Institut für Pharmazeutische Wissenschaften der Universität Graz

Institute of Pharmaceutical Sciences of University of Graz

We work for **tomorrow**

UNI GRAZ

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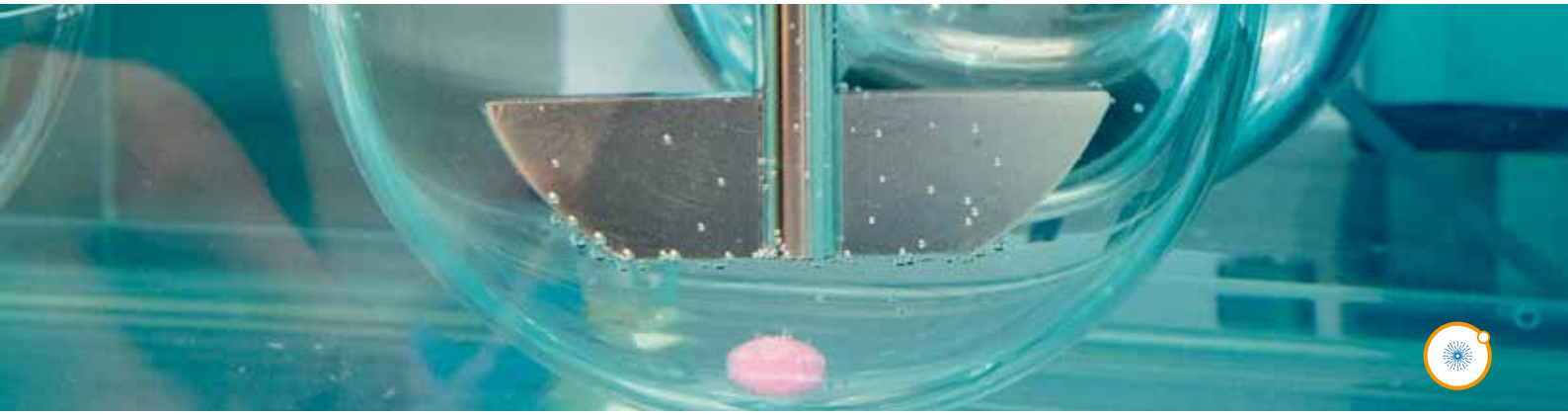

Preface

The Institute of Pharmaceutical Sciences is one of the biggest institutes of the University of Graz and responsible for education and research in this field. Currently it has 43 academic and 40 technical and administrative staff members. In addition, we are continuously supported by graduate students, research fellows and exchange students.

The Institute houses state-of-the-art facilities of an internationally high standard level. The main focus of research is in the fields of natural product chemistry, drug lead discovery, cellular signaling, molecular drug targets, pharmacogenomics, bioanalysis and nanotechnology. The results lead either to publications in top journals and/or to filings of intellectual property rights. Research is mainly funded by national and international grants as well as by the pharmaceutical and food industry. Several scientists of the Institute are members of centres of excellence or multinational research networks. Plenty international collaborations guarantee a continuous exchange of students, scientists and know-how.

In addition, the Institute provides up-to-date teaching to undergraduate students within the pharmacy curricula by incorporating research progress into lectures as well as into practical courses. Moreover, we offer interesting postgraduate programs within the mentioned research areas leading to doctorate degrees in natural sciences. Pharmacy students of Graz have proven to be successful at the national and international level thus coping with the challenges of modern medical life sciences. Since the Institute is actively participating in different mobility programs (Erasmus, Ceepus, Eurasia-Pacific Uninet, ASEA Uninet, WTZ) with the University of Graz being a member of the Arqus University Alliance, exchange of researchers and students is strongly supported, leading to an internationalization of pharmaceutical sciences in Graz.

In summary, the Institute of Pharmaceutical Sciences is an attractive and internationally competitive location for students and researchers alike, offering high standards in a wide variety of pharmaceutical disciplines.

