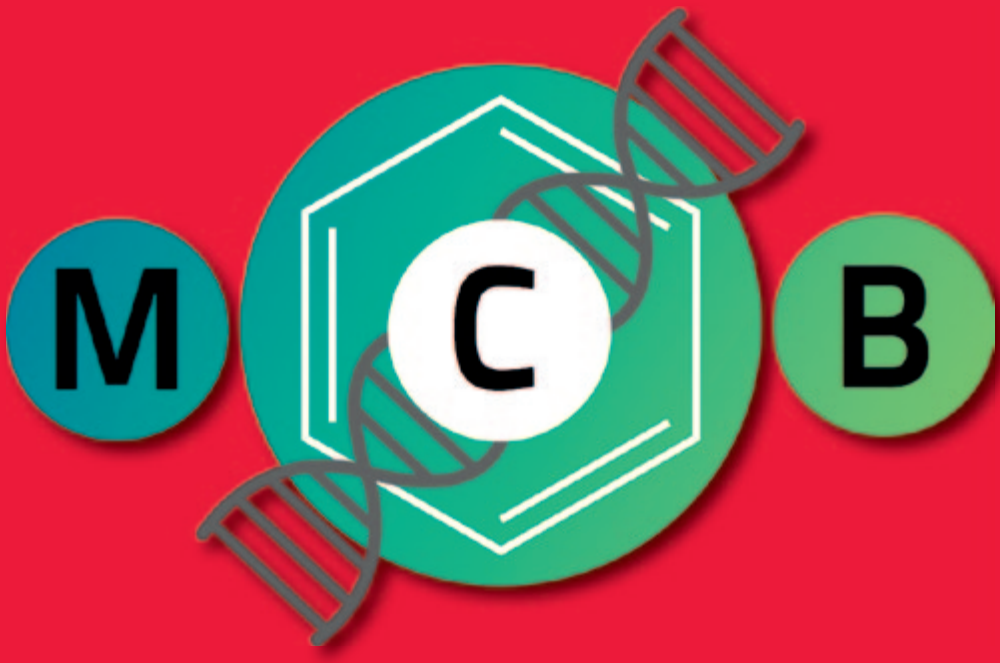
university of groningen

2014 | 400 years



The Medicinal Chemistry & Bioanalysis (MCB) Program

GUIDE

Graduate School for Drug Exploration

The Medicinal Chemistry and Bioanalysis (MCB) program comprises 3 core groups and 3 associated groups. Together the MCB program combines expertise in analytical chemistry with that in medicinal chemistry and chemical biology. The program forms a link between chemistry and biomedically oriented programs within GUIDE.

Full members
Drug Design: Alexander Dömling (chair), Matthew Groves
Pharmaceutical Analysis: Sabeth Verpoorte (chair)
Analytical Biochemistry: Rainer Bischoff (chair), Peter Horvatovich

Associate members
Sustainable Catalysis: Gerrit Poelarends
Medicinal Inorganic Chemistry: Angela Casini
Medicinal Chemistry: Frank Dekker

