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Ecology and genomics of Actinobacteria and their specialised metabolism

Bergeijk, D.A. van

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References

- 1 Cimermancic, P. *et al.* Insights into secondary metabolism from a global analysis of prokaryotic biosynthetic gene clusters. *Cell* **158**, 412-421 (2014).
- 2 van der Meij, A., Worsley, S. F., Hutchings, M. I. & van Wezel, G. P. Chemical ecology of antibiotic production by actinomycetes. *FEMS Microbiol Rev* **41**, 392-416 (2017).
- 3 Sadeghi, A. *et al.* Diversity of the ectoines biosynthesis genes in the salt tolerant *Streptomyces* and evidence for inductive effect of ectoines on their accumulation. *Microbiol Res* **169**, 699-708 (2014).
- 4 Takano, E. Gamma-butyrolactones: *Streptomyces* signalling molecules regulating antibiotic production and differentiation. *Curr Opin Microbiol* **9**, 287-294 (2006).
- 5 Kramer, J., Ozkaya, O. & Kummerli, R. Bacterial siderophores in community and host interactions. *Nat Rev Microbiol* **18**, 152-163 (2020).
- 6 Becher, P. G. *et al.* Developmentally regulated volatiles geosmin and 2-methylisoborneol attract a soil arthropod to *Streptomyces* bacteria promoting spore dispersal. *Nat Microbiol* **5**, 821-829 (2020).
- 7 Wright, E. S. & Vetsigian, K. H. Inhibitory interactions promote frequent bistability among competing bacteria. *Nat Commun* **7**, 11274 (2016).
- 8 Abrudan, M. I. *et al.* Socially mediated induction and suppression of antibiosis during bacterial coexistence. *Proc Natl Acad Sci U S A* **112**, 11054-11059 (2015).
- 9 Berdy, J. Bioactive microbial metabolites. *J Antibiot (Tokyo)* **58**, 1-26 (2005).
- 10 Katz, L. & Baltz, R. H. Natural product discovery: past, present, and future. *J Ind Microbiol Biotechnol* **43**, 155-176 (2016).
- 11 Newman, D. J. & Cragg, G. M. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod* **83**, 770-803 (2020).
- 12 Fleming, A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae*. 1929. *Bull World Health Organ* **79**, 780-790 (2001).
- 13 Sakula, A. Selman Waksman (1888-1973), discoverer of streptomycin: a centenary review. *Br J Dis Chest* **82**, 23-31 (1988).
- 14 Berdy, J. Thoughts and facts about antibiotics: where we are now and where we are heading. *J Antibiot (Tokyo)* **65**, 385-395 (2012).
- 15 Murray, C. J. L. *et al.* Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* **399**, 629-655 (2022).
- 16 Baltz, R. H. Renaissance in antibacterial discovery from actinomycetes. *Curr Opin Pharmacol* **8**, 557-563 (2008).
- 17 Cooper, M. A. & Shlaes, D. Fix the antibiotics pipeline. *Nature* **472**, 32 (2011).
- 18 Hutchings, M. I., Truman, A. W. & Wilkinson, B. Antibiotics: past, present and future. *Curr Opin Microbiol* **51**, 72-80 (2019).
- 19 Martin, M. F. & Liras, P. Organization and expression of genes involved in the biosynthesis of antibiotics and other secondary metabolites. *Annu Rev Microbiol* **43**, 173-206 (1989).
- 20 Bentley, S. D. *et al.* Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3(2). *Nature* **417**, 141-147 (2002).
- 21 Ikeda, H. *et al.* Complete genome sequence and comparative analysis of the industrial microorganism *Streptomyces avermitilis*. *Nat Biotechnol* **21**, 526-531 (2003).
- 22 Wright, L. F. & Hopwood, D. A. Identification of the antibiotic determined by the SCP1 plasmid of *Streptomyces coelicolor* A3(2). *J Gen Microbiol* **95**, 96-106 (1976).

