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## Environmental and metabolomic study of antibiotic production by actinomycetes

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# **R**efferences

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- Agate, A. D. & Bhat, J. V. (1963).** A method for the preferential isolation of actinomycetes from soils. *Antonie van Leeuwenhoek* **29**, 297-304.
- Abel, C. B. L., Lindon, J. C., Noble, D., Rudd, B. A. M., Sidebottom, P. J. & Nicholson, J. K. (1999).** Characterization of metabolites in Intact *Streptomyces citricolor* culture supernatants using high-resolution nuclear magnetic resonance and directly coupled high-pressure liquid chromatography–nuclear magnetic resonance spectroscopy. *Anal Biochem* **270**, 220-230.
- Aharonowitz, Y. (1980).** Nitrogen metabolite regulation of antibiotic biosynthesis. *Annu Rev Microbiol* **34**, 209-233.
- Ahmed, S., Craney, A., Pimentel-Elardo, S. M. & Nodwell, J. R. (2013).** A synthetic, species-specific activator of secondary metabolism and sporulation in *Streptomyces coelicolor*. *Chembiochem* **14**, 83-91.
- Alali, F. Q., Gharaibeh, A., Ghawanmeh, A., Tawaha, K. & Oberlies, N. H. (2008).** Colchicinoids from *Colchicum crocifolium* Boiss.: a case study in dereplication strategies for (-)-colchicine and related analogues using LC-MS and LC-PDA techniques. *Phytochem Anal* **19**, 385-394.
- Alexander, D. C., Rock, J., He, X., Brian, P., Miao, V. & Baltz, R. H. (2010).** Development of a genetic system for combinatorial biosynthesis of lipopeptides in *Streptomyces fradiae* and heterologous expression of the A54145 biosynthesis gene cluster. *Appl Environ Microbiol* **76**, 6877-6887.
- Allen, J., Davey, H. M., Broadhurst, D., Heald, J. K., Rowland, J. J., Oliver, S. G. & Kell, D. B. (2003).** High-throughput classification of yeast mutants for functional genomics using metabolic footprinting. *Nat Biotechnol* **21**, 692-696.
- Allenby, N. E., Laing, E., Bucca, G., Kierzek, A. M. & Smith, C. P. (2012).** Diverse control of metabolism and other cellular processes in *Streptomyces coelicolor* by the PhoP transcription factor: genome-wide identification of *in vivo* targets. *Nucleic Acids Res* **40**, 9543-9556.
- Altermann, E. & Klaenhammer, T. R. (2005).** PathwayVoyager: pathway mapping using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. *BMC Genomics* **6**, 60.
- Altschul, S. F., Gish, W., Miller, W., Myers, E. W. & Lipman, D. J. (1990).** Basic local alignment search tool. *J Mol Biol* **215**, 403-410.
- Angell, S., Schwarz, E. & Bibb, M. J. (1992).** The glucose kinase gene of *Streptomyces coelicolor* A3(2): its nucleotide sequence, transcriptional analysis and role in glucose repression. *Mol Microbiol* **6**, 2833-2844.
- Angell, S., Lewis, C. G., Buttner, M. J. & Bibb, M. J. (1994).** Glucose repression in *Streptomyces coelicolor* A3(2): a likely regulatory role for glucose kinase. *Mol Genet* **244**, 135-143.
- Anthony, M. L., McDowell, P. C., Gray, T. J., Blackmore, M. & Nicholson, J. K. (1996).**  $^1\text{H}$  NMR spectroscopic studies on the characterization of renal cell lines and identification of novel potential markers of *in vitro* nephrotoxicity. *Biomarkers* **1**, 35-43.
- Aparicio, J. F., Colina, A. J., Ceballos, E. & Martin, J. F. (1999).** The biosynthetic gene cluster for the 26-membered ring polyene macrolide pimaricin. A new polyketide synthase organization encoded by two subclusters separated by functionalization genes. *J Biol Chem* **274**, 10133-10139.
- Arias, C. A. & Murray, B. E. (2009).** Antibiotic-resistant bugs in the 21st century--a clinical super-challenge. *N Engl J Med* **360**, 439-443.
- Aziz, R. K., Bartels, D., Best, A. A. & other authors (2008).** The RAST server: Rapid annotations using subsystems technology. *BMC Genomics* **9**.
- Bachmann, B. O. & Ravel, J. (2009).** Chapter 8. Methods for *in silico* prediction of microbial polyketide and nonribosomal peptide biosynthetic pathways from DNA sequence data. *Methods Enzymol* **458**, 181-217.
- Baltz, R. H. (2007).** Antimicrobials from actinomycetes: back to the future. *Microbe* **2**, 125-131.
- Baltz, R. H. (2008).** Renaissance in antibacterial discovery from actinomycetes. *Current Opin Pharmacol* **8**, 557-563.
- Baltz, R. H. (2011).** Function of MbtH homologs in nonribosomal peptide biosynthesis and applications in secondary metabolite discovery. *J Ind Microbiol Biotechnol* **38**, 1747-1760.
- Barreto, T. R., da Silva, A. C., Soares, A. C. & de Souza, J. T. (2008).** Population densities and genetic diversity of actinomycetes associated to the rhizosphere of *Theobroma cacao*. *Braz J Microbiol* **39**, 464-470.
- Beck, H. C., Hansen, A. M. & Lauritsen, F. R. (2003).** Novel pyrazine metabolites found in polymyxin biosynthesis by *Paenibacillus polymyxa*. *FEMS Microbiol Lett* **220**, 67-73.

- Beltrametti, F., Rossi, R., Selva, E. & Marinelli, F. (2006).** Antibiotic production improvement in the rare actinomycete *Planobispora rosea* by selection of mutants resistant to the aminoglycosides streptomycin and gentamycin and to rifamycin. *J Ind Microbiol Biotechnol* **33**, 283-288.
- Bentley, R. & Meganathan, R. (1981).** Geosmin and methylisoborneol biosynthesis in streptomycetes. Evidence for an isoprenoid pathway and its absence in non-differentiating isolates. *FEBS Lett* **125**, 220-222.
- Bentley, S. D., Chater, K. F., Cerdeno-Tarraga, A. M. & other authors (2002).** Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3(2). *Nature* **417**, 141-147.
- Bérdy, J. (2005).** Bioactive microbial metabolites. *J Antibiot (Tokyo)* **58**, 1-26.
- Berger, J., Jampolsky, L. M. & Goldberg, M. W. (1949).** Borrelidin, a new antibiotic with anti-borrelia activity and penicillin enhancement properties. *Arch Biochem* **22**, 476-478.
- Bibb, M. J. (2005).** Regulation of secondary metabolism in streptomycetes. *Curr Opin Microbiol* **8**, 208-215.
- Bibb, M. J. & Hesketh, A. (2009).** Chapter 4. Analyzing the regulation of antibiotic production in streptomycetes. *Methods Enzymol* **458**, 93-116.
- Birko, Z., Bialek, S., Buzas, K. & other authors (2007).** The secreted signaling protein factor C triggers the A-factor response regulon in *Streptomyces griseus*: overlapping signaling routes. *Mol Cell Proteomics* **6**, 1248-1256.
- Biró, S., Békési, I., Vitális, S. & Szabó, G. (1980).** A substance effecting differentiation in *Streptomyces griseus*. *Eur J Biochem* **103**, 359-363.
- Biró, S., Birkó, Z. & van Wezel, G. P. (2000).** Transcriptional and functional analysis of the gene for factor C, an extracellular signal protein involved in cytodifferentiation of *Streptomyces griseus*. *Antonie van Leeuwenhoek* **78**, 277-285.
- Bitzer, J., Kopcke, B., Stadler, M., Heilwig, V., Ju, Y. M., Seip, S. & Henkel, T. (2007).** Accelerated dereplication of natural products, supported by reference libraries. *Chimia* **61**, 332-338.
- Blow, N. (2008).** Metabolomics: Biochemistry's new look. *Nature* **455**, 697-700.
- Bok, J. W., Chiang, Y. M., Szewczyk, E. & other authors (2009).** Chromatin-level regulation of biosynthetic gene clusters. *Nat Chem Biol* **5**, 462-464.
- Bose, N., Ogawa, A., von Reuss, S. H., Yim, J. J., Ragsdale, E. J., Sommer, R. J. & Schroeder, F. C. (2012).** Complex small-molecule architectures regulate phenotypic plasticity in a nematode. *Angew Chem Int Ed Engl* **51**, 12438-12443.
- Boucher, H. W. & Corey, G. R. (2008).** Epidemiology of Methicillin-Resistant *Staphylococcus aureus*. *Clin Inf Diseases* **46**, S344-S349.
- Boucher, H. W., Talbot, G. H., Bradley, J. S., Edwards, J. E., Gilbert, D., Rice, L. B., Scheld, M., Spellberg, B. & Bartlett, J. (2009).** Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. *Clin Inf Diseases* **48**, 1-12.
- Brescia, M. A., Caldarola, V., De Giglio, A., Benedetti, D., Fanizzi, F. P. & Sacco, A. (2002).** Characterization of the geographical origin of Italian red wines based on traditional and nuclear magnetic resonance spectrometric determinations. *Anal Chim Acta* **458**, 177-186.
- Brückner, R. & Titgemeyer, F. (2002).** Carbon catabolite repression in bacteria: choice of the carbon source and autoregulatory limitation of sugar utilization. *FEMS Microbiol Lett* **209**, 141-148.
- Bundy, J. G., Willey, T. L., Castell, R. S., Ellar, D. J. & Brindle, K. M. (2005).** Discrimination of pathogenic clinical isolates and laboratory strains of *Bacillus cereus* by NMR-based metabolomic profiling. *FEMS Microbiol Lett* **242**, 127-136.
- Bull, A. T., Ward, A. C. & Goodfellow, M. (2000).** Search and discovery strategies for biotechnology: the paradigm shift. *Microbiol Mol Biol Rev* **64**, 573-606.
- Burt, S. (2004).** Essential oils: their antibacterial properties and potential applications in foods—a review. *Int J Food Microbiol* **94**, 223-253.
- Butler, M. S. & Buss, A. D. (2006).** Natural products—the future scaffolds for novel antibiotics? *Biochem Pharmacol* **71**, 919-929.
- Caboche, S., Pupin, M., Leclerc, V., Fontaine, A., Jacques, P. & Kucherov, G. (2008).** NORINE: a database of nonribosomal peptides. *Nucleic Acids Res* **36**, D326-331.

