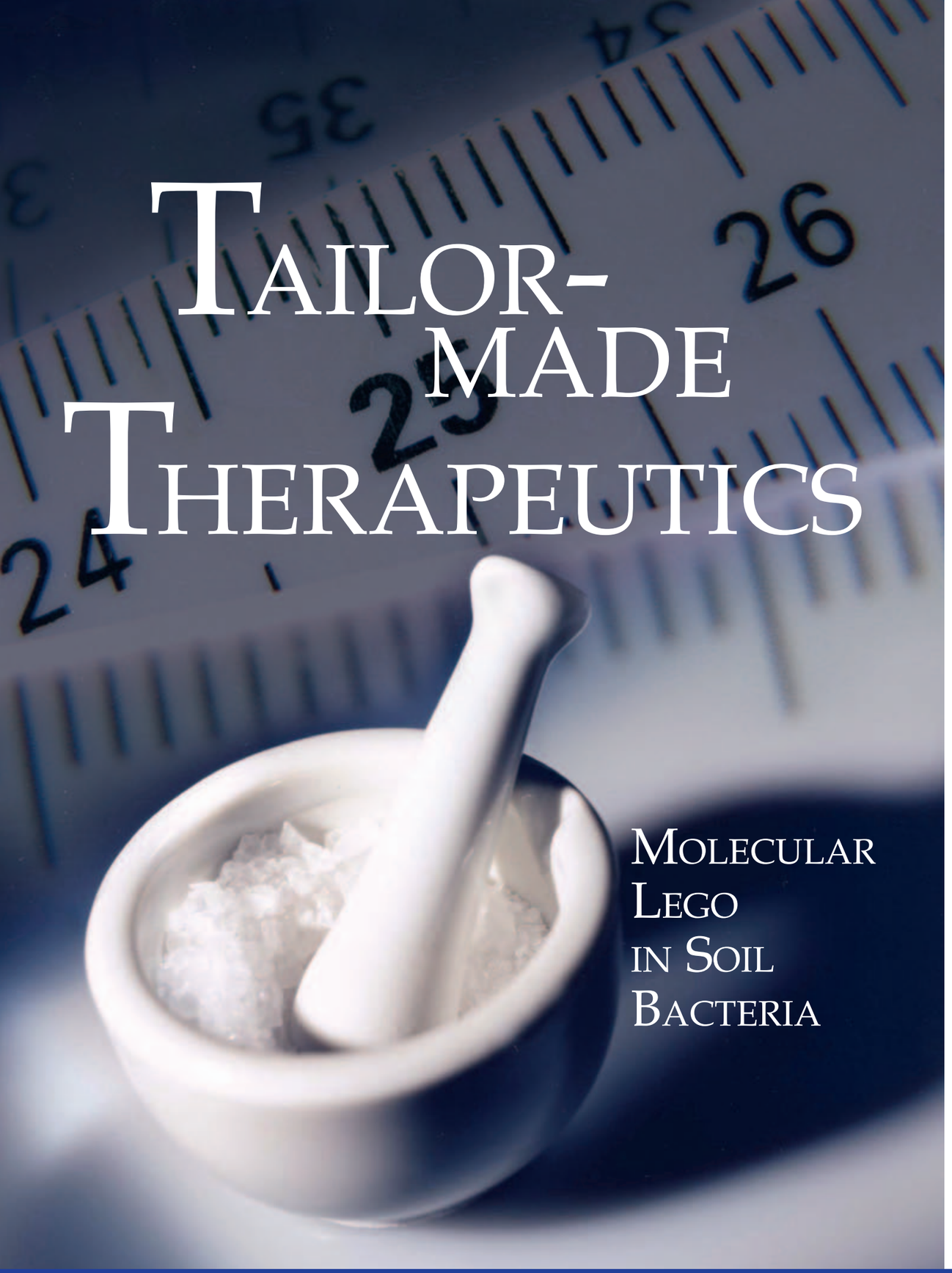


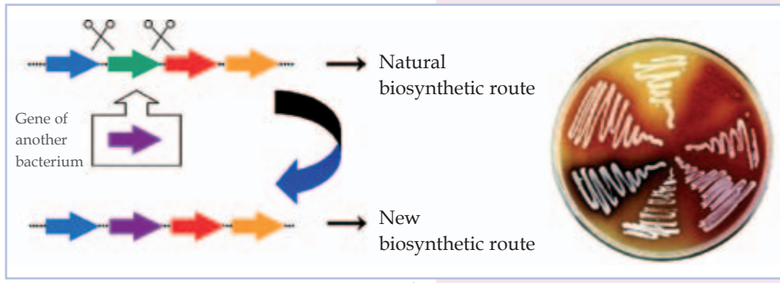
Tailor-made Therapeutics

Molecular Lego in Soil Bacteria

To combat a risky bacterial infection almost everyone has taken them at some point in their lives: Antibiotics such as ***tetracycline***, ***erythromycin*** or ***chloramphenicol***. But who would actually assume them to represent natural products rather than synthetic substances, with many being produced in the backyard? In fact, these agents originate from soil bacteria, so-called actinomycetes, which are also responsible for the typical smell of fresh soil. Although their name is reminiscent of fungi, the only thing they have in common is their appearance: The mycelia-like growth and the reproduction through spore formation. Besides antibiotics, actinomycetes also produce other compounds used for the treatment of fungal or yeast infections, such as ***candicidin***. Doxorubicin, another well-known agent isolated from actinomycetes, inhibits cell division and is therefore successfully applied in cancer therapy.

Natural Products Become Drugs

It appears feasible that microorganisms produce certain compounds to protect themselves from other microorganisms and to defend their natural habitat, a strategy that became optimized over millions of years. Their application to combat human pathogens is relatively new since ***actinomycetes*** were not recognized as useful producers of ***antibiotics*** until the middle of the 20th century. Nowadays about two-thirds of natural product derived antibiotics originate from these soil bacteria. However, isolated compounds are not automatically suitable for their application as drugs for a number of reasons: Amongst others they might cause unpleasant side effects, could be eliminated too quickly or possess insufficient solubility. Thus, bioactive natural products often demand an individual modification to adapt them to their medical application. A chemical-synthetic approach for the production of such highly complex molecules could result in outrageous prices for these