Univ.-Prof. Dr. Dr. h.c. Rudolf Bauer,
Head of the Institute

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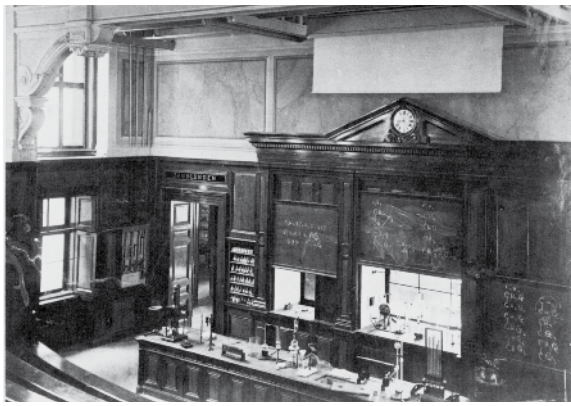
Studies and Teaching

The University of Graz trains students to be independent and interdisciplinary thinking, critical graduates with high professional, social and intercultural competence. Good teaching promotes a reflected and confident handling of students with science. And good science therefore can always be measured against good teaching. In the mission statement of the university is stipulated that research-led teaching and interdisciplinary teaching are of particular importance.

The Institute of Pharmaceutical Sciences is participating in the following study programmes:

- Bachelor of Science in Pharmaceutical Sciences
- Master of Science in Pharmacy
- Master of Science in Chemical and Pharmaceutical Engineering (NAWI Graz Master Programme)
- PhD in Natural Sciences

Brief History



Already in the 18th century, Empress Maria Theresa established a new state-run educational system for pharmacists. They were no longer trained within the guilds alone, but had to attend newly established courses at the medical faculties of the universities. They graduated as Masters of Pharmacy ("Magister pharmaciae").

Franz Hruschauer, a former student of Liebig, became the first chairman of the newly established Institute of Chemistry (1850-1858) at the University of Graz, which conducted the first pharmacy course in 1853. Education in pharmacy was performed in close cooperation with Joanneum, which had been established in 1811 by Archduke Johann as a center for continuing education and scientific research, and as a museum with large natural science collections that were used for teaching at the University.

Until the end of the 19th century, the curriculum of pharmacy included courses in the fields of zoology, botany, chemistry, physics, mineralogy, and pharmacognosy, which were all given by the particular experts and professors in these fields. In 1855, a laboratory was opened for pharmacy students in order to shift the main focus of education from lectures to practical courses. From 1858 to 1861, Johann Gottlieb taught the students in pharmaceutical chemistry. In 1878, under the guidance of Leopold von Pebal, a former student of Bunsen, a new Institute of Chemistry was built. Pebal also organized modern equipment for the laboratories. His successors were Zdenko Hans Skraup (1887-1906) and Roland Scholl (1907-1914). In the era of Anton Skrabal (1917-1943), the Institute of Chemistry separated into Organic and Pharmaceutical Chemistry, plus two additional institutes. The chairman of the new institute was Alois Zinke (1943-1963), followed by Erich Ziegler (1963-1978). In 1964, the Institute of Pharmaceutical Chemistry became a separate branch with Gustav Zigeuner as head (1964-1990), followed by Werner Korsatko (1991-1995), and Ernst Haslinger (1995-2004).

In 1909, Otto Loewi, the later Nobel Prize winner, became the chairman of the Institute of Pharmacology and Pharmacognosy at University of Graz (1909-1938), which was part of the Medical Faculty. A separate chair for Pharmacognosy, headed by Rudolf Müller (1909-1937), was established at the same institute. In 1939, Pharmacognosy became a separate institute, which was shifted to the Faculty of Philosophy and later in 1976, to the newly established Faculty of Natural Sciences. At the Institute of Pharmacognosy, Willibald Hauser (1937-1939), Robert Fischer (1939-1973), Theodor Kartnig (1973-1999), Alois Hiermann (1999-2002), and Rudolf Bauer (2002-2004) were chairmen.