- Carpenterbogs, L., Loynachan, T. E. & Stahl, P. D. (1995).** Spore germination of *Gigaspora margarita* stimulated by volatiles of soil-isolated actinomycetes. *Soil Biol Biochem* **27**, 1445-1451.
- Carter, R. A., Worsley, P. S., Sawers, G. & other authors (2002).** The *vbs* genes that direct synthesis of the siderophore vicibactin in *Rhizobium leguminosarum*: their expression in other genera requires ECF sigma factor Rpol. *Mol Microbiol* **44**, 1153-1166.
- Cavaleiro, C., Pinto, E., Goncalves, M. J. & Salgueiro, L. (2006).** Antifungal activity of *Juniperus* essential oils against dermatophyte, *Aspergillus* and *Candida* strains. *J Appl Microbiol* **100**, 1333-1338.
- Challis, G. L. & Hopwood, D. A. (2003).** Synergy and contingency as driving forces for the evolution of multiple secondary metabolite production by *Streptomyces* species. *Proc Natl Acad Sci U S A* **100**, 14555-14561.
- Charlton, A. J., Farrington, W. H. H. & Brereton, P. (2002).** Application of  $^1\text{H}$  NMR and multivariate statistics for screening complex mixtures: quality control and authenticity of instant coffee. *J Agric Food Chem* **50**, 3098-3103.
- Charusanti, P., Fong, N. L., Nagarajan, H., Pereira, A. R., Li, H. J., Abate, E. A., Su, Y., Gerwick, W. H. & Palsson, B. O. (2012).** Exploiting adaptive laboratory evolution of *Streptomyces clavuligerus* for antibiotic discovery and overproduction. *PLoS One* **7**, e33727.
- Chater, K. F. (2006).** *Streptomyces* inside-out: a new perspective on the bacteria that provide us with antibiotics. *Philos Trans R Soc Lond B Biol Sci* **361**, 761-768.
- Chauton, M. S., Optun, O. I., Bathen, T. F., Volent, Z., Gribbestad, I. S. & Johnsen, G. (2003).** HR MAS  $^1\text{H}$  NMR spectroscopy analysis of marine microalgal whole cells. *Mar Ecol Prog Ser* **256**, 57-62.
- Chen, H., Xiao, X., Wang, J., Wu, L. J., Zheng, Z. M. & Yu, Z. L. (2008).** Antagonistic effects of volatiles generated by *Bacillus subtilis* on spore germination and hyphal growth of the plant pathogen, *Botrytis cinerea*. *Biotechnol Lett* **30**, 919-923.
- Chimura, H., Sawa, T., Kumada, Y., Naganawa, H. & Matsuzaki, M. (1975).** New isoflavones, inhibiting catechol-O-methyltransferase, produced by *Streptomyces*. *J Antibiot (Tokyo)* **28**, 619-626.
- Choi, Y. H., Kim, H. K., Hazekamp, A., Erkelens, C., Lefeber, A. W. M. & Verpoorte, R. (2004).** Metabolomic differentiation of *Cannabis sativa* cultivars using  $^1\text{H}$  NMR spectroscopy and principal component analysis. *J Nat Prod* **67**, 953-957.
- Chuanchuen, R. & Schweizer, H. P. (2012).** Global transcriptional responses to tricosan exposure in *Pseudomonas aeruginosa*. *Int J Antimicrob Agents* **40**, 114-122.
- Clardy, J., Fischbach, M. A. & Walsh, C. T. (2006).** New antibiotics from bacterial natural products. *Nat Biotechnol* **24**, 1541-1550.
- Collins, R. P. & Gaines, H. D. (1964).** Production of hydrogen sulfide by *Streptomyces odorifer*. *Appl Microbiol* **12**, 335-336.
- Colson, S., Stephan, J., Hertrich, T., Saito, A., van Wezel, G. P., Titgemeyer, F. & Rigali, S. (2007).** Conserved cis-acting elements upstream of genes composing the chitinolytic system of streptomycetes are DasR-responsive elements. *J Mol Microbiol Biotechnol* **12**, 60-66.
- Colson, S., van Wezel, G. P., Craig, M., Noens, E. E., Nothaft, H., Mommaas, A. M., Titgemeyer, F., Joris, B. & Rigali, S. (2008).** The chitobiase-binding protein, DasA, acts as a link between chitin utilization and morphogenesis in *Streptomyces coelicolor*. *Microbiology* **154**, 373-382.
- Colombo, V., Fernandez-de-Heredia, M. & Malpartida, F. (2001).** A polyketide biosynthetic gene cluster from *Streptomyces antibioticus* includes a LysR-type transcriptional regulator. *Microbiology* **147**, 3083-3092.
- Comroe, J. H., Jr. (1978).** Pay dirt: the story of streptomycin. Part I. From Waksman to Waksman. *Am Rev Respir Dis* **117**, 773-781.
- Corre, C., Song, L., O'Rourke, S., Chater, K. F. & Challis, G. L. (2008).** 2-Alkyl-4-hydroxymethylfuran-3-carboxylic acids, antibiotic production inducers discovered by *Streptomyces coelicolor* genome mining. *Proc Natl Acad Sci U S A* **105**, 17510-17515.
- Craig, M., Lambert, S., Jourdan, S. & other authors (2012).** Unsuspected control of siderophore production by N-acetylglucosamine in Streptomycetes. *Env Microbiol Rep*.
- Craney, A., Ozimok, C., Pimentel-Elardo, S. M., Capretta, A. & Nodwell, J. R. (2012).** Chemical perturbation of secondary metabolism demonstrates important links to primary metabolism. *Chem Biol* **19**, 1020-1027.
- Cruz-Morales, P., Vijgenboom, E., Iruegas-Bocardo, F. & other authors (2013).** The genome sequence of

- Streptomyces lividans* 66 reveals a novel tRNA-dependent peptide biosynthetic system within a metal-related genomic island. *Genome Biol Evol* **5**, 1165-1175.
- Davies, J. E. (1993). The Rise and Fall of Antibiotics. *Recherche* **24**, 1354-1361.
- D'Alia, D., Eggle, D., Nieselt, K., Hu, W. S., Breitling, R. & Takano, E. (2011). Deletion of the signalling molecule synthase ScbA has pleiotropic effects on secondary metabolite biosynthesis, morphological differentiation and primary metabolism in *Streptomyces coelicolor* A3(2). *Microb Biotechnol* **4**, 239-251.
- de Jong, A., van Heel, A. J., Kok, J. & Kuipers, O. P. (2010). BAGEL2: mining for bacteriocins in genomic data. *Nucleic Acids Res* **38**, W647-651.
- Demain, A. L. (1989). Carbon source regulation of idiolite biosynthesis. in Regulation of Secondary Metabolism in Actinomycetes. CRC Press, Boca Raton, FL, 127-134.
- Demain, A. L. (1999). Pharmaceutically active secondary metabolites of microorganisms. *Appl Microbiol Biotechnol* **52**, 455-463.
- Demilo, A. B., Lee, C.-J., Moreno, D. S. & Martinez, A. J. (1996). Identification volatiles derived from *Citrobacter freundii* fermentation of a trypticase soy broth. *J Agric Food Chem* **44**, 607-612.
- Dickschat, J. S., Martens, T., Brinkhoff, T., Simon, M. & Schulz, S. (2005). Volatiles released by a *Streptomyces* species isolated from the North Sea. *Chem Biodivers* **2**, 837-865.
- Dobretsov, S., Dahms, H. U., Yili, H., Wahl, M. & Qian, P. Y. (2007). The effect of quorum-sensing blockers on the formation of marine microbial communities and larval attachment. *FEMS Microbiol Ecol* **60**, 177-188.
- Duarte, I., Barros, A., Belton, P. S., Righelato, R., Spraul, M., Humpfer, E. & Gil, A. M. (2002). High-resolution nuclear magnetic resonance spectroscopy and multivariate analysis for the characterization of beer. *J Agric Food Chem* **50**, 2475-2481.
- Dorman, H. J. & Deans, S. G. (2000). Antimicrobial agents from plants: antibacterial activity of plant volatile oils. *J Appl Microbiol* **88**, 308-316.
- Dulaney, E. L. (1948). Observations on *Streptomyces griseus*: II. Nitrogen sources for growth and streptomycin production. *J Bacteriol* **56**, 305-313.
- Dulaney, E. L., Larsen, A. H. & Stapley, E. O. (1955). A note on the isolation of microorganisms from natural sources. *Mycologia* **47**, 420-422.
- El-Nakeeb, M. A. & Lechevalier, H. A. (1963). Selective isolation of aerobic Actinomycetes. *Appl Microbiol* **11**, 75-77.
- Eriksson, L., Johansson, E., Kettaneh-Wold, N., Trygg, J., Wikstrom, C. & Wold, S. (2006). Multi- and megavariate data analysis. Umeå: Umetrics Academy.
- Eriksson, L., Johansson, E., Kettaneh-Wold, N. & Wold, S. (2001). Multi- and Megavariate Data Analysis. Principles and Applications. Umetrics AB, Umeå, Sweden.
- Fedorova, D., Moktali, V. & Medema, H. (2012). Bioinformatics approaches and software for detection of secondary metabolic gene clusters. In *Fungal Secondary Metabolism*, pp. 23-45. Edited by N. P. Keller & G. Turner: Humana Press.
- Fernando, W. G. D., Ramarathnam, R., Krishnamoorthy, A. S. & Savchuk, S. C. (2005). Identification and use of potential bacterial organic antifungal volatiles in biocontrol. *Soil Biol Biochem* **37**, 955-964.
- Flärdh, K. & Buttner, M. J. (2009). *Streptomyces* morphogenetics: dissecting differentiation in a filamentous bacterium. *Nat Rev Microbiol* **7**, 36-49.
- Fleming, A. (1929). The antibacterial action of a *Penicillium*, with special reference to their use for the isolation of *B. influenzae*. *Brit J Exp Pathol* **10**, 226-236.
- Florian, C. L., Preece, N. E., Bhakoo, K. K., Williams, S. R. & Noble, M. D. (1995). Cell type-specific fingerprinting of meningioma and meningeal cells by proton nuclear magnetic resonance spectroscopy. *Cancer Res* **55**, 420-427.
- Floriano, B. & Bibb, M. (1996). *afrS* is a pleiotropic but conditionally required regulatory gene for antibiotic production in *Streptomyces coelicolor* A3(2). *Mol Microbiol* **21**, 385-396.
- Forreffe, L., Vercauteren, J. & Rutledge, D. N. (1996). Multivariate statistical analysis of two-dimensional NMR data to differentiate grapevine cultivars and clones. *Food Chem* **57**, 441-450.
- Fredenhagen, A., Derrien, C. & Gassmann, E. (2005). An MS/MS library on an ion-trap instrument for efficient

