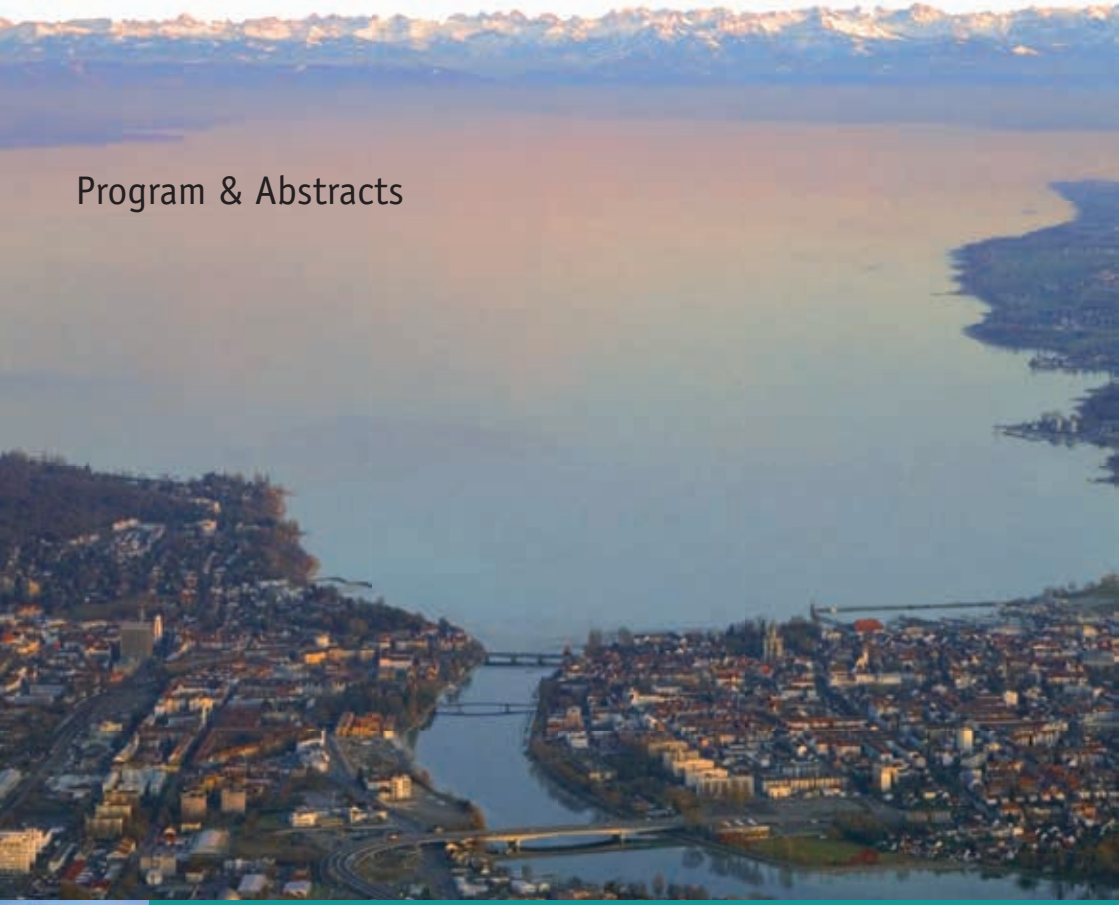
10 - 11 October 2013
University of Konstanz | A 704

Konstanz Symposium Chemical Biology

Program & Abstracts



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Organisation

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Program

Thursday, October 10 Location: University of Konstanz, A 704

Session I: **Chair: Andreas Marx**

09:00 - 09:40 h **Wei Yang**
Human DNA Polymerase: from Chemistry to Cancer Biology

09:40 - 10:20 h **Maja Köhn**
Chemical Probes for the Modulation of Phosphatase Activity

10:20 - 10:50 h **Poster Talks**

10:50 - 11:20 h **Coffee Break**

Chair: Jörg Hartig

11:20 - 12:00 h **Marie-Paule Teulade-Fichou**
Small Molecules for Targeting and Imaging Nucleic Acid Structures

12:00 - 12:40 h **Valentin Wittmann**
Function and Fate of Cellular Carbohydrates

12:50 - 14:00 h **Lunch**

Session II: **Chair: Christof Hauck**

14:00 - 14:40 h **Markus Sauer**
Localization Microscopy Coming of Age:
From Concepts to Biological Impact

14:40 - 15:20 h **Daniel Summerer**
Synthetic Protein Functions for Nucleic Acid Targeting

15:20 - 15:50 h **Poster Talks**

15:50 - 16:20 h **Coffee Break**

Chair: Thomas Mayer

16:20 - 17:00 h **Timothy Mitchison**
New Mechanisms for Old Chemotherapy Drugs

17:00 - 17:40 h **Elke Deuerling**
Ribosome-Associated Chaperones as Key Players in Proteostasis

17:40 - 18:20 h **Poster Talks**

18:30 h **Dinner & Poster Session**

The Poster Prize is sponsored by DECHEMA Biotechnologie

Friday, October 11 Location: University of Konstanz, A 704

Session I: **Chair: Elisa May**

09:00 - 09:40 h **Ashraf Brik**
Chemistry and Biology with the Ubiquitin Signal

09:40 - 10:20 h **Dorit Merhof**
Image Analysis and -Visualization for Biomedical Applications

10:20 - 11:00 h **Andreas Zumbusch**
Growth of Lipid Droplets: Insights from Live Cell Microscopy

11:00 - 11:30 h **Coffee Break**

Chair: Valentin Wittmann

11:30 - 12:10 h **Anna Mapp**
Allosteric Modulators of Protein-Protein Interactions

12:10 - 12:50 h **Thorsten Berg**
Inhibition of Protein-Protein Interactions and Transcription Factors by Small Organic Molecules

12:50 - 14:00 h **Lunch**

Session II: **Chair: Marcus Groettrup**

14:00 - 14:40 h **Christopher Kirk**
Towards Optimized Utility of Proteasome Inhibitors with Peptide Epoxyketones

14:40 - 15:20 h **Udo Oppermann**
Targeting the Histone Demethylome

15:20 - 16:00 h **Chuan He**
Dynamic DNA and RNA Methylation/Demethylation in Biological Regulation

16:00 h **Concluding Remarks**

Speakers & Abstracts

Dr. Wei Yang

Wei Yang majored in Biochemistry at Fudan University (Shanghai, China) and graduated 1991 from Professor Wayne Hendrickson's group at Colombia University (USA) with a degree in Biochemistry and Molecular Biophysics. After postdoctoral stays at Colombia and Yale University she joined the National Institutes of Health (NIH), Washington.

Since 2000 Yang is working as a senior investigator and section chief at NIH. Also she is adjunct professor at Johns Hopkins University and a member of the National Academy of Sciences.

Her current research is focused on DNA translesion synthesis and mismatch repair. Goal is to discover molecular mechanism of maintenance of genomic stability and use our knowledge to benefit mankind. Taking a multifaceted approach of X-ray, electron microscopy, mutagenesis, enzymology, protein and nucleic acid chemistry, her research group discovered the ATPase activity in MutL, the proofreading function of the MutS ATPase, and mechano-chemical coupling of ATP hydrolysis in a molecular motor. In addition, Yang's group has uncovered the mechanisms of translesion DNA synthesis in cancer avoidance and chemotherapy resistance.

Human DNA Polymerase: from Chemistry to Cancer Biology

Wei Yang, Teruya Nakamura, Ye Zhao, Mark Gregory, Christian Biertuempfel, Fumio Hanaoka

LMB, NIDDK, NIH, Bethesda, MD 20892, Kumamoto University (Japan), Zhejiang University (China), Max Planck Institute of Biochemistry (Germany), Gakushuin University (Japan)

Human DNA pol η is essential for UV survival. Deficiency of DNA pol η causes the variant form of Xeroderma Pigmentosum (XPV), characterized by sunlight-induced pigmentation changes and a highly elevated incidence of skin malignancies. Interestingly, DNA pol η is a "double agent" in cancer biology. It counteracts the DNA-damaging effect of cisplatin in anti-cancer treatment by carrying out accurate translesion synthesis opposite intra-strand cisplatin crosslinked guanines. Taking the advantage of (1) the slow reaction rate and (2) the absence of large conformational change throughout the catalytic cycle of human DNA pol η, we were able to follow the chemical steps of DNA synthesis in crystallo with the native enzyme and substrates. We found that the two well-characterized Mg^{2+} align and juxtapose the 3´-OH with the incoming nucleotide such that deprotonation of the 3´-OH doesn't depend on a specific proton acceptor. We also uncovered a third Mg^{2+} ion, which arrives with the new bond and stabilizes the intermediate and product state. The third divalent cation may be an unappreciated feature of the two-metal-ion mechanism. Finally, I will compare the mechanisms of translesion synthesis bypassing different lesions by human DNA pol η with the goal of increasing the efficiency of chemotherapy.

Speakers & Abstracts

Dr. Maja Köhn

Maja Köhn, born 1975 in Kiel (Germany), studied chemistry at the University of Kiel (Germany) 1996 to 2001. She graduated from Prof. Herbert Waldmann's group at the Max-Planck-Institute of Molecular Physiology and the University of Dortmund (Germany) in 2005 in the field of organic chemistry and chemical biology working on peptide- and small molecule microarrays. Afterwards, she joined Professor G. Verdine's group at Harvard University (USA) as a DAAD postdoctoral fellow working on polynucleotide inhibitors of the hepatitis C virus. At the end of 2007 she started her current position as a group leader at the European Molecular Biology Laboratory.