Logo design: Andreia de Almeida (Medicinal Inorganic Chemistry)
Lay-out: Marcel Zinger (Grafimedia)
Print: Grafimedia (University Services Department)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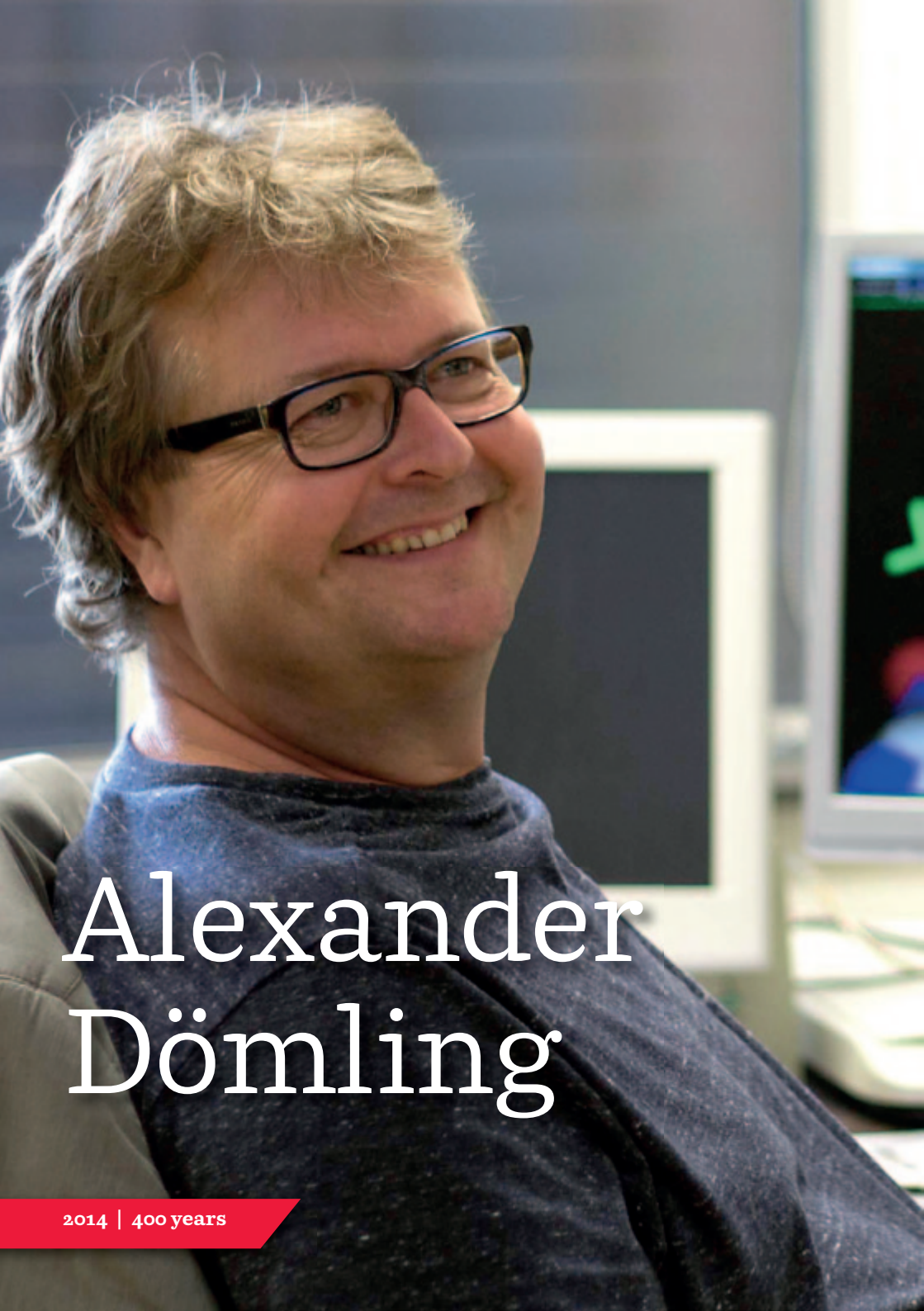


Alexander Dömling

2014 | 400 years

The research of the Dömling group for Drug Design aims at the development of novel tools for the rapid and efficient discovery of novel drugs for unmet medical needs. The tools are extensively applied to the design and discovery of novel drugs in the areas of cancer, infectious and inflammatory, orphan and neglected tropical diseases. We aim to make the expression "from bench to bedside" become true. Several collaborations with Biotech and Pharma companies secure the applied relevance of the research performed.

A key technology developed in our laboratory is multicomponent reaction chemistry (MCR). MCR is applied in the European Lead Factory, a very large Innovative Medicines Initiative (IMI) project sponsored by the European Union and the partners of The European Federation of Pharmaceutical Industries and Associations (EFPIA). Newly developed scaffolds are also feeded into our designer software ANCHOR.QUERY a collaborative approach to virtual drug discovery codeveloped with Carlos Camacho from the University of Pittsburgh. ANCHOR.QUERY, a unique open-access "google-like" technology promises to expand chemical space and the exploration of the human interactome by leveraging in-house small-scale assays and user-friendly chemistry to rationally design ligands for PPIs with known structure. In collaboration with the positron emission tomography (PET) unit (P. Elsinga, UMCG) we are developing novel chemical approaches to rapidly assemble PET labeled drugs using MCR for their time and space resolved detection in humans.

