

## **Summaries Petersen/Amstutz (eds): Natural Compounds as Drugs II**

### **Summary**

**Axel A. Brakhage, Julia Schuemann, Sebastian Bergmann, Kirstin Scherlach, Volker Schroeckh and Christian Hertweck**

#### **Activation of fungal silent gene clusters: An new avenue to drug discovery**

The ongoing exponential growth of DNA sequence data will lead to the discovery of many natural-product biosynthesis pathways by genome mining for which no actual product has been characterised. In many cases, these clusters remain silent under laboratory conditions. New technologies based on genetic engineering are available to induce silent genes. Heterologous expression of a silent gene cluster under the control of defined promoters can be applied. Alternatively, promoters of biosynthesis genes within the genome can be exchanged by defined promoters. Most promising, however, is the activation of pathway-specific regulatory genes, which was recently demonstrated. Such regulatory genes are present in many secondary metabolite gene clusters. This approach is rendered feasible by the fact that all of the genes encoding the large number of enzymes required for the synthesis of a typical secondary metabolite are clustered and that in some cases, a single regulator controls the expression of all members of a gene cluster to a certain extent. The advantage of this technique is that only a small gene needs to be handled, and that an ectopic integration is sufficient, bypassing all limitations of homologous recombination. Most conveniently, this strategy can trigger the concerted expression of all pathway genes. The vast amount of DNA sequence in the public database represents only the beginning of this new genomics era. The activation of these gene clusters by genetic engineering will lead to the discovery of many so far unknown products and therefore represents a novel avenue to drug discovery.

### **Summary**

**Matthew L. Maddess, Miles N. Tackett and Steven V. Ley**

#### **Total synthesis studies on macrocyclic pipecolic acid natural products: FK506, the antascomycins and rapamycin**

This chapter derives its inspiration from the challenges presented to total synthesis chemists, by a particular group of macrocyclic pipecolic acid natural products. Although there is considerable emphasis on the completed syntheses of the main characters (FK506, the antascomycins and rapamycin), the overall complexity of the molecular problem has stimulated a wealth of new knowledge, including the development of novel strategies and the invention of new synthetic methods. The ingenious and innovative approaches to these targets have enabled new generations of analogues, and provided material to further probe the biology of these fascinating molecules. With pharmaceutical application as an immunosuppressant, as well as potential use for the treatment of cancer and neurodegenerative diseases, this family of natural products continues to inspire new and interesting science while providing solutions to healthcare problems of the world.

### **Summary**

**Lisa A. Marcaurelle and Charles W. Johannes**

#### **Application of natural product-inspired diversity-oriented synthesis to drug discovery**

Natural products have played a critical role in the identification of numerous medicines. Synthetic organic chemistry and combinatorial chemistry strategies such as diversity-oriented synthesis (DOS) have enabled the synthesis of natural product-like compounds. The

combination of these approaches has both improved the desired biological properties of natural products as well as the identification of novel compounds. Diversity concepts and strategies to access novel compounds inspired by natural products will be reviewed.

## **Summary**

**Peter Ertl and Ansgar Schuffenhauer**

### **Cheminformatics analysis of natural products: Lessons from nature inspiring the design of new drugs**

Natural products (NPs) have evolved over a very long natural selection process to form optimal interactions with biological macromolecules. NPs are therefore an extremely useful source of inspiration for the design of new drugs. In the present study we report the results of a cheminformatics analysis of more than 130,000 NP structures. The physicochemical properties of NPs and their typical structural features are compared to those of bioactive molecules and average organic molecules. The relationship between the structure of NPs and the type of organism from which they have come has also been analyzed. The aim of this study was to identify those properties and structural features which are typical for NPs and discriminate this class of molecules from common synthetic molecules, with the ultimate goal being to provide a guide for the design of novel NP-like bioactive structures. Hopefully the results of this analysis help to eliminate the old myth about NPs as being ‘too complex’ or having ‘bad properties’, as well as help us to focus on these areas of NP structural space which are essential for biological activity, taking advantage of the process of natural selection over billions of years to guide us to new and as yet unexplored areas of the Chemical Structure Universe.