In 2010 she became a DFG Emmy Noether Research group leader. Her research interests are to control and investigate phosphatases using interdisciplinary approaches comprising synthetic chemistry, biochemistry, and molecular cell biology. The focus lies on phosphatases that promote diseases. Chemical tools include peptide- and phosphoinositide-based modulators of phosphatase activity and semisynthetic proteins for mechanistic studies.chemotherapy resistance.

Chemical Probes for the Modulation of Phosphatase Activity

Maja Köhn

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Within intracellular signaling networks, phosphatases are counter players of kinases and play crucial roles in health and disease. The investigation of phosphatases is challenging, which is also due to the lack of tools to selectively study particular phosphatases. Understanding of phosphatase function, regulation and substrate interaction is therefore still quite limited.

The development of chemical modulators of phosphatases, that is activators or inhibitors, faces several difficulties. Active site inhibitors are hardly selective due to structurally conserved active sites. They are also rarely bioavailable because phosphatases prefer to bind negatively charged molecules, which is due to their substrates being phosphorylated proteins or second messengers. For the design of chemical activators no general strategies are available, and allosteric sites that can be used for this purpose need to be identified.

I present here approaches for the design of specific chemical activators and inhibitors of protein phosphatases that are based on the natural interaction partners of phosphatases and are active inside cells.

Speakers & Abstracts

Doctor Marie-Paule Teulade-Fichou

Dr. Marie-Paule Teulade-Fichou is a Research Director at CNRS, Paris, France. She was educated both at University Denis Diderot (first doctorate in 1984 in Pharmaceutical Chemistry) and at University Pierre & Marie Curie (second doctorate in 1986 in Organic Chemistry). Then she took up a position at CNRS in 1986, to develop research on new organophosphorus compounds at the Ecole Polytechnique (Palaiseau) in the group of Professor François Mathey. In 1991 she joined the group of Professor Jean-Marie Lehn at the College de France (Paris), where she developed macrocylic chemistry towards recognition of nucleic acids. In 2007, she was nominated as deputy director of the Chemical Biology Laboratory of Institut Curie and she is currently team-leader of the group "Structure and Fluorescent Probes for Nucleic Acids". Her current interest is focused on the design of new nucleic acids targeted drugs for anticancer research and for elucidating DNA-related molecular basis of cancer. In detail the research of the group is focused on the design of synthetic probes for structural recognition and fluorescent sensing of unusual DNA and RNA structures (quadruplexes, hairpins, mismatches). The first objective is to interfere with the binding and the processing of the related protein machineries (helicases, repair proteins, telomere capping proteins). In particular the conception of quadruplex ligands has constituted a central research topic in the last years (more than 40 articles). In fine the objective is to provide new nucleic acid targeted drugs for anticancer research and for elucidating DNA-related molecular basis of cancer. More recently new research for conception of new fluorescent probes for biphotonic microscopy has been initiated.

Dr. Marie-Paule Teulade-Fichou has published over 120 articles in the field of organic chemistry and bioorganic chemistry of nucleic acids and she is co-inventor of five patents in the field of anticancer drugs and fluorescent probes for nucleic acids.

Small Molecules for Targeting and Imaging Nucleic Acid Structures

Marie-Paule Teulade-Fichou

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For many years our research efforts have been focused on the design of structure and fluorescent probes for nucleic acids. Our targets are more specifically alternative secondary structures such as G-quadruplexes that can be found in G-rich regions and local pairing defects such as base mismatches that result from base misincorporation or damages. These structures are involved in various genomic dysfunctions and may ultimately cause genetic instability related to cancer development. Our aim is to provide chemical biology tools for better understanding the roles of these structures and their processing by proteins. In parallel the new compounds may be considered as prototypes for anticancer drug development.

Along these lines, we have developed a number of new heterocyclic scaffolds that have been engineered to display on the one hand selective recognition of the target DNA structure and on the other hand a switchable fluorescence emission acting as reporter. Selected examples illustrating our main achievements in the field will be described:

1) Design of bisquinolinium scaffolds acting as G-quadruplex DNA probes [1,3]
2) Design of Cyclobismacrocycles binding to homopyrimidine mismatches [4,6]
3) Design of Vinyl-Triphenylamine dyes shaped for two-photon absorption and AT-rich regiospecificity [7,9]

In each case, we will give a short overview of the synthetic approaches, the structure of the interaction with DNA identified by NMR or modelling and the practical applications for in vitro analysis and in-cell probing.

References:

[1] De Cian et al Highly efficient Bisquinolinum compounds for quadruplex recognition J.Amer. Chem.Soc. 2007, 129, 1856.
[2] P. Yang et al. Engineering Bisquinolinium-Thiazole orange conjugates for fluorescent sensing of G-quadruplex DNA Angew.Chem. Int Ed. 2009,48, 2188-2191.
[3] E.Largy et al. Visualizing quadruplexes: from fluorescent ligands to light up probes Topics in Current Chem. 2013, Vol 330, 111.
[4] M. Bahr et al. Recognition of Pyrimidine-pyrimidine DNA mismatches by distance-constrained macrocyclic Bisintercalators. Nucleic Acids Res. 2008, 36, 5000.
[5] A. Granzhan, M.-P. Teulade-Fichou A Fluorescent Bisanthracene Macrocycle discriminates between matched and mismatch-containing DNA. Chemistry Eur.J. 2009, 15, 1314.
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[7] G. Bordeau et al. Trinaphthylamines as robust organic material for two-photon-induced fluorescence J. Am. Chem. Soc. 2008, 130,16836. WO2008/055969.
[8] B. Dumat et al. Vinyl-Triphenylamine Dyes, a New Family of Switchable Fluorescent Probes for Targeted Two-photon Cellular Imaging: from DNA to Protein Labeling, Org Biomol.Chem special issue 2012, 30, 6054.
[9] B. Dumat et al. DNA switches on the two-photon efficiency of an ultrabright triphenylamine dye with exquisite AT regiospecificity. Submitted.

Speakers & Abstracts

Professor Valentin Wittmann

Valentin Wittmann studied Chemistry at the Goethe-University of Frankfurt (Germany). In 1994 he obtained a PhD from the Technical University of Munich (Germany) for his work on C-glycopeptides under the supervision of Prof. Horst Kessler. Subsequently, he carried out postdoctoral research with Prof. Christian Griesinger at the Goethe-University of Frankfurt (Germany) in the field of stable-isotope-labeled oligonucleotides and with Prof. Chi-Huey Wong at The Scripps Research Institute in La Jolla, California (USA) working on the chemoenzymatic synthesis of oligosaccharides. In 1997 he returned to Frankfurt to start independent research. Since 2003 he is professor of organic/bioorganic chemistry at the University of Konstanz (Germany).

From 2006 until 2011 he was the Dean of Studies of the Department of Chemistry. His main research area is the chemical biology of carbohydrates including the investigation of multivalent carbohydrate-protein interactions, development of ligation reactions, metabolic oligosaccharide engineering, and RNA-targeting antibiotics.

Function and Fate of Cellular Carbohydrates

Valentin Wittmann

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Carbohydrates are involved in a myriad of cellular functions. In the form of glycoconjugates they modulate activity and physicochemical properties of proteins and lipids, and they are themselves involved in molecular recognitions processes. However, our understanding of the underlying mechanisms is just at the beginning and methods for their elucidation need further development. Challenges in current glycobiology include the elucidation of the mechanisms of multivalent carbohydrate-protein interactions and the development of tools to monitor glycan structures in cells and organisms. This lecture gives an overview of our group's activities in these fields. To unravel the molecular details of carbohydrate-protein interactions we employed X-ray crystallography and, more recently, distance measurements in the nanometer range by EPR spectroscopy using spin-labeled carbohydrates. In contrast to proteins, that are routinely labeled by genetic methods, such as expression as GFP fusion proteins, comparable methods are not available for glycans. We employed metabolic oligosaccharide engineering for monitoring glycans in different cell lines as well as in zebrafish. To increase the repertoire of existing bioorthogonal ligation reaction, we developed a new ligation method based on a Diels-Alder reaction with inverse-electron-demand of electron deficient 1,2,4,5-tetrazines and terminal alkenes. Since this reaction is orthogonal to the azide-alkyne cycloaddition (click reaction), detection of two different sugars (one alkene-labeled the other azide-labeled) is possible within one experiment.

Speakers & Abstracts

Professor Markus Sauer

Markus Sauer, born 1965 in Pforzheim (Germany), studied chemistry at the Universities of Karlsruhe, Saarbrücken and Heidelberg. He graduated at the University of Heidelberg in 1995 in the field of time-resolved fluorescence spectroscopy and design of new fluorophore. After finishing his PhD his research focused on single-molecule fluorescence spectroscopy and imaging, and the development of single-molecule DNA sequencing. After a short-term visit at LBNL Berkeley where he was engaged with time-resolved fluorescence imaging of QDs in living cells he was decorated with the BioFuture award of the BMBF to build up his own research group on single-molecule fluorescence detection, identification and analysis at the Institute of Physical Chemistry, University of Heidelberg. After finishing his habilitation in Physical Chemistry in 2002 he accepted an offer from the Physics Department of Bielefeld University and moved to Bielefeld as full Professor for Applied Laser Physics and Laser Spectroscopy (C4) in 2003. 2009 he moved to the Julius-Maximilians-University Würzburg as full Professor for Biotechnology and Biophysics (W3). In the last 10 years he invented direct optical reconstruction microscopy (dSTORM) a powerful super-resolution fluorescence imaging method based reversible photoswitching of standard fluorescent probes in the presence of thiols.