## References

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- dereplication of natural products. Different fragmentation patterns for [M + H]<sup>+</sup> and [M + Na]<sup>+</sup> ions. *J Nat Prod* **68**, 385-391.
- Firn, R. D. & Jones, C. G. (2003).** Natural products--a simple model to explain chemical diversity. *Nat Prod Rep* **20**, 382-391
- Gaunt, L. F., Higgins, S. C. & Hughes, J. F. (2005).** Interaction of air ions and bactericidal vapours to control micro-organisms. *J Appl Microbiol* **99**, 1324-1329.
- Gerber, N. N. & Lecheval, H. A. (1965).** Geosmin an earthy-smelling substance isolated from actinomycetes. *Appl Microbiol* **13**, 935-938.
- Gerber, N. N. (1967).** Geosmin an earthy-smelling substance isolated from actinomycetes. *Biotechnol Bioeng* **9**, 321-327.
- Gill, J. S., Sivasithamparam, K. & Smettem, K. R. J. (2001).** Effect of soil moisture at different temperatures on Rhizoctonia root rot of wheat seedlings. *Plant and Soil* **231**, 91-96.
- Giske, C. G., Monnet, D. L., Cars, O. & Carmeli, Y. (2008).** Clinical and economic impact of common multidrug-resistant Gram-negative *Bacilli*. *Antimicrob Agents Chemother* **52**, 813-821.
- Goodacre, R., Vaidyanathan, S., Dunn, W. B., Harrigan, G. G. & Kell, D. B. (2004).** Metabolomics by numbers: acquiring and understanding global metabolite data. *Trends Biotechnol* **22**, 245-252.
- Goodfellow, M. & Williams, E. (1986).** New strategies for the selective isolation of industrially important bacteria. *Biotechnology and Genetic Engineering Reviews* **4**, 213-262.
- Goosen, N. & van de Putte, P. (1995).** The regulation of transcription initiation by integration host factor. *Mol Microbiol* **16**, 1-7.
- Görke, B. & Stölke, J. (2008).** Carbon catabolite repression in bacteria: many ways to make the most out of nutrients. *Nat Rev Microbiol* **6**, 613-624.
- Griffin, J. L. (2003).** Metabonomics: NMR spectroscopy and pattern recognition analysis of body fluids and tissues for characterisation of xenobiotic toxicity and disease diagnosis. *Curr Opin Chem Biol* **7**, 648-654.
- Gross, H. (2009).** Genomic mining--a concept for the discovery of new bioactive natural products. *Curr Opin Drug Discov Devel* **12**, 207-219.
- Gu, Y. Q., Mo, M. H., Zhou, J. P., Zou, C. S. & Zhang, K. Q. (2007).** Evaluation and identification of potential organic nematicidal volatiles from soil bacteria. *Soil Biol Biochem* **39**, 2567-2575.
- Gubbens, J., Janus, M., Florea, B. I., Overkleeft, H. S. & van Wezel, G. P. (2012).** Identification of glucose kinase dependent and independent pathways for carbon control of primary metabolism, development and antibiotic production in *Streptomyces coelicolor* by quantitative proteomics. *Mol Microbiol* **86**, 1490-1507.
- Gubbens, J., Girard, G., Song, L., Florea, B.I., Aston, P., Choi, Y.H., Overkleeft, H.S., Challis, G.L. and van Wezel, G.P.** Proteomining, a novel quantitative proteomics-based platform for rapid and positive identification of biosynthetic genes specifying natural products. *Submitted for publication*.
- Gürtler, H., Pedersen, R., Anthoni, U., Christophersen, C., Nielsen, P. H., Wellington, E. M., Pedersen, C. & Bock, K. (1994).** Albaflavone, a sesquiterpene ketone with a zizaene skeleton produced by a *streptomycete* with a new rope morphology. *J Antibiot* **47**, 434-439.
- Habibi, D., Ogloff, N., Jalili, R., Yost, A., Weng, A., Ghahary, A. & Ong, C. (2012).** Borrelidin, a small molecule nitrile-containing macrolide inhibitor of threonyl-tRNA synthetase, is a potent inducer of apoptosis in acute lymphoblastic leukemia. *Invest New Drugs* **30**, 1361-1370.
- Hansen, M. E., Smedsgaard, J. & Larsen, T. O. (2005).** X-Hitting: an algorithm for novelty detection and dereplication by UV spectra of complex mixtures of natural products. *Anal Chem* **77**, 6805-6817.
- Hara, H., Ohnishi, Y. & Horinouchi, S. (2009).** DNA microarray analysis of global gene regulation by A-factor in *Streptomyces griseus*. *Microbiology* **155**, 2197-2210.
- Harris, N. D., Karahadian, C. & Lindsay, R. C. (1986).** Musty aroma compounds produced by selected molds and actinomycetes on agar and whole wheat bread. *J Food Protect* **49**, 964-970.
- Haupt, I., Wahner, U., Pitra, C., Lober, G., Luck, G. & Eckardt, K. (1975).** Effects of the antibiotic resistomycin on the synthesis of macromolecules. *Z Allg Mikrobiol* **15**, 411-421.
- Hayakawa, M. & Nonomura, H. (1987).** Humic acid-vitamin agar, a new medium for the selective isolation of soil actinomycetes. *Journal of Fermentation Technology* **65**, 501-509.

- Hayakawa, M. & Nonomura, H. (1989).** A new method for the intensive isolation of actinomycetes from soil. *Actinomycetol* **3**, 95-104.
- Hayakawa, M., Tamura, T. & Nonomura, H. (1991).** Selective isolation of *Actinoplanes* and *Dactylosporangium* from soil by using  $\gamma$ -collidine as the chemoattractant. *Journal of Fermentation and Bioengineering* **72**, 426-432.
- Hayakawa, M., Yoshida, Y. & Iimura, Y. (2004).** Selective isolation of bioactive soil actinomycetes belonging to the *Streptomyces violaceusniger* phenotypic cluster. *J Appl Microbiol* **96**, 973-981.
- Hegde, V. R., Wittreich, H., Patel, M. G., Horan, A. C., Hart, R. F., Troyanovich, J. J., Puar, M. S. & Gullo, V. P. (1989).** Naturally produced isocoumarins - inhibitors of calmodulin-sensitive cyclic guanosine 3',5'-monophosphate phosphodiesterase. *J Ind Microbiol* **4**, 209-213.
- Hiard, S., Maree, R., Colson, S., Hoskisson, P. A., Titgemeyer, F., van Wezel, G. P., Joris, B., Wehenkel, L. & Rigali, S. (2007).** PREDetector: a new tool to identify regulatory elements in bacterial genomes. *Biochem Biophys Res Commun* **357**, 861-864.
- Himmelreich, U., Somorjai, R. L., Dolenko, B., Lee, O. C., Daniel, H. M., Murray, R., Mountford, C. E. & Sorrell, T. C. (2003).** Rapid identification of *Candida* species by using nuclear magnetic resonance spectroscopy and a statistical classification strategy. *Appl Environ Microb* **69**, 4566-4574.
- Hirano, S., Tanaka, K., Ohnishi, Y. & Horinouchi, S. (2008).** Conditionally positive effect of the TetR-family transcriptional regulator AtrA on streptomycin production by *Streptomyces griseus*. *Microbiology* **154**, 905-914.
- Hockelmann, C., Moens, T. & Juttner, F. (2004).** Odor compounds from cyanobacterial biofilms acting as attractants and repellents for free-living nematodes. *Limnol Oceanogr* **49**, 1809-1819.
- Holmes, E., Nicholls, A. W., Lindon, J. C. & other authors (2000).** Chemometric models for toxicity classification based on NMR spectra of biofluids. *Chem Res Toxicol* **13**, 471-478.
- Hopwood, D. A. (1997).** Genetic contributions to understanding polyketide synthases. *Chem Rev* **97**, 2465-2498.
- Hopwood, D. A. (1999).** Forty years of genetics with *Streptomyces*: from *in vivo* through *in vitro* to *in silico*. *Microbiology* **145**, 2183-2202.
- Hopwood, D. A. (2006).** Soil to genomics: the *Streptomyces* chromosome. *Annu Rev Genet* **40**, 1-23.
- Hopwood, D. A. (2007).** *Streptomyces in nature and medicine: the antibiotic makers*. New York: Oxford University Press.
- Horinouchi, S. & Beppu, T. (1994).** A-factor as a microbial hormone that controls cellular differentiation and secondary metabolism in *Streptomyces griseus*. *Mol Microbiol* **12**, 859-864.
- Horinouchi, S. and T. Beppu. (1992).** Autoregulatory factors and communication in *actinomycetes*. *Annu Rev Microbiol* **46**, 377-398.
- Hosaka, T., Ohnishi-Kameyama, M., Muramatsu, H., Murakami, K., Tsurumi, Y., Kodani, S., Yoshida, M., Fujie, A. & Ochi, K. (2009).** Antibacterial discovery in actinomycetes strains with mutations in RNA polymerase or ribosomal protein S12. *Nat Biotechnol* **27**, 462-464.
- Hsiao, N. H., Gottelt, M. & Takano, E. (2009).** Chapter 6. Regulation of antibiotic production by bacterial hormones. *Methods Enzymol* **458**, 143-157.
- Huang, J., Shi, J., Molle, V. & other authors (2005).** Cross regulation among disparate antibiotic biosynthetic pathways of *Streptomyces coelicolor*. *Mol Microbiol* **58**, 1276-1287.
- Ichinose, K., Ozawa, M., Itou, K., Kunieda, K. & Ebizuka, Y. (2003).** Cloning, sequencing and heterologous expression of the medermycin biosynthetic gene cluster of *Streptomyces* sp. AM-7161: towards comparative analysis of the benzoisochromanone gene clusters. *Microbiology* **149**, 1633-1645.
- Ikeda, H., Ishikawa, J., Hanamoto, A., Shinose, M., Kikuchi, H., Shiba, T., Sakaki, Y., Hattori, M. & Omura, S. (2003).** Complete genome sequence and comparative analysis of the industrial microorganism *Streptomyces avermitilis*. *Nat Biotechnol* **21**, 526-531.
- Inaoka, T., Takahashi, K., Yada, H., Yoshida, M. & Ochi, K. (2004).** RNA polymerase mutation activates the production of a dormant antibiotic 3,3'-neotrehalosadiamine via an autoinduction mechanism in *Bacillus subtilis*. *J Biol Chem* **279**, 3885-3892.
- Inaoka, T. & Ochi, K. (2011).** Scandium stimulates the production of amylase and bacilysin in *Bacillus subtilis*. *Appl Environ Microbiol* **77**, 8181-8183
- Inouye, S., Tsuruoka, T., Watanabe, M., Takeo, K., Akao, M., Nishiyama, Y. & Yamaguchi, H. (2000).** Inhibitory