- 23 Wright, L. F. & Hopwood, D. A. Actinorhodin is a chromosomally-determined antibiotic in *Streptomyces coelicolor* A3(2). *J Gen Microbiol* **96**, 289-297 (1976).
- 24 Feitelson, J. S., Malpartida, F. & Hopwood, D. A. Genetic and biochemical characterization of the red gene cluster of *Streptomyces coelicolor* A3(2). *J Gen Microbiol* **131**, 2431-2441 (1985).
- 25 Chong, P. P. *et al.* Physical identification of a chromosomal locus encoding biosynthetic genes for the lipopeptide calcium-dependent antibiotic (CDA) of *Streptomyces coelicolor* A3(2). *Microbiology (Reading)* **144** (Pt 1), 193-199 (1998).
- 26 Gomez-Escribano, J. P. *et al.* Structure and biosynthesis of the unusual polyketide alkaloid coelimycin P1, a metabolic product of the cpk gene cluster of *Streptomyces coelicolor* M145. *Chemical Science* **3**, 2716-2720 (2012).
- 27 Gavriilidou, A. *et al.* Compendium of specialized metabolite biosynthetic diversity encoded in bacterial genomes. *Nat Microbiol* **7**, 726-735 (2022).
- 28 Medema, M. H. & Fischbach, M. A. Computational approaches to natural product discovery. *Nat Chem Biol* **11**, 639-648 (2015).
- 29 Rutledge, P. J. & Challis, G. L. Discovery of microbial natural products by activation of silent biosynthetic gene clusters. *Nat Rev Microbiol* **13**, 509-523 (2015).
- 30 Moon, K., Xu, F. & Seyedsayamdost, M. R. Cebulantin, a cryptic lanthipeptide antibiotic uncovered using bioactivity-coupled HiTES. *Angew Chem Int Ed Engl* **58**, 5973-5977 (2019).
- 31 Moon, K., Xu, F., Zhang, C. & Seyedsayamdost, M. R. Bioactivity-HiTES unveils cryptic antibiotics encoded in actinomycete bacteria. *ACS Chem Biol* **14**, 767-774 (2019).
- 32 van der Heul, H. U., Bilyk, B. L., McDowall, K. J., Seipke, R. F. & van Wezel, G. P. Regulation of antibiotic production in Actinobacteria: new perspectives from the post-genomic era. *Nat Prod Rep* **35**, 575-604 (2018).
- 33 Bibb, M. J. Regulation of secondary metabolism in streptomycetes. *Curr Opin Microbiol* **8**, 208-215 (2005).
- 34 Hoskisson, P. A. & Fernández-Martínez, L. T. Regulation of specialised metabolites in Actinobacteria - expanding the paradigms. *Environ Microbiol Rep* **10**, 231-238 (2018).
- 35 Traxler, M. F., Watrous, J. D., Alexandrov, T., Dorrestein, P. C. & Kolter, R. Interspecies interactions stimulate diversification of the *Streptomyces coelicolor* secreted metabolome. *mBio* **4**, e00459-13 (2013).
- 36 Rigali, S. *et al.* Feast or famine: the global regulator DasR links nutrient stress to antibiotic production by *Streptomyces*. *EMBO Rep* **9**, 670-675 (2008).
- 37 Zhu, H., Sandiford, S. K. & van Wezel, G. P. Triggers and cues that activate antibiotic production by actinomycetes. *J Ind Microbiol Biotechnol* **41**, 371-386 (2014).
- 38 Smanski, M. J., Schlatter, D. C. & Kinkel, L. L. Leveraging ecological theory to guide natural product discovery. *J Ind Microbiol Biotechnol* **43**, 115-128 (2016).
- 39 NCOH. About Netherlands Centre for One Health, <<https://ncoh.nl/about>>
- 40 Chevette, M. G. & Handelsman, J. Needles in haystacks: reevaluating old paradigms for the discovery of bacterial secondary metabolites. *Nat Prod Rep* **38**, 2083-2099 (2021).