Application of the ANCHOR.QUERY approach to the MDM2/p53 cancer target led to high hit rates (>50%), resulting in a large and diverse set of confirmed inhibitors. Multiple crystal structures of our compounds demonstrate that anchor-bound docked models significantly enhanced the quality of the predictions, strongly supporting our interactive approach to drug design. Optimized compounds are highly potent inducers of apoptosis in certain patient-derived leukemia cells. Collaborators in the p53 area are Angela Casini (RUG), Philip Elsinga (UMCG), Tadeuz Holak (Jagelonian University, Poland), Aart Jochemsen (Leiden University Medical Centre) and Barbara Beck (Helmholz Center for Hematology, Munich).

Other design projects of novel drugs include MERS-CoV and flu targeting hemagglutinin (A Huckriede, UMCG; S. Goda, Qatar), food poisoning and autoimmune diseases (S. Goda, Qatar), mixed linage leukemia targeting MLL-menin (B. Beck, Munich), allosteric site PIF pockets in AGC kinases for diabetes (M. Engel, University of Saarbrücken), caspases for inflammation (P. Spanu, Sassari, Italy) and arginase for asthma (H. Meurs, RUG). Much of the structural biology part of the Drug Design research line is performed in collaboration with Matthew Groves (Ass. Prof. in the group Drug Design).

Highlights of Drug Design

Protein protein interaction antagonists using the disruptive technology ANCHOR.QUERY.

Fast, convergent and efficient muticomponent reaction chemistry (MCR) covering a very large and diverse chemical space. Dömling et al. (2012) Chemistry and biology of muticomponent reactions. Chem. Rev. 112, 3083-3135.

Koes et al. (2012) Enabling Large-Scale Design, Synthesis and Validation of Small Molecule Protein-Protein Antagonists. PLoS ONE 7: e32839. doi:10.1371/journal.pone.0032839.

Matthew Groves

The research in my group is in the field of Structural Biology. In particular the use of macromolecular X-ray crystallography to generate high-resolution (atomic) models of proteins that play a role in human health. My group operates in close collaboration with that of the Chair of Drug Design, Alexander Dömling. In addition to performing structure based analysis of proteins and protein:compound complexes we will also perform biophysical analysis of proteins, protein:protein interactions and protein:compound interactions.

The new laboratory for protein crystallisation is designed to be high throughput in approach. We have the specific intention to install cutting edge technology and implement pipelines that will allow non-expert researchers to rapidly overexpress, purify and crystallize their targets of interest. This open-access philosophy will be guided by expert supervision at all stages of the structure pipeline – from gene to structure. These high throughput pipelines are intended to provide significant structural biology support for the groups within the Department of Pharmacy – evidenced by the number of new in-house collaborative projects (Cassini, Hirsch, Meurs, Dekker and Dömling). While the group was only established in April 2013, we already possess a large library of overexpression cell lines, coupled with stocks of over 50 expression vector systems. Establishment of pipelines for cloning (LIC-based) and purification are currently underway and full crystallisation operations will be established by the end of July 2013.

The group has a successful track record in a variety of medically relevant fields, with a recent particular emphasis on carbon metabolism from the malarial parasite. We will continue this line of research utilizing the same high throughput approach. Close links with other groups within the Department of Pharmacy will result in an efficient generation and analysis of novel compounds that can be screened for their efficacy as biomarkers, in vivo research tools as well as leads for therapeutics. The group's expertise in cloning, overexpression, crystallisation, biochemistry and biophysics is complemented by current and on-going collaborations with international researchers that provide opportunities for in vitro and in vivo assays that are currently unavailable within RUG/UMCG.

The group has a focus on the pressing health concerns of humanity: contributing to the understanding and development of novel treatments for the world's most lethal pathogens (malaria & tuberculosis) as well as initiating investigations into cancer-relevant targets. The diversity of targets under examination is linked by a keen interest in analyzing and perturbing sites of protein:protein interaction or oligomerization – a particular emphasis of the group's recent publications. The recent projects also involve new collaborations with groups in the UK, US, Poland, Germany and Qatar. Currently a group member is performing a 3 month placement in the laboratory of a major collaborator in Sao Paulo, Brazil where he has successfully isolated and overexpressed 10 novel targets from *P. falciparum*, *S. aureus*, *M. tuberculosis* and *H. sapiens*.

