

# How can actinomycete taxonomy and natural product research work together?

## The Sanofi-Aventis approach



**Joachim Wink**

Sanofi-Aventis Germany  
R&D LGCR  
Industriepark Höchst  
65926 Frankfurt am Main  
Germany  
Email Joachim.wink@  
sanofi-aventis.com

**The role of taxonomy in natural product research can be estimated in different ways. As the biological active secondary metabolite is in the focus, different companies have developed their own philosophy, as Sanofi-Aventis has done. Surveying the patent literature and journals for the description of natural products, for example, the *Journal of Antibiotics*, it is found that most actinomycetes reported to produce biological active compounds are described only to the genus level<sup>1</sup> or with an invalid taxonomic name. Many of them belong to novel species, as shown in our studies of members of the genus *Actinoplanes* during a research program for new lantibiotics<sup>2</sup> which resulted in the validation of *Actinoplanes liguriensis* and *A. teichnomyceticus*<sup>3</sup> which have been invalidly published by Parenti and co-workers<sup>4,5</sup>. The characterisation and description of the antibiotic-producing actinomycetes at Sanofi-Aventis or its predecessors has a long history going back to the publication of three novel species of the genus *Streptomyces* that produce moenomycin<sup>6</sup>, an antibiotic compound which is still in fermentative production today.**

In this paper, three facets from the Sanofi-Aventis approach to the discovery of new secondary metabolites being correlated to taxonomy are presented: novel species of actinomycetes produce new compounds, correlations between antibiotic formation and taxonomy within the genus *Amycolatopsis* and the method to identify and characterise novel species within our collection using the *Compendium of Actinomycetales*<sup>7</sup>.

Natural product research has a long tradition at Sanofi-Aventis in the research programs at different locations of its various predecessor companies. In Frankfurt (Germany) screening for

antibiotics started in 1951 and was continued from 1972 until 1998 through cooperation with Hoechst India Ltd. in Mulund, Mumbai (India). In parallel there was also chemical screening done in Frankfurt from 1983 to 1992. Since 1993 all natural product screening activities are concentrated in Frankfurt, together with the company's strain collection.

The basis of all the screening concepts is having a diverse strain collection. The size and diversity of the Sanofi-Aventis collection is the product of the mergers of different companies. The two major parts of the present collection are the Höchst collection from antibiotic screening as well as that from chemical screening (37%) and the natural product screening collection from Rhone Poulenc in Vitry (Paris, France; 45%). We also have a taxonomic reference collection of strains acquired from international collections (DSMZ, ATCC, and IFO and so on), the Romainville (Rusell Pharma Paris/France) and Labège (Sanofi Toulouse/France) collection i (Figure 1). The strains are mainly actinomycetes (69%) and fungi (26%). The actinomycetes were primarily isolated from soil material, but some were isolated from marine sediments or plant material.

In all our screening approaches the most important lead compounds are produced by novel species. The first example is moenomycin (Figure 2) which is produced by several different novel *Streptomyces* species, *S. ederensis*, *S. ghanaensis* and *S. geysiriensis*<sup>6</sup>. From the screening program in India a number of novel *Amycolatopsis* species were described, which all produce new compounds. These species and their respective compounds are *A. balhimycina* (balhimycin/glycopeptides)<sup>8,9</sup>, *A. decaplanina* (decaplanin/glycopeptides)<sup>10,11</sup>, *A. keratiniphila* subsp. *nogabecina* (nogabecin/glycopeptides)<sup>9,12</sup> and *A.*

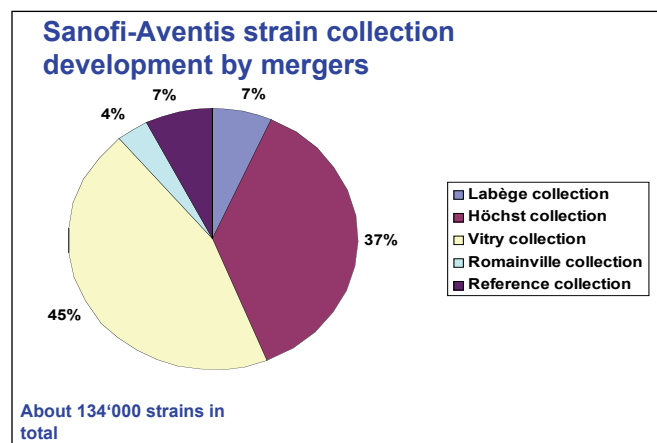


Figure 1. The actual composition of the Sanofi-Aventis strain collection.