## **Summary**

**Andres Lopez, Ainslie B. Parsons, Corey Nislow, Guri Giaever and Charles Boone**

### **Chemical-genetic approaches for exploring the mode of action of natural products**

Determining the mode of action of bioactive compounds, including natural products, is a central problem in chemical biology. Because many genes are conserved from the yeast *Saccharomyces cerevisiae* to humans and a number of powerful genomics tools and methodologies have been developed for this model system, yeast is making a major contribution to the field of chemical genetics. The set of barcoded yeast deletion mutants, including the set of ~5000 viable haploid and homozygous diploid deletion mutants and the complete set of ~6000 heterozygous deletion mutants, containing the set of ~1000 essential genes, are proving highly informative for identifying chemical–genetic interactions and deciphering compound mode of action. Gene deletions that render cells hypersensitive to a specific drug identify pathways that buffer the cell against the toxic effects of the drug and thereby provide clues about both gene and compound function. Moreover, compounds that show similar chemical–genetic profiles often perturb similar target pathways. Gene dosage can be exploited to discover connections between compounds and their targets. For example, haploinsufficiency profiling of an antifungal compound, in which the set of ~6000 heterozygous diploid deletion mutants are scored for hypersensitivity to a compound, may identify the target directly. Creating deletion mutant collections in other fungal species, including the major human fungal pathogen *Candida albicans*, will expand our chemical genomics tool set, allowing us to screen for antifungal lead drugs directly. The yeast deletion mutant collection is also being exploited to map large-scale genetic interaction data obtained from genome-wide synthetic lethal screens and the integration of this data with chemical genetic data should provide a powerful system for linking compounds to their target pathway.

Extensive application of chemical genetics in yeast has the potential to develop a small molecule inhibitor for the majority of all ~6000 yeast genes.

**Keywords:** yeast, *S. cerevisiae*, marine natural products, cyclopeptides, Papuamide B, gene deletion collection, haploinsufficiency, chemical-genetics, alamethicin, theopalauamide, stichloroside, cinnamycin, barcode micro-array, parallel fitness, synthetic genetic interactions, synthetic genetic array

## Summary

**Karl-Heinz Altmann and Klaus Memmert**

### **Epothilones as lead structures for new anticancer drugs – pharmacology, fermentation, and structure-activity-relationships**

Epothilones (Epo's) A and B are naturally occurring microtubule-stabilizers, which inhibit the growth of human cancer cells *in vitro* at low nM or sub-nM concentrations. In contrast to taxol (paclitaxel, Taxol®) epothilones are also active against different types of multidrug-resistant cancer cell lines *in vitro* and against multidrug-resistant tumors *in vivo*. Their attractive preclinical profile has made epothilones important lead structures in the search for improved cytotoxic anticancer drugs and Epo B (EPO906, patupilone) is currently undergoing Phase III clinical trials. Numerous synthetic and semisynthetic analogs have been prepared since the absolute stereochemistry of epothilones was first disclosed in mid-1996 and their *in vitro* biological activity has been determined. Apart from generating a wealth of SAR information, these efforts have led to the identification of at least six compounds (in addition to Epo B), which are currently at various stages of clinical evaluation in humans, the most advanced compound being the Epo B lactam BMS-247550 (ixabepilone). This chapter will first provide a summary of the basic features of the biological profile of Epo B *in vitro* and *in vivo*. This will be followed by a review of the processes that have been developed for the fermentative production of Epo B. The main part of the chapter will focus on the most relevant aspects of the epothilone SAR with regard to effects on tubulin polymerization, *in vitro* antiproliferative activity, and *in vivo* antitumor activity. Particular emphasis will be placed on work conducted in the authors' own laboratories, but data from other groups will also be included. In a final section, the current status of those epothilone analogs undergoing clinical development will be briefly discussed.