- effect of essential oils on apical growth of *Aspergillus fumigatus* by vapour contact. *Mycoses* **43**, 17-23.
- Inouye, S., Takizawa, T. & Yamaguchi, H. (2001). Antibacterial activity of essential oils and their major constituents against respiratory tract pathogens by gaseous contact. *J Antimicrob Chemother* **47**, 565-573.
- Iqbal, M., Mast, Y., Amin, R., Hodgson, D. A., Wohlleben, W. & Burroughs, N. J. (2012). Extracting regulator activity profiles by integration of de novo motifs and expression data: characterizing key regulators of nutrient depletion responses in *Streptomyces coelicolor*. *Nucleic Acids Res* **40**, 5227-5239.
- Islam, M. & Tiedemann, A. (2008). Zoosporogenesis and differentiation of grapevine downy mildew pathogen *Plasmopara viticola* in host-free system. *Phytopathology* **98**, S72-S72.
- Jellema, R. H. (2009). *Comprehensive chemometrics, chemical and biochemical data analysis*. Oxford: Elsevier.
- Johansen, S. K., Maus, C. E., Plikaytis, B. B. & Douthwaite, S. (2006). Capreomycin binds across the ribosomal subunit interface using tlyA-encoded 2'-O-methylations in 16S and 23S rRNAs. *Mol Cell* **23**, 173-182.
- Jones, J. B. & Pinder, A. R. (1958). Some synthetical investigations in isocoumarin chemistry. *J Chem Soc*, 2612-2618.
- Jornvall, H., Hedlund, J., Bergman, T., Oppermann, U. & Persson, B. (2010). Superfamilies SDR and MDR: from early ancestry to present forms. Emergence of three lines, a Zn-metalloenzyme, and distinct variabilities. *Biochem Biophys Res Commun* **396**, 125-130.
- Juttner, F. & Watson, S. B. (2007). Biochemical and ecological control of geosmin and 2-methylisoborneol in source waters. *Appl Environ Microbiol* **73**, 4395-4406.
- Kai, M., Effmert, U., Berg, G. & Piechulla, B. (2007). Volatiles of bacterial antagonists inhibit mycelial growth of the plant pathogen *Rhizoctonia solani*. *Arch Microbiol* **187**, 351-360.
- Karnetová, J., Tax, J., Stajner, K., Vaněk, Z. & Krumphanzl, V. (1983). Production of phenazines by *Streptomyces cinnamonensis*. *Folia Microbiol* **28**, 51-53.
- Kawai, K., Wang, G., Okamoto, S. & Ochi, K. (2007). The rare earth, scandium, causes antibiotic overproduction in *Streptomyces* spp. *FEMS Microbiol Lett* **274**, 311-315.
- Kato, J.-y., Funai, N., Watanabe, H., Ohnishi, Y. & Horinouchi, S. (2007). Biosynthesis of  $\gamma$ -butyrolactone autoregulators that switch on secondary metabolism and morphological development in *Streptomyces*. *Proc Natl Acad Sci U S A* **104**, 2378-2383.
- Kataoka, M., Ueda, K., Kudo, T., Seki, T. & Yoshida, T. (1997). Application of the variable region in 16S rDNA to create an index for rapid species identification in the genus *Streptomyces*. *FEMS Microbiol Lett* **151**, 249-255.
- Katoh, K. & Toh, H. (2008). Recent developments in the MAFFT multiple sequence alignment program. *Brief Bioinform* **9**, 286-298.
- Kawachi, R., Akashi, T., Kamitani, Y., Sy, A., Wangchaisoonthorn, U., Nihira, T. & Yamada, Y. (2000). Identification of an AfsA homologue (BarX) from *Streptomyces virginiae* as a pleiotropic regulator controlling autoregulator biosynthesis, virginiamycin biosynthesis and virginiamycin M1 resistance. *Mol Microbiol* **36**, 302-313.
- Kemsley, E. K. (1998). *Discriminant Analysis and Class Modeling of Spectroscopic Data*. Chichester, UK.
- Kennedy, A. C. (1999). Bacterial diversity in agroecosystems. *Agr Ecosyst Environ* **74**, 65-76.
- Kersten, R. D., Yang, Y. L., Xu, Y., Cimermancic, P., Nam, S. J., Fenical, W., Fischbach, M. A., Moore, B. S. & Dorrestein, P. C. (2011). A mass spectrometry-guided genome mining approach for natural product peptidogenomics. *Nat Chem Biol* **7**, 794-802.
- Kieser, T., Bibb, M. J., Buttner, M. J., Chater, K. F. & Hopwood, D. A. (2000). *Practical Streptomyces genetics*: The John Innes Foundation, Norwich, United Kingdom.
- Kim, H. K., Choi, Y. H. & Verpoorte, R. (2010). NMR-based metabolomic analysis of plants. *Nat Protoc* **5**, 536-549.
- Kim, H. K., Saifullah, Khan, S. & other authors (2010). Metabolic classification of South American Ilex species by NMR-based metabolomics. *Phytochemistry* **71**, 773-784.
- Kingston, D. G. I. (2011). Modern natural products drug discovery and its relevance to biodiversity conservation. *J Nat Prod* **74**, 496-511.
- Kitani, S., Yamada, Y. & Nihira, T. (2001). Gene replacement analysis of the butyrolactone autoregulator receptor (FarA) reveals that FarA acts as a Novel regulator in secondary metabolism of *Streptomyces lavendulae* FRI-5. *J Bacteriol* **183**, 4357-4363.

- Klevens, R. M., Edwards, J. R., Tenover, F. C., McDonald, L. C., Horan, T., Gaynes, R. & System, N. N. I. S. (2006).** Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. *Clin Inf Diseases* **42**, 389-391.
- Klevens, R. M., Morrison, M. A., Nadle, J. & other authors (2007).** Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA : the journal of the American Medical Association* **298**, 1763-1771.
- Koitabashi, M., Kajitani, Y. & Hirashima, K. (2004).** Antifungal substances produced by fungal strain Kyu-W63 from wheat leaf and its taxonomic position. *J Gen Plant Pathol* **70**, 124-130.
- König, W. A., Hochmuth, D. & Joulain, D. (2005).** *Massfinder 3*. Hamburg: Dr Hochmuth Scientific Consulting.
- Konishi, Y., Kiyota, T., Draghici, C., Gao, J. M., Yeboah, F., Acoca, S., Jarussophon, S. & Purisima, E. (2007).** Molecular formula analysis by an MS/MS/MS technique to expedite dereplication of natural products. *Anal Chem* **79**, 1187-1197.
- Kuester, E. & Williams, S. T. (1964).** Selection of Media for Isolation of *Streptomyces*. *Nature* **202**, 928-929.
- Labeda, D. P. & Lyons, A. J. (1991).** Deoxyribonucleic-Acid Relatedness among Species of the *Streptomyces-Cyaneus* Cluster. *Syst Appl Microbiol* **14**, 158-164.
- Lahana, R. (1999).** How many leads from HTS? *Drug Discov Today* **4**, 447-448.
- Lam, K. S. (2007).** New aspects of natural products in drug discovery. *Trends Microbiol* **15**, 279-289.
- Laouer, H., Meriem el, K., Prado, S. & Baldovini, N. (2009).** An antibacterial and antifungal phenylpropanoid from *Carum montanum* (Coss. et Dur.) Benth. et Hook. *Phytother Res* **23**, 1726-1730.
- Laureti, L., Song, L., Huang, S., Corre, C., Leblond, P., Challis, G. L. & Aigle, B. (2011).** Identification of a bioactive 51-membered macrolide complex by activation of a silent polyketide synthase in *Streptomyces ambofaciens*. *Proc Natl Acad Sci U S A* **108**, 6258-6263.
- Lautru, S. & Challis, G. L. (2004).** Substrate recognition by nonribosomal peptide synthetase multi-enzymes. *Microbiology* **150**, 1629-1636.
- Lazzarini, A., Cavaletti, L., Toppo, G. & Marinelli, F. (2000).** Rare genera of actinomycetes as potential producers of new antibiotics. *Antonie van Leeuwenhoek* **78**, 399-405.
- Lee, J., Hwang, Y., Kim, S., Kim, E. & Choi, C. (2000).** Effect of a global regulatory gene, *afsR2*, from *Streptomyces lividans* on avermectin production in *Streptomyces avermitilis*. *J Biosci Bioeng* **89**, 606-608.
- Lee, P. C., Umeyama, T. & Horinouchi, S. (2002).** *afsS* is a target of *AfsR*, a transcriptional factor with ATPase activity that globally controls secondary metabolism in *Streptomyces coelicolor* A3(2). *Mol Microbiol* **43**, 1413-1430.
- Leipe, D. D. & Landsman, D. (1997).** Histone deacetylases, acetoins utilization proteins and acetylpolyamine amidohydrolases are members of an ancient protein superfamily. *Nucleic Acids Res* **25**, 3693-3697.
- Linares, J. F., Gustafsson, I., Baquero, F. & Martinez, J. L. (2006).** Antibiotics as intermicrobial signaling agents instead of weapons. *Proc Natl Acad Sci U S A* **103**, 19484-19489.
- Lingappa, Y. & Lockwood, J. L. (1961).** A chitin medium for isolation, growth and maintenance of actinomycetes. *Nature* **189**, 158-159.
- Lipinski, C. A., Lombardo, F., Dominy, B. W. & Feeney, P. J. (2001).** Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* **46**, 3-26.
- Liu, G., Chater, K. F., Chandra, G., Niu, G. & Tan, H. (2013).** Molecular regulation of antibiotic biosynthesis in *Streptomyces*. *Microbiol Mol Biol Rev* **77**, 112-143.
- Liu, M., Kirpekar, F., Van Wezel, G. P. & Douthwaite, S. (2000).** The tylosin resistance gene *tlrB* of *Streptomyces fradiae* encodes a methyltransferase that targets G748 in 23S rRNA. *Mol Microbiol* **37**, 811-820.
- Liu, X., Ng, C. & Ferenci, T. (2000).** Global adaptations resulting from high population densities in *Escherichia coli* cultures. *J Bacteriol* **182**, 4158-4164.
- Lohmeier-Vogel, E. M., Hahn-Hagerdal, B. & Vogel, H. J. (1995).** Phosphorus-31 and carbon-13 nuclear magnetic resonance study of glucose and xylose metabolism in agarose-immobilized *Candida tropicalis*. *Appl Environ Microbiol* **61**, 1420-1425.
- Lukashin, A. V. & Borodovsky, M. (1998).** GeneMark.hmm: new solutions for gene finding. *Nucleic Acids Res* **26**, 1107-1115.