In 1919, Otto Loewi established the first course for Pharmaceutical Technology at the Medical Faculty, which was supported by the Styrian government. Fritz Wischos, head of the hospital pharmacy, lectured this course from 1921 to 1932, followed by Ludwig Zechner from 1933 to 1938, and Norbert Schniderschitsch from 1938 onwards. During his period, education in pharmaceutical technology was shifted from the hospital pharmacy to the university, where a Institute for Applied Pharmacy was established within the Institute of Pharmaceutical Chemistry. Between 1959 and 1969, L. Zechner was again chairman of the Institute of Galenics. Christian Knopp (1969-1989), Werner Korsatko (1989-2000), and Ernst Haslinger (2000-2004) headed the Institute of Pharmaceutical Technology. From 1995 to 2001 the Institute was an independent institute.

In 1973, the Institute of Pharmacodynamics and Toxicology split off from the Institute of Experimental and Clinical Pharmacology of the Medical Faculty. From 1973 to 1997, Walter Kukovetz was head of this new Institute of Pharmacodynamics and Toxicology, which was established within the Faculty of Natural Sciences, and renamed into Institute of Pharmacology and Toxicology in 1992. From 1998 to 2004, Bernd-Michael Mayer was head of the institute.

In April 2004, today's Institute of Pharmaceutical Sciences was established as a result of merging the previously separate pharmaceutical institutes, in order to synergize administration, research and teaching. Rudolf Bauer was appointed head of this institute, which became one of the biggest in the university. The Institute has been structured into four sections: Pharmacognosy, Pharmacology and Toxicology, Pharmaceutical Chemistry, and Pharmaceutical Technology and Biopharmacy.

Pharmacognosy

Starting from microscopic investigations of herbal drugs, pharmacognosy has developed into a high-tech science during the last 50 years. Today it plays an integral role in the field of pharmaceutical sciences by discovering, identifying, and evaluating bioactive compounds from natural sources. Studies of plants used in European, North American, African and Asian traditional medicine are regularly conducted with the goal of identifying bioactive constituents for explaining pharmacological activities, and for discovering new drug leads.

Pharmacological screening

The main focus is on plant constituents with anti-inflammatory, immunomodulatory, anti-cancer, and/or anti-microbial activity. Extracts, fractions, and pure compounds are screened in-house in various in-vitro systems. Assays are established to test for inhibition of prostaglandin biosynthesis by COX-1 and COX-2 enzymes, for inhibition of NO production in stimulated mouse macrophages, and for inhibition on COX-2 expression in human THP-1 cells. Anti-proliferative activity is tested in various human cancer cell lines, with a particular focus on melanoma cells. Assays on modification of anti-microbial resistance with special focus on bacterial efflux pumps are established. Intensive collaborations for testing in other assays and conducting mechanistic studies have been established with Medical University of Graz, University of Vienna, University of Mainz, University of Ljubljana and University of London. A close collaboration with the China Academy of Chinese Medical Sciences is existing to study Chinese plants with anti-diabetic activity.

Isolation, identification and structure elucidation of natural products

International collaborations are providing access to sources of interesting new plant material with diverse and unexplored constituents. Besides also domestic and European plants are investigated. Isolation of bioactive compounds is conducted by a wide variety of chromatographic separation methods (LC, MPLC, HPLC, FCPC), using a bioactivity guided and/or a metabolomics and chemometrics based approach. MS and NMR are used for structural elucidation in close in-house collaboration with colleagues in Pharmaceutical Chemistry.

Analysis and quality control

Research in analysis and quality control of medicinal plants and herbal medicinal products is conducted on a regular basis using instrumental HPTLC, GC-MS, HPLC, and LC-MS. A major focus is on development of monographs for the European Pharmacopoeia and on quality control methods for herbs used in traditional Chinese medicine. LC-MS metabolomics and chemometrics based methods are investigated for a future, more holistic approach in the quality control of herbal medicinal products. Expertise in European regulatory affairs for herbal medicinal products and dietary supplements can also be offered.

Microbiome & Health Initiative Graz

In close collaboration with Medical University of Graz and Graz University of Technology, a research platform for microbiome research has been established, which is investigating the interaction of herbal products and gut microbiota, studying the impact of plant constituents on the microbial populations by Illumina next generation sequencing on the one side, and the metabolites produced by gut microbiota from secondary plant constituents by LC-HRMS on the other side. These investigations are conducted within the collaborative initiative BioTechMed, the BioHealth Field of Excellence of University of Graz, and the NAWI Graz Central Lab Environmental, Plant & Microbial Metabolomics.