*vancoresmycina* (vancoresmycin/tetramic acid derivative)<sup>9,13</sup>. Balhimycin, for example, is one of the glycopeptide antibiotics which have been used for biosynthetic and molecular biological modifications studies by university groups<sup>14,15</sup>. During chemical screening with members of different genera of actinomycetes not belonging to the genus *Streptomyces* (so called neglected genera), a strain of the genus *Actinoplanes* displayed several bands in thin layer chromatography and also exhibited antibacterial activity. The strain was isolated from a soil sample collected in the Italian province Friaul, so the new lipopeptide compound was named Friulimycin (Figure 3) and the strain was described as *Actinoplanes friuliensis*<sup>16</sup>. This compound is now under development within the company Merlion.

The last example is the lantibiotic labyrinthopeptin. This is an example where the taxonomic position of the novel species *Actinomadura namibiensis* was investigated and published much earlier than the structure of this unusual peptide and its activity in the pain model<sup>17,18</sup>. The peptide includes a new amino acid named labionin and the biosynthesis was studied by the group of Prof Suessmuth at the University of Berlin<sup>19</sup>.

During our studies of novel species in the genus *Amycolatopsis* by use of Riboprinter® analysis, it was found that the species producing glycopeptides and rifampicin-like compounds cluster separately and the two clusters were proposed as the

“mediterranei” cluster and the “orientalis” cluster based on the significant species in each<sup>20</sup>. The “mediterranei” cluster includes strains which produce ansamycin antibiotics of the rifamycin group like *A. vancoresmycina* (homorifamycin), *A. tolypomycina* (tolipomycin) and *A. mediterranei* (rifamycin). *A. balhimycina*, one of the glycopeptide producers, is also placed in this group. Molecular biological studies of this strain in the laboratory of Prof Wohlleben at the University of Tübingen showed that the genome of *A. balhimycina* includes genes for the biosynthesis of rifamycin antibiotics (personal communication) beside the genes for balhimycin biosynthesis. The “orientalis” cluster contains the glycopeptide producers like *A. alba*, *A. coloradensis*, *A. decaplanina*, *A. orientalis*, *A. lurida* and *A. keratiniphila* subsp. *nogabecina*. Similar clusters are also observed in the phylogeny calculated from 16S rDNA sequences (Figure 4).

For the identification of *Actinobacteria* to the species level a number of different techniques must be used in the polyphasic approach as described by Vandamme *et al.*<sup>21</sup>.

To differentiate between known and novel species within the collection it is important to compare the isolates with the known species of *Actinobacteria*. Therefore, we use the reference part of the collection, to which about 90% of the validly described species of this class belong. All these strains were characterised by use of a number of methods which have been chosen based