## References

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- MacNeil, D. J., Gewain, K. M., Ruby, C. L., Dezeny, G., Gibbons, P. H. & MacNeil, T. (1992).** Analysis of *Streptomyces avermitilis* genes required for avermectin biosynthesis utilizing a novel integration vector. *Gene* **111**, 61-68.
- Maharjan, S., Oh, T. J., Lee, H. C. & Sohng, J. K. (2009).** Identification and functional characterization of an *afsR* homolog regulatory gene from *Streptomyces venezuelae* ATCC 15439. *J Microbiol Biotechnol* **19**, 121-127.
- Malpartida, F. & Hopwood, D. A. (1986).** Physical and genetic characterisation of the gene cluster for the antibiotic actinorhodin in *Streptomyces coelicolor* A3(2). *Mol Gen Genet* **205**, 66-73.
- Manteca, A., Fernandez, M. & Sanchez, J. (2005).** A death round affecting a young compartmentalized mycelium precedes aerial mycelium dismantling in confluent surface cultures of *Streptomyces antibioticus*. *Microbiology* **151**, 3689-3697.
- Manteca, A., Fernandez, M. & Sanchez, J. (2005).** Mycelium development in *Streptomyces antibioticus* ATCC11891 occurs in an orderly pattern which determines multiphase growth curves. *BMC Microbiol* **5**, 51.
- Mao, X., Cai, T., Olyarchuk, J. G. & Wei, L. (2005).** Automated genome annotation and pathway identification using the KEGG Orthology (KO) as a controlled vocabulary. *Bioinformatics* **21**, 3787-3793.
- Martin, J. F. & Demain, A. L. (1980).** Control of antibiotic biosynthesis. *Microbiol Rev* **44**, 230-251.
- Martin, J. F. & Aparicio, J. F. (2009).** Enzymology of the polyenes pimaricin and candicidin biosynthesis. *Methods Enzymol* **459**, 215-242.
- Martin, J. F. & Liras, P. (2010).** Engineering of regulatory cascades and networks controlling antibiotic biosynthesis in *Streptomyces*. *Curr Opin Microbiol* **13**, 263-273.
- Martin, J. F., Sola-Landa, A., Santos-Benito, F., Fernandez-Martinez, L. T., Prieto, C. & Rodriguez-Garcia, A. (2011).** Cross-talk of global nutritional regulators in the control of primary and secondary metabolism in *Streptomyces*. *Microb Biotechnol* **4**, 165-174.
- Martín, J. F. (2004).** Phosphate control of the biosynthesis of antibiotics and other secondary metabolites is mediated by the PhoR-PhoP system: an unfinished story. *J Bacteriol* **186**, 5197-5201.
- Martín, J. F., and A. Demain. (1980).** Control of antibiotic biosynthesis. *MicrobiolRev* **44**, 230-251.
- Martinez, A., Kolvek, S. J., Hopke, J., Yip, C. L. & Osburne, M. S. (2005).** Environmental DNA fragment conferring early and increased sporulation and antibiotic production in *Streptomyces* species. *Appl Environ Microbiol* **71**, 1638-1641.
- Matsumoto, A., Ishizuka, H., Beppu, T. & Horinouchi, S. (1995).** Involvement of a small ORF downstream of the *afsR* gene in the regulation of secondary metabolism in *Streptomyces coelicolor* A3(2). *Actinomycetologica* **9**, 37-43.
- McDowall, K. J., Thamchaipenet, A. & Hunter, I. S. (1999).** Phosphate control of oxytetracycline production by *Streptomyces rimosus* is at the level of transcription from promoters overlapped by tandem repeats similar to those of the DNA-binding sites of the OmpR family. *J Bacteriol* **181**, 3025-3032.
- McLafferty, F. W. (2005).** *Wiley Registry™ of Mass Spectral Data*, 7th edn. New York, USA: John Wiley & Sons, Ltd.
- Medema, M., Blin, K., Cimermancic, P., de Jager, V., Zakrzewski, P., Fischbach, M. A., Weber, T., Takano, E. & Breitling, R. (2011a).** antiSMASH: rapid identification, annotation and analysis of secondary metabolite biosynthesis gene clusters in bacterial and fungal genome sequences. *Nucleic Acids Res* **39**, W339-W346.
- Medema, M. H., Breitling, R., Bovenberg, R. & Takano, E. (2011b).** Exploiting plug-and-play synthetic biology for drug discovery and production in microorganisms. *Nat Rev Microbiol* **9**, 131-137.
- Mendes, M. V., Tunca, S., Anton, N., Recio, E., Sola-Landa, A., Aparicio, J. F. & Martin, J. F. (2007).** The two-component *phoR-phoP* system of *Streptomyces natalensis*: Inactivation or deletion of *phoP* reduces the negative phosphate regulation of pimaricin biosynthesis. *Metabolic engineering* **9**, 217-227.
- Miyadoh, S. (1993).** Research on antibiotic screening in Japan over the last decade: a producing microorganism approach. *Actinomycetol* **7**, 100-106.
- Moore, J. M., Bradshaw, E., Seipke, R. F., Hutchings, M. I. & McArthur, M. (2012).** Use and discovery of chemical elicitors that stimulate biosynthetic gene clusters in *Streptomyces* bacteria. *Methods Enzymol* **517**, 367-385.
- Myers, P. L. (1997).** Will combinatorial chemistry deliver real medicines? *Curr Opin Biotechnol* **8**, 701-707.
- Nair, R. & Chanda, S. (2006).** Activity of some medicinal plants against certain pathogenic bacterial strains. *Ind J Pharmacol* **38**, 142-144.

- Nazari, B., Kobayashi, M., Saito, A., Hassaninasab, A., Miyashita, K. & Fujii, T. (2012).** Chitin-induced gene expression involved in secondary metabolic pathways in *Streptomyces coelicolor* A3(2) grown in soil. *Appl Environ Microbiol* **79**, 707-713.
- Nett, M., Ikeda, H. & Moore, B. S. (2009).** Genomic basis for natural product biosynthetic diversity in the actinomycetes. *Nat Prod Rep* **26**, 1362-1384.
- Newman, D. J. & Cragg, G. M. (2007).** Natural products as sources of new drugs over the last 25 years. *J Nat Prod* **70**, 461-477.
- Newman, D. J. & Cragg, G. M. (2012).** Natural products as sources of new drugs over the 30 Years from 1981 to 2010. *J Nat Prod* **75**, 311-335.
- Ng, Z. Y. & Amsaveni, S. (2012).** Isolation, screening and characterization of antibiotic-producing actinomycetes from rhizosphere region of different plants from a farm of Sungai Ramal Luar, Malaysia. *J Adv Biomed Pathobiol* **2**, 96-107.
- Nikaido, H. & Vaara, M. (1985).** Molecular basis of bacterial outer membrane permeability. *Microbiol Rev* **49**, 1-32.
- Nodwell, J. R. and R. Losick. (1998).** Purification of an extracellular signaling molecule involved in production of the aerial mycelium by *Streptomyces coelicolor*. *J Bacteriol* **180**, 1334-1337.
- Nieselt, K., Battke, F., Herbig, A. & other authors (2010).** The dynamic architecture of the metabolic switch in *Streptomyces coelicolor*. *BMC Genomics* **11**, 10.
- Nolan, R. D. & Cross, T. (1988).** Isolation and screening of actinomycetes. In M. Goodfellow, S.T. Williams, and M. Mordarski (eds.), *Actinomycetes in biotechnology*. Academic Press, London, 2-8.
- Nord, L. I., Kenne, L. & Jacobsson, S. P. (2001).** Multivariate analysis of  $^1\text{H}$  NMR spectra for saponins from *Quillaja saponaria* Molina. *Anal Chim Acta* **446**, 197-207.
- Nothaft, H., Dresel, D., Willimek, A., Mahr, K., Niederweis, M. & Titgemeyer, F. (2003).** The phosphotransferase system of *Streptomyces coelicolor* is biased for *N*-acetylglucosamine metabolism. *J Bacteriol* **185**, 7019-7023.
- Nothaft, H., Rigali, S., Boomsma, B., Swiatek, M., McDowall, K. J., van Wezel, G. P. & Titgemeyer, F. (2010).** The permease gene *nagE2* is the key to *N*-acetylglucosamine sensing and utilization in *Streptomyces coelicolor* and is subject to multi-level control. *Mol Microbiol* **75**, 1133-1144.
- Novakova, R., Rehakova, A., Kutas, P., Feckova, L. & Kormanec, J. (2011).** The role of two SARP family transcriptional regulators in regulation of the auricin gene cluster in *Streptomyces aureofaciens* CCM 3239. *Microbiology* **157**, 1629-1639.
- O'Callaghan, J., Caddick, M. X. & Dobson, A. D. (2003).** A polyketide synthase gene required for ochratoxin A biosynthesis in *Aspergillus ochraceus*. *Microbiology* **149**, 3485-3491.
- O'Rourke, S., Wietzorek, A., Fowler, K., Corre, C., Challis, G. L. & Chater, K. F. (2009).** Extracellular signalling, translational control, two repressors and an activator all contribute to the regulation of methylenomycin production in *Streptomyces coelicolor*. *Mol Microbiol* **71**, 763-778.
- Ochi, K. & Okamoto, S. (2012).** A magic bullet for antibiotic discovery. *Chem Biol* **19**, 932-934.
- Ochi, K. & Hosaka, T. (2013).** New strategies for drug discovery: activation of silent or weakly expressed microbial gene clusters. *Appl Microbiol Biotechnol* **97**, 87-98.
- Ohnishi, Y., Kameyama, S., Onaka, H. & Horinouchi, S. (1999).** The A-factor regulatory cascade leading to streptomycin biosynthesis in *Streptomyces griseus*: identification of a target gene of the A-factor receptor. *Mol Microbiol* **34**, 102-111.
- Ohnishi, Y., Ishikawa, J., Hara, H., Suzuki, H., Ikenoya, M., Ikeda, H., Yamashita, A., Hattori, M. & Horinouchi, S. (2008).** Genome sequence of the streptomycin-producing microorganism *Streptomyces griseus* IFO 13350. *J Bacteriol* **190**, 4050-4060.
- Ohnishi Y. K. S., Onaka H, Horinouchi S. (1999).** The A-factor regulatory cascade leading to streptomycin biosynthesis in *Streptomyces griseus*: identification of a target gene of the A-factor receptor. *Mol Microbiol* **34**, 102-111.
- Okami, Y. & Hotta, K. (1988).** Search and discovery of new antibiotics. In *Actinomycetes in biotechnology*, pp. 33-67. Edited by M. Goodfellow, S. T. Williams & M. Mordarski. California: Academic Press.
- Oliynyk, M., Samborskyy, M., Lester, J. B., Mironenko, T., Scott, N., Dickens, S., Haydock, S. F. & Leadlay, P. F. (2007).** Complete genome sequence of the erythromycin-producing bacterium *Saccharopolyspora erythraea*