- 41 Sayed, A. M. *et al.* Extreme environments: microbiology leading to specialized metabolites. *J Appl Microbiol* **128**, 630-657 (2020).
- 42 van Bergeijk, D. A., Terlouw, B. R., Medema, M. H. & van Wezel, G. P. Ecology and genomics of Actinobacteria: new concepts for natural product discovery. *Nat Rev Microbiol* **18**, 546-558 (2020).
- 43 Chevette, M. G. *et al.* The antimicrobial potential of *Streptomyces* from insect microbiomes. *Nat Commun* **10**, 516 (2019).

- 44 van der Meij, A. *et al.* Inter- and intracellular colonization of *Arabidopsis* roots by endophytic Actinobacteria and the impact of plant hormones on their antimicrobial activity. *Antonie Van Leeuwenhoek* **111**, 679-690 (2018).
- 45 Liu, Y. *et al.* Deciphering microbial landscapes of fish eggs to mitigate emerging diseases. *ISME J* **8**, 2002-2014 (2014).
- 46 Scott, J. J. *et al.* Bacterial protection of beetle-fungus mutualism. *Science* **322**, 63 (2008).
- 47 Mendes, R. *et al.* Deciphering the rhizosphere microbiome for disease-suppressive bacteria. *Science* **332**, 1097-1100 (2011).
- 48 Sit, C. S. *et al.* Variable genetic architectures produce virtually identical molecules in bacterial symbionts of fungus-growing ants. *Proc Natl Acad Sci U S A* **112**, 13150-13154 (2015).
- 49 Whitman, W. B. *et al.* *Bergey's Manual of Systematic Bacteriology: Volume 5: The Actinobacteria.* (Springer Science & Business Media, 2012).
- 50 Barka, E. A. *et al.* Taxonomy, physiology, and natural products of Actinobacteria. *Microbiol Mol Biol Rev* **80**, 1-43 (2016).
- 51 Hopwood, D. A. *Streptomyces in nature and medicine: the antibiotic makers.* (Oxford University Press, 2007).
- 52 Vrancken, K. & Anne, J. Secretory production of recombinant proteins by *Streptomyces*. *Future Microbiol* **4**, 181-188 (2009).
- 53 Newman, D. J. & Cragg, G. M. Natural products as sources of new drugs over the last 25 years. *J Nat Prod* **70**, 461-477 (2007).
- 54 Davies, J. & Davies, D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* **74**, 417-433 (2010).
- 55 Payne, D. J., Gwynn, M. N., Holmes, D. J. & Pompliano, D. L. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nat Rev Drug Discov* **6**, 29-40 (2007).
- 56 Baltz, R. H. Antimicrobials from actinomycetes: back to the future. *Microbe* **2**, 125-131 (2007).
- 57 van den Berg, M. A. *et al.* Genome sequencing and analysis of the filamentous fungus *Penicillium chrysogenum*. *Nat Biotechnol* **26**, 1161-1168 (2008).
- 58 Bode, H. B., Bethe, B., Hofs, R. & Zeeck, A. Big effects from small changes: possible ways to explore nature's chemical diversity. *Chembiochem* **3**, 619-627 (2002).
- 59 Romano, S., Jackson, S. A., Patry, S. & Dobson, A. D. W. Extending the "One Strain Many Compounds" (OSMAC) principle to marine microorganisms. *Mar Drugs* **16** (2018).
- 60 Wu, C. *et al.* Lugdunomycin, an angucycline-derived molecule with unprecedented chemical architecture. *Angew Chem Int Ed Engl* **58**, 2809-2814 (2019).
- 61 Wright, E. S. & Vetsigian, K. H. Inhibitory interactions promote frequent bistability among competing bacteria. *Nat Commun* **7**, 11274 (2016).