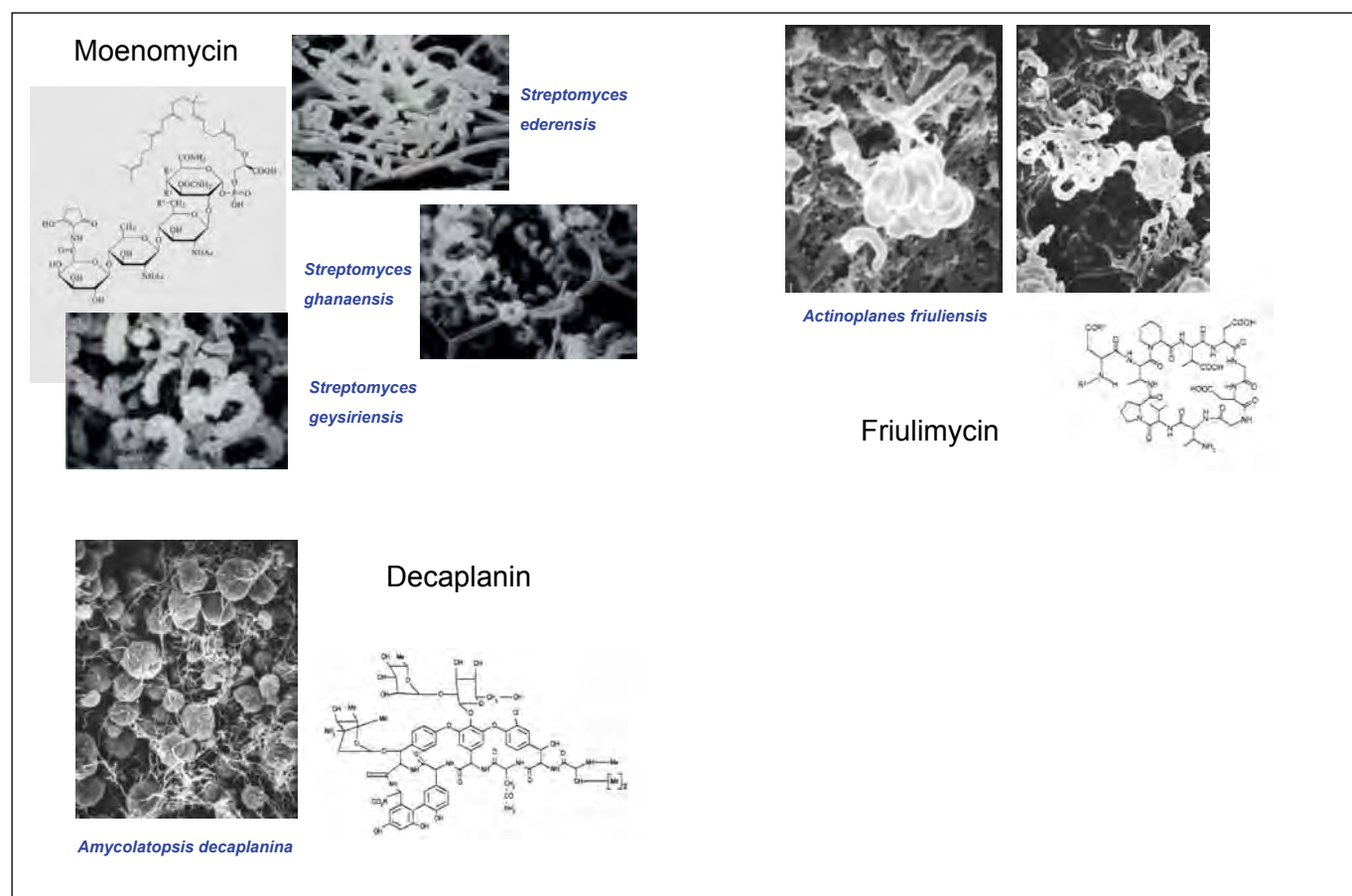


Figure 2. Examples of new antibiotics produced by novel species of actinomycetes from different screening approaches at Sanofi-Aventis and its predecessors.

on lengthy experience with morphological and physiological characterisation. The results are documented in reports including pictures of the strains. These reports are now publicly available as a link on the home page of the German Culture Collection DSMZ (<http://www.gbif-prokarya.de/microorganisms/wink.html>), where actually more than 1200 species from 160 genera of *Actinobacteria* are described<sup>7</sup>.

The methods used for this basic data of nearly all species are the following:

### Characterisation of colony growth

Characterisation of the morphology is a basic tool in actinomycete description<sup>22</sup>. The different strains were grown on the media of the International Streptomyces Project<sup>23</sup> by use of six well plates. Media were ISP 2 (yeast extract-malt extract agar), ISP 3 (oatmeal agar), ISP 4 (inorganic salt-starch agar), ISP 5 (glycerol-asparagine agar), ISP 6 (peptone-yeast extract iron agar) and ISP 7 (tyrosine agar). Characterised were the colour of the substrate mycelium (SM), the formation and colour of the aerial mycelium (AM) and the production of a soluble pigment (SP).

### Scanning electron microscopy

For the observation of the fine structure in scanning electron microscopy an agar plate of a well-grown and aerial mycelium-forming culture was prepared according to the method described previously<sup>24</sup>. The sample is fixed with glutaraldehyde, the water is substituted with acetone, a critical point drying with carbon dioxide follows and finally the sample is sputtered with gold.

### Carbon utilisation

The utilisation of carbohydrates plays an important role in species differentiation by bacteria and also the *Actinobacteria*<sup>25,26</sup>. The ability of strains to use nine compounds was tested on a 12-well plate based on the method of the ISP project<sup>23</sup>. Glucose, arabinose, sucrose, xylose, inositol, mannitol, fructose, rhamnose and raffinose were used as carbon sources.

### Physiological fingerprints with the api® strips

The api® system (bioMérieux) includes different strips with micro tubes that contain dehydrated substrates for the demonstration of enzymatic activity like the fermentation of carbohydrates. Two tests were used for the *Actinomycetales*:

1. Api® Coryne, a test kit especially for the *Propionibacterineae*, *Micrococcineae* and *Corynebacterineae*<sup>27,28</sup>, which also works with *Pseudonocardiaceae*.
2. Api® Zym, a simple rapid system for the detection of bacterial enzymes<sup>29</sup>, which has been successfully used for identification of *Actinomycetaceae* and related bacteria<sup>30</sup>.