Localization Microscopy Coming of Age: From Concepts to Biological Impact

Markus Sauer

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Super-resolution fluorescence imaging by single-molecule photoactivation or photo-switching and position determination (localization microscopy) has the potential to fundamentally revolutionize our understanding of how cellular function is encoded at the molecular level. Among all powerful high-resolution imaging techniques introduced in recent years localization microscopy excels at it delivers single-molecule information about the distribution and, adequate controls presupposed, even absolute numbers of proteins present in subcellular compartments. This provides insights into biological systems at a level we are used to think about and model biological interactions. We briefly introduce basic requirements of localization microscopy, its potential use for quantitative molecular imaging, discuss present obstacles and ways to bypass them, and give future prospects how the refined understanding of photoswitching mechanisms can pave the way to further increase the spatial resolution of localization microscopy approaching real molecular dimensions.

Speakers & Abstracts

Dr. Daniel Summerer

Daniel Summerer, born 1975 in Cologne (Germany), studied chemistry from 1994 to 2000 at the University of Bonn (Germany) and graduated 2004 from Prof. Andreas Marx group were he did research on the chemical biology of DNA replication. Afterwards, he joined Professor Peter G. Schultz´s group at the Scripps Research Institute (USA) as a Humboldt fellow, working on the chemical biology of RNA translation / expansion of the genetic code. In 2006 he started as project manager at febit holding, based in Heidelberg (Germany) and Lexington (USA) in the field of genomics (microarrays and next-generation-sequencing), where he became Head of Application Development in 2007. In 2011, he moved as Fellow of the Zukunftskolleg to the University of Konstanz to pursue his independent academic career. His research circles around the molecular mechanisms of gene expression. Here, a particular emphasis is the design of artificial protein functions that offer principles of nucleic acid recognition and chemical conversion not offered by natural proteins and thus enable otherwise inaccessible insights into nucleic acid function. This research involves the organic synthesis of unnatural amino acids and nucleic acid analogs, genetic code expansion, protein evolution and genomics/transcriptomics.

Synthetic Protein Functions for Nucleic Acid Targeting

Daniel Summerer

Department of Chemistry and Zukunftskolleg, University of Konstanz

DNA-binding proteins that discriminate between cytosine and 5-methylcytosine (mC) are important analytical tools in epigenetics. However, proteins currently in use are either not sequence-selective or exhibit sequence constraints, which restricts the flexibility and resolution of locus-specific mC-detection. We report that transcription-activator-like effectors (TALEs) enable the highly resolved detection of mC at user-defined loci within large, eukaryotic genomes. Their free programmability of sequence-recognition makes TALEs a general alternative to nucleic acid probes in a wide range ofgenomics techniques that offer the direct and simultaneous read-out of both the genetic and epigenetic information of DNA.

Speakers & Abstracts

Professor Timothy J. Mitchison

Dr. Mitchison received his Ph.D. in Biochemistry and Biophysics from the University of California, San Francisco. During his postdoctoral work at the University of California, San Francisco with Dr. Marc Kirschner, he discovered dynamic Instability of microtubules, a fundamental aspect of cytoskeleton biology and since then has studied the biochemistry, dynamics and spatial organization of microtubules and actin filaments with a focus on cell division mechanisms. Much of his lab's work in this area is based on live fluorescence imaging and has been at the forefront of the application of novel optical methodologies to living cells. In 1997 he moved to Harvard Medical School to Co-direct the Institute of Chemistry and Cell Biology, a collaboration between chemists and cell biologists, to develop and apply small molecule screening capabilities in academia. As part of this effort, Dr. Mitchison's developed a strong interest in cancer chemotherapy and in more rational approaches to drug development in general. In 2004 he co-founded a new department, Systems Biology, that aims to bring systematic and quantitative methods to bear on problems in basic cell biology and medicine and in 2011 he helped found the Systems Pharmacology initiative at Harvard Medical School, a major interest area within the department, co-Directed by Peter Sorger and himself.

Dr. Mitchison is the Hasib Sabbagh Professor of Systems Biology, co-Director of the Initiative in Systems Pharmacology, and Deputy Chair for the Department of Systems Biology at Harvard Medical School.

New Mechanisms for Old Chemotherapy Drugs

Timothy Mitchison

Harvard Medical School, Boston MA 02115, USA

Cancer chemotherapeutic drugs can be broadly divided into cytoxic, hormonal and targeted, but new modalities are needed to combat metastatic disease. We are approaching this problem by analyzing the biochemical and cellular mechanisms of successful and failed drugs. Anti-microtubule drugs such as paclitaxel are though to selectively kill dividing cells via mitotic arrest. We compared responses to anti-microtubule and targeted anti-mitosis drugs in cell culture and xenograft models using single cell imaging. We propose that the mechanism in common to the two drug classes, death via mitotic arrest, is responsible for the anti-proliferative side effects of chemotherapy. Tumor killing efficacy appears to arise from a novel interphase cell killing pathway unique to the anti-microtubule drugs and the tumor environment, which we are trying to recapitulate in cell culture. Another approach to chemotherapy is to activate tumor resident innate immune cells to damage the tumor. We have analyzed the mechanism of the anti-tumor flavonoids FAA and DMXAA that cure mouse tumors by this mechanism, but failed in man. We have identified a candidate protein target in mouse macrophages, and find that the human homolog does not bind the drugs, which may explain lack of efficacy in man. These studies identify a promising target for a new class of chemotherapy drugs that works by activating innate immunity.

Speakers & Abstracts

Professor Elke Deuerling

Elke Deuerling, born in 1967 in Lichtenfels (Germany), studied Molecular Biology from 1986 to 1991 at the Universities of Erlangen-Nürnberg and Bayreuth (Germany). She graduated from Prof. W. Schumann's group at the University of Bayreuth in 1995 in the field of genetics. In 1996, she joined Prof. Bernd Bukau at the University of Freiburg (Germany) as a postdoctoral fellow and later on as an assistant professor working on E. coli Trigger Factor. In 2003 she obtained her Habilitation and venia legendi for Molecular Biology and Biochemistry at the University of Freiburg. 2002 - 2003 she was an assistant professor at the Center for Molecular Biology (ZMBH) in the group of Prof. B. Bukau, Ruprecht-Karls-University Heidelberg, and from 2004-2007 an independent Heisenberg fellow. Since April 2007 she is a full professor at the University of Konstanz (Germany), Department of Biology, and holds the chair of Molecular Microbiology. Elke Deuerling is Speaker of the Collaborative Research Center 969 "Chemical and Biological Principles of Cellular Proteostasis" funded by the Deutsche Forschungsgemeinschaft (DFG). The aim of her research is to understand the structural, functional and mechanistic principles of molecular chaperones in the process of de novo protein folding in health and disease. Genetic and biochemical investigations of molecular chaperones are performed using three different model organisms, i.e. the bacterium Escherichia coli, the yeast Saccharomyces cerevisiae as well as the nematode Caenorhabditis elegans.

Ribosome-Associated Chaperones as Key Players in Proteostasis

Elke Deuerling

Molecular Microbiology, University of Konstanz

The synthesis and folding of new proteins is a fundamental and essential biological process in living cells. This process is delicate and error-prone and thus requires the guidance by molecular chaperones. Besides cytosolic or organelle-specific chaperones, all organisms evolved ribosome-associated chaperones that support early folding events and prevent protein misfolding and aggregation. The loss of chaperone functions can cause severe cellular defects and contributes to the development of protein misfolding diseases such as Alzheimer´s and Huntington´s disease.

Data will be presented on the in vivo roles of eukaryotic ribosome-associated chaperone systems NAC and Ssb-RAC. Besides supporting cotranslationally the folding of newly synthesized proteins, these chaperone systems also regulate the influx of new proteins into the cellular proteome by modulating ribosome biogenesis and protein synthesis. In addition, these chaperones associate with protein aggregates and modulate the toxicity of polyQ proteins in yeast. Thus, ribosome-associated chaperones are potent modulators of cellular proteostasis by controlling protein synthesis, folding and aggregation processes.

Speakers & Abstracts

Professor Ashraf Brik

Professor Ashraf Brik completed his B.Sc. in Chemistry in 1996 at the Ben-Gurion University of the Negev (BGU) and his M.Sc. in 1998 in the Technion-Israel Institute of Technology. In 1998, he moved to The Scripps Research Institute (TSRI) where he worked with Professor Ehud Keinan and Professor Philip Dawson in the area of chemical synthesis of proteins. From 2002-2004 he was a postdoctoral fellow and later a Sr. Research Associate working with Professor Chi-Huey Wong (TSRI) in the area of enzyme inhibition and glycoprotein synthesis. In 2007, Professor Brik returned to his Alma Mater as an Assistant Professor in the Chemistry Department at BGU and was promoted to Associate Professor in 2011 and to Full Professor in 2012. Prof Brik is the recipient of the Israel Chemical Society Prize for the Outstanding Young Investigator Award for 2011 and the Tetrahedron Young Investigator Award in Bioorganic and Medicinal Chemistry for 2013.

