Reinhard Fässler
Max-Planck-Institute of Biochemistry, Martinsried, Germany
>> Daniela Pietrobon
Dept. of Biomedical Sciences, University of Padova, Italy

CMBI - seminar series

seminars

The CMBI seminars are a very important integrative and multidisciplinary activity of the CMBI and are also part of the PhD programs established within the CMBI. So far, it hosted 114 lectures from renowned scientists from the US, Canada, Australia, Sweden, Denmark, Netherlands, Poland, France, Italy, UK, Germany, Belgium, Switzerland, and Austria. It also provides a forum for excellent scientists from the Innsbruck Universities. Seminar speakers of the last four years are listed here:

2021

Susanne Wegmann, Ph.D.
Dipl.-Ing., Protein Actions in Neurodegeneration, DZNE, Berlin, GE
Barbara Bakker, Ph.D.
Professor of Medical Systems Biology, Faculty of Medical Sciences, University of Groningen, NL
Christine Sers, Ph.D.
Institute of Pathology, Charité Berlin, GE
Lars Dölken, Ph.D.
Julius-Maximilians-Universität Würzburg, DE

2020

Bernhard Lendl, Ph.D.
Institute of Chemical Technologies and Analytics, TU Wien, Austria
Andreas Koeberle, Ph.D.
Michael Popp Research Institute, University of Innsbruck, Austria
Robert Konrat, Ph.D.
Professor, Max F. Perutz Laboratories, University of Vienna, Austria
Norbert Polacek, Ph.D.
Department of Chemistry and Biochemistry, University of Bern, Switzerland

2019

Angela Peron, Ph.D.
Dipartimento di Scienze della Salute, Universita' degli Studi di Milano, Italy
Doriano Fabbro, Ph.D.
Chief Scientific Officer, PIQUR Therapeutics AG, Basel, Switzerland
Ulrich Stelzl, Ph.D.
Institut für Pharmazeutische Wissenschaften, Universität Graz, Austria
Jacek Jaworski, Ph.D.
International Institute of Molecular and Cell Biology in Warsaw, Poland

CMBI - seminar series

seminars

Floris Foijer, Ph.D.
European Research Institute for the Biology of Ageing, University of Groningen, NL
Thomas Brand, Ph.D.
Imperial College London, UK
Kathrin Thedieck, Ph.D.
Institute of Biochemistry, University of Innsbruck, A
Nikolay Ninov, Ph.D.
DFG-Center for Regenerative Therapies, Technical University of Dresden, GE
Patrick Eyers, Ph.D.
Institute of Integrative Biology, University of Liverpool, GB
Bernhard Grimm, Ph.D.
Institute of Biology, Plant Physiology, Faculty of Life Science, Humboldt-University Berlin, GE
Veronika Sexl, Ph.D.
Institute of Pharmacology and Toxicology, University of Veterinary Medicine, Vienna, A
Werner Zwerschke, Ph.D.
Research Institute for Biomedical Aging Research, University of Innsbruck, A
Alexandra Koschak, Ph.D.
Department of Pharmacy, Pharmacology and Toxicology, University of Innsbruck, A

2018

Jörn Piel, Ph.D.
Institute of Microbiology, ETH Zurich, Switzerland
Antonio Feliciello, Ph.D.
MD, Università degli Studi di Napoli Federico II, Italy
Thomas Magauer, Ph.D.
Institute of Organic Chemistry, University of Innsbruck, Austria
Jürgen Popp, Ph.D.
Institute of Physical Chemistry, Jena University, Jena, Germany

contact

Centrum für
Molekulare Biowissenschaften Innsbruck
Universität Innsbruck

Office: Innrain 80-82
A-6020 Innsbruck
Tel: +43 512 507-57501
Fax: +43 512 507-57599
cmbi@uibk.ac.at
www.uibk.ac.at/cmbi