- NRRL23338. *Nat Biotechnol* **25**, 447-453.
- Omura, S., Ikeda, H., Ishikawa, J. & other authors (2001).** Genome sequence of an industrial microorganism *Streptomyces avermitilis*: deducing the ability of producing secondary metabolites. *Proc Natl Acad Sci U S A* **98**, 12215-12220.
- Onaka H, Mori Y, Igarashi Y & T, F. (2011).** Mycolic acid-containing bacteria induce natural-product biosynthesis in *Streptomyces* species. *Appl Environ Microbiol* **77**, 400-406.
- Paradkar, A. (2013).** Clavulanic acid production by *Streptomyces clavuligerus*: biogenesis, regulation and strain improvement. *J Antibiot (Tokyo)* **66**, 411-420.
- Parajuli, N., Viet, H. T., Ishida, K., Tong, H. T., Lee, H. C., Liou, K. & Sohng, J. K. (2005).** Identification and characterization of the *afsR* homologue regulatory gene from *Streptomyces peucetius* ATCC 27952. *Res Microbiol* **156**, 707-712.
- Pawlak, K., Kotowska, M., Chater, K. F., Kuczak, K. & Takano, E. (2007).** A cryptic type I polyketide synthase (*cpk*) gene cluster in *Streptomyces coelicolor* A3(2). *Arch Microbiol* **187**, 87-99.
- Payne, D. J., Gwynn, M. N., Holmes, D. J. & Pompili, D. L. (2007).** Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nat Rev Drug Discov* **6**, 29-40.
- Petersen, C. d. V., Beck, H. C. & Lauritsen, F. R. (2004).** On-line monitoring of important organoleptic methyl-branched aldehydes during batch fermentation of starter culture *Staphylococcus xylosus* reveal new insight into their production in a model fermentation. *Biotechnol Bioeng* **85**, 298-305.
- Piepersberg, W. & Distler, J. (1997).** Aminoglycosides and sugar components in other secondary metabolites. In *Products of Secondary Metabolism*, pp. 397-488. Edited by H. J. Rehm & G. Reed. Weinheim: VCH-Verlagsgesellschaft.
- Polkowski, K. & Mazurek, A. P. (2000).** Biological properties of genistein. A review of in vitro and in vivo data. *Acta Pol Pharm* **57**, 135-155.
- Pierre, P. S., Jansen, J. J., Hordijk, C. A., van Dam, N. M., Cortesero, A. M. & Dugravot, S. (2011).** Differences in volatile profiles of turnip plants subjected to single and dual herbivory above- and belowground. *J Chem Ecol* **37**, 368-377.
- Pimm, S. L., Russell, G. J., Gittleman, J. L. & Brooks, T. M. (1995).** The future of biodiversity. *Science* **269**, 347-350.
- Ping, L. & Boland, W. (2004).** Signals from the underground: bacterial volatiles promote growth in *Arabidopsis*. *Trends Plant Sci* **9**, 263-266.
- Pyun, M. S. & Shin, S. (2006).** Antifungal effects of the volatile oils from *Allium* plants against *Trichophyton* species and synergism of the oils with ketoconazole. *Phytomedicine* **13**, 394-400.
- Raamsdonk, L. M., Teusink, B., Broadhurst, D. & other authors (2001).** A functional genomics strategy that uses metabolome data to reveal the phenotype of silent mutations. *Nat Biotechnol* **19**, 45-50.
- Qiu, X., Yan, X., Liu, M. & Han, R. (2012).** Genetic and proteomic characterization of *rpoB* mutations and their effect on nematicidal activity in *Photobacterium luminescens* LN2. *PLoS One* **7**, e43114.
- Queiroz, E. F., Wolfender, J. L. & Hostettmann, K. (2009).** Modern approaches in the search for new lead antiparasitic compounds from higher plants. *Curr Drug Targets* **10**, 202-211.
- Rademaker, J. L. W., Louws, F. J. & De Bruijn, F. J. (1997).** Characterization of the diversity of ecologically important microbes by rep-PCR genomic fingerprinting. In *Molecular Microbial Ecology Manual*, pp. 1-26. Edited by A. D. L. Akkermans, J. D. Van Elsas & J. D. De Bruijn. Dordrecht: Kluwer Academic Publishers
- Ramos, A., Lolkema, J. S., Konings, W. N. & Santos, H. (1995).** Enzyme Basis for pH Regulation of Citrate and Pyruvate Metabolism by *Leuconostoc oenos*. *Appl Environ Microbiol* **61**, 1303-1310.
- Ratcliff, W. C. & Denison, R. F. (2011).** Microbiology. Alternative actions for antibiotics. *Science* **332**, 547-548.
- Reading, C. & Cole, M. (1977).** Clavulanic acid: a beta-lactamase-inhibiting beta-lactam from *Streptomyces clavuligerus*. *Antimicrob Agents Chemother* **11**, 852-857.
- Recio, E., Colinas, A., Rumbero, A., Aparicio, J. F. & Martín, J. F. (2004).** PI factor, a novel type quorum-sensing inducer elicits pimaricin production in *Streptomyces natalensis*. *J Biol Chem* **279**, 41586-41593.
- Reyes-Dominguez, Y., Boedi, S., Sulyok, M., Wiesenberger, G., Stoppacher, N., Krksa, R. & Strauss, J. (2012).** Heterochromatin influences the secondary metabolite profile in the plant pathogen *Fusarium graminearum*. *Fungal Genet Biol* **49**, 39-47.

- Rice, L. B. (2008).** Federal funding for the study of antimicrobial resistance in nosocomial pathogens: No ESKAPE. *J Infect Dis* **197**, 1079-1081.
- Rigali, S., Nothaft, H., Noens, E. E. & other authors (2006).** The sugar phosphotransferase system of *Streptomyces coelicolor* is regulated by the GntR-family regulator DasR and links N-acetylglucosamine metabolism to the control of development. *Mol Microbiol* **61**, 1237-1251.
- Rigali, S., Titgemeyer, F., Barends, S., Mulder, S., Thomae, A. W., Hopwood, D. A. & van Wezel, G. P. (2008).** Feast or famine: the global regulator DasR links nutrient stress to antibiotic production by *Streptomyces*. *EMBO Rep* **9**, 670-675.
- Rivero-Cruz, B., Rivero-Cruz, I., Rodríguez, J. M., Cerdá-García-Rojas, C. M. & Mata, R. (2006).** Qualitative and quantitative analysis of the active components of the essential oil from *Brickellia veronicaefolia* by nuclear magnetic resonance spectroscopy. *J Nat Prod* **69**, 1172-1176.
- Rochfort, S. (2005).** Metabolomics reviewed: a new "omics" platform technology for systems biology and implications for natural products research. *J Nat Prod* **68**, 1813-1820.
- Rodríguez-García, A., Sola-Landa, A., Apel, K., Santos-Benito, F. & Martin, J. F. (2009).** Phosphate control over nitrogen metabolism in *Streptomyces coelicolor*: direct and indirect negative control of *glnR*, *glnA*, *glnII* and *amtB* expression by the response regulator PhoP. *Nucleic Acids Res* **37**, 3230-3242.
- Roggo, B. E., Petersen, F., Delmendo, R., Jenny, H. B., Peter, H. H. & Roesel, J. (1994).** 3-Alkanoyl-5-hydroxymethyl tetronic acid homologues and resistomycin: new inhibitors of HIV-1 protease. I. Fermentation, isolation and biological activity. *J Antibiot (Tokyo)* **47**, 136-142.
- Römer, A. (1982).**  $^1\text{H}$  NMR spectra of substituted phenazines. *Org Magn Res* **19**, 66-68.
- Romero, D., Traxler, M. F., Lopez, D. & Kolter, R. (2011).** Antibiotics as signal molecules. *Chem Rev* **111**, 5492-5505.
- Roemer, T., Xu, D., Singh, S. B., Parish, C. A., Harris, G., Wang, H., Davies, J. E. & Bills, G. F. (2011).** Confronting the challenges of natural product-based antifungal discovery. *Chem Biol* **18**, 148-164.
- Ruan, B., Bovee, M. L., Sacher, M., Stathopoulos, C., Poralla, K., Francklyn, C. S. & Söll, D. (2005).** A unique hydrophobic cluster near the active site contributes to differences in borrelidin inhibition among threonyl-tRNA synthetases. *J Biol Chem* **280**, 571-577.
- Ryu, C. M., Farag, M. A., Hu, C. H., Reddy, M. S., Wei, H. X., Pare, P. W. & Klopper, J. W. (2003).** Bacterial volatiles promote growth in *Arabidopsis*. *Proc Natl Acad Sci U S A* **100**, 4927-4932.
- Ryu, C. M., Farag, M. A., Hu, C. H., Reddy, M. S., Klopper, J. W. & Pare, P. W. (2004).** Bacterial volatiles induce systemic resistance in *Arabidopsis*. *Plant Physiol* **134**, 1017-1026.
- Saitou, N. & Nei, M. (1987).** The neighbor-joining method: a new method for reconstructing phylogenetic trees. *Mol Biol Evol* **4**, 406-425.
- Sajid, I., Shaaban, K. & Hasnain, S. (2011).** Antitumour compounds from a saline soil isolate, *Streptomyces griseoincarnatus* CTF15. *Nat Prod Res* **25**, 549-559.
- Sanchez, S., Chavez, A., Forero, A. & other authors (2010).** Carbon source regulation of antibiotic production. *J Antibiot (Tokyo)* **63**, 442-459.
- Santos-Benito, F., Rodriguez-Garcia, A., Sola-Landa, A. & Martin, J. F. (2009).** Cross-talk between two global regulators in *Streptomyces*: PhoP and AfsR interact in the control of *afsS*, *pstS* and *phoRP* transcription. *Mol Microbiol* **72**, 53-68.
- Santos-Benito, F., Barriuso-Iglesias, M., Fernandez-Martinez, L. T., Martinez-Castro, M., Sola-Landa, A., Rodriguez-Garcia, A. & Martin, J. F. (2011).** The RNA polymerase omega factor RpoZ is regulated by PhoP and has an important role in antibiotic biosynthesis and morphological differentiation in *Streptomyces coelicolor*. *Appl Environ Microbiol* **77**, 7586-7594.
- Schatz, A., Bugle, E. & Waksman, S. A. (1944).** Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. *Exptl Biol & Med* **55**, 66-69.
- Scherrer, R. & Gerhardt, P. (1971).** Molecular sieving by the *Bacillus megaterium* cell wall and protoplast. *J Bacteriol* **107**, 718-735.
- Schöller, C. E. G., Gürtler, H., Pedersen, R., Molin, S. & Wilkins, K. (2002).** Volatile Metabolites from Actinomycetes. *Journal of Agricultural and Food Chemistry* **50**, 2615-2621.
- Schripsema, J. (2010).** Application of NMR in plant metabolomics: techniques, problems and prospects. *Phytochem*