- 62 Hibbing, M. E., Fuqua, C., Parsek, M. R. & Peterson, S. B. Bacterial competition: surviving and thriving in the microbial jungle. *Nat Rev Microbiol* **8**, 15-25 (2010).
- 63 Traxler, M. F. & Kolter, R. Natural products in soil microbe interactions and evolution. *Nat Prod Rep* **32**, 956-970 (2015).
- 64 Traxler, M. F., Watrous, J. D., Alexandrov, T., Dorrestein, P. C. & Kolter, R. Interspecies interactions stimulate diversification of the *Streptomyces coelicolor* secreted metabolome. *MBio* **4**, e00459-13 (2013).
- 65 Gueriot, M. L. Microbial iron transport. *Annu Rev Microbiol* **48**, 743-772 (1994).
- 66 Li, C., Ji, C. & Tang, B. Purification, characterisation and biological activity of melanin from *Streptomyces* sp. *FEMS Microbiol Lett* **365** (2018).

- 67 Sadeghi, A. *et al.* Diversity of the ectoines biosynthesis genes in the salt tolerant *Streptomyces* and evidence for inductive effect of ectoines on their accumulation. *Microbiol Res* **169**, 699-708 (2014).
- 68 Kroiss, J. *et al.* Symbiotic streptomycetes provide antibiotic combination prophylaxis for wasp offspring. *Nat Chem Biol* **6**, 261-263 (2010).
- 69 Raaijmakers, J. M. & Mazzola, M. Diversity and natural functions of antibiotics produced by beneficial and plant pathogenic bacteria. *Annu Rev Phytopathol* **50**, 403-424 (2012).
- 70 Doroghazi, J. R. & Metcalf, W. W. Comparative genomics of actinomycetes with a focus on natural product biosynthetic genes. *BMC Genomics* **14**, 611 (2013).
- 71 Cimermancic, P. *et al.* Insights into secondary metabolism from a global analysis of prokaryotic biosynthetic gene clusters. *Cell* **158**, 412-421 (2014).
- 72 Sriswasdi, S., Yang, C. C. & Iwasaki, W. Generalist species drive microbial dispersion and evolution. *Nat Commun* **8**, 1162 (2017).
- 73 Shimkets, L. J. in *Bacterial genomes: physical structure and analysis* (eds F. J. de Bruijn, J. R. Lupski, & G. M. Weinstock), 5-11 (Chapman & Hall, 1998).
- 74 Fraser, C. M. *et al.* The minimal gene complement of *Mycoplasma genitalium*. *Science* **270**, 397-403 (1995).
- 75 Salem, H. *et al.* Drastic genome reduction in an herbivore's pectinolytic symbiont. *Cell* **171**, 1520-1531.e1513 (2017).
- 76 Davies, J. Millennium bugs. *Trends Cell Biol* **9**, M2-5 (1999).
- 77 Claessen, D., Rozen, D. E., Kuipers, O. P., Sogaard-Andersen, L. & van Wezel, G. P. Bacterial solutions to multicellularity: a tale of biofilms, filaments and fruiting bodies. *Nat Rev Microbiol* **12**, 115-124 (2014).
- 78 Flårdh, K. & Buttner, M. J. *Streptomyces* morphogenetics: dissecting differentiation in a filamentous bacterium. *Nat Rev Microbiol* **7**, 36-49 (2009).
- 79 Chater, K. F. & Losick, R. in *Bacteria as multicellular organisms* (eds J. A. Shapiro & M. Dworkin), 149-182 (New York: Oxford University Press, 1997).
- 80 Merrick, M. J. A morphological and genetic mapping study of bald colony mutants of *Streptomyces coelicolor*. *J Gen Microbiol* **96**, 299-315. (1976).
- 81 Hopwood, D. A., Wildermuth, H. & Palmer, H. M. Mutants of *Streptomyces coelicolor* defective in sporulation. *J Gen Microbiol* **61**, 397-408 (1970).
- 82 Bibb, M. J. Regulation of secondary metabolism in streptomycetes. *Curr Opin Microbiol* **8**, 208-215 (2005).
