The cover picture shows the binding of a ruthenium half-sandwich complex to the ATP binding site of glycogen synthase kinase 3 (GSK-3) and how its structure and potency evolved from a brief structure–activity relationship. With a binding constant ($K_i$) of, at most, 5 pM, this organometallic compound is several orders of magnitude more potent than the natural product staurosporine, which itself served as an inspiration for the design. The crystal structure of the organoruthenium inhibitor with GSK-3 demonstrates that the metal itself is not involved in any direct interactions with the active site of GSK-3, but solely serves as a structural center. Further details can be found in the article by E. Meggers, et al. on p. 2933 ff.

Dissecting the proteome. Platforms are available to investigate the events that occur from gene to protein. These, combined with our ability to manipulate the genome and proteome by RNAi and chemical probes alike, are transforming the biomedical field. The opportunities arising to investigate disease, develop therapies and to explore the proteome with chemistry-based approaches are rapidly increasing in number and will be discussed here.
Allosteric Regulation of Proteases

An alternative grip on proteases: Allosteric small-molecule regulation of proteases opens up new opportunities for specific control of cellular proteolytic activities and complements existing active-site-directed approaches. This review discusses natural proteinaceous and designed small molecules that act as allosteric protease regulators, highlighting a general mechanism that accounts for allostery in proteases.

K. J. Weissman*

2929 – 2931

Taking a Closer Look at Fatty Acid Biosynthesis

Crystal structure of a multienzyme:
Ban et al. recently reported a breakthrough in understanding fatty acid synthesis in animals. Determination of a 3.2 Å crystal structure of porcine fatty acid synthase (FAS) reveals a multienzyme of startling architectural complexity.

G. E. Atilla-Gokcumen, N. Pagano, C. Streu, J. Maksimoska, P. Filippakopoulos, S. Knapp, E. Meggers*

2933 – 2936

Perfect match: An organoruthenium complex with at most a low picomolar binding constant for glycogen synthase kinases 3 is reported, whose binding to the ATP-binding site has been analyzed by X-ray crystallography. The complex, (R,R)-NP549, is one of the most potent protein kinase inhibitors reported to date, almost four orders of magnitude more potent than the related natural product staurosporine.

D. D. Young, H. Lusic, M. O. Lively, J. A. Yoder, A. Deiters*

2937 – 2940

Gene Silencing in Mammalian Cells with Light-Activated Antisense Agents

On and off the spot: The spatio-temporal light-activation of gene silencing was achieved through the complete inactivation of phosphorothioate antisense agents by installing light-removable (caged) groups at specific sites, as illustrated here. Full antisense activity was restored through a brief irradiation with UV light at 365 nm.
Get to NOE MAG: Partial structures of GQ1bα, the natural ligand of the myelin-associated glycoprotein (MAG), have been synthesized and subjected to NOE experiments to determine their bioactive conformations. The experiments show that the flexible α(2→3)-glycosidic linkage between N-acetylneuraminic acid and galactose present in all ligands adopts a “sialyl Lewis x-type” binding mode. This information is valuable for the future design of conformationally preorganized MAG inhibitors.

MAgnificent analysis to remove ambiguity: The binding epitopes of tri- and tetrasaccharide ligands in their interactions with the myelin-associated glycoprotein (MAG) have been studied by using saturation transfer difference NMR, in which the signal intensities can help to resolve overlapped HSQC signals. In the figure, the signals of the protons with the closest proximity to the protein are shown in red (30–60%) or blue (61–100%).

Detecting heparin: We report a new fluorescent approach to the detection and quantification of the biologically relevant molecule heparin. We designed and prepared a cyclic peptide that is able to catalyse the hydrolysis of a fluorogenic anionic ester (green) under low-concentration conditions. Then we demonstrated that the inhibition of this artificial enzyme (grey) by heparin (red) allows its fluorescent sensing with a remarkable sensitivity of 13 nM.