- Anal* **21**, 14-21.
- Schulz, S. & Dickschat, J. S. (2007).** Bacterial volatiles: the smell of small organisms. *Nat Prod Rep* **24**, 814-842.
- Schulz, S., Fuhlendorff, J. & Reichenbach, H. (2004).** Identification and synthesis of volatiles released by the myxobacterium *Chondromyces crocatus*. *Tetrahedron* **60**, 3863-3872.
- Sekurova, O., Sletta, H., Ellingsen, T. E., Valla, S. & Zotchev, S. (1999).** Molecular cloning and analysis of a pleiotropic regulatory gene locus from the nystatin producer *Streptomyces noursei* ATCC11455. *FEMS Microbiol Lett* **177**, 297-304.
- Shapiro, S. (1989).** Nitrogen assimilation in *actinomycetes* and the influence of nitrogen nutrition on *actinomycete* secondary metabolism. In: *Shapiro S, editor Regulation of secondary metabolism in actinomycetes* Boca Raton, FL: CRC Press, 135-211.
- Shiono, Y., Shiono, N., Seo, S., Oka, S. & Yamazaki, Y. (2002).** Effects of polyphenolic anthrone derivatives, resistomycin and hypericin, on apoptosis in human megakaryoblastic leukemia CMK-7 cell line. *Z Naturforsch C* **57**, 923-929.
- Sidda, J. D. & Corre, C. (2012).** Gamma-butyrolactone and furan signaling systems in *Streptomyces*. *Methods Enzymol* **517**, 71-87.
- Singh, L. S., Baruah, I. & Bora, T. C. (2006).** Actinomycetes of Loktak habitat: isolation and screening for antimicrobial activities. *Biotechnology* **5**, 217-221.
- Skinner, R., Cundliffe, E. & Schmidt, F. J. (1983).** Site of action of a ribosomal RNA methylase responsible for resistance to erythromycin and other antibiotics. *J Biol Chem* **258**, 12702-12706.
- Sola-Landa, A., Moura, R. S. & Martín, J. F. (2002).** The two-component PhoR-PhoP system controls both primary metabolism and secondary metabolite biosynthesis in *Streptomyces lividans*. *Proc Natl Acad Sci U S A* **100**, 6133-6138.
- Sola-Landa, A., Moura, R. S. & Martin, J. F. (2003).** The two-component PhoR-PhoP system controls both primary metabolism and secondary metabolite biosynthesis in *Streptomyces lividans*. *Proc Natl Acad Sci U S A* **100**, 6133-6138.
- Song, Q., Huang, Y. & Yang, H. (2012).** Optimization of fermentation conditions for antibiotic production by Actinomycetes YJ1 strain against *Sclerotinia sclerotiorum*. *Journal of Agricultural Science* **4**, 95.
- Sorensen, J. L., Nielsen, K. F. & Sondergaard, T. E. (2012).** Redirection of pigment biosynthesis to isocoumarins in *Fusarium*. *Fungal Genet Biol* **49**, 613-618.
- Souli, M., Galani, I. & Giamarellou, H. (2008).** Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. *Euro Surveill* **13**.
- Spellberg, B., Guidos, R., Gilbert, D., Bradley, J., Boucher, H. W., Scheld, W. M., Bartlett, J. G. & Edwards, J. (2008).** The epidemic of antibiotic-resistant infections: a call to action for the medical community from the infectious diseases society of America. *Clin Inf Diseases* **46**, 155-164.
- Stackebrandt, E. & Ebers, J. (2006).** Taxonomic parameters revisited: tarnished gold standards. *Microbiol Today* **4**, 152-155.
- Sterner, D. E. & Berger, S. L. (2000).** Acetylation of histones and transcription-related factors. *Microbiol Mol Biol Rev* **64**, 435-459.
- Stinson, M., Ezra, D., Hess, W. M., Sears, J. & Strobel, G. (2003).** An endophytic *Gliocladium* sp of *Eucryphia cordifolia* producing selective volatile antimicrobial compounds. *Plant Sci* **165**, 913-922.
- Strauss, J. & Reyes-Dominguez, Y. (2011).** Regulation of secondary metabolism by chromatin structure and epigenetic codes. *Fungal Genet Biol* **48**, 62-69.
- Strobel, G. A., Dirkse, E., Sears, J. & Markworth, C. (2001).** Volatile antimicrobials from *Muscodorum albus*, a novel endophytic fungus. *Microbiology* **147**, 2943-2950.
- Suzuki, S., Takahashi, K., Okuda, T. & Komatsubara, S. (1998).** Selective isolation of *Actinobispora* on gellan gum plate. *Can J Microbiol* **44**, 1-5.
- Sveshnikova, M. A., Chormonova, N. T., Lavrova, N. V., Terekhova, L. P. & Preobrazhenskaya, T. P. (1976).** Isolation of Soil Actinomycetes on Selective Media with Novobiocin. *Antibiot Med Bioteck* **21**, 784-787.
- Swiatek, M. A., Tenconi, E., Rigali, S. & van Wezel, G. P. (2012a).** Functional analysis of the N-acetylglucosamine metabolic genes of *Streptomyces coelicolor* and role in the control of development and antibiotic production. *J*

- Bacteriol* **194**, 1136-1144.
- Swiatek, M. A., Urem, M., Tenconi, E., Rigali, S. & van Wezel, G. P. (2012b).** Engineering of *N*-acetylglucosamine metabolism for improved antibiotic production in *Streptomyces coelicolor* A3(2) and an unsuspected role of NagA in glucosamine metabolism. *Bioengineered* **3**, 280-285.
- Swiatek, M. A., Gubbens, J., Bucca, G., Song, E., Yang, Y. H., Laing, E., Kim, B. G., Smith, C. P. & van Wezel, G. P. (2013).** The ROK family regulator RokB7 pleiotropically affects xylose utilization, carbon catabolite repression, and antibiotic production in *Streptomyces coelicolor*. *J Bacteriol* **195**, 1236-1248.
- Takahashi, Y. & Omura, S. (2003).** Isolation of new actinomycete strains for the screening of new bioactive compounds. *J Gen Appl Microbiol* **49**, 141-154.
- Tamehiro, N., Hosaka, T., Xu, J., Hu, H., Otake, N. & Ochi, K. (2003).** Innovative approach for improvement of an antibiotic-overproducing industrial strain of *Streptomyces albus*. *Appl Environ Microbiol* **69**, 6412-6417.
- Tamura, K., Peterson, D., Peterson, N., Stecher, G., Nei, M. & Kumar, S. (2011).** MEGA5: molecular evolutionary genetics analysis using maximum likelihood, evolutionary distance, and maximum parsimony methods. *Mol Biol Evol* **28**, 2731-2739.
- Tanaka, Y., Komatsu, M., Okamoto, S., Tokuyama, S., Kaji, A., Ikeda, H. & Ochi, K. (2009).** Antibiotic overproduction by *rpsL* and *rsmG* mutants of various actinomycetes. *Appl Environ Microbiol* **75**, 4919-4922.
- Tanaka, Y., Hosaka, T. & Ochi, K. (2010).** Rare earth elements activate the secondary metabolite-biosynthetic gene clusters in *Streptomyces coelicolor* A3(2). *J Antibi* **63**, 477-481.
- Thakur, D., Yadav, A., Gogoi, B. K. & Bora, T. C. (2007).** Isolation and screening of *Streptomyces* in soil of protected forest areas from the states of Assam and Tripura, India, for antimicrobial metabolites. *Journal de Mycologie Médicale / Journal of Medical Mycology* **17**, 242-249.
- Titgemeyer, F., Reizer, J., Reizer, A. & Saier, M. H., Jr. (1994).** Evolutionary relationships between sugar kinases and transcriptional repressors in bacteria. *Microbiology* **140**, 2349-2354.
- Titgemeyer, F. (2007).** Carbon and nitrogen regulation in Gram-positive bacteria: a tribute to Milton H. Saier, Jr. *J Mol Microbiol Biotechnol* **12**, 5-8.
- Tormo, J. R., Garcia, J. B., DeAntonio, M., Feliz, J., Mira, A., Diez, M. T., Hernandez, P. & Pelaez, F. (2003).** A method for the selection of production media for actinomycete strains based on their metabolite HPLC profiles. *J Ind Microbiol Biot* **30**, 582-588.
- Trygg, J. & Wold, S. (2003).** O2-PLS, a two-block (X-Y) latent variable regression (LVR) method with an integral OSC filter. *J Chemom* **17**, 53-64.
- Trygg, J. & Lundstedt, T. (2007).** Chemometrics techniques for metabolomics. In *The Handbook of Metabonomics and Metabolomics* pp. 171-200. Edited by J. C. Lindon, J. K. Nicholson & E. Holmes. Amsterdam, The Netherlands: Elsevier.
- Tweeddale, H., Notley-McRobb, L. & Ferenci, T. (1998).** Effect of slow growth on metabolism of *Escherichia coli*, as revealed by global metabolite pool ("Metabolome") analysis. *J Bacteriol* **180**, 5109-5116.
- Tweeddale, H., Notley-McRobb, L. & Ferenci, T. (1999).** Assessing the effect of reactive oxygen species on *Escherichia coli* using a metabolome approach. *Redox Rep* **4**, 237-241.
- Udwary, D. W., Zeigler, L., Asolkar, R. N., Singan, V., Lapidus, A., Fenical, W., Jensen, P. R. & Moore, B. S. (2007).** Genome sequencing reveals complex secondary metabolome in the marine actinomycete *Salinispora tropica*. *Proc Natl Acad Sci U S A* **104**, 10376-10381.
- Uguru, G. C., Stephens, K. E., Stead, J. A., Towle, J. E., Baumberg, S. & McDowall, K. J. (2005).** Transcriptional activation of the pathway-specific regulator of the actinorhodin biosynthetic genes in *Streptomyces coelicolor*. *Mol Microbiol* **58**, 131-150.
- van Wezel, G. P., White, J., Hoogvliet, G. & Bibb, M. J. (2000).** Application of *redD*, the transcriptional activator gene of the undecylprodigiosin biosynthetic pathway, as a reporter for transcriptional activity in *Streptomyces coelicolor* A3(2) and *Streptomyces lividans*. *J Mol Microbiol Biotechnol* **2**, 551-556.
- van Wezel, G. P., Krabben, P., Traag, B. A., Keijser, B. J., Kerste, R., Vijgenboom, E., Heijnen, J. J. & Kraal, B. (2006a).** Unlocking *Streptomyces* spp. for use as sustainable industrial production platforms by morphological engineering. *Appl Environ Microbiol* **72**, 5283-5288.
- van Wezel, G. P., Titgemeyer, F. & Rigali, S. (2006b).** Methods and means for metabolic engineering and improved