TCM Research Center Graz

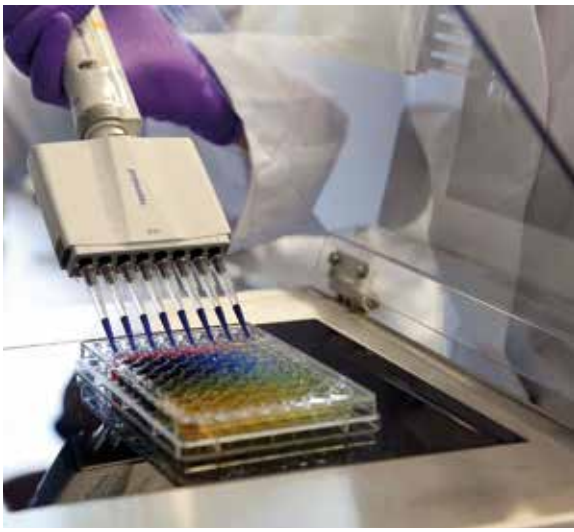
TCM Research Center Graz has been founded in 2007 by University of Graz and Medical University Graz, and subsequently became a competence center that is unique worldwide. Rudolf Bauer has been investigating the active ingredients and quality of Chinese medicinal herbs for almost 30 years. Close collaboration has been established with several Chinese research institutions, like the Sino-Austrian Joint Laboratory for TCM Research with Guangxi Botanical Garden of Medicinal Plants in Nanning, a Collaborative TCM Research Center with the Shanghai Research Center of Modernization of Traditional Medicine at Shanghai Institute of Materia Medica, Chinese Academy of Sciences, a Co-Research Center for herbal medicine research with the China Academy of Chinese Medial Sciences, Beijing, and a joint laboratory with Baotou Medical College.

Pharmaceutical Chemistry

In the section of Pharmaceutical Chemistry, we are scientifically investigating and teaching our students on how drugs and new drug candidates are made, how to detect and quantify drugs and their metabolites, how drugs act on their targets and if/how we can improve their mode/range of action. The Institute is sub-structured into five working groups:

Network Pharmacology

The group is focusing on the analysis of molecular interaction networks with the aim to understand the dynamics of molecular networks underlying cellular processes related to human disease. Experimental functional genomics techniques, e.g. HTP Y2H screening, are utilized in combination with biochemical, cell biological and computational methods. Current DNA sequencing approaches and mass spectrometry based proteomics technologies allow the simultaneous measurements of gene/protein variants for series of cell types, conditions or disease states. In particular the discovery of new somatic mutations in health and disease has vastly outpaced our ability to assess their functional roles. As most of the variation alone is not causal with respect to the observed phenotype, the question arises how to systematically analyse the large number of molecular variations and how to assess the importance of combined changes for cellular function, disease development and drug action? In our work we focus on the systematic analyses of the functional impact of genetic variation and post-translational protein modification on protein-protein interaction, which as universal protein function underlies cellular phenotypes. Using deep scanning mutagenesis approaches we bridge the knowledge gap between nucleotide resolution genomics and protein resolution proteomics. Network biology offers a more comprehensive understanding of biological processes. Advances in systems biology indicate that complex diseases may not be treated effectively by interventions at single drug targets and with single drugs. Network biology will advance our understanding of drug action and will be an important piece in developing individualized medicine.