Chemistry and Biology with the Ubiquitin Signal

Ashraf Brik

Department of Chemistry, Ben-Gurion University of the Negev

In this talk, I will present our novel synthetic approaches for peptide and protein ubiquitination to shed light on the various unknown aspects of the ubiquitin signal in cellular pathways. The attachment of ubiquitin protein to a specific protein target is a widely utilized posttranslational modification in eukaryotes, which is involved in various aspects of cellular functions e.g. protein degradation and DNA repair. Notably, ubiquitination has been implicated in several diseases including cancer and neurodegenerative diseases. In this process, three distinct enzymes, known as the E1-E3 systems, collaborate to achieve a site-specific tagging of the lysine residue(s) in the target protein. The overwhelming majority of studies in the field rely on the in vitro enzymatic reconstitution of this complex posttranslational modification for the protein of interest. However, this process is often challenged by the heterogeneity of the modified protein, the isolation of the specific ligase (E3) and obtaining reasonable quantities of the ubiquitinated protein. Our group reported a highly efficient and site-specific peptide and protein ubiquitination utilizing our developed thiolysine residue and synthetic ubiquitin bearing C-terminal thioester functionality to emulate the action of the enzymatic machinery. This battery of chemical tools allowed for the first semisynthesis of homogeneous ubiquitinated alpha-synuclein to support the ongoing efforts aiming at studying the effect of ubiquitination in health and disease. Additionally, we also achieved the total chemical synthesis of all di-ubiquitin chains as well as the K48-linked tetra-ubiquitin, composed of 304 amino acids. More recently, the synthesis of ubiquitinated peptides linked to mono-, di-, tri-, and tetra-ubiquitin was also made possible, which enabled us to examine the behavior of these novel bioconjugates with several deubiquitinases. We also expanded these approaches to target different deubiquitinases in the ubiquitin system to shed light on their role in health and disease, and ultimately, for drug development.

Speakers & Abstracts

Professor Dorit Merhof

Dorit Merhof, born 1978 in Erlangen (Germany), studied computer science at the University of Erlangen-Nuremberg (Germany) from 1998 to 2003. She graduated from Prof. Günther Greiner's group at the University of Erlangen-Nuremberg in 2007 in the field of Computer Graphics and Visualization, working with medical image data. Afterwards, she joined Siemens Molecular Imaging (SMI), Oxford (UK) as a research scientist. In October 2009, she followed a call of the University of Konstanz (Germany) for an assistant professorship in Visual Computing. At the University of Konstanz, Dorit Merhof established the INCIDE research center, which specifically supports interdisciplinary research. INCIDE provides and develops algorithms for the analysis and visualization of highly complex scientific data repositories, i.e. efficient methods for (semi) automated data analysis, data mining, numerical simulation and parameter estimation, and for visual and interactive data exploration. In July 2013, Dorit Merhof followed a call of the RWTH Aachen University for a chair in Imaging & Computer Vision. Her current research comprises image analysis and visualization for data originating from various applications in the natural and life sciences, which often requires dedicated processing and analysis.

Image Analysis and -Visualization for Biomedical Applications

Dorit Merhof

Institute of Imaging and Computer Vision, RWTH Aachen University

Nowadays, a wealth of image data is generated in biology and associated sciences, which requires expert knowledge for analysis and visualization. The INCIDE center (Interdisciplinary Center for Interactive Data Analysis, Modelling and Visual Exploration) at the University of Konstanz provides and develops algorithms for automated analysis and for interactive exploration of complex scientific data repositories comprising microscopy images and high-throughput screening data.
Since analysis and visualization have become a real bottleneck in biological sciences, this data provides interesting and challenging research questions from a computer science point of view. In this talk, a selection of interdisciplinary projects completed in INCIDE is presented.

Speakers & Abstracts

Professor Andreas Zumbusch

Andreas Zumbusch studied Chemistry and Experimental Physics at Ludwig-Maximilians Universität (LMU) Munich, Germany. He graduated 1992 from Prof. Orrit's group at the Centre de Physique Moleculaire Optique et Hertzienne, CNRS, Bordeaux, France. His doctoral thesis was carried out at the Institue of Inorganic Chemistry at Universität Karlsruhe. In 1997 Zumbusch received a Feodor-Lynen fellowship of the Alexander von Humboldt-Foundation and a Post-doctoral fellowship of the Associated Western Universities and stayed at the Pacific Northwest National Laboratory, Richland, WA, USA, in the group of Prof. Dr. X. S. Xie. He obtained his Habilitation and venia legendi in Physical Chemistry at LMU in 2003. Afterwards he worked as a Reader in Biophysics, at Department of Physics and Astronomy, University College London and served as Head of Unit in Natural Sciences and Technology at the Austrian Science Fund. Since 2006 he is a full Professor of Physical Chemistry at the University of Konstanz. His research interests are based in the field of Coherent Anti-Stokes Raman Scattering (CARS) microscopy, spectroscopy and microscopy of single and the synthesis and spectroscopic characterization of new fluorophores. He applies these techniques to solve problems from soft matter physics and lipid biology.

Growth of Lipid Droplets: Insights from Live Cell Microscopy

Andreas Zumbusch, Christian Jüngst, Martin Winterhalder, Matthias Klein

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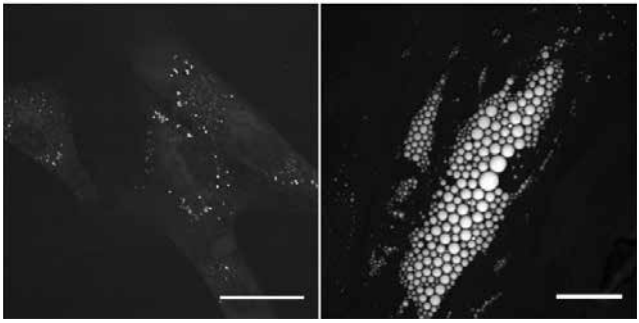
Lipid droplets (LD) are lipid rich structures which are found in many prokaryotic and eukaryotic cells. Depending on the cell type, their sizes can vary greatly, with diameters ranging from some tens of nm in most cells to several tens of µm in adipocytes. Work of the last decade has shown that LDs have to be regarded as true cellular organelles with a broad variety of functions. Despite the grown awareness of their importance, little is known so far about the growth and degradation processes of LDs. In this presentation, we will show how long-term studies of unlabeled mesenchymal stem cells based on CARS microscopy shed light on the growth of LDs during adipogenic differentiation. Our findings hint at the possibility that a protein stabilized fusion pore is involved. We analyze the lipid transfer data obtained in the microscopy studies in the framework of a Hagen-Poiseuille model. For the data analysis, the viscosity of the transferred material has to be known. We demonstrate that a viscosity dependent molecular rotor dye can be used to measure LD viscosities in live cells. On this basis, we calculate the diameter of a putative lipid transfer channel to lie in the range of 2-20 nm depending on the size of the involved LDs.



CARS image of lipid droplets in undifferentiated (left) and adipogenically differentiated (right) mesenchymal stem cells. Scale bar 30 µm.

Speakers & Abstracts

Professor Anna Mapp

Anna Mapp completed her A.B. in chemistry at Bryn Mawr College (US) in 1992 before moving to the University of California-Berkeley to obtain the PhD in Organic Chemistry working with Professor Clayton Heathcock. She then carried out postdoctoral research as an NRSA Postdoctoral Fellow at Caltech before joining the faculty in the Department of Chemistry at the University of Michigan in 2000. Dr. Mapp was promoted to Associate Professor in 2006, Full Professor in 2010, and was named the Edwin Vedejs Collegiate Professor of Chemistry and a Research Professor of the Life Sciences Institute in 2013. Additionally she has since 2010 served as the Director of the Program in Chemical Biology at the University of Michigan after having played a leadership role in its development and implementation. Anna Mapp has established a multidisciplinary research program focused on the discovery and in situ characterization of the protein-protein interactions that transcriptional activator proteins use to regulate transcription in healthy and diseased tissue; these data are used to discover novel drug-like small molecules that either promote or inhibit these protein-protein interactions in cancer. Mapp has received a number of awards based on research achievements including the Presidential Early Career Award for Scientists and Engineers, the Eli Lilly Award in Biological Chemistry, and the Arthur C Cope Scholar Award.

Allosteric Modulators of Protein-Protein Interactions

Anna Mapp

University of Michigan, USA

Most essential cellular functions are accomplished by dynamic macromolecular assemblies comprised of least one enzymatic component surrounded by non-enzymatic moieties that enforce timing, location and specificity. In the case of transcription, transcriptional activators direct the assembly of the RNA polymerase II holoenzyme at specific gene promoters at particular time points; once the polymerase is engaged, the complex disassembles as transcription initiates. This is accomplished through transient protein-protein interactions (PPIs) between conformationally dynamic binding partners. Mis-regulation of activator-transcriptional machinery assembly events is at the heart of many human diseases and the PPIs that direct these dynamic processes are critical for probe development and for therapeutic targeting. We will discuss two new strategies for the discovery of small molecule modulators of activator-transcriptional machinery PPIs, strategies that have produced molecules with unique potency and specificity profiles due to their allosteric mechanism.

Speakers & Abstracts

Professor Thorsten Berg

Thorsten Berg, born in 1967, studied chemistry at the University of Cologne (Germany). After obtaining his Doctorate in Organic Chemistry in 1996 from Prof. Dieter Enders' group at RHTH Aachen University (Germany), he joined Prof. K. D. Janda's group at The Scripps Research Institute (USA) as a DAAD post-doctoral fellow. Subsequently, he joined the group of Prof. P.K. Vogt at The Scripps Research Institute (USA), where he worked on small-molecule inhibitors of transcription factor dimerization. In 2001, he started his own research group within the Department of Molecular Biology (Director: Prof. A. Ullrich) at the Max Planck Institute of Biochemistry in Martinsried (Germany). From 2003 to 2008, he carried out his habilitation in Organic Chemistry and Biochemistry at the Technical University of Munich (Prof. H. Kessler, Germany). In 2009, he took up a Professorship for Organic Chemistry / Chemical Biology at the University of Leipzig (Germany), where he is currently Director of the Institute of Organic Chemistry. The overall aim of his research is to devise innovative methods for the efficient design, development, and identification of small organic modulators of protein-protein interactions.