For the identification of actinobacterial genera, different chemotaxonomic markers play a very important role<sup>31-42</sup>. We have chosen the fatty acids as the fastest and highly reproducible chemotaxonomic marker for the determination of the genus of potential novel isolates.

The fatty acids can be separated by gas chromatography as methylesters. We used the modified TMSH method<sup>43</sup>, in which the cells were cultivated on cellulose acetate filters on a medium containing glucose (1%), starch (1%), glycerol (1%), cornsteep liquor (0.25%), peptone (0.5%), yeast extract (0.2%), NaCl (0.1%) and CaCO<sub>3</sub> (0.3%). On this medium most of the actinomycetes express their differentiation stages and produce high amounts of biomass. The biomass which was harvested after 14 days of incubation was directly extracted with TMSH (trimethylsulphonium hydroxide). After evaporation the sample was dissolved in methanol and analysed in the gas chromatograph. The fatty acid pattern can be used for taxon identification as well as for species separation.

In the area of molecular biological tools we have chosen one simple and fast technology for the differentiation between isolates within a genus, the characterisation of proteins with the MALDI-TOF mass spectrometry<sup>44-46</sup>. Strain samples were collected

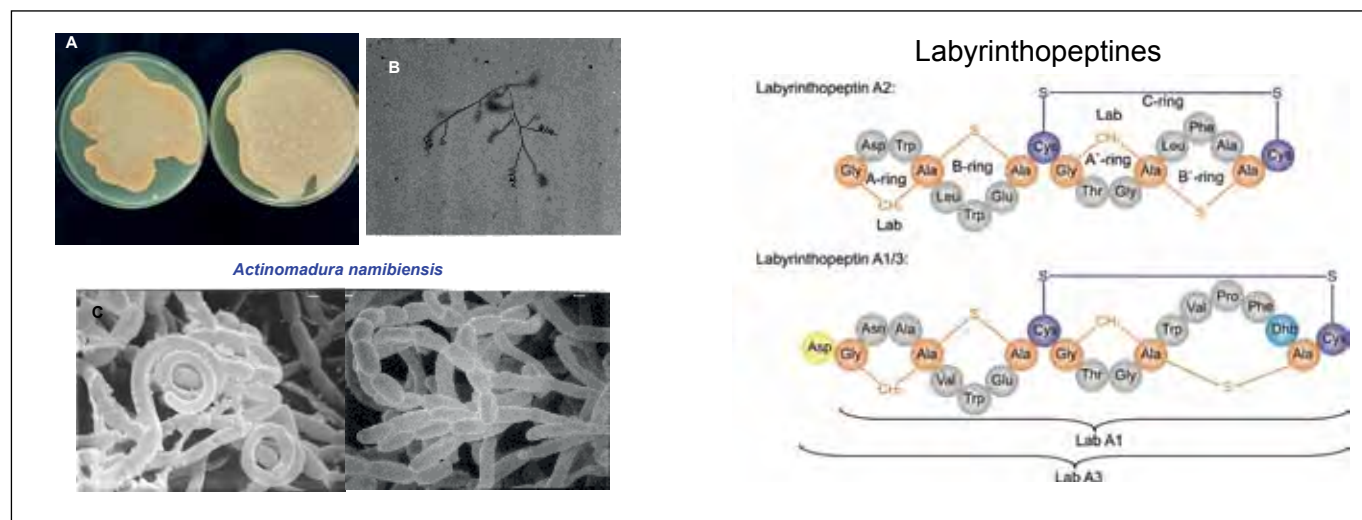


Figure 3. Labyrinthopeptins, new antibiotics from *Actinomadura namibiensis*.