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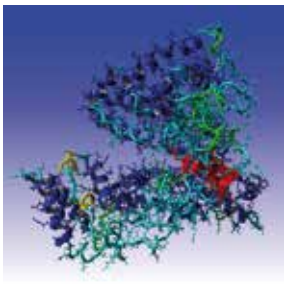
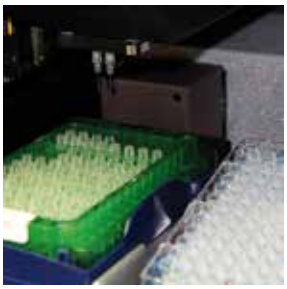




Biopharmaceuticals

For diseases in which cell-cell communication is malfunctioning – like chronic inflammation and cancer – a certain class of signalling molecules play a crucial role: the so-called chemokines. Our group is engineering these proteins with the two-fold aim of i) to better understand the complex extracellular network which leads to cell migration and ii) to translate this knowledge into novel drugs. Of particular interest in this context is the interaction of chemokines with glycans of the cell surface and the extracellular matrix. This complex matrix is responsible for immune and tumor cell recruitment in the context of inflammation and metastasis. Our method toolbox consists of molecular and cellular biology, protein and glycan engineering, biophysics and proteomics. Our drug candidates are typical biologics/biopharmaceuticals, i.e. they comprise protein mutants, which show anti-inflammatory or anti-tumorigenic activity in animal models. The combination of basic and applied research has proven to be a successful model resulting in the spin-off of two biotech companies: ProtAffin Biotechnology AG (incorporated 2005) and Antagonis Biotherapeutics GmbH (established 2015).

Drug Development

Protozoan parasites of the genus plasmodium are the causative pathogens of malaria killing about 400.000 people every year. New antiplasmodial drugs are urgently needed, because resistant strains have become prevalent across an expanding area of Southeast Asia even to recommended artemisinin-based combination therapies (ACTs). A spread of these strains to Africa is of great concern, because there are hardly any therapeutic alternatives.

We have a strong focus on the synthesis of new antiplasmodial drugs. Initial drug design is followed by synthesis, isolation and purification of compounds. The structures are revealed and characterized by NMR spectroscopy and high resolution mass spectrometry. Physicochemical parameters of the synthesized compounds are calculated in silico or estimated experimentally. In conjunction with the results of antiplasmodial in vitro tests they lead to structure-activity relationships enabling the selection of leads for next generation antimalarials. Only the most promising drug candidates are selected for in vivo testing. In addition, ADME and toxicity parameters are determined in assays.

Pharmaceutical Analysis

We are developing methods for enantiomer separation by High Performance Liquid Chromatography (HPLC) and Capillary Electrophoresis (CE). This topic involves synthesis of new chiral selectors for HPLC, CE and the new principle of capillary electrochromatography (CEC). These methods are applied to the separation of the enantiomers of compounds of biological interest, drugs and pesticides. Furthermore, we are designing electrochemical (bio)sensors for determining biologically active substances in complex matrices and as screening tools for diagnostic applications. The sensors are based on carbon paste and screen-printed electrodes.

The main interest of our research work is focussed on the development of methods for the determination of biological active compounds in the picomole or femtomole range in biological materials. This includes pharmacokinetic studies of drugs and metabolites in blood, plasma, serum and urine as well as pesticide quantification in water and other materials, analysis of cosmetic products, or prostaglandin and phospholipid determination in different human materials. In order to enhance sensitivity and selectivity derivatization agents for fluorescence or electrochemical detection in combination with chromatographic separation techniques are being designed. Photolytic processes and recently, problems dealing with clinical pharmacy are under investigation.

Another technique that is used in pharmaceutical analysis is the nuclear magnetic resonance (NMR) spectroscopy. The structure of synthetic compounds and natural products – usually secondary plant metabolites – is determined by homonuclear and heteronuclear two-dimensional NMR experiments.

Molecular Pharmacy

Research focus of the group is on biology and pharmacology of oxidized phospholipids (OxPLs). These pleiotropic lipid mediators demonstrate a variety of activities relevant to acute and chronic inflammation, blood coagulation, angiogenesis, pain sensation, and other pathological processes. The major goal of these studies is to identify new drug targets and drug candidates preventing deleterious proinflammatory action of OxPLs. In parallel, OxPLs are investigated as a prototype chemical scaffold for synthesis of stabilized derivatives that can be used for treatment of sepsis and lung edema. Finally, the group develops analytical methods based on mass spectrometry and monoclonal antibodies that allow quantification of OxPLs and mechanisms of their neutralization in blood of patients with cardiovascular disease. In summary, OxPLs are investigated as potential drug targets, drug leads and disease biomarkers.

