Summaries Petersen/Amstutz (eds): Natural Compounds as Drugs I

Summary
Mark S. Butler and David J. Newman
Mother Nature's gifts to diseases of man: the impact of natural products on anti-infective, anticholestemics and anticancer drug discovery

This chapter is designed to demonstrate that compounds derived from nature are still in the forefront of drug discovery in diseases such as microbial and parasitic infections, carcinomas of many types and control of cholesterol/lipids in man. In each disease area we have provided short discussions of past, present and future agents, in general only considering compounds currently in clinical Phase II or later, that were/are derived from nature's chemical skeletons. Finishing with a discussion of the current and evolving role(s) of microbes (bacteria and fungi) in the production of old and new agents ostensibly produced by higher organisms.

Summary
Olivier Potterat and Matthias Hamburger
Drug discovery and development with plant-derived compounds

An overview is given on current efforts in drug development based on plant-derived natural products. Emphasis is on projects which have advanced to clinical development. Therapeutic areas covered include cancer, viral infections including HIV, malaria, inflammatory diseases, nociception and vaccine adjuvants, metabolic disorders, and neurodegenerative diseases. Aspects which are specific to plant-based drug discovery and development are also addressed, such as supply issues in the commercial development, and the Convention on Biological Diversity.

Summary
Holger Jenke-Kodama, Rolf Müller and Elke Dittmann
Evolutionary mechanisms underlying secondary metabolite diversity

The enormous chemical diversity and the broad range of biological activities of secondary metabolites raise many questions about their role in nature and the specific traits leading to their evolution. The answers to these questions will not only be of fundamental interest but may also provide lessons that could help to improve the screening protocols of pharmaceutical companies and strategies for rational secondary metabolite engineering. In this review, we try to dissect evolutionary principles leading to the emergence, distribution, diversification and selection of genes involved in secondary metabolite biosyntheses. We give an overview about recent insights into the evolution of the different types of polyketide synthases (PKS) in microorganisms and plants and highlight unique mechanisms underlying polyketide diversity. Although phylogenetic and experimental data have significantly increased our knowledge about the role and evolution of secondary metabolites in the last decades there is still much dissent about the impact of natural selection. In order to understand the evolution towards metabolic diversity we therefore need more thorough investigations of the ecological role of secondary metabolites in the future.

Summary
Sheo B. Singh and Fernando Pelaez
Biodiversity, chemical diversity and drug discovery

Drugs developed from microbial natural products are in the fundaments of modern pharmaceutical companies. Despite decades of research, all evidences suggest that there must remain many interesting natural molecules with potential therapeutic application yet to be discovered. Any efforts to successfully exploit the chemical diversity of microbial secondary metabolites need to rely heavily on a good understanding of microbial diversity, being the working hypothesis that maximizing biological diversity is the key strategy to maximizing chemical diversity. This chapter presents an overview of diverse topics related with this basic principle, always in relation with the discovery of novel secondary metabolites. The types of microorganisms more frequently used for natural products discovery are briefly reviewed, as well as the differences between terrestrial and marine habitats as sources of bioactive secondary metabolite producers. The concepts about microbial diversity as applied to prokaryotes have evolved in the last years, but recent data suggest the existence of true biogeographic patterns of bacterial diversity, which are also discussed. Special attention is dedicated to the existing strategies to exploit the microbial diversity that is not easy to tackle by conventional approaches. This refers explicitly to the current attempts to isolate and cultivate the previously uncultured bacteria, including the application of high throughput techniques. Likewise, the advances of microbial molecular biology has allowed the development of metagenomic approaches, i.e., the expression of biosynthetic pathways directly obtained from environmental DNA and cloned in a suitable host, as another way of accessing microbial genetic resources. Also, approaches relying on the genomics of metabolite producers are reviewed.

Summary
Frank E. Koehn
High impact technologies for natural products screening

Natural products have historically been a rich source of lead molecules in drug discovery. However, natural products have been de-emphasized as high throughput screening resources in the recent past, in part because of difficulties in obtaining high quality natural products screening libraries, or in applying modern screening assays to these libraries. In addition, natural products programs based on screening of extract libraries, bioassay-guided isolation, structure elucidation and subsequent production scale-up are challenged to meet the rapid cycle times that are characteristic of the modern HTS approach. Fortunately, new technologies in mass spectrometry, NMR and other spectroscopic techniques can greatly facilitate the first components of the process – namely the efficient creation of high-quality natural products libraries, bimolecular target or cell-based screening, and early hit characterization.
The success of any high throughput screening campaign is dependent on the quality of the chemical library. The construction and maintenance of a high quality natural products library, whether based on microbial, plant, marine or other sources is a costly endeavor. The library itself may be composed of samples that are themselves mixtures – such as crude extracts, semi-pure mixtures or single purified natural products. Each of these library designs carries with it distinctive advantages and disadvantages. Crude extract libraries have lower resource requirements for sample preparation, but high requirements for identification of the bioactive constituents. Pre-fractionated libraries can be an effective strategy to alleviate interferences encountered with crude libraries, and may shorten the time needed to identify the active

principle. Purified natural product libraries require substantial resources for preparation, but offer the advantage that the hit detection process is reduced to that of synthetic single component libraries. Whether the natural products library consists of crude or partially fractionated mixtures, the library contents should be profiled to identify the known components present – a process known as dereplication. The use of mass spectrometry and HPLC-mass spectrometry together with spectral databases is a powerful tool in the chemometric profiling of bio-sources for natural product production. High throughput, high sensitivity flow NMR is an emerging tool in this area as well. Whether by cell based or biomolecular target based assays, screening of natural product extract libraries continues to furnish novel lead molecules for further drug development, despite challenges in the analysis and prioritization of natural products hits.
Spectroscopic techniques are now being used to directly screen natural product and synthetic libraries. Mass spectrometry in the form of methods such as ESI-ICRFTMS, and FACS-MS as well as NMR methods such as NMR-SAR and STD-NMR have been utilized to effectively screen molecular libraries. Overall, emerging advances in mass spectrometry, NMR and other technologies are making it possible to overcome the challenges encountered in screening natural products libraries in today's drug discovery environment. As we apply these technologies and develop them even further, we can look forward to increased impact of natural products in the HTS based drug discovery.