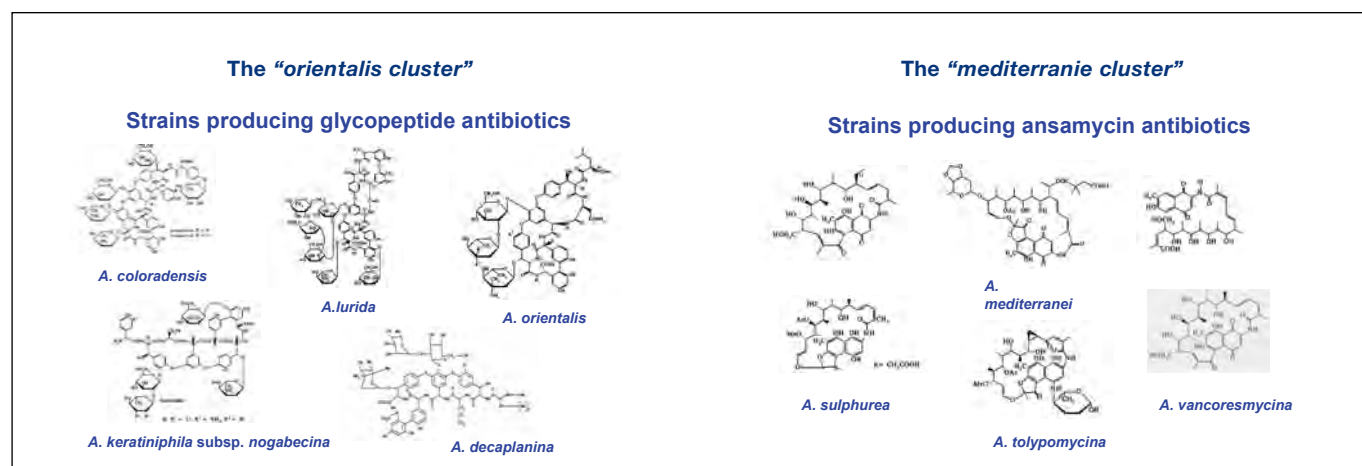


Figure 4. The two clusters within the genus *Amycolatopsis*. The orientalis cluster with the glycopeptides (upper left) and the mediterranei cluster with the ansamycin antibiotics (upper right) and both clusters in the phylogenetic trees based on 16S rDNA homology (lower left) and ribotype pattern (lower right).

from cellulose acetate filter, transferred onto a stainless steel template and immediately mixed with 1  $\mu$ l of matrix [10 mg/ml 2,5-dihydroxybenzoic acid in water/acetonitrile (1:1) with 0.03% trifluoroacetic acid]. The cell/matrix mixture was air-dried at room temperature. Positive ion mass spectra were recorded from each colony using a MALDI-TOF mass spectrometer (Voyager DE-PRO, Applied Biosystems, USA). Mass spectra were obtained from 2,000 to 20,000 Da. All analyses were carried out in the linear and delayed extraction mode, giving separation of protein peaks and a mass accuracy of at least 200 ppm. *Escherichia coli* strain DH5 $\alpha$  with known mass values of ribosomal proteins was used for external calibration.

The MALDI-TOF MS spectra were smoothed, baseline-corrected and peak detected using the Applied Biosystems Data Explorer software. The peak lists of the strains were imported in AnagnosTec "SARAMIS" (Spectral ARchiving And Microbial Identification System) software for used for spectra comparison, allowing classification of microorganisms<sup>47</sup>.

The novelty of isolates from our collection which were identified during one of our screening approaches has to be verified. This was carried out in collaboration with the German Culture Collection DSMZ using different molecular biological methods using 16S rDNA sequencing, DNA-DNA hybridisation and Riboprinter<sup>®</sup> analysis<sup>48-52</sup>. From this collaboration more than 30 novel species of different actinomycetes genera have been described<sup>3,9,10,16,17,47,53,54</sup>.

## Conclusions

The Sanofi-Aventis approach shows that actinomycetes taxonomy can be a very important and helpful tool in natural product screening. Also the postulated paradigm shift in biotechnology points out the importance of taxonomy in this important industrial field of research<sup>55</sup>.

Natural products diversity is still the pool for new compounds filling the pipeline for drug discovery<sup>56</sup>. As the number of isolates which have to be screened to detect new biological active

metabolites is rising, it is even more important to work with strains which have never been used for screening processes<sup>57</sup>. This can be achieved by isolating microorganisms from unusual habitats, trying to cultivate organisms which are difficult to handle or isolate new species and genera<sup>58-65</sup>. In all these cases the taxonomic characterisation of isolates plays an important role.