Pharmaceutical Technology and Biopharmacy

Pharmaceutical Technology is one of the main traditional core competences in the field of pharmaceutical sciences since centuries. In the 1800s the compounding of medicines – which also was called Galenics – was transformed from a handmade manufacturing to an industrialized process. Drugs which were dispensed as single powders or liquids before, were then formulated and prepared by tableting, later by capsules or by sterile formulations as parenteral dosage forms. During the 50s and 60s of the last century Biopharmacy was established as a new part of pharmaceutical sciences describing the effects of a biological environment on the drug formulation as an interdisciplinary field of research and education between the traditional Galenics and the modern scientific area of Pharmacology and Toxicology.

Todays section of Pharmaceutical Technology and Biopharmacy is covering a broad area of competences in pharmaceutical education and research. We offer lectures and practical lab courses in compounding of personalized medicines as well as industrial manufacturing such as tableting or manufacturing of sterile formulations in a state-of-the-art clean room environment.

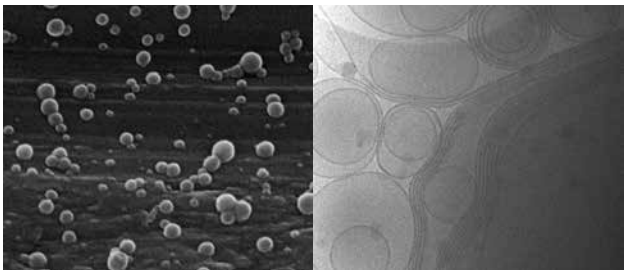
The research interest of our section is focused on Pharmaceutical Nanotechnology and covers all kinds of colloidal drug delivery systems and dosage forms:

- Micro- and Nanoparticles, Dispersions and Emulsions
- Liposomes
- Micelles and Microemulsions

Further, thin film technologies of drugs are applied on surfaces to manipulate the solid state properties including dissolution behavior and stability. New crystal growth and polymorphic structures are investigated in the nanometer scale.

In our lab, biopharmaceutical investigations are performed with a strong focus on the oral uptake route. Established in vitro and ex vivo models enable state-of-the-art investigations to be carried out for industrial and scientific partners and students as part of the Bachelor's or Master's programs. The complexity of investigations cover:

- Dissolution Tests
- Cell-free Drug Permeation Test
- In vitro Cell-Culture Tests
- Ex vivo Tissue Permeation Tests

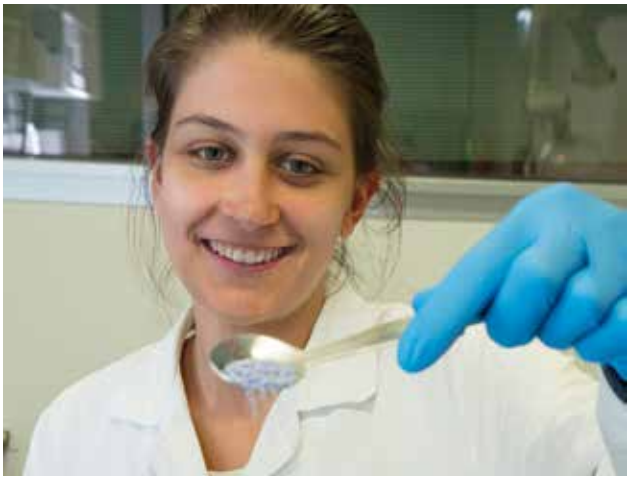


Pharmaceutical Nanotechnology

Nanomedicines and applications using Pharmaceutical Nanotechnology are investigated for nucleic acids and peptide based Drug Delivery Systems in terms of Drug Targeting and formulations with modified release behavior. Nucleic acid drugs such as:

- Oligonucleotides
- siRNA and microRNA

represent a new class of therapeutic substances used for several targets including metabolic diseases, viral infections and cancer. In contrast to gene therapies, which involve the replacement and substitution of genetic material, antisense drugs or siRNA and microRNA do not alter or substitute the endogenous genetic material during therapy. These oligonucleotides are effective blocking agents for protein expression with a high sequence specificity. The latest improvements for those systems are Protamine-Oligonucleotide-Particles – so called Proticles – which enable efficacious drug delivery and drug targeting potential not only for oligonucleotides but also peptides and proteins.