Inhibition of Protein-Protein Interactions and Transcription Factors by Small Organic Molecules

Thorsten Berg

Institute of Organic Chemistry, University of Leipzig

According to current thinking, only one in seven human proteins can be targeted by small organic molecules. Since most biological processes are performed by protein complexes, inhibitors of specific protein-protein interactions are likely to influence the functions of most proteins. Therefore, the inhibition of protein-protein interactions represents a powerful approach by which to expand the proportion of proteins that can be targeted by small organic molecules. In support of this notion, we have previously demonstrated that dimeric transcription factors can be efficiently and selectively inhibited by small molecules that interfere with the protein-protein interactions required for their activity. Moreover, small-molecule inhibitors of protein-protein interactions can provide alternative methods by which to interfere with the function of established small-molecule targets, i.e. protein kinases. In collaboration with Prof. K. Strebhardt (University of Frankfurt, Germany), we have provided proof-of-principle that the serine/threonine kinase Plk1 can be targeted by small-molecules which do not target its ATP binding pocket, but instead inhibit the protein-protein interactions required for correct intracellular localization of the enzyme.

Stimulated by our discoveries of small molecules which inhibit protein-protein interactions and transcription factors, we hypothesized that known bioactive molecules could possess similar activities. In the course of these studies, we have identified hitherto unknown activities of certain natural products and FDA-approved drugs on transcription factors and protein-protein interactions, which will be detailed in the presentation. Our data give new insights into the molecules' biological activities. In addition, they highlight the role of known bioactive compounds as a prominent source of lead structures for the development of inhibitors of protein-protein interactions and transcription factors.

Speakers & Abstracts

Christopher J. Kirk, Ph.D.

Christopher Kirk received his doctorate at the University of Michigan (US) where he studied T-cell signal transduction in the laboratory of Richard Miller. He remained at Michigan for a postdoctoral fellowship focused on gene-modified dendritic cell cancer vaccines under James Mulé. Since 2001, Christopher has been in the biotechnology industry focused on drug discovery research and drug development in the areas of cancer and inflammation. At Deltagen, Inc., he focused on discovering novel drug targets through high throughput gene knockout technology. In 2004, he became one of the original scientists at Proteolix, Inc. where the cancer drug Kyprolis™ (carfilzomib) was discovered and developed. In 2009, Proteolix was acquired by Onyx Pharmaceuticals, which continues to perform research and development on proteasome inhibitors and protein degradation and homeostasis as a therapeutic strategy to treat cancer and inflammatory diseases.

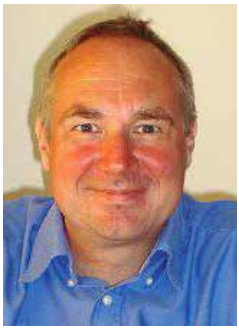
Towards Optimized Utility of Proteasome Inhibitors with Peptide Epoxyketones

Christopher J. Kirk

Vice President Research, Onyx Pharmaceuticals, San Francisco, USA

The ubiquitin/proteasome pathway is the primary means by which intracellular protein degradation occurs. The 26S proteasome, a multicatalytic proteolytic machine, plays a central role in regulating most facets of cell physiology and has been the target of drug discovery programs in cancer and inflammatory diseases. Proteasome inhibition is a validated therapeutic strategy for the treatment of B-cell neoplasms. Originating from the natural product epoxomicin, we have generated several peptide epoxyketones, with distinct pharmaceutic and pharmacologic profiles as proteasome inhibitors. One of these compounds, carfilzomib, has recently received FDA approval for the treatment of relapsed and refractory myeloma. A second compound, oprozomib, which is an orally bioavailable analog of carfilzomib, has entered clinical trials with encouraging initial results in the treatment of multiple myeloma. Another focus of our research is subunit selective inhibitors of the proteasome. Our discovery of subunit-selective peptide epoxyketones has helped elucidate distinct roles for both the immunoproteasome and constitutive proteasome in immune cell biology. Immunoproteasome selective inhibitors are highly efficacious in mouse models of autoimmunity and represent a new class of therapeutics for the treatment of inflammatory diseases.

Speakers & Abstracts



Professor Udo Oppermann

Udo Oppermann obtained a Diploma in Human Biology in 1990 and PhD in Pharmacology and Toxicology in 1994, both with distinctions from Philipps University Marburg, Germany. He went on to become Associate Professor at Karolinska Institutet, Stockholm, in the Department of Medical Biochemistry and Biophysics where he stayed until 2004. After a sabbatical stay at Yale University, he has been a Principal Investigator of the Structural Genomics Consortium (SGC) in Oxford since its inception in 2003. In 2008 he became Professor in Molecular Biology at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, and he is now Deputy Director of the Institute of Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, as well as a Fellow of St Catherine's College.

The research in the Oppermann group focuses on the biology and structure-activity relationships of human metabolic protein families of all types but with emphasis on oxidoreductases such as short- or medium chain dehydrogenases/reductases (SDR, MDR), or oxidative enzymes such as the ketoglutarate dependent oxygenases. The use of chemical biology to understand human biology is a major focus of the group and is currently applied to the field of epigenetic mechanisms in stem cell biology, as well as chronic inflammatory and metabolic diseases.

Targeting the Histone Demethylome

Udo Oppermann

Botnar Research Centre, University of Oxford, OX3 7LD, UK
Structural Genomics Consortium, University of Oxford, UK

The reversible Ne-methylation of lysyl side-chains in histones, catalyzed by distinct classes of methyl transferases and demethylases, has emerged as an important mechanism in orchestration of chromatin state, gene regulation and DNA repair. Despite the progress achieved over the past years in understanding regulation and interactions of these enzymes, chemical tools to interrogate their biological functions, especially for the histone demethylases, are lacking. This impasse is addressed in a public-private partnership that aims to develop potent, selective and cell-active chemical probes to investigate chromatin modification.

Covalent modifications of histone tails play essential roles in mediating chromatin structures and epigenetic regulation. JmjD3 and UTX are Jmj-type histone demethylases, belong to the KDM6 subfamily, and catalyze the removal of methyl groups of methylated lysine 27 on histone 3 (H3K27), a critical mark to promote polycomb mediated repression and gene silencing. The importance of these demethylase enzymes in e.g. cancer biology or immunology has been shown by molecular genetic approaches, however it is unclear if their roles are mediated by protein-protein interaction in transcriptional complexes or by their enzymatic function.

Here we report the first highly selective and potent small molecule enzyme inhibitor for the KDM6 histone demethylase subfamily that is used to probe cellular functions of H3K27 demethylases. The inhibitor is active in HeLa cells and promotes a dose-dependent increase of global H3K27 methylation in both JmjD3 transfected or untransfected cells. This presentation will provide insight how the KDM6 enzymes control critical pathways in inflammation, oncology and development.

Our results resolve the ambiguity associated with the H3K27 demethylase function of KDM6 members, demonstrate the relevance and pharmacological tractability of JmjD3 and UTX, and provide a possible path to selective pharmacological intervention across the Jmj family of histone demethylases.

Speakers & Abstracts

Professor Chuan He

Chuan He is a Professor in the Department of Chemistry and Director of the Institute for Biophysical Dynamics at the University of Chicago. He is also a joint Professor in the Department of Chemical Biology and Director of the Synthetic and Functional Biomolecules Center at Peking University. He was born in P. R. China in 1972 and received his B.S. (1994) from the University of Science and Technology of China. He received his Ph. D. degree from Massachusetts Institute of Technology in chemistry in 2000. After being trained as a Damon-Runyon postdoctoral fellow at Harvard University from 2000-2002, he joined the University of Chicago as an assistant professor, and was promoted to associate professor in 2008 and full professor in 2010. He is also a member of the Cancer Research Center at the University of Chicago. He has been recently selected as an Investigator of the Howard Hughes Medical Institute. His research spans a broad range of chemical biology, cell biology, molecular biology, biochemistry, structural biology, and genomics. His recent research concerns reversible RNA and DNA methylation in biological regulation.

Dynamic DNA and RNA Methylation/Demethylation in Biological Regulation

Chuan He

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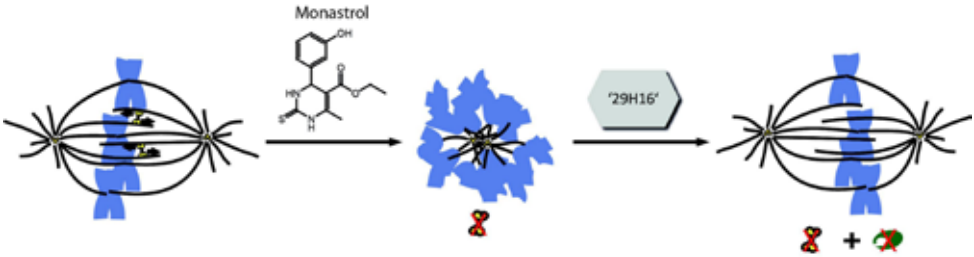
Reversible chemical modifications on nucleic acids and proteins determine cell fates. The five bases that comprise nucleic acids —adenine, guanine, cytosine, thymine, and uracil —can be chemically and enzymatically modified. These chemical events can have significant biological consequences, particularly for gene expression. I will present chemical strategies we have developed to enrich, sequence, and study novel nucleic acid modifications that include 5-hydroxymethylcytosine and its further oxidized forms in mammalian genome. Several AlkB family proteins have been identified in the human genome that may mediate nucleic acids oxidation. Some of these proteins play critical roles in obesity/diabetes and various cancers. I will present our recent results that reveal demethylation of mammalian messenger RNA catalyzed by some of these intriguing enzymes. Based on these discoveries we propose a new mode of biological regulation that depends on reversible RNA modification, for which we termed “RNA Epigenetics”.