## References

- Wink, J. *et al.* (2002) Cyclipostins: Novel hormone-sensitive lipase inhibitors from *Streptomyces* sp. DSM 13381. Taxonomic studies of the producer microorganism and fermentation results. *J. Antibiotics* 55, 472-479.
- Vertesy, L. *et al.* (1999) Ala(O)-actagardine, a new lantibiotic from cultures of *Actinoplanes liguriae* ATCC 31048. *J. Antibiotics* 52, 730-741.
- Wink, J. *et al.* (2004) *Actinoplanes liguriae* sp. nov. and *Actinoplanes teichomyceticus* sp. nov., two new species of the genus *Actinoplanes*. *Int. J. Syst. Evol. Microbiol.* 56, 2125-2130.
- Parenti, F. *et al.* (1976) Gardimycin, a new antibiotic from *Actinoplanes* I. Description of the producer strain and fermentation studies. *J. Antibiotics* 29, 501-506.
- Parenti, F. *et al.* (1978) Teichomycins, new antibiotics from *Actinoplanes teichomyceticus* sp. nov. I. Description of the producer strain, fermentation studies and biological properties. *J. Antibiotics* 31, 276-283.
- Wallhäuser, K-H. *et al.* (1966) Moenomycin, a new antibiotic. I. Fermentation and isolation. *Antimicrob. Agents Chemother.* 5, 734-735
- Wink, J. *Compendium of Actinobacteria* <http://www.gbif-prokaryota.de/microorganisms/wink.html>
- Nadkarni, S.R. *et al.* (1994) Balhimycin, a new glycopeptide antibiotic produced by *Amycolatopsis* sp. Y-86, 21022. *J. Antibiotics* 47, 985-994.
- Wink, J. *et al.* (2003) Three new antibiotic producing species of the genus *Amycolatopsis*, *Amycolatopsis balhimycina* sp. nov., *A. tolypomycina* sp. nov., *A. vancoresmycina* sp. nov. and description of *Amycolatopsis keratiniphila* subsp. *keratiniphila* subsp. nov. and *A. keratiniphila* subsp. *nogabecina* subsp. nov. *System. Appl. Microbiol.* 26, 38-46.
- Wink, J. *et al.* (2004) *Amycolatopsis decaplanina* sp. nov., a novel member of the genus with unusual morphology. *Int. J. Syst. Evol. Microbiol.* 54, 235-239.
- Franco, C.M.M. *et al.* (1990) Glycopeptide antibiotic decaplanin. EP 356894.
- Nadkarni, S. *et al.* (1991) A process for the production of a new glycopeptide antibiotic nogabecin F with *Nocardia*. IN 169250.
- Hopmann, C.M. *et al.* (2002) Isolation and structure elucidation of vancoresmycin - a new antibiotic from *Amycolatopsis* sp. ST 101170. *Tetrahedron Letters* 43, 435-438.
- Butz, D. *et al.* (2008) Module extension of a non ribosomal peptide synthetase of the glycopeptide antibiotic balhimycin produced by *Amycolatopsis balhimycina*. *ChemBioChem* 9, 1195-1200
- Pelzer, S. *et al.* (1999) Identification and analysis of the balhimycin biosynthetic gene cluster and its use for manipulating glycopeptide biosynthesis in *Amycolatopsis mediterranei* DSM5908. *Antimicrob. Agents Chemother.* 43, 1565-1573.