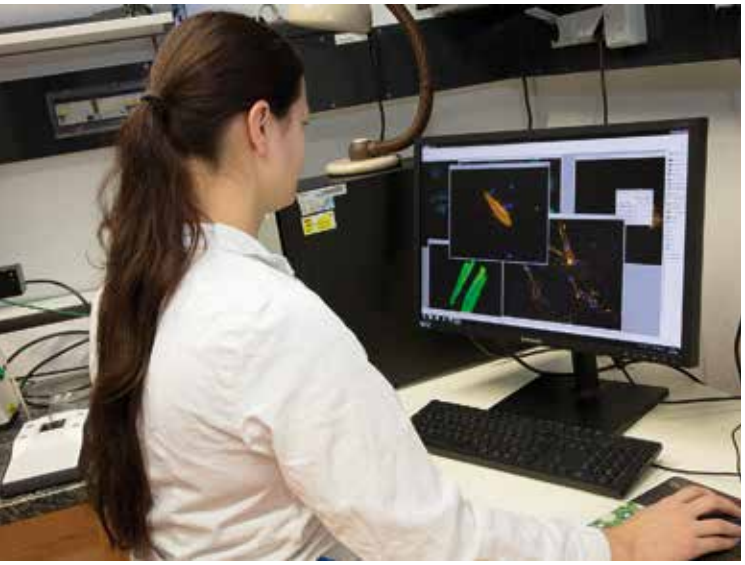


Preformulation

Drug Preformulation focuses on the solid state arrangement of drugs and aims to define physiochemical properties, stability, solubility and bioavailability of respective drug candidates during formulation and application. Using new crystal growth strategies and investigations, new polymorphic forms are generated within thin layers, which might be thin as a nanometer up to some hundreds of nanometers. Also a generation of thin amorphous layers in the same thickness range can be achieved. The new polymorphs as well as amorphous states within thin films enable overcoming solubility limitation for most drugs. Variable control on the drug release can then be achieved by superior stimulus responsive coatings derived from chemical vapor depositions processes. These coatings additionally prolong stability of either, crystalline or amorphous states sufficient to improve already used drug applications by line extension strategies.

Pharmacology and Toxicology

The scientific world of the pharmacologists and toxicologists of the University of Graz ranges from basic research of molecular mechanisms up to the research into clinical applications, and to toxicological counseling. In the center of interest are questions on how chemical entities interfere with living systems and how these effects can be used for the treatment of diseases as well as the undesired biological effects of these interferences.



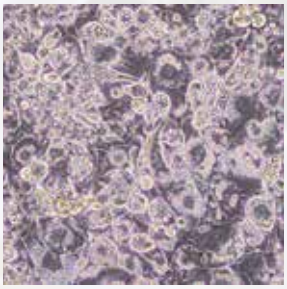
Molecular Pharmacology

A main interest lies in the biosynthesis and biological actions of nitric oxide (NO). Special emphasis is placed on the characterization of NO synthases (NOS), in particular on the role of the pterin cofactor tetrahydrobiopterin. Moreover, the selective action of the gaseous transmitter hydrogen sulfide (H_2S) on different NOS isoforms has become an interesting topic.

Further research investigates the mechanism of action of NO-releasing drugs, in particular the pathways involved in the bioactivation of nitroglycerin, which has been used to treat coronary artery disease since the second half of the 19th century.

Vascular NO/cGMP signaling

NO/cyclic GMP signaling in blood vessels is a further main research topic. The aim of the scientific studies is to clarify the molecular mechanisms involved in NO/cGMP signaling under physiological and pathophysiological conditions. Used are in vitro models with isolated tissues (organ bath experiments, Langendorff perfusion of isolated hearts) cultured endothelial and smooth muscle cells, as well as purified enzymes including NOS isoforms, soluble guanylate cyclase (sGC), and aldehyde dehydrogenase II (Aldh2). The outcome of the research aims at contributing to a better understanding of the role of NO/cGMP as regulator of blood pressure in health and disease.