Summary
Judith M. Rollinger, Hermann Stuppner and Thierry Langer
Virtual screening for the discovery of bioactive natural products

In this survey the impact of the virtual screening concept is discussed in the field of drug discovery from nature. Confronted by a steadily increasing number of secondary metabolites and a growing number of molecular targets relevant in the therapy of human disorders, the huge amount of information needs to be handled. Virtual screening filtering experiments already showed great promise for dealing with large libraries of potential bioactive molecules. It can be utilized for browsing databases for molecules fitting either an established pharmacophore model or a three dimensional (3D) structure of a macromolecular target. However, for the discovery of natural lead candidates the application of this in silico tool has so far almost been neglected. There are several reasons for that. One concerns the scarce availability of natural product (NP) 3D databases in contrast to synthetic libraries; another reason is the problematic compatibility of NPs with modern robotized high throughput screening (HTS) technologies. Further arguments deal with the incalculable availability of pure natural compounds and their often too complex chemistry. Thus research in this field is time-consuming, highly complex, expensive and ineffective. Nevertheless, naturally derived compounds are among the most favorable source of drug candidates. A more rational and economic search for new lead structures from nature must therefore be a priority in order to overcome these problems.
Here we demonstrate some basic principles, requirements and limitations of virtual screening strategies and support their applicability in NP research with already performed studies. A sensible exploitation of the molecular diversity of secondary metabolites however asks for virtual screening concepts that are interfaced with well-established strategies from classical pharmacognosy that are used in an effort to maximize their efficacy in drug discovery. Such integrated virtual screening workflows are outlined here and shall help to motivate NP researchers to dare a step towards this powerful in silico tool.

Summary
Arnold L. Demain and Jose L. Adrio
Strain improvement for production of pharmaceuticals and other microbial metabolites by fermentation

Microbes have been good to us. They have given us thousands of valuable products with novel structures and activities. In nature, they only produce tiny amounts of these secondary metabolic products as a matter of survival. Thus, these metabolites are not overproduced in nature, but they must be overproduced in the pharmaceutical industry. Genetic manipulations are used in industry to obtain strains that produce hundreds or thousands of times more than that produced by the originally isolated strain. These strain improvement programs traditionally employ mutagenesis followed by screening or selection; this is known as 'brute-force' technology. Today, they are supplemented by modern strategic technologies developed via advances in molecular biology, recombinant DNA technology, and genetics. The progress in strain improvement has increased fermentation productivity and decreased costs tremendously. These genetic programs also serve other goals such as the elimination of undesirable products or analogs, discovery of new antibiotics, and deciphering of biosynthetic pathways.

Summary
Prakash S. Masurekar
Nutritional and engineering aspects of microbial process development

Today we use many drugs produced by microorganisms. However, when these drugs were discovered it was found that the yields were low and a substantial effort had to be put in to develop commercially viable processes. A key part of this endeavor was the studies of the nutritional and the engineering parameters. In this chapter, the basic principles of optimizing the nutritional and engineering aspect of the production process are described with appropriate examples. It was found that two critical components of nutritional medium, carbon and nitrogen source regulated the synthesis of the compounds of interest. Rapidly utilizable carbon source such as glucose supported the growth but led to catabolite repression and alternative carbon sources or methods of addition had to be devised. Inorganic nitrogen sources led to undesirable changes in pH of the medium. Organic nitrogen sources could influence the yields positively or negatively and had to be chosen carefully. Essential nutrients like phosphates often inhibited the synthesis and its concentration had to be maintained below the inhibitory levels. On many occasions, trace nutrients like metal ions and vitamins were found to be critical for good production. Temperature and pH were important environmental variables and their optimum values had to be determined. The media were designed and optimized initially with 'one variable at a time' approach and later with experimental design based on statistics. The latter approach is preferred because it is economical, considers interactions between medium components and allows a rapid optimization of the process. The engineering aspects like aeration, agitation, medium sterilization, heat transfer, process monitoring and control, become critical as the process is scaled-up to the production size. Aeration and agitation are probably the most important variables. In many processes dissolved oxygen concentration had to be maintained above a critical value to obtain the best yields. The rheological properties of fermentation broth significantly affect the aeration and mixing efficiency. The removal of heat from the large fermentors can be difficult under certain conditions. However, new designs of impellers, availability of sensors to monitor important physiological and process variables and advent of computers have facilitated successful scale-up of fermentation processes.

Summary
Elizabeth McCoy and Sarah E. O'Connor
Natural products from plant cell cultures

Plants produce complex small molecules – natural products – that exhibit anticancer, antimalarial and antimicrobial activity. These molecules play a key role in human medicine. However, plants typically produce these compounds in low quantities, and harvesting plant natural products is frequently expensive, time-consuming and environmentally damaging. Plant cell culture provides a renewable, easily scalable source of plant material. In this chapter we discuss the successes and pitfalls associated with natural product production in plant cell cultures.

http://www.springer.com/978-3-7643-8098-4

Natural Compounds as Drugs, Volume I
Petersen, F.; Amstutz, R. (Eds.)
2008, XII, 372 p., Hardcover
ISBN: 978-3-7643-8098-4
A product of Birkhäuser Basel