16. Aretz, W. *et al.* (2000) Friulimicins: Novel lipopeptide antibiotics with peptidoglycan synthesis inhibiting activity from *Actinoplanes friuliensis* sp. nov. Taxonomic studies of the producing microorganism and fermentation *J. Antibiotics* 53, 807–815.
17. Wink, J. *et al.* (2003) *Actinomadura namibiensis* sp. nov. *Int. J. Syst. Evol. Microbiol.* 53, 721–724.
18. Broenstrup, M. *et al.* (2009) Highly bridged peptides from *Actinomadura namibiensis* and their derivatives WO2009121483
19. Meindl, K. *et al.* (2010) Labyrinthopeptine – eine neue Klasse carbacyclischer Lantibiotika. *Angewandte Chemie* 122, 1169–1173
20. Wink, J. (2003) Polyphasic taxonomy and antibiotic formation in some closely related genera of the family *Pseudonocardiaceae*. In *Recent Research Developments in Antibiotics* (S.G. Pandalai, ed.), pp. 97–140, Transworld Research Network, Kerala, India.
21. Vandamme, P. *et al.* (1996) Polyphasic taxonomy, a consensus approach to bacterial systematics. *Microbiol. Rev.* 60, 407–438.
22. Pridham, T.G. *et al.* (1958) A guide for the classification of *Streptomyces* according to selected groups. Placement of strains in morphological sections. *Appl. Microbiol.* 6, 52–79.
23. Shirling, E.B. and Gottlieb, D. (1966) Methods for characterization of *Streptomyces* species. *Int. J. System. Bacteriol.* 16, 313–340.
24. Wink, J. *et al.* (1992) Secondary metabolites by chemical screening. 8. Decarstrictines, a new family of inhibitors of cholesterol biosynthesis from *Penicillium* sp. *J. Antibiotics* 45, 56–65.
25. Pridham, T.G. and Gottlieb, D. (1948) The utilization of carbon compounds by some *Actinomycetales* as an aid for species determination *J. Bacteriol.* 56, 107–114.
26. Benedict, R.G. *et al.* (1955) Further studies in the evaluation of carbohydrate utilization tests as aids in the differentiation of species of *Streptomyces*. *Appl. Microbiol.* 3, 1–6.
27. Gavin, S.E. *et al.* (1992) Evaluation of the rapid Coryne identification system for *Corynebacterium* species and other Coryneforms. *J. Clin. Microbiol.* 30, 1692–1695.
28. Freney, J. *et al.* (1991) Evaluation of API Coryne in comparison with conventional methods for identifying Coryneform bacteria *J. Clin. Microbiol.* 29, 38–41.
29. Humble, M.W. *et al.* (1977) API ZYM: a simple rapid system for the detection of bacterial enzymes. *J. Clin. Pathol.* 30, 275–277.
30. Kilian, M. (1978) Rapid identification of *Actinomycetaceae* and related bacteria *J. Clin. Microbiol.* 8, 127–133.
31. Collins, M.D. and Kroppenstedt, R.M. (1983) Lipid composition as a guide to the classification of some coryneform bacteria – containing an A4 type peptidoglycan (Schleifer and Kandler). *Syst. Appl. Microbiol.* 4, 95–104.
32. Collins, M.D. *et al.* (1982) Chemical studies as a guide to the classification of *Corynebacterium baumlyticum*. *J. Gen. Microbiol.* 128, 335–341.
33. Cummins, C.S. and Harris, H. (1956) The chemical composition of the cell wall in some Gram-positive bacteria and its possible value as a taxonomic character *J. Gen. Microbiol.* 14, 583–600.
34. Cummins, C.S. and Harris, H. (1958) Studies on cell-wall composition and taxonomy of *Actinomycetales* and related groups *J. Gen. Microbiol.* 18, 173–189.
35. Kroppenstedt, R.M. (1985) Fatty acid and menaquinone analysis of actinomycetes and related organisms. In *Chemical methods in bacterial systematics* No. 20 SAB Technical Series (Goodfellow, M. and D.E. Minnikin eds), pp. 173–199, Academic Press.
36. Kroppenstedt, R.M. and Kutzner, H.J. (1976) Biochemical markers in the taxonomy of Actinomycetes *Experientia* 32, 318.
37. Kroppenstedt, R.M. and Kutzner, H.J. (1978) Biochemical taxonomy of some problem Actinomycetes. *Zentralblatt Bacteriol., I. Abt., Suppl.* 6, 125–133.
38. Lechevalier, M.P. (1968) Identification of aerobic actinomycetes of clinical importance *J. Lab. Clin. Med.* 71, 934–944.
39. Lechevalier, H.A. (1989) A practical guide to generic identification of Actinomycetes. In *Bergey's Manual of Systematic Bacteriology* Vol. 4. (Williams, S.T. *et al.*, eds), pp. 2344–2347, Williams and Wilkins, Baltimore, USA.
40. Lechevalier, M.P. *et al.* (1981) Phospholipids in the taxonomy of Actinomycetes *Zbl. Bakt. Mikrobiol. Hyg. I. Abt. Suppl.* 11, 335–354.
41. Minnikin, D.E. *et al.* (1975) Differentiation of *Mycobacterium*, *Nocardia* and related taxa by thin-layer chromatography analysis of whole organism methanolysates *J. Gen. Microbiol.* 88, 200–204.
42. Minnikin, D.E. *et al.* (1978) Menaquinone patterns in the classification of nocardioform and related bacteria *Zentralbl. Bakteriologie Parasitenkd. Infektionskr. U. Hyg. I. Abt., Suppl.* 6, 85–90.