Cardiac adenosine signaling

Another research interest lies in studying the protective effects of adenosine signaling in the heart. Special emphasis is given to the role of adenosine kinase (ADK), which catalyzes the conversion of adenosine into adenosine monophosphate (AMP). Modulation of cardiac adenosine levels is achieved by pharmacological inhibition or genetic manipulations in mice. Studies are performed with isolated cardiomyocytes and mouse models. In this context, the link between adenosine metabolism and cardiac protein quality control is of special interest.

Adipocyte signaling

Nowadays, adipose tissue is no longer regarded as passive storage unit for excessive energy but rather represents a highly active endocrine organ that secretes vasoactive hormones and inflammatory cytokines. A research focus is to unravel the role of adipose tissue in the development of cardiovascular disease. Special emphasis is placed on perivascular adipose tissue inflammation. To this purpose, studies with cultivated fat cells, isolated tissues, and transgenic mouse models are performed. These studies should provide in depth insight into the adipose-vessel axis and may pave the way for the development of novel therapeutic strategies for metabolically-induced cardiovascular disorders.

Thank you to our Partners

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Science for a **better life**

BAYER

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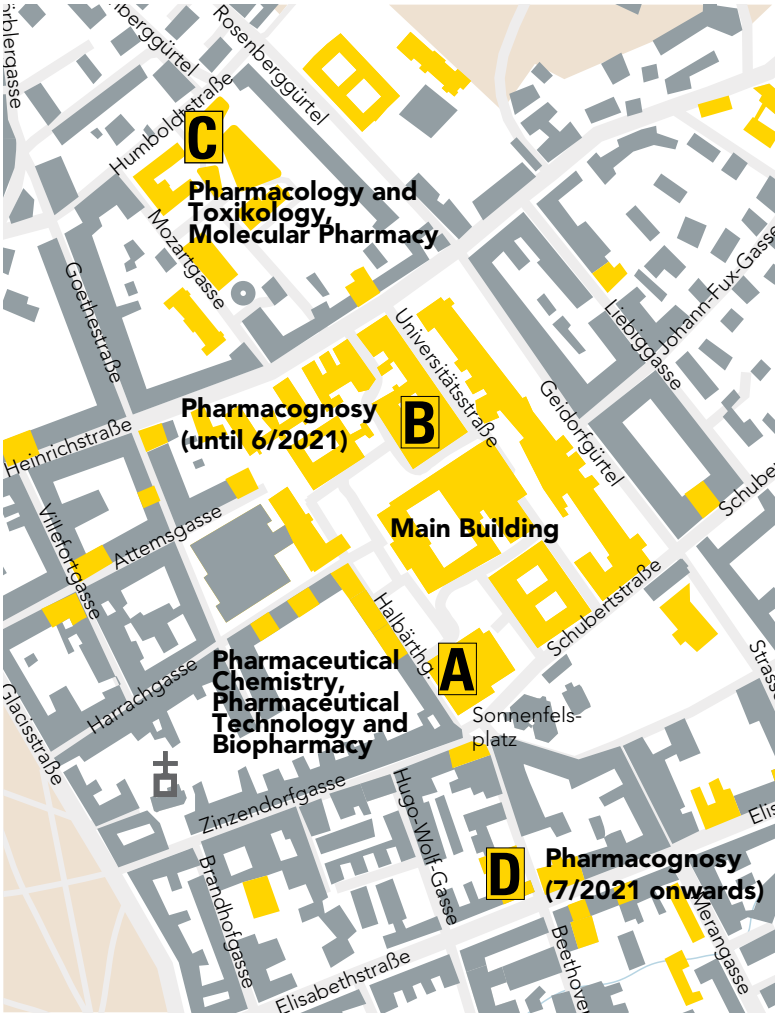

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