- product formation by micro-organisms Patent application WO/2007/094667.
- van Wezel, G. P., Konig, M., Mahr, K., Nothaft, H., Thomae, A. W., Bibb, M. & Titgemeyer, F. (2007).** A new piece of an old jigsaw: glucose kinase is activated posttranslationally in a glucose transport-dependent manner in *Streptomyces coelicolor* A3(2). *J Mol Microbiol Biotechnol* **12**, 67-74.
- van Wezel, G. P., McKenzie, N. L. & Nodwell, J. R. (2009).** Chapter 5. Applying the genetics of secondary metabolism in model actinomycetes to the discovery of new antibiotics. *Methods Enzymol* **458**, 117-141.
- van Wezel, G. P. & McDowall, K. J. (2011).** The regulation of the secondary metabolism of *Streptomyces*: new links and experimental advances. *Nat Prod Rep* **28**, 1311-1333.
- Verdrehngh, M., Collins, L. V., Bergin, P. & Tarkowski, A. (2004).** Phytoestrogen genistein as an anti-staphylococcal agent. *Microbes Infect* **6**, 86-92.
- Verpoorte, R., Choi, Y. H. & Kim, H. K. (2007).** NMR-based metabolomics at work in phytochemistry. *Phytochem Rev* **6**, 3-14.
- Verpoorte, R., Choi, Y. H., Mustafa, N. R. & Kim, H. K. (2008).** Metabolomics: back to basics. *Phytochem Rev* **7**, 525-537.
- Versalovic, J., Schneider, M., de Bruijn, F. J. & Lupski, J. R. (1994).** Genomic fingerprinting of bacteria using repetitive sequence-based Polymerase Chain Reaction. *Methods Mol Cell Biol* **5**, 25-40.
- Vespermann, A., Kai, M. & Piechulla, B. (2007).** Rhizobacterial volatiles affect the growth of fungi and *Arabidopsis thaliana*. *Appl Environ Microbiol* **73**, 5639-5641.
- Vigliotta, G., Tredici, S. M., Damiano, F., Montinaro, M. R., Pulimeno, R., di Summa, R., Massardo, D. R., Gnoni, G. V. & Alifano, P. (2005).** Natural merodiploidy involving duplicated *rpoB* alleles affects secondary metabolism in a producer actinomycete. *Mol Microbiol* **55**, 396-412.
- Vijayabharathi, R., Bruheim, P. R., Andreassen, T., Raja, D. S., Devi, P. B., Sathyabama, S. & Priyadarisini, V. B. (2011).** Assessment of resistomycin, as an anticancer compound isolated and characterized from *Streptomyces aurantiacus* AA5. *J Microbiol* **49**, 920-926.
- Vining, L. C. (1992).** Secondary metabolism, inventive evolution and biochemical diversity: a review. *Gene* **115**, 135-140.
- Vogels, J. T. W. E., Terwel, L., Tas, A. C., van den Berg, F., Dukel, F. & van der Greef, J. (1996).** Detection of adulteration in orange juices by a new screening method using proton NMR spectroscopy in combination with pattern recognition techniques. *J Agric Food Chem* **44**, 175-180.
- Vogtli, M., Chang, P. C. & Cohen, S. N. (1994).** *afsR2*: a previously undetected gene encoding a 63-amino-acid protein that stimulates antibiotic production in *Streptomyces lividans*. *Mol Microbiol* **14**, 643-653.
- Vukovic, N., Milosevuc, T., Sukdolak, S. & Solujic, S. (2008).** The chemical composition of the essential oil and the antibacterial activities of the essential oil and methanol extract of *Teucrium montanum*. *J Serb Chem Soc* **73**, 299-305.
- Waksman, S. A. & Woodruff, H. B. (1940).** Bacteriostatic and bactericidal substances produced by a soil *Actinomycetes*. *Exp Biol Med* **45**, 609-614.
- Waksman, S. A. & Woodruff, H. B. (1942).** Streptothrin, a new selective bacteriostatic and bactericidal agent, particularly active against Gram-negative bacteria. *Exp Biol Med* **49**, 207-210.
- Wan, M. G., Li, G. Q., Zhang, J. B., Jiang, D. H. & Huang, H. C. (2008).** Effect of volatile substances of *Streptomyces platensis* F-1 on control of plant fungal diseases. *Biol Control* **46**, 552-559.
- Ward, J. L. & Beale, M. H. (2006).** NMR spectroscopy in plant metabolomics. In *Plant Metabolomics*, pp. 81-91. Edited by K. Saito, R. Dixon & L. Willmitzer: Springer Berlin Heidelberg.
- Ward, J. L., Baker, J. M. & Beale, M. H. (2007).** Recent applications of NMR spectroscopy in plant metabolomics. *Febs J* **274**, 1126-1131.
- Watrous, J., Roach, P., Alexandrov, T. & other authors (2012).** Mass spectral molecular networking of living microbial colonies. *Proc Natl Acad Sci U S A* **109**, E1743-1752.
- Watve, M., Tickoo, R., Jog, M. & Bhole, B. (2001).** How many antibiotics are produced by the genus *Streptomyces*? *Arch Microbiol* **176**, 386-390.
- Weber, T., Welzel, K., Pelzer, S., Vente, A. & Wohlleben, W. (2003).** Exploiting the genetic potential of polyketide producing streptomycetes. *J Biotechnol* **106**, 221-232.

- WHO-Media-centre (2012).** Antimicrobial resistance WHO.
- Wietzorek, A. & Bibb, M. J. (1997).** A novel family of proteins that regulates antibiotic production in *Streptomyces* appears to contain an OmpR-like DNA-binding fold. *Mol Microbiol* **25**, 1181-1184.
- Willey, J. M. & Gaskell, A. A. (2011).** Morphogenetic signaling molecules of the streptomycetes. *Chem Rev* **111**, 174-187.
- Williams, S. T. & Davies, F. L. (1965).** Use of antibiotics for selective isolation and enumeration of Actinomycetes in soil. *J Gen Microbiol* **38**, 251-261.
- Wolfender, J.-L., Marti, G. & Ferreira Queiroz, E. (2010).** Advances in techniques for profiling crude extracts and for the rapid identification of natural products: dereplication, quality control and metabolomics. *Curr Org Chem* **14**, 1808-1832.
- Woodruff, H. B. & Ruger, M. (1948).** Studies on the physiology of a streptomycin-producing strain of *Streptomyces griseus* on proline medium. *J Bacteriol* **56**, 315-321.
- Xu, Q., van Wezel, G. P., Chiu, H. J. & other authors (2012).** Structure of an *mmyB*-like regulator from *C. aurantiacus*, Member of a new transcription factor family linked to antibiotic metabolism in Actinomycetes. *PLoS One* **7**, e41359.
- Yamada, Y. & Nihira, T. (1999).** Microbial hormones and microbial chemical ecology. In *Comprehensive natural products chemistry*, pp. 377-413. Edited by K. Mori. Dordrecht, The Netherlands.: Elsevier Scientific Publishers.
- Yamamoto, S., He, Y., Arakawa, K. & Kinashi, H. (2008).**  $\gamma$ -butyrolactone-dependent expression of the streptomycetes antibiotic regulatory protein gene *srrY* plays a central role in the regulatory cascade leading to lankacidin and lankamycin production in *Streptomyces rochei*. *J Bacteriol* **190**, 1308-1316
- Yang, Y. H., Song, E., Willemse, J. & other authors (2012).** A novel function of *Streptomyces* integration host factor (IHF) in the control of antibiotic production and sporulation in *Streptomyces coelicolor*. *Antonie van Leeuwenhoek* **101**, 479-492.
- Yang, Y. L., Xu, Y., Straight, P. & Dorrestein, P. C. (2009).** Translating metabolic exchange with imaging mass spectrometry. *Nat Chem Biol* **5**, 885-887.
- Yu, Z., Zhu, H., Dang, F., Zhang, W., Qin, Z., Yang, S., Tan, H., Lu, Y. & Jiang, W. (2012).** Differential regulation of antibiotic biosynthesis by DraR-K, a novel two-component system in *Streptomyces coelicolor*. *Mol Microbiol* **85**, 535-556.
- Zerbino, D. R. & Birney, E. (2008).** Velvet: Algorithms for de novo short read assembly using de Bruijn graphs. *Genome Res* **18**, 821-829.
- Zerikly, M. & Challis, G. L. (2009).** Strategies for the discovery of new natural products by genome mining. *Chembiochem* **10**, 625-633.
- Zhang, J. (1985).** Microbial Taxonomy. *Fudan University Press*, 214-218.
- Zhu, H., Sandiford, S.K. & van Wezel, G.P.** Triggers and cues that activate antibiotic production by actinomycetes. *J Ind Microbiol Biotechnol*, in press.
- Zinad, D. S., Shaaban, K. A., Abdalla, M. A., Islam, M. T., Schuffler, A. & Laatsch, H. (2011).** Bioactive isocoumarins from a terrestrial *Streptomyces* sp. ANK302. *Nat Prod Commun* **6**, 45-48.