Customizing enzymes: We demonstrate that cytochrome c552 (Cyt c552) from Thermus thermophilus HB8 can be transformed into a thermally tolerant peroxidase by a design process modeled on the catalytic mechanism of peroxidases. At temperatures above 50 °C, the enzymatic activity of the engineered Cyt c552 surpasses that of a myoglobin variant that is known to exhibit the highest activity among artificial peroxidases.
M. Muona, A. S. Aranko, H. Iwai*

2958 – 2961

Segmental Isotopic Labelling of a Multidomain Protein by Protein Ligation by Protein Trans-Splicing

Structure–function relationships of intact multidomain proteins: Segmental isotopic labelling of multidomain proteins could open a new avenue for studying particular domains in intact proteins, because it could simplify the NMR spectra through the incorporation of stable isotopes in a region-specific manner. We have demonstrated that the necessary protein ligation can be easily achieved both in vivo and in vitro by protein trans-splicing.

L. Betancor, M.-J. Fernández, K. J. Weissman, P. F. Leadlay*

2962 – 2966

Improved Catalytic Activity of a Purified Multienzyme from a Modular Polyketide Synthase after Coexpression with Streptomyces Chaperonins in Escherichia coli.

Folding helpers: Coexpression of Streptomyces coelicolor chaperonins GroEL1, GroEL2 and GroES with an actinomycete-derived polyketide synthase multi-enzyme in Escherichia coli has beneficial effects on yield, folding and specific activity of the purified enzyme. The results strongly suggest the utility of chaperones derived from polyketide-producing actinomycete bacteria in optimising the recombinant production of PKS proteins in E. coli for detailed studies of structure and function.

FULL PAPERS

L. Smith, H. Hong, J. B. Spencer, P. F. Leadlay*

2967 – 2975

Analysis of Specific Mutants in the Lasalocid Gene Cluster: Evidence for Enzymatic Catalysis of a Disfavoured Polyether Ring Closure

Baldwin’s rules bent: The biosynthesis of the polyether ionophore lasalocid in Streptomyces lasaliiensis involves a kinetically disfavoured ring closure to form a six-membered tetrahydropyran. In a mutant lacking the novel epoxide hydrolase LasB, the intermediate instead forms the five-membered ring product predicted by Baldwin’s rules; this shows the key role of LasB in stereocontrol.

J. Chelliserrykattil, H. Lu, A. H. F. Lee, E. T. Kool*

2976 – 2980

Polymerase Amplification, Cloning, and Gene Expression of Benzo-Homologous “yDNA” Base Pairs

Large bases encoding information: Here, we study whether DNA base pairs widened by addition of benzene can correctly store and transfer genetic information. Although the efficiency and selectivity in replication are low, the bases yT and yC were correctly amplified by PCR a substantial fraction of the time. Moreover, they correctly encoded amino acids in green fluorescent protein in bacterial cells.
Lighten up! 7-Azidomethoxycoumarins constitute phosphine-sensitive profluorophores. A DNA-templated Staudinger reduction removes the azidomethyl substituent and activates coumarin fluorescence. This method detects nucleic acid sequences with significant single mismatch discrimination and amplification of the fluorescence signal.

Chain reaction: The total chemical synthesis of desB30 insulin analogues by Fmoc-based, solid-phase synthesis of single-chain precursors that folded to give yields of up to 25% (11% after purification) and that were transformed into two-chain insulin by a protease from *Achromobacter lyticus* is reported. The overall insulin yield was as much as 6%, and the method was not labour intensive. An example of insulin with the unnatural amino acid *α*-aminoisobutyric acid (Aib) is shown.

Outsiders giving insights: Myxobacteria are talented producers of bioactive secondary metabolites. However, *Nannocystis* spp. have hardly been investigated. Phenylannolones from *Nannocystis exedens*, as illustrated here, represent a unique type of polyketide and reverse the multidrug resistance of cancer cells. The biosynthesis of the phenylannolones comprises novel biochemical reactions.