43. Müller, K.D. *et al.* (1990) A new and rapid method for the assay of bacterial fatty acids using high resolution capillary gas chromatography and trimethylsulfonium hydroxide *Zbl. Bakt.* 274, 174–182.
44. Erhard, M. *et al.* (1977) Rapid typing and elucidation of new metabolites of intact cyanobacteria using MALDI-TOF mass spectrometry. *Nature Biotechnol.* 15, 906–909.
45. Mellmann, A. *et al.* (2008) Evaluation of Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) in comparison to 16S rRNA gene sequencing for species identification of nonfermenting bacteria *J. Clin. Microbiology* 46, 1946–1954.
46. Seng, P. *et al.* (2009) Ongoing revolution in bacteriology routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry *Clin. Infect. Dis.* 49, 543–551.
47. Kroppenstedt, R.M. *et al.* (2005) Eight new species of the genus *Micromonospora*, *Micromonospora citrea* sp. nov., *Micromonospora ecbinaurantiaca* sp. nov., *Micromonospora ecbinofusca* sp. nov., *Micromonospora fulviviridis* sp. nov., *Micromonospora inyonensis* sp. nov., *Micromonospora peucetia* sp. nov., *Micromonospora sagamiensis* sp. nov., and *Micromonospora viridifaciens* sp. nov. *Syst. Appl. Microbiol.* 28, 328–339.
48. Bruce, J. (1996) Automated system rapidly identifies and characterizes microorganisms in food. *Food Technol.* 50, 77–81.
49. Escara, J.F. and Hutton, J.R. (1980) Thermal stability and renaturation of DNA in dimethyl sulfoxide solutions: acceleration of renaturation rate *Biopolymers* 19, 1315–1327.
50. Felsenstein, J. (1993) PHYLIP Phylogeny inference package, version 3.5.1. Seattle: Department of Genetics, University of Washington.
51. Huss, V.A.R. (1983) Studies on the spectrophotometric determination of DNA hybridization from renaturation rates. *Syst. Appl. Microbiol.* 4, 184–192.
52. Jahnke, K.-D. (1992) BASIC computer program for evaluation of spectroscopic DNA renaturation data from GILFORD SYSTEM 2600 spectrophotometer on a PC/XT/AT type personal computer. *J. Microbiol. Meth.* 15, 61–73.
53. Stackebrandt, E. *et al.* (2001) *Nonomuraea dietzii* sp. nov. *Int. J. Syst. Evol. Microbiol.* 51, 1437–1441.
54. Stackebrandt, E. *et al.* (2004) Reclassification of *Amycolatopsis orientalis* subsp. *lurida* Lechevalier *et al.* 1986 as *Amycolatopsis lurida* sp. nov., comb. nov. *Int. J. Syst. Evol. Microbiol.* 54, 267–268.
55. Bull, A.T. *et al.* (2000) Search and discovery strategies for biotechnology: the paradigm shift. *Microbiol. Mol. Biol. Rev.* 64, 573–606.
56. Newman, D.J. and Laird, S.A. (1999) The influence of natural products on 1997 pharmaceutical sales figures. In *The commercial use of biodiversity* (ten Kate, K. and Laird, S.A., eds), pp. 333–335, Earthscan Publications Ltd., London.
57. Goodfellow, M. and O'Donnel, A.G. (1989) Search and discovery of industrially significant actinomycetes. In *Microbial Products* (Baumberg, S. *et al.*, eds), pp. 343–383, Cambridge University Press.
58. Clardy, J. (2006) New antibiotics from bacterial natural products *Nature Biotechnol.* 24, 1541–1550.
59. Donadinio, S. (2010) Antibiotic discovery in the twenty-first century: current trends and future perspectives *J. Antibiot.* 63, 423–430.
60. Berdy, J. (2005) Bioactive microbial metabolites. *J. Antibiot.* 58, 1–26.
61. Balz, R.H. (2006) Marcel Faber Roundtable: Is our antibiotic pipeline unproductive because of starvation, constipation or lack of inspiration? *J. Ind. Microbiol. Biotechnol.* 33, 507–513.
62. Li, J., W.-H. and Verderas, J.C. (2009) Drug discovery and natural products: end of an era or an endless frontier? *Science* 325, 161–165.
63. Harvey, A.L. (2008) Natural products in drug discovery. *Drug Discov. Today* 13, 894–901.
64. Newman, D.J. (2008) Natural products as leads to potential drugs: an old process or the new hope for drug discovery? *J. Med. Chem.* 51, 2589–2599.
65. Balz, R.H. (2008) Renaissance in antibacterial discovery from actinomycetes *Curr. Op. Pharmacol.* 8, 557–563.

## Biography

**Joachim M Wink** has been a research scientist at Sanofi-Aventis, Germany, and its predecessors in Frankfurt, Germany, for more than 25 years. He is responsible for the strain library and actinomycetes natural product screening. He is a lecturer at the University of Braunschweig in the field of applied microbiology. His special interests are in actinomycetes taxonomy and correlations to secondary metabolite production and the role of secondary metabolites in the environment of the microorganisms. He has published about 40 novel species of *Actinobacteria* in collaboration with the German Culture Collection DSMZ in Braunschweig.