Poster Abstracts

Target Identification of a Small Molecule Rescuing Monastrol-Induced Spindle Defects

Naowras Al-Obaidi[1], Craig M. Crews[2], Thomas U. Mayer[1]

[1] *Konstanz Research School Chemical Biology, University of Konstanz, 78457 Konstanz*
[2] *Department of Molecular, Cellular & Developmental Biology, Yale University, New Haven, CT, USA.*



During mitosis, accurate segregation of DNA into two daughter cells is achieved by the dynamic function of a microtubule-based bipolar structure, the mitotic spindle. A major driving force for spindle pole separation is the kinesin Eg5. Small molecule inhibitors of Eg5 such as monastrol induce collapse of the bipolar spindle. There is increasing evidence for further players that contribute to the formation and maintenance of the bipolar spindle whose identity and mode of action, however, remain elusive.

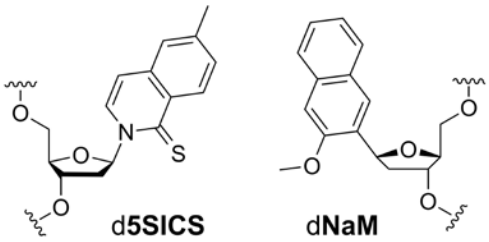
In a phenotype-based screen, we identified a compound, termed 29H16, that rescued spindle bipolarity in Eg5-inhibited cells. Notably, 29H16 also restored the bipolar shape of the spindle in Xenopus egg extract supplemented with monastrol indicating that the target of 29H16 is conserved in evolution. To identify the molecular target of 29H16, we first verified the rescue by live-cell imaging showing that a considerable percentage of cells could overcome the monastrol-induced mitotic arrest and divide again upon treatment with 29H16. Next, we optimized an assay which allows the assessment and quantification of the biological activity of 29H16. This assay was used to test commercially available derivatives of 29H16 to gain information on structure-activity-relationship. We further extended the derivative library by synthesizing additional structures and could find both more potent derivatives and a position in the molecule that tolerates modification. Using this knowledge, we immobilized the small molecule and applied affinity chromatography coupled mass spectrometry to identify potential biological targets of 29H16. We aim to use 29H16 as a means to dissect the process of spindle formation in cells. This goal implies the identification of the molecular target of 29H16. In our work, we characterized the effect of 29H16 on mammalian cells and evaluated the structural requirements for its function. Using the tools we have generated, we aim to identify interaction partners and validate their role in assembly of a bipolar spindle.

Structural Basis for the Enzymatic Incorporation of a Hydrophobic Artificial Base Pair into DNA

Karin Betz, Kay Diederichs, Wolfram Welte & Andreas Marx

Department of Chemistry and Biology and Konstanz Research School Chemical Biology, University of Konstanz

The genetic alphabet is comprised of two base pairs, and the development of a third, unnatural base pair would enhance the potential of numerous chemical and biological applications based on DNA. Therefore, the development of an artificial base pair which is processed by DNA polymerases with efficiencies and selectivities comparable to the natural base pairs is an important task. The Romesberg group at the Scripps Research Institute in California developed the artificial hydrophobic base pair d**NaM**-d**5SICS** which is one of the most efficiently replicated unnatural base pairs identified to date.[1] Its pairing is based only on hydrophobic and packing forces and in free duplex DNA it forms a cross-strand intercalated structure.[2,3] This mode of pairing maximizes packing interactions but the structure is difficult to reconcile with efficient polymerase recognition. In collaboration with the Romesberg group we aim to investigate the structural basis for the incorporation and elongation of d**NaM**-d**5SICS** by crystallographic studies using the well characterized KlenTaq DNA polymerase as a model.



The d**5SICS**-d**NaM** unnatural base pair

[1] D. A. Malyshev, K. Dhami, H. T. Quach, T. Lavergne, P. Ordoukhanian, A. Torkamani, F. E. Romesberg, Proc. Natl. Acad. Sci. U.S.A. 2012, 109, 12005-12010.

[2] K. Betz, D. A. Malyshev, T. Lavergne, W. Welte, K. Diederichs, T. J. Dwyer, P. Ordoukhanian, F. E. Romesberg, A. Marx, Nature Chem. Biol. 2012, 8, 612-614

[3] D. A. Malyshev, D.A. Pfaff, S. I. Ippoliti, G. T. Hwang, T. J. Dwyer, F. E. Romesberg, Chem. Eur. J. 2010, 16, 12650-12659.

Poster Abstracts

Thiazolides, GSTP1 and Colon Cancer Cell Apoptosis

Anette Brockmann[1,3], Tobias Strittmatter[2,3], Sarah May[1], Eva Oechsle[1], Andreas Marx[2,3] and T. Brunner[1,3]

[1] *Chair of Biochemical Pharmacology, Department of Biology, University of Konstanz*
[2] *Chair of Organic Chemistry/Cellular Chemistry, Department Chemistry, University of Konstanz*
[3] *Konstanz Research School Chemical Biology, University of Konstanz*

Thiazolides are antibiotics with potent anti-microbial activities used for the treatment of intestinal infections. Although so far no (side) effects on mammalian cells have been described, our lab has recently shown that thiazolides promote apoptosis in colon cancer cells. Thiazolides potently synergized with other apoptosis inducers, such as chemotherapeutic drugs and TRAIL. As the main mammalian target of thiazolides we identified the glutathione S-transferase, GSTP1. Interestingly, GSTP1 enzymatic activity was required for the apoptosis inducing activity of thiazolides. Furthermore, we have seen that cell cycle progression was a prerequisite for Thiazolide-induced apoptosis in colon cancer cells. We are currently investigating the molecular requirements of the thiazolide structure and derivatives to induce a GSTP1-dependent apoptotic cell death in colon cancer cells. Various thiazolides differ in their apoptosis promoting activity in Caco-2 cells. The thiazolide RM4819 induced activation of JNK and p38- MAP kinase, and their inhibition strongly blocked thiazolide-induced cell death. They also induced the expression of the Jun kinase target Bim, a BH3-only protein. Furthermore downregulation of Bim attenuated thiazolide-induced apoptosis. As GSTP1 sequesters and inhibits Jun kinase and other signaling molecules we are currently investigating whether thiazolides induce Jun kinase and p38 activation and subsequent apoptosis induction via the release of these MAP kinases from GSTP1. Interestingly, GSTP1 is barely expressed in normal colonic mucosa, but abundantly expressed in colorectal tumor cells. As we have previously shown that inhibition of cell cycle progression blocks thiazolide-induced cell death in Caco-2 cells, we are examining whether cell cycle arrest causes reduced GSTP1 expression in colon cancer cells or affects GSTP1 enzymatic activity. Current data indicate that GSTP1 expression is not affected by cell cycle arrest.
Our study proposes thiazolides as a novel therapeutic for the treatment of colorectal tumors and GSTP1 as an Achilles' heel of thiazolide-induced cell death.

Identification of Negative Regulators of Integrin-Mediated Cell Adhesion

Nina Dierdorf

University of Konstanz

Cells recognize and respond to their microenvironment through a multitude of transmembrane proteins such as the well characterized integrin superfamily. These tightly regulated receptors mediate transmembrane signaling by connecting the actin cytoskeleton via cytoplasmic adapter proteins to the extracellular matrix. Regulation of integrin activity is a fundamental process involved in a lot of physiological events like angiogenesis, tissue formation, migration or survival. The regulation of their ligand affinity based on conformational changes has been intensively studied. In the recent years a lot of proteins have been identified that positively affect integrin activity like talin and kindlins. In contrast, only few factors that negatively regulate integrins are currently known.

We identified the serine/threonine phosphatase Popx2 as a negative regulator of integrin activation in a shRNA-based screening approach. The knockdown of Popx2 results in an increased cell adhesion potential coinciding with enhanced ?1 integrin activation. These findings establish Popx2 as a novel regulator of integrin-mediated cell adhesion.

A detailed understanding of the mechanism of integrin affinity modulation will give us new starting points to manipulate integrin-mediated cell adhesion and the turnover of focal adhesion sites, both physiological events involved in a lot of pathological processes like cancer, asthma or multiple sclerosis.

Poster Abstracts

Synthesis of Purine Analogues with Trifluoromethyl-Substituents

Johannes Drexler, Ulrich Groth

Department of Chemistry, University of Konstanz

Fluoro- and trifluoromethyl-substituents of organic compounds play an important role for pharmaceutical active compounds. These substituents can increase the activity and/or bioavailability of bioactive molecules by tuning the electronical and sterical effects. It is currently in discussion if trifluoromethyl substituents have the capacity to form hydrogen bonds which would lead to interesting interactions with e.g. proteins.[1] A variety of purine analogues in the form of pyrollo[2,3-d]pyrimidines, respectively 7-deazapurines were found in nature as pharmaceutical active compounds such as tubercidin.[2] While these natural materials act as anti-viral, anti-bacterial or respectively anti-tumor agents, they also show a high toxicity and severely lack selectivity. Therefore these compounds are not suitable as pharmaceuticals.