therapeutics. Therefore, in most cases it is reasonable to pass the job to the bacteria, which are capable of assembling complex structures out of simple building blocks like acetic acid or sugar molecules. The required blueprint is encoded in their ***DNA***. The „DNA program“ decides on the ***enzymes*** to be build, which in turn define the assembly pattern of the different building blocks. To some extent these enzymes even compose molecular assembly lines on which the single components are put together like building blocks in a factory. Here, each enzyme has a certain task in one or more steps of the biosynthesis before the intermediate is passed on to the next enzyme.



Principle of the “combinatorial biosynthesis”. Through the exchange of genes (marked by colored arrows) altered biosynthetic routes emerge. Agar plate with bacteria producing new antibiotics.

Genetic Engineering Modeled by Nature

Microbiologists studying the genetic programming of actinomycetes and the biosynthesis of the compounds they produce were wondering whether it is possible to rewrite the building plan for antibiotics in a way to make the bacteria produce altered compounds. The required genetic tools only became available in the 1980s. However, the breakthrough was achieved by a team of scientists around Hopwood: They mixed genes of two different antibiotic-producing microorganisms and came up with a new metabolite isolated from the genetically modified bacteri-

Actinomycetes
Gram –positive, often filamentous bacteria producing mycelia similar to that of fungi. They represent a significant component of the soil's microflora and exhibit outrageous properties concerning the production of bioactive natural products.

Antibiotics
Substances of mainly microbial origin with the capability to kill bacteria (bactericidal) or to avoid their reproduction (bacteriostatic).

Candicidin
See glossary p. 103.

Chloramphenicol
See glossary p. 103.

DNA
De(s)oxyribonucleic acid; carrier of the genetic information.

Enzymes
Proteins that accelerate chemical reactions by acting as a catalyst.