**Keywords:** epothilone, microtubule stabilizer, anticancer, drug discovery, structure-activity relationship, natural products, antiproliferative, medicinal chemistry

## Summary

**Yuhta Masuoka, Nobuaki Shindoh and Noriaki Inamura**

### **Histone deacetylase inhibitors from microorganisms: The Astellas experience**

Histone deacetylase (HDAC) inhibitors, such as trichostatin A and trapoxin, which were first found in microorganisms, potently and selectively inhibit HDAC enzymes. They have made a strong contribution to research on HDACs, chromatin control, abnormal epigenetic control in various diseases and the significance of acetylation in posttranslational modification.

Recently, HDAC inhibitors have been focused on as potential drugs for the treatment of several diseases, including cancer, although trichostatin A and trapoxin show no effects in animal models because of their metabolic instability *in vivo*. Chemical modification has been conducted in order to overcome this drawback.

We discovered the microbial metabolites FK228 (also known as FR901228, romidepsin, depsipeptide, NSC-630176 and NSC-630176D) and YM753 (spiruchostatin A). Both

compounds have bicyclic structures and represent a novel structural class of HDAC inhibitor. The enzyme and tumor cell growth inhibitory activities of FK228 were found to be very potent. It also showed potent HDAC inhibitory activity *in vivo*. FK228 is the first potent HDAC inhibitor to undergo clinical development as a potential treatment for solid and hematological cancers. Due to its dramatic effect in patients with refractory cutaneous T-cell lymphoma (CTCL), in October 2004 the US Food & Drug Administration (FDA) granted fast-track status to FK228 as monotherapy for the treatment of CTCL in patients who have relapsed following, or become refractory to, another systemic therapy. Thus HDAC inhibitors such as FK228 and YM753 have potential as tools for life science studies and also as therapeutic agents for various intractable diseases.

### **Summary**

**Peter C. Hiestand, Martin Rausch, Daniela Piani Meier and Carolyn A. Foster**  
**Ascomycete derivative to MS therapeutic: S1P receptor modulator FTY720**

Fingolimod (FTY720) represents the first in a new class of immune-modulators whose target is sphingosine-1-phosphate (S1P) receptors. It was first identified by researchers at Kyoto University and Yoshitomi Pharmaceutical as a chemical derivative of the ascomycete metabolite ISP-1 (myriocin). Unlike its natural product parent, FTY720 does not interfere with sphingolipid biosynthesis. Instead, its best characterized mechanism of action upon *in vivo* phosphorylation, leading to the active principle FTY720-P, is the rapid and reversible inhibition of lymphocyte egress from peripheral lymph nodes. As a consequence of S1P<sub>1</sub> receptor internalization, tissue-damaging T-cells can not recirculate and infiltrate sites of inflammation such as the central nervous system (CNS). Furthermore, FTY720-P modulation of S1P receptor signaling also enhances endothelial barrier function. Due to its mode of action, FTY720 effectively prevents transplant rejection and is active in various autoimmune disease models. The most striking efficacy is in the multiple sclerosis (MS) model of experimental autoimmune encephalomyelitis, which has now been confirmed in the clinic. FTY720 demonstrated promising results in Phase II trials and recently entered Phase III in patients with relapsing MS. Emerging evidence suggests that its efficacy in the CNS extends beyond immunomodulation to encompass other aspects of MS pathophysiology, including an influence on the blood-brain-barrier and glial repair mechanisms that could ultimately contribute to restoration of nerve function. FTY720 may represent a potent new therapeutic modality in MS, combined with the benefit of oral administration.

### **Summary**

**Thomas Kuhn and Ying Wang**  
**Artemisinin – an innovative cornerstone for anti-malaria therapy**

Artemisinin-based Combination Therapies (ACT) are recommended by the World Health Organization (WHO) to treat especially multidrug resistant forms of malaria, as currently used medications have become increasingly ineffective. In this chapter, the discovery of artemisinin from Traditional Chinese Medicine and its further development to ACT are reviewed. It is highlighted how the complex supply chain to the naturally occurring endoperoxide artemisinin, required to produce ACT-based drugs, was established; thus addressing the significant therapeutic needs and high demands for the medication.

Natural Compounds as Drugs, Volume II

Petersen, F.; Amstutz, R. (Eds.)

2008, X, 428 p. 212 illus., 27 illus. in color., Hardcover

ISBN: 978-3-7643-8594-1

A product of Birkhäuser Basel