Highlights of Structural Biology

Esch D, Vahokoski J, Groves MR, Pogenberg V, Cojocaru V, Vom Bruch H, Han D, Drexler HC, Araúzo-Bravo MJ, Ng CK, Jauch R, Wilmanns M & Schöler HR. (2013) A unique Oct4 interface is crucial for reprogramming to pluripotency. Nat Cell Biol. 15, 295-301.

Butzloff S, Groves MR, Wrenger C & Müller IB. (2012) Cytometric quantification of singlet oxygen in the human malaria parasite Plasmodium falciparum. Cytometry A. 81, 698-703.

Sabeth Verpoorte

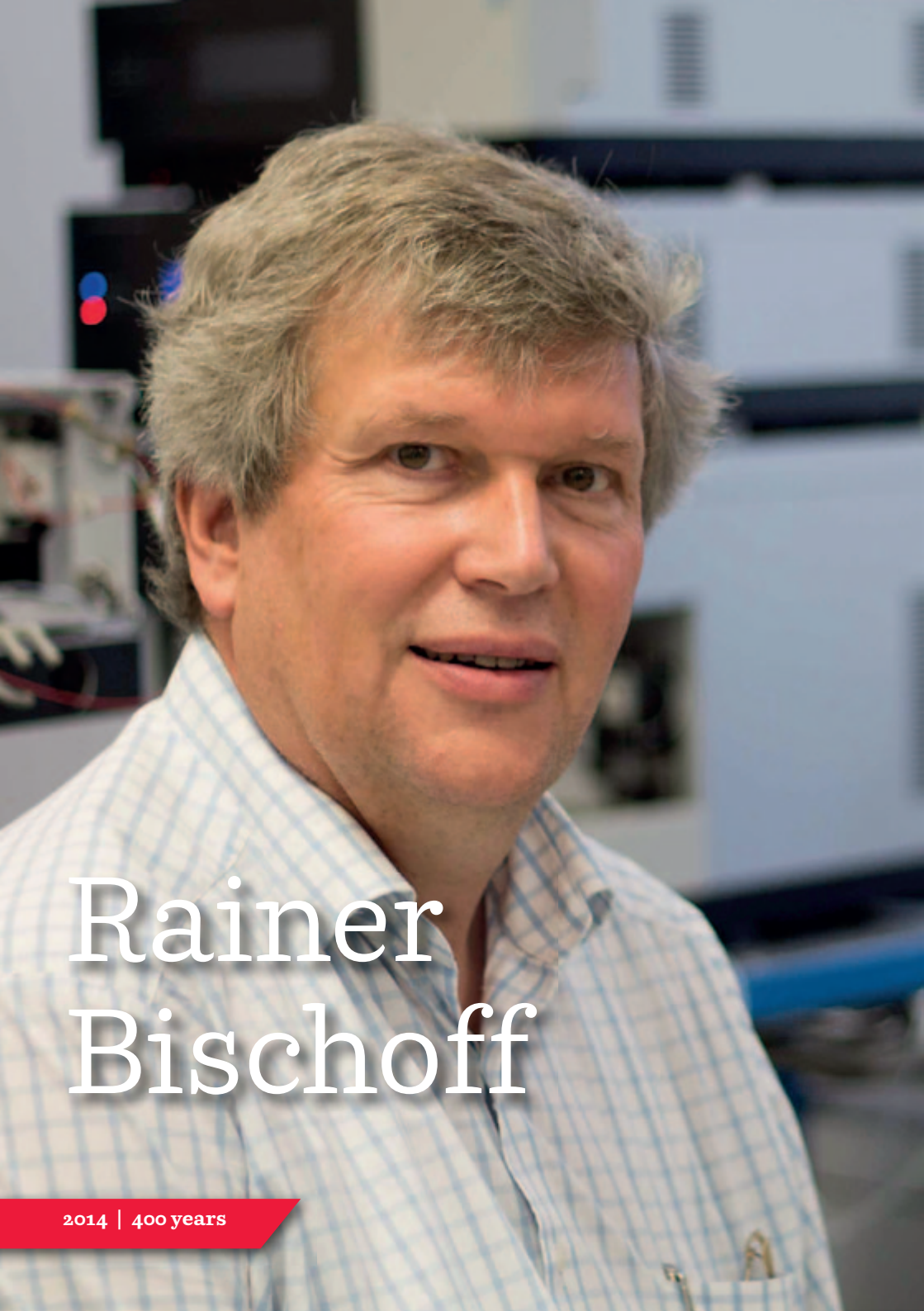
2014 | 400 years

Micro- and nanotechnologies are poised to play an integral role in the realm of modern-day science and ultimately the betterment of human life, as they offer an unprecedented means to directly probe and manipulate our molecular and cellular worlds. Research in the Pharmaceutical Analysis group over the past decade has been primarily devoted to better understanding micro- and nanofluidic systems and how they can be applied to chemical and cell biological problems. The application of microfluidics / lab-on-a-chip technologies to biological, medical and pharmaceutical questions involving the study of cells or tissue is cutting-edge. The first papers describing microfluidic devices for cell studies appeared in the late 1990's, making this area one that has seen phenomenal growth in the past decade. However, the continued success of micro- and nanofluidics in the biological and medical realms is critically dependent on multidisciplinary collaborations between scientists in these different areas. A major driving force for our research has been and continues to be projects involving scientists from the chemical, life sciences, and physics disciplines and focusing on relevant questions related to drug development and unraveling the underlying mechanisms of disease.

Ongoing projects involve the development of advanced tools for cell analysis in conjunction with drug screening (chip-based human endothelial cell culture and analysis; development of an intestine–liver chip for ADME-Tox screening). Recent acquisition of EU funding have helped expand our efforts in both these areas to include research related to the development of 1) a new nanotechnology-based paradigm for engineering vascularized liver tissue for transplantation (www.nanobio-4trans.eu/) and 2) an innovative biophotonic platform for the diagnosis of cardiovascular disease (www.liphos.eu/). Efforts have also focused on new particle separation strategies exploiting a unique recirculating flow pattern accessible only at the micrometer scale, as well as new approaches for two-phase flow control and continuous glucose monitoring. Specific projects include the development of universal miniaturized electrospray interfaces for miniaturized mass spectrometers, modules for improved multidimensional chromatography for analysis of complex samples, and a flow-based electrokinetic technique for the separation of polymer microspheres and biological particles (e.g. cells, DNA). The recent arrival of Adjunct Professor Thomas Cremers will see the introduction of techniques such as microdialysis and micro-biosensors for the analysis of living systems.