- 83 van der Heul, H. U., Bilyk, B. L., McDowall, K. J., Seipke, R. F. & van Wezel, G. P. Regulation of antibiotic production in Actinobacteria: new perspectives from the post-genomic era. *Nat Prod Rep* **35**, 575-604 (2018).
- 84 Manteca, A. A death round affecting a young compartmentalized mycelium precedes aerial mycelium dismantling in confluent surface cultures of *Streptomyces antibioticus*. *Microbiology* **151**, 3689-3697 (2005).
- 85 Manteca, A., Mader, U., Connolly, B. A. & Sanchez, J. A proteomic analysis of *Streptomyces coelicolor* programmed cell death. *Proteomics* **6**, 6008-6022 (2006).
- 86 Tenconi, E., Traxler, M. F., Hoebreck, C., van Wezel, G. P. & Rigali, S. Production of prodiginines is part of a programmed cell death process in *Streptomyces coelicolor*. *Front Microbiol* **9**, 1742 (2018).
- 87 Gomez-Escribano, J. P. *et al.* Structure and biosynthesis of the unusual polyketide alkaloid coelimycin P1, a metabolic product of the cpk gene cluster of *Streptomyces coelicolor* M145. *Chem Sci* **3**, 2716-2720 (2012).

- 88 Ohnishi, Y. *et al.* Genome sequence of the streptomycin-producing microorganism *Streptomyces griseus* IFO 13350. *J Bacteriol* **190**, 4050-4060 (2008).
- 89 Wu, C. *et al.* Expanding the chemical space for natural products by *Aspergillus-Streptomyces* co-cultivation and biotransformation. *Sci Rep* **5**, 10868 (2015).
- 90 Challis, G. L. & Hopwood, D. A. 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 (2003).
- 91 Ling, L. L. *et al.* A new antibiotic kills pathogens without detectable resistance. *Nature* **517**, 455-459 (2015).
- 92 Wilson, M. C. *et al.* An environmental bacterial taxon with a large and distinct metabolic repertoire. *Nature* **506**, 58-62 (2014).
- 93 Amos, G. C. A. *et al.* Comparative transcriptomics as a guide to natural product discovery and biosynthetic gene cluster functionality. *Proc Natl Acad Sci U S A* **114**, E11121-E11130 (2017).
- 94 Machado, H., Tuttle, R. N. & Jensen, P. R. Omics-based natural product discovery and the lexicon of genome mining. *Curr Opin Microbiol* **39**, 136-142 (2017).
- 95 Martinet, L. *et al.* A single biosynthetic gene cluster is responsible for the production of bagremycin antibiotics and ferroverdin iron chelators. *mBio* **10**, e01230-19 (2019).
- 96 Seipke, R. F., Kaltenpoth, M. & Hutchings, M. I. *Streptomyces* as symbionts: an emerging and widespread theme? *FEMS Microbiol Rev* **36**, 862-876 (2012).
- 97 Jensen, P. R., Williams, P. G., Oh, D.-C., Zeigler, L. & Fenical, W. Species-specific secondary metabolite production in marine actinomycetes of the genus *Salinispora*. *Appl Environ Microbiol* **73**, 1146-1152 (2007).
- 98 Yang, A. *et al.* Nitrosporeusines A and B, unprecedented thioester-bearing alkaloids from the Arctic *Streptomyces nitrosporeus*. *Org Lett* **15**, 5366-5369 (2013).
- 99 Zipperer, A. *et al.* Human commensals producing a novel antibiotic impair pathogen colonization. *Nature* **535**, 511-516 (2016).
- 100 Ziemert, N. *et al.* Diversity and evolution of secondary metabolism in the marine actinomycete genus *Salinispora*. *Proc Natl Acad Sci U S A* **111**, E1130-E1139 (2014).