Aim of this work is the synthesis of substituted 7-deazapurines and purines, containing at least one fluorine moiety. By introducing trifluoromethyl-substituents, one hopes to achieve a higher selectivity in biological evaluations.[3] The de novo synthetic pathways start from fluorine containing buildings blocks and are first fused to functionalized pyrimidine heterocycles and subsequently to the purine analogue bicycles. A limited amount of synthetic steps are to introduce various substituents in order to establish substance libraries. Subsequent biological evaluations can yield information about the structure-activity relationship of these compounds.

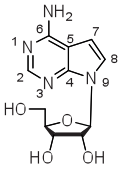


Figure 1: Tubercidin

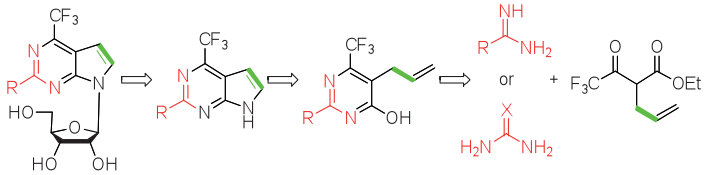


Figure 2: Synthetic pathway to yield 7-deazapurines

[1] R. Filler, Organofluorine compounds in medicinal chemistry and biomedical applications, Elsevier, 1993.
[2] R. Kazlauskas, P. Murphy, R. Wells et al., Aust. J. Chem., 1983, 36, 165-170.
[3] P. Naus, R. Pohl, I. Votruba et al., J. Med. Chem., 2010, 53, 460-470.

Chain Length Dependent Conformation of PolyQ Sequences as Molecular Origin for Fibril Formation

Benjamin Heck

University of Konstanz

Extended polyglutamine (PolyQ) chains are associated with many neurodegenerative diseases e.g. Huntington disease. In the affected protein, so called huntingtin, the PolyQ repeats are longer than ~ 36 Qs. These repeats are responsible for intracellular aggregates. A longer PolyQ chain results in an earlier onset of Huntington disease. We studied the folding mechanisms of synthesised polyQ sequences in dependence of the chain length, concentration, temperature and pD. We used FTIR and CD spectroscopy to study the polyQ peptides in thermal equilibrium. A conformational change is induced upon heating from 5-80°C in 5°C steps. Nano - to microsecond folding/unfolding dynamics are studied by a laser - excited temperature jump.

Poster Abstracts

Folding of a Protein into a Membrane

Katharina Henke[1], Meike Potschies[2], Wolfram Welte[2], Karin Hauser[1]

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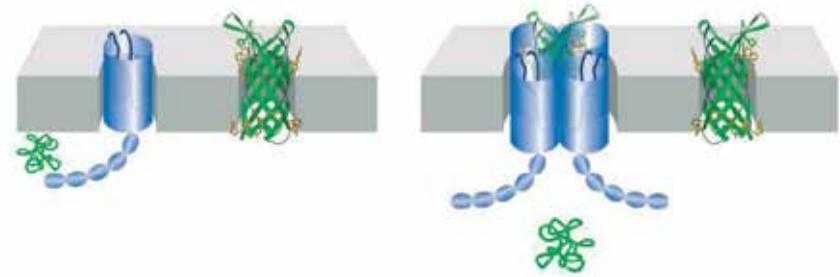
The process during which a protein assumes its native structure is still poorly understood after many decades of research. The outer membrane protein TtoA from Thermus thermophilus forms a ß-barrel with eight ß-strands. FTIR measurements are well-suited to observe ß-structures due to the fingerprint peaks for intermolecular and intramolecular ß-structure interactions as well as aggregates. Expression, purification and solubilization of His-tagged TtoA have successfully yielded native protein. FTIR spectra show a typical ß-structure, and heating studies of the protein reveal a very high thermostability. Unfolding does not occur up to 110°C. Previous studies have shown that, in the presence of TtOmp85, another Thermus thermophilus ß-barrel OMP, TtoA folds into liposomes. Thus, TtOmp85 might function as a chaperone or insertase. Different hypothesis about the insertion mechanism exist.
We assume that unfolded TtoA is able to fold into its native state in the presence of liposomes and that in presence of reconstituted TtOmp85 the insertion of TtoA is much more efficient. To verify these assumptions TtOmp85 has been reconstituted into liposomes and mixed with native and denatured TtoA, respectively. The refolding of TtoA and insertion into the liposomes can be observed with the help of FTIR difference spectra. Time-resolved stopped-flow and ATR approaches are used to monitor the folding mechanism of TtoA into a membrane.



Two hypotheses for the insertion of the OMP TtoA into a membrane
left: insertion of TtoA at the lipid-protein interface of a single TtOmp85
right: funneling through a pore formed by multiple TtOmp85, followed by a lateral shift into the membrane. Adapted from Tomassen, J. (2007), Science 317, 903-904

Monitoring Kinetics of Enzymatic ATP Consumption by EPR Spectroscopy

Christian Hintze, Stephan Hacker, Andreas Marx, Malte Drescher

Department of Chemistry, Konstanz Research School Chemical Biology, and Zukunftskolleg, University of Konstanz

Life uses ATP in cells to supply processes with energy. It also is an important signaling molecule that helps regulating the metabolism of cells and transmits extracellular signals to trigger intracellular processes. Therefore, many enzymes use ATP as an energy or phosphate transferring substrate. Due to this ubiquitous occurrence, the kinetics of enzymatic consumption of ATP is of high interest. Unfortunately, existing methods of investigation are hindered by their need of auxiliary reagents, since these might interfere with the enzymatic process, and thus invalidate the results.

In this work a new tool to monitor the kinetics of enzymatic consumption of ATP by applying EPR spectroscopy is presented. For this purpose doubly spin labeled ATP analogues have been synthesized. Their inter-spin distance ranges up to 3.8 nm as determined by DEER. Due to the high flexibility of the linkers this distribution is very broad and has considerable probability below 1.5 nm. Hence, the corresponding cw EPR spectrum exhibits dipolar broadening as long as the ATP remains intact. After enzymatic cleavage of the ATP, both labels are separated spatially and the dipolar broadening vanishes. The spectrum of a sample with only a fraction of the ATP split is a superposition of the spectra of these two extremes. After proper data analysis, the ratio between cleaved and intact ATP can be extracted from the spectrum. By measuring time resolved cw EPR spectra, the kinetics of ATP consumption are studied.

Thus, one can investigate the inhibition and stimulation of enzymes when consuming ATP without the need for auxiliary reagents. In contrast to fluorescence spectroscopy, EPR can also be applied in opaque media.

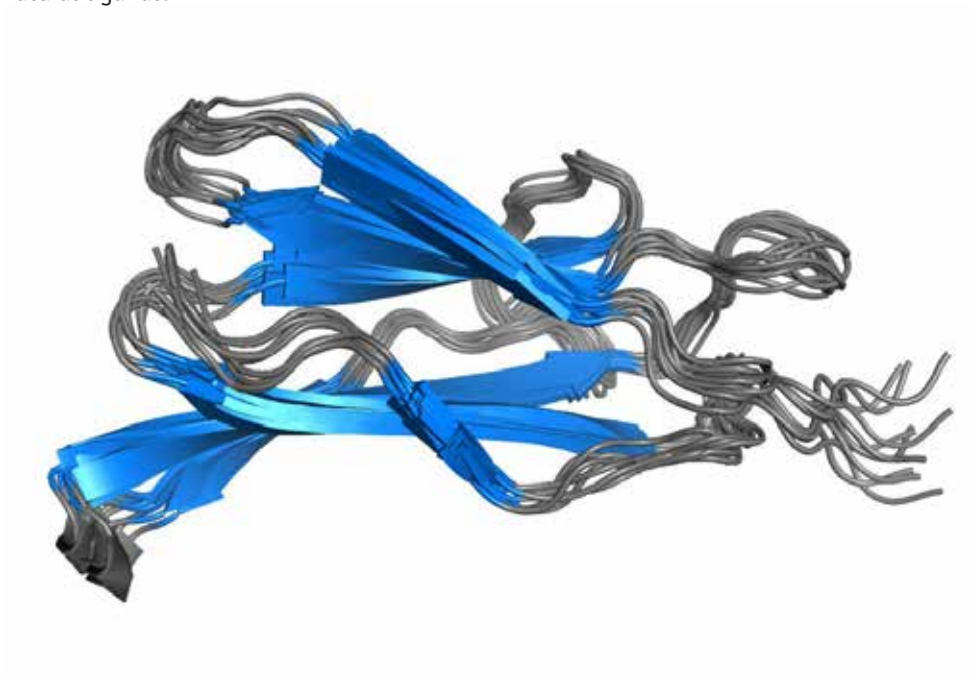
Poster Abstracts

Neurons Seeking for the Right Connection: a Molecular Study

Žarko Kulić, Claudia A.O. Stürmer, Günter Fritz, Heiko M. Möller

Fachbereich Chemie/Biologie and Konstanz Research School Chemical Biology, University of Konstanz

During development of the nervous system, neurons are growing on highly ordered routes to find their target. On a molecular level, multiple cell surface receptors participate in the correct path finding and bundling of neurons. In the present study, one of these receptors is characterized in structure, dynamics and it's interaction to inhibitors and natural ligands.