Highlights of Pharmaceutical Analysis

In collaboration with Prof. Geny Groothuis (Drug Metabolism and Toxicology, Groningen Research Institute of Pharmacy), we have demonstrated organ interaction between the intestine and liver in the regulation of bile acid synthesis by the liver.
Van Midwoud, Paul M. et al., "A microfluidic approach for in vitro assessment of interorgan interactions in drug metabolism using intestinal and liver slices", Lab Chip 2010, 10(20), 2778-2786.
In collaboration with Prof. Jerry Westerweel, we have reported a new, tunable hydrodynamic chromatography approach to size-based particle separation of micrometer-diameter particles.
Jellema, Laurens-Jan C. et al., "Tunable hydrodynamic chromatography of microparticles localized in short microchannels", Anal. Chem. 2010, 82(10), 4027-4035.



Rainer Bischoff

2014 | 400 years

The research of the Bischoff group aims at the discovery and validation of disease-relevant biomarkers, the quantification of proteins (e.g. biopharmaceuticals) in complex biological matrices and the development of novel analytical techniques. Our main analytical approach is based on LC-MS/(MS) although we have a wide range of analytical tools at our disposal.

The Biomarker research line collaborates with clinical research groups at the UMCG, for example the groups of Dirkje Postma (Pulmonary Disease) and Ate van der Zee (Gynecological Oncology). This line is further connected to joint projects with the group of Theo Luider at the EMC in Rotterdam (e.g. on Multiple Sclerosis). As part of this research line we focus on how the outcome of proteomics, peptidomics and metabolomics studies is affected by pre-analytical factors. We are currently validating a number of biomarkers for the early diagnosis of cervical cancer that were discovered by serum and tissue analysis.

The Biopharmaceutical research line is performed in collaboration with Nico van de Merbel (professor by special appointment in the group) and the group of Wim Quax (Pharmaceutical Biology). As part of this research line, we developed a number of LC-MS/MS methods that allow quantifying recombinant and endogenous proteins in serum and plasma according to international guidelines for bioanalysis. This know-how is amongst others being applied in the biomarker validation line of research (e.g. in a collaboration with the Clinical Chemistry Department at the UMCG (Ido Kema)).