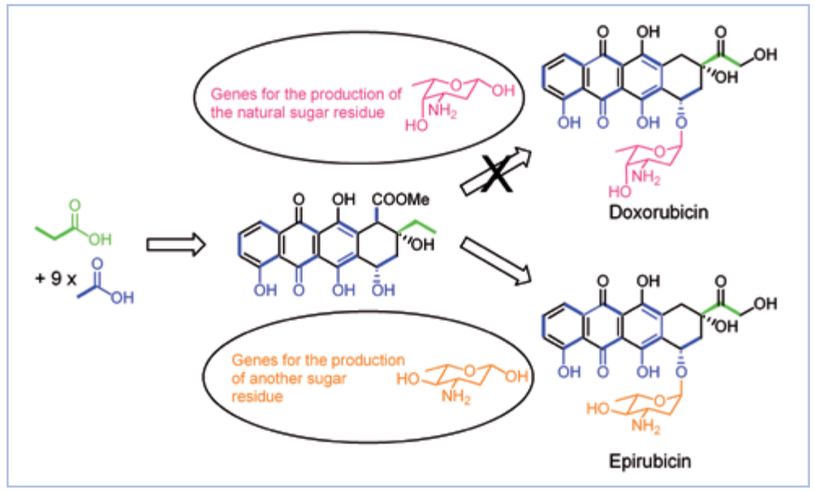
Erythromycin
see glossary p. 103

Tetracycline
see glossary p. 109

Avermectin and doramectin
Anti-parasitic drugs of the polyketide class produced by ***Streptomyces*** spp. and modified semi-synthetically, respectively, which specifically damage nerve cells of parasites, worms, mites and insects.

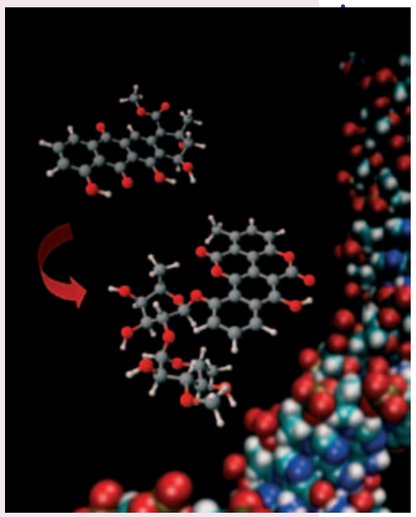
Combinatorial biosynthesis
Genetic engineering method for the biological production of structurally altered compounds through the combination of genes originating from different organisms.

Formation of resistance
Aquirement of the ability to withstand toxic compounds.



Small change, high impact: the introduction of another sugar residue results in a 20-fold more active anti-tumor drug.

um. To date numerous genes involved in the production of bioactive agents are known. Their comparison revealed that genes are swapped between microorganisms, thus supporting the hypothesis that new bacterial strains with altered assembly programs evolved constantly in evolution. Those bacteria reconstructing a new and more efficient antibiotic through such a gene swap prevailed in their natural habitat. Nowadays these natural processes can be mimicked by scientists via the modern methods of genetic engineering.



Enzymatic conversion of a molecule's framework to a potential anti-cancer drug

First Achievements in Pharmaceutical Research

The technique used to combine different genes in a way to obtain novel potential bioactive agents is called combinatorial biosynthesis. Several impressive examples proved its effectiveness: For instance, the anti-cancer drug epirubicin differs from the naturally occurring bioactive agent doxorubicin only in one sugar residue thereby exhibiting a 20-fold higher activity against tumor cells. Before, epirubicin was produced by a complicated chemical modification. However, now it is possible to combine the genes of different bacterial strains, creating a single bacterial culture capable of producing an optimized anti-cancer drug. Likewise, in the case of the anti-parasite drug avermectin, significant improvements were achieved via combinatorial biosynthesis, since doramectin, its derivative, could protect thousands of Africans from the dreaded river blindness caused by parasitic worms. Through the directed genetic modification of the avermectin producer and the introduction of genes required for the production of the unusual building block, the anti-parasite drug became biotechnologically available. These pioneering successes inspired scientists from across the world to decipher and change the so far undiscovered programming of the biosynthesis of bioactive agents in actinomycetes. The final goal is to understand and eventually exploit the functioning of these mini-factories to develop new drugs with improved therapeutic properties. The rapid formation of resistances of dangerous pathogens and malign tumors constantly requires new drugs to successfully fight infections. In this race the molecular Lego can make a contribution to remain one step ahead.