Investigation of a FAK-Displacing Small Molecule Inhibitor – STOP MOTION with Foot Locker

Christoph Paone, Alexander Buntru, Christof R. Hauck

Cell Biology, University of Konstanz, Christof.Hauck@uni-konstanz.de

Focal adhesion kinase (FAK) is a protein tyrosine kinase crucial for the regulated assembly and disassembly of focal adhesion protein complexes at integrin-dependent cell adhesion sites, a process important for cell migration. At focal adhesions, FAK exhibits important signaling, but also scaffolding functions. For the recruitment and integrity of FAK at focal adhesions its C-terminal focal adhesion targeting (FAT) domain is necessary. This domain is also crucial for interactions with the focal adhesion proteins paxillin and talin [1]. Due to its contribution to cell migration, which is crucial for pathological processes such as cancer cell invasion and tumor metastasis and its elevated expression in different tumor cells, FAK is an interesting target for the development of new anti-cancer strategies. Targeting only the kinase domain neglects the importance of FAK scaffolding function in tumor progression [2]. Thus, a fast-acting, small molecule inhibitor, which could delocalize FAK from focal adhesions, would probably improve the possibilities of cancer therapy. In addition such compound will be highly interesting in basic research on the regulation of focal adhesion dynamics. A microscopy-based high-content screen revealed to two promising candidates (Foot Locker 1 and 2), which efficiently can displace FAK and paxillin from focal adhesions (Buntru et al., unpublished). These inhibitors were further characterized using biochemical, microscopic and spectroscopic measurements to identify the molecular target(s) and investigate its applicability in basic research and cancer therapy.

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Poster Abstracts

Identifying the Function of GGGAATC Repeat Sequences in Xanthomonas Campestris

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Keywords: Non-canonical nucleic acid conformations, G-quadruplex, osmoadaption, potassium sensor

G-Quadruplex structures can be adopted by G-rich DNA and RNA sequences. Proof of the existence of quadruplexes in vivo is still scarce, as is evidence for their suggested functions. We are focusing on a potential quadruplex forming sequence in the plant-pathogenic bacteria Xanthomonas campestris pv. campestris and its role in gene regulation. We identified 97 GGGAATC repeats in the X. campestris genome. The repeats are primarily found in intergenic regions. In vitro analysis of the DNA oligo (GGGAATC)3GGG indicated formation of a (3+1) hybrid G-quadruplex in the presence of K^+. Analysis of the neighboring genes revealed various genes coding for proteins involved in cell wall synthesis, motility, energy metabolism, adaption and in particular osmoadaption. This is of special interest as a massive uptake of K^+ ions from the environment occurs in many non-halophilic bacteria after an osmotic upshift. X. campestris also faces high K^+ concentration when infecting host plants. We hypothesize that GGGAATC repeats could be involved in osmoregulation. There the motif may act as potassium sensor affecting gene expression upon increase of intracellular potassium.

α-Synuclein binds Alpha-Helically to Mitochondria

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α-Synuclein, an intrinsically-disordered protein associated with Parkinson's disease, interacts with mitochondria, and can produce mitochondrial dysfunction including impairment of complex I, oxidative stress, mitochondrial lipid abnormalities, and mitochondrial fission. However, the details of physiological and pathophysiological synuclein-mitochondria interactions of these protein remain poorly defined.
We probed the interaction of α-synuclein with isolated mitochondria by using site-directed spin labeling in combination with pulsed electron paramagnetic resonance spectroscopy (EPR). The obtained experimental data reveal that α-synuclein bound to mitochondria is in an α-helical arrangement and the N-terminal part of the protein in crucial for binding.
The results advance our understanding of α-synuclein's interactions with mitochondrial membranes and thus should help elucidate the role of the protein in the mitochondria dysfunction associated with neurodegenerative diseases.

Poster Abstracts

Synthesis of Alkene-Derivatized Fucose for Application in Metabolic Oligosaccharide Engineering

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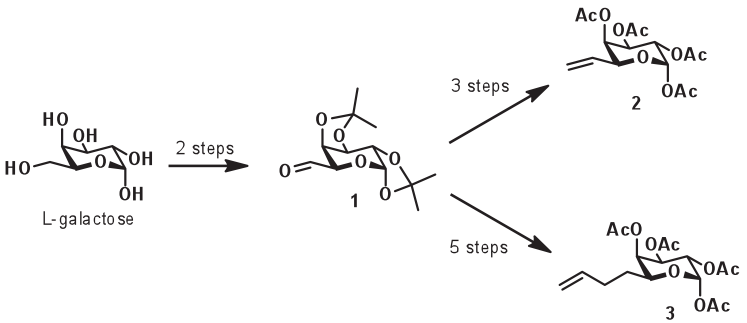
Glycosylation is one of the most common post-translational modifications and influences the function of glycoproteins in many ways. In particular, L-fucose is important for cell-cell interactions, regulation of protein function and for many developmental processes.[1] This is why investigation of fucosylated glycans is of great interest. A promising approach to visualize glycoconjugates is metabolic oligosaccharide engineering (MOE) that allows to monitor glycans by using a chemical ligation reaction.
Recently, we could show that terminal alkenes can be successfully used in a Diels-Alder reaction with inverse electron demand (DARinv) with a tetrazine to label cell-surface sialic acids.[2] The advantage of terminal alkenes is that they are small and thus accepted by metabolic processes. Moreover, the DARinv has been shown to be bioorthogonal as well as orthogonal to click chemistry and therefore is suitable for dual labeling.[2]
C6-modified fucose derivatives are known to be accepted by the fucose salvage pathway and incorporated into fucosylated glycanes.[1,3] Here we show the synthesis of two L-fucose derivatives bearing terminal alkenes at the C6 position for use in MOE. Starting from aldehyde 1, which is available in two steps from L-galactose, sugars 2 und 3 were prepared in three and five steps, respectively.



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Synthesis of Strained and Electron-Rich Dienophiles for Diels-Alder Reactions with Inverse Electron Demand and their Application in Metabolic Oligosaccharide Engineering

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Within the last years, metabolic oligosaccharide engineering (MOE) (Figure 1) has been established as an important tool to monitor carbohydrates in vivo and in vitro.[1] Different ligation methods can be used to detect the unnatural sugars that have been metabolically incorporated. In addition to the well-established azide-alkyne cycloaddition, our lab also uses Diels-Alder reactions with inverse electron demand (DAR_{inv}) as ligation reaction. One of the advantages of the DAR_{inv} is that it does not require catalysis by toxic metals and that the release of nitrogen during the reaction makes it irreversible. Moreover, the DAR_{inv} can be carried out in the presence of azides, and it is, thus, possible to label two different metabolically incorporated sugars in the same experiment.[2] This DAR_{inv} with an electron-poor tetrazine and an alkene and following retro-Diels-Alder reaction may be further improved by using dienophiles with a higher electron density or strained alkenes. Thus, new sugars (Figure 2) fulfilling these criteria were synthesized to make the reaction more efficient.

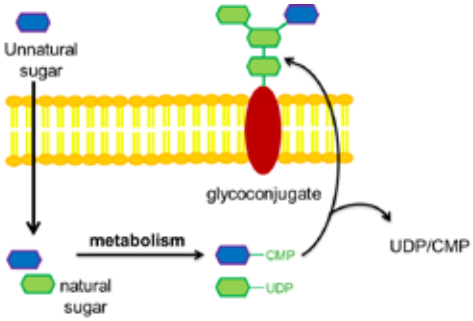

Figure 1: MOE principle

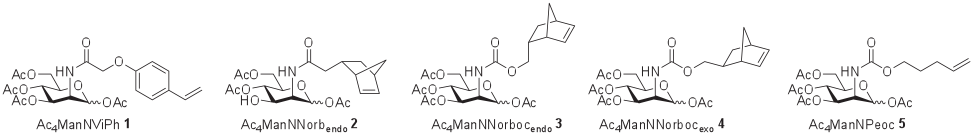

Figure 2: Novel dienophiles for DAR_{inv}

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Poster Abstracts

PolyQ Aggregation Processes Studied with ATR-IR Spectroscopy

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Several neurodegenerative diseases, including Huntington's diseases (HD), are caused by the expansion of polyglutamine (polyQ) repeats in proteins. The age of the disease onset is inversely correlated to the polyQ repeat length [1]. Detailed information of changes in the structure of polyQ proteins is therefore essential in order to understand the mechanisms underlying pathogenesis and to design therapeutic strategies. We study the aggregation process of glutamine repeats in polyQ proteins (His-SUMO-N17-PolyQ-FLAG) with varying glutamine length. Designed polyQ constructs mimic the native extended polyglutamine sequence in the Huntingtin. The SUMO (Small Ubiquitin-like Modifier) protein part keeps the fusion protein soluble and a protease recognition sequence allows Ulp protease cleavage. The aggregation process of the polyQ protein is initiated by adding Ulp cleavage and the aggregation of the glutamine sequence Q_N starts. The polyQ constructs are immobilized on a internal reflection element (IRE) with a help of a solid supported lipid bilayer (SSLB), modified with a NTA (nitrilotriacetic acid)[2] . Aggregation process is investigated by attenuated total reflectance infrared (ATR-FTIR) spectroscopy. ATR spectra of constructs showed that aggregates of N17-Q_N-FLAG with N = 56 exhibit three major bands, a band at 1607 cm^{-1}, assigned to the NH_2 deformation vibrations of the Gln side chain, a band at 1626 cm^{-1}, assigned to ß-sheet, and a band at 1655 cm^{-1}, assigned to C=O stretching of the Gln side chains.

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