The precise and accurate quantification of proteins and metabolites is a cornerstone technology for the recently founded Systems Biology Center (SBC-EMA). As part of SBC-EMA we developed a wide range of protein and metabolite quantification methods. These quantitative data form the basis for systems biology modeling of cellular ageing in yeast and mice.

Our core business is the development of novel analytical methods and their application to real-life bioanalytical problems as summarized above. As part of this work we develop methods that target post-translational protein modifications (e.g. tyrosine nitration – collaboration with Frank Dekker). It is without doubt that we currently miss much of the diversity of proteomes due to the fact that post-translational modifications are not taken into account or cannot be detected. Another part of this research line develops electrochemistry-based methods to study Phase-I drug metabolism as well as protein and peptide oxidations leading to cleavage of the peptide bond.

Highlights of Analytical Biochemistry

In collaboration with the EMC in Rotterdam, we have discovered a number of biomarkers for Multiple Sclerosis in an animal model and evaluated their response to treatment with minocycline.
Stoop, M. P., et al., (2012) Minocycline Effects on the Cerebrospinal Fluid Proteome of Experimental Autoimmune Encephalomyelitis Rats. J. Proteome Res. 11, 4315-4325

In collaboration with the Mass Spectrometry Core Facility (Hjalmar Permentier), we have shown that peptides can be electrochemically cleaved at tyrosine and tryptophan residues.
Roeser, J., et al., (2013) Boron-Doped Diamond Electrodes for the Electrochemical Oxidation and Cleavage of Peptides. Anal. Chem. 85, 6626-6632

Péter Horvatovich

2014 | 400 years

The research of the Horvatovich group aims at the development of novel computational methods for processing, analysis and interpreting mass spectrometry data of complex biological samples, both covering quantitative and compound identification aspects. In modern mass spectrometry based proteomics, peptidomics and metabolomics computational algorithms play a pivotal role to process, analyse and interpret the large amount of complex data that these experimental tools generate.

The main research line consists of developing quantitative LC-MS data pre-processing workflows including accurate automatic alignment of complex proteomics, peptidomics and metabolomics LC-MSn data. This research includes assessment of the accuracy of data pre-processing workflows and statistical analyses using differentially spiked datasets and the adaption of workflows for diverse sample preparation scenarios such as multidimensional fractionation. This research is embedded in the research activities of the Bischoff group, and performed in collaboration with IBM (Frank Suits) regarding the development of quantitative data processing pipelines and time alignment and the Biomedical Data Analysis group (Age Smilde, UvA) for statistical analysis and validation.

Other research activities include development of comprehensive data management and processing solution for proteomics analysis including quantification from LC-MS data, workflow for peptide and protein identification from LC-MSn data, selection of set of discriminating features using statistically validated methods and identification of pathways or interaction networks based on the list of discriminating peptides, proteins or metabolites. This research aims further at providing a comprehensive easy-to-use data management and processing solution for the activities of Interfaculty Mass Spectrometry Center using high-performance computational hardware in collaboration with Morris Swertz (Genomic Coordination Center, RUG) and multiple Dutch universities such as UU, WUR, ErasmusMC and the AMC.

Development of comprehensive processing and analysis platforms for Imaging Mass Spectrometry data in collaboration with IBM (Frank Suits) and glycopeptide identification workflows in collaboration with Manfred Wuhrer (VU) and Henry Lam (HKUST) have been initiated recently.

Highlights of Computational Mass Spectrometry

In collaboration with IBM development of Imaging Mass Spectrometry Data processing and analysis platform to discover spatial correlated compounds:
Suits F, Fehniger TE, Végvári A, Marko-Varga G, Horvatovich P., Correlation Queries for Mass Spectrometry Imaging, Anal Chem. 2013, 85: 4398-4404.
Assessment of feature selection methods identify set of discriminating compounds in discovery LC-MS quantitative profiling studies:
Christin C, Hoefsloot HC, Smilde AK, Hoekman B, Suits F, Bischoff R, Horvatovich P., A critical assessment of feature selection methods for biomarker discovery in clinical proteomics, Mol Cell Proteomics. 2013, 12: 263-276.