A chemical romance: Trisporic acids (TSAs) control the sexual reproduction of opposite mating types of many zygomycetes fungi. Cultures of *Blakeslea trispora* were supplemented with a series of deuterium-labeled apocarotenoid precursors. The isolated metabolites allowed for the reconstruction of the biosynthetic sequence between β-carotene and the different series of TSAs.
Investigation of Biosynthetic Pathways to Hydroxycoumarins During Post-Harvest Physiological Deterioration in Cassava Roots by Using Stable Isotope Labelling

Rooting out the right pathway: Isotopic labelling studies show that cinnamate goes via ferulate to scopoletin, whereas esculetin is biosynthesised from umbelliferone in cassava roots during post-harvest physiological deterioration. The lactonisation step proceeds by ortho-hydroxylation and not via a proposed spirrolactone-dienone.

Importance of Translation–Replication Balance for Efficient Replication by the Self-Encoded Replicase

Express yourself: We have devised a self-encoding system in which RNA was replicated by the self-encoded RNA replicase (Rep) produced by the translation reaction, and the ribosome (Rib) and replicase competed for the RNA. We evaluated the competition effect for RNA replication by constructing a kinetic model, as illustrated. The results indicated that the balance between translation and replication was critical for an efficient self-encoded system.

Orientation of the Monomeric Porin OmpG in Planar Lipid Bilayers

The orientations of single OmpG pores in planar lipid bilayers were determined from the sidedness of the response of an extracellular disulfide bond to dithiothreitol (DTT). With this knowledge, the binding of a cyclodextrin adapter presented to OmpG from the extracellular or periplasmic side was investigated. The information on the interaction between the cyclodextrin and OmpG serves to advance the use of OmpG as a biosensor.

Differential Inhibitory Activities and Stabilisation of DNA Aptamers against the SARS Coronavirus Helicase

Non-Hoogsteen or Hoogsteen? DNA aptamers evolved against the SCV helicase were split into two classes: non-G-quadruplex and G-quadruplex. The non-G-quadruplex aptamers inhibited the helicase activities but the G-quadruplex aptamers did not. Understanding this structure-based inhibition will be critical for further aptamer development against helicases.

www.chembiochem.org © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim ChemBioChem 2008, 9, 2899 – 2907
Photocontrol of Bcl-xL binding affinity has been achieved with short peptides alkylated with azobenzene crosslinkers. Helix-stabilized peptides exhibited up to 20-fold enhancements in affinity relative to their helix-destabilized forms, and more than 200-fold selectivity for binding to Bcl-xL over Hdm2. Such photocontrollable peptide-based switches may be used to interfere specifically with biomacromolecular interactions.

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In situ production of amyloid β (Aβ) 1–42: A novel photo-“click peptide” has nearly 100-fold higher water solubility than Aβ1–42 and no self-assembling tendencies. The click peptide is able to produce intact Aβ1–42 quickly under physiological conditions (pH 7.4, 37 °C) upon photoirradiation followed by an O–N intramolecular acyl migration.

Tales of the unexpected: Microviridin K (1) is a potent elastase inhibitor. It is biosynthesized from a linear prepeptide that is triply cross-linked by ester and amide bonds between the ω-functional groups of glutamic acid residues and serine, threonine and lysine. This unprecedented post-translational modification process and the N-terminal acetylation have been reconstituted in vitro.

DKP photoaffinity probes: Based on a new vascular-disrupting agent, NPI-2358, biotin-tagged photoaffinity probes with antimicrotubule activity were designed and synthesized. A tubulin photoaffinity labeling study revealed that the synthesized compounds are useful chemical probes for NPI-2358.

Tubulin Photoaffinity Labeling with Biotin-Tagged Derivatives of Potent Diketopiperazine Antimicrotubule Agents

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