Christian Hertweck and Stefan Pelzer
Translation: Daniela Böttger

Additional Literature

Staunton J, Wilkinson B: Combinatorial biosynthesis of polyketides and nonribosomal peptides (2001), Curr Opin Chem Biol. 5, 159-164

Weissman KJ, Leadlay PF: Combinatorial biosynthesis of reduced polyketides (2005), Nat Rev Microbiol. 3, 925-936

Reeves CD: The enzymology of combinatorial biosynthesis (2003), Crit Rev Biotechnol. 23, 95-147

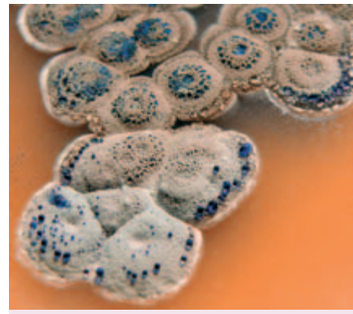
Cropp TA, Kim BS, Beck BJ, Yoon YJ, Sherman DH, Reynolds KA: Recent developments in the production of novel polyketides by combinatorial biosynthesis (2002), Biotechnol Genet Eng Rev. 19, 159-172

Walsh CT: Combinatorial biosynthesis of antibiotics: challenges and opportunities (2002), Chembiochem. 3, 125-134

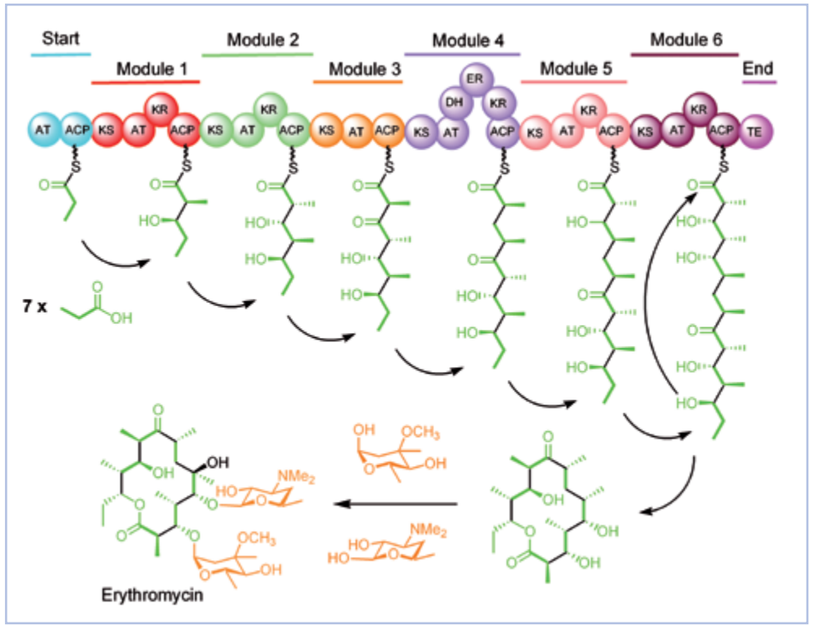
Rix U, Fischer C, Remsing LL, Rohr J: Modification of post-PKS tailoring steps through combinatorial biosynthesis (2002), Nat Prod Rep. 19, 542-580

Links on the Web

Texys
www.texys.de/biodata/biosynthese.html



New bioactive agents from actinomycetes, a group of soil bacteria. An antibiotic produced by this strain accumulates within the blue drops.



Some enzymes work like molecular assembly lines, exemplified on the production of the antibiotic erythromycin.