Gerrit Poelarends

2014 | 400 years

The research of the Poelarends group is aimed at the discovery and design of novel biocatalysts and biosynthetic pathways for the production of pharmaceutically relevant products. One research line focuses on the identification, characterization, and development of new biocatalysts for stereo- and regioselective addition reactions that lead to optically active α- and β-amino acids. In collaboration with other groups at the RUG, we have developed various enzymatic routes (using ammonia lyases) for the selective synthesis of substituted aspartic acids. These non-proteinogenic amino acids are highly valuable as tools for biological research and as chiral building blocks for pharmaceuticals and food additives. We have also employed laboratory evolution strategies to design ammonia lyases with improved catalytic activity, selectivity and/or an expanded substrate spectrum. Further work is currently underway to develop and apply engineered ammonia lyases for the chemo-enzymatic synthesis of various new amino compounds, including derivatives of threo-(2S,3S)-3-(benzyloxy) aspartate, an important inhibitor of glutamate transporters in the central nervous system. Another area of interest is the development of enantioselective proline-based biocatalysts for general alkylation, Michael addition, and aldol reactions as broadly useful synthetic bond-forming methodologies for the production of pharmaceuticals and fine chemicals. Attention has been focussed on the use of tautomerases in asymmetric C-C bond formation. Using 4-oxalocrotonate tautomerase (4-OT), which has the unique feature of using a nucleophilic amino-terminal proline in catalysis, we have recently developed efficient protocols for enantioselective Michael-type reactions of a variety of aldehydes with various nitroolefins. These reactions yield chiral building blocks for the synthesis of various GABA-B receptor agonists such as Baclofen, Pregabalin, Phenibut, and derivatives thereof, which are important pharmaceuticals and valuable as tools for neurobiology research. Further work is currently underway applying directed evolution to 4-OT and other tautomerases to increase the activity and scope of these proline-based enzymes in C-C bond formation. All of our projects involve an interplay of several disciplines including organic synthesis, mechanistic enzymology, enzyme kinetics, protein engineering, X-ray crystallography, spectroscopy and mass spectrometry.

Highlights of Sustainable Catalysis

In collaboration with DSM Pharmaceutical Products and several research groups at the RUG, we have developed new enzymatic routes for the stereoselective synthesis of a large variety of aspartic acid derivatives, which are highly valuable as tools for biological research and as chiral building blocks for pharmaceuticals and food additives.
Raj et al. (2012) Engineering methylaspartate ammonia lyase for the asymmetric synthesis of unnatural amino acids. Nat. Chem. 4:478-484.
Using a proline-based biocatalyst, we have developed new protocols for Michael-type reactions of a variety of aliphatic aldehydes with various nitroolefins, yielding important chiral building blocks (nitroaldehydes) for pharmaceutical synthesis. High stereoselectivity and water as reaction medium characterize this methodology.
Zandvoort et al. (2012) Bridging between organocatalysis and biocatalysis: asymmetric addition of acetaldehyde to β-nitrostyrenes catalyzed by a promiscuous proline-based tautomerase. Angew. Chem. Int. Ed. 51:1240-1243.

Angela Casini

2014 | 400 years

The research in my group is in the fields of Bioinorganic and Medicinal Inorganic Chemistry. In particular the study of the role of metal ions in biological systems and of the mechanisms of action of metal-based anticancer agents are active topics of our research program. Besides synthetic chemistry and structural characterization of new metal complexes we strongly focus on an intensive biological evaluation of the new compounds as possible anticancer agents, and on the investigation of their mechanisms of action. Of note, the peculiar chemical properties of metal-based compounds impart innovative pharmacological profiles to this class of therapeutic and diagnostic agents, most likely in relation to novel molecular mechanisms still poorly understood. The development of improved metallodrugs requires clearer understanding of their physiological processing and molecular basis of actions. Our research in the field constitutes the basis of a systematic and interdisciplinary approach to address some of the critical issues in the study of the molecular mechanisms of metallodrugs' action via the implementation of high-resolution biophysical techniques coupled with more pharmacological methods. Thus, biophysical techniques such as high-resolution mass spectrometry (both molecular and elemental sensitive), various spectroscopies and X-ray crystallography, are complemented by fluorescence microscopy, protein expression and purification, screening of enzyme activity, as well as in vitro and ex vivo screening of drug toxicity, accumulation and metabolism.
An important task of our research is to discover the unique properties of metal compounds as modulators (inhibitors or activators) of proteins/enzyme activities, and to exploit them for different therapeutic and imaging purposes or as molecular biological tools. As an example, we have identified the aquaporins (AQPs), membrane water channels with crucial roles in normal human physiology and pathophysiology, as possible target systems for metal compounds. Certainly, there is considerable potential for translating knowledge of AQP structure, function and physiology to the clinic, and there is great translational potential in aquaporin-based therapeutics. Overall, these projects encompass a variety of metal ions and different ligand systems studied by various techniques, as well as numerous collaborations in the field. Our research is highly interdisciplinary ranging from Inorganic and Bioinorganic Chemistry to Molecular Biology, Biochemistry, Toxicology and Molecular Pharmacology.

Highlights of Medicinal Inorganic Chemistry

Since several years we are involved in the identification of protein targets for metallodrugs and in the study of the metal-protein interactions at a molecular level.
Emerging protein targets for metallodrugs: new insights. A. de Almeida, B. Oliveira, J. G. Correia, G. Soveral, A. Casini,* CoordChemRev, 2013, 257, 2689-2704.
In collaboration with the University of Lisbon we have identified poten an selective inhibitors of the membrane protein channels aquaporins.
Targeting Aquaporin Function: Potent Inhibition of Aquaglyceroporin-3 by a Gold-based Compound. A. P. Martins, A. Marrone, A. Ciancetta, A. G. Cobo, M. Echevarría, T. F. Moura, N. Re, A. Casini,* G. Soveral, PlosONE 2012, 7(5), e37435.

Frank Dekker

2014 | 400 years

The research of the Dekker group aims at the development of chemistry-based techniques to investigate enzyme activity in its cellular and physiological contexts. Ultimately, these newly developed detection methods and small molecule inhibitors open up opportunities for drug discovery and diagnosis.

Enzymes play a crucial regulatory role in inflammation and represent potential drug targets. Nevertheless, the activities of these enzymes are poorly studied due to a lack of convenient tools for modulation and detection of enzyme activity in its physiological context. To address this problem further, we develop novel detection methods and small molecule inhibitors to study inflammatory signal transduction pathways.

A main line of our research is focused on protein lysine acetylations, which are known to have a broad regulatory scope in cellular signaling. Acetylations of histones form a major part of the histone code for epigenetic regulation of gene-transcription. In addition, reversible acetylations of non-histone proteins proved to be crucial for regulation of nuclear factor κB (NF-κB) mediated gene transcription. We aim to develop a novel bioorthogonal ligation strategy for chemical labeling of protein acetylation in cells. Secondly, we will systematically investigate changes in protein acetylation in response to activation of the NF-κB pathway using a proteomics strategy. Thirdly, we will develop small molecule inhibitors of acetyltransferases and study their impact on acetylations that regulate the NF-κB signaling pathway. In addition, we aim to investigate the role of oxidative enzymes such as lipoxygenases in histone acetylation and the NF-kB pathway.

The research of Frank Dekker aims to integrate different chemical and pharmaceutical disciplines to innovate drug discovery. Therefore, local collaborations have been established with Prof. Minnaard (Bioorganic chemistry), Prof. Poelarends (Pharmaceutical Biology), Prof Bischoff (Analytical biochemistry) and Prof. Schmidt (Pharmacology). In addition, productive international collaborations have been established with Prof. Zheng, (Biochemistry, Georgia State University, Atlanta, USA), Prof. Piwocka (Cell biology, Nencki Insitute, Warsaw, Polen) and Prof. Bartova (Cell biology, Institute of Biophysics, Brno, Czech Republic).

Highlights of Medicinal Chemistry

We have developed a novel inhibitor of histone acetylation, which is currently under investigation for its ability to inhibit inflammatory responses.
Ghizzoni M. et al. 6-alkylsalicylates are selective Tip60 inhibitors and target the acetyl-CoA binding site. Eur. J. Med. Chem. 2012, 47(1), 337-344.
We have developed a novel strategy for antibody free-detection on tyrosine nitration in collaboration with the group of Rainer Bischoff.
Wisastra R et al. Antibody-free detection of protein tyrosine nitration in tissue sections. Chembiochem. 2011, 12(13), 2016-2020.