- 101 Adamek, M. *et al.* Comparative genomics reveals phylogenetic distribution patterns of secondary metabolites in *Amycolatopsis* species. *BMC Genomics* **19**, 426 (2018).
- 102 Andam, C. P., Choudoir, M. J., Vinh Nguyen, A., Sol Park, H. & Buckley, D. H. Contributions of ancestral inter-species recombination to the genetic diversity of extant *Streptomyces* lineages. *ISME J* **10**, 1731-1741 (2016).
- 103 Tidjani, A. *et al.* Massive gene flux drives genome diversity between sympatric *Streptomyces* conspecifics. *MBio* **10**, e01533-19 (2019).
- 104 McDonald, B. R. & Currie, C. R. Lateral gene transfer dynamics in the ancient bacterial genus *Streptomyces*. *mBio* **8**, e00644-17 (2017).
- 105 Medema, M. H., Cimermancic, P., Sali, A., Takano, E. & Fischbach, M. A. A systematic computational analysis of biosynthetic gene cluster evolution: lessons for engineering biosynthesis. *PLoS Comp Biol* **10**, e1004016 (2014).
- 106 Joynt, R. & Seipke, R. F. A phylogenetic and evolutionary analysis of antimycin biosynthesis. *Microbiology* **164**, 28-39 (2018).
- 107 Chevrette, M. G. *et al.* Taxonomic and metabolic incongruence in the ancient genus *Streptomyces*. *Front Microbiol* **10**, 2170 (2019).

- 108 Navarro-Munoz, J. C. *et al.* A computational framework to explore large-scale biosynthetic diversity. *Nat Chem Biol* **16**, 60-68 (2020).
- 109 Bruns, H. *et al.* Function-related replacement of bacterial siderophore pathways. *ISME J* **12**, 320-329 (2018).
- 110 Jensen, P. R. Natural products and the gene cluster revolution. *Trends Microbiol* **24**, 968-977 (2016).
- 111 Chater, K. F. & Chandra, G. The evolution of development in *Streptomyces* analysed by genome comparisons. *FEMS Microbiol Rev* **30**, 651-672 (2006).
- 112 Ventura, M. *et al.* Genomics of Actinobacteria: tracing the evolutionary history of an ancient phylum. *Microbiol Mol Biol Rev* **71**, 495-548 (2007).
- 113 Choulet, F. *et al.* Evolution of the terminal regions of the *Streptomyces* linear chromosome. *Mol Biol Evol* **23**, 2361-2369 (2006).
- 114 Bilyk, B., Horbal, L. & Luzhetskyy, A. Chromosomal position effect influences the heterologous expression of genes and biosynthetic gene clusters in *Streptomyces albus* J1074. *Microb Cell Fact* **16**, 5 (2017).
- 115 Letzel, A.-C. *et al.* Genomic insights into specialized metabolism in the marine actinomycete *Salinispora*. *Environ Microbiol* **19**, 3660-3673 (2017).
- 116 Ghinet, M. G. *et al.* Uncovering the prevalence and diversity of integrating conjugative elements in Actinobacteria. *PLoS One* **6**, e27846 (2011).
- 117 Kinashi, H., Shimaji, M. & Sakai, A. Giant linear plasmids in *Streptomyces* which code for antibiotic biosynthesis genes. *Nature* **328**, 454-456 (1987).
- 118 Medema, M. H. *et al.* The sequence of a 1.8-mb bacterial linear plasmid reveals a rich evolutionary reservoir of secondary metabolic pathways. *Genome Biol Evol* **2**, 212-224 (2010).
- 119 Mochizuki, S. *et al.* The large linear plasmid pSLA2-L of *Streptomyces rochei* has an unusually condensed gene organization for secondary metabolism. *Mol Microbiol* **48**, 1501-1510 (2003).
- 120 Huang, J. *et al.* Cross-regulation among disparate antibiotic biosynthetic pathways of *Streptomyces coelicolor*. *Mol Microbiol* **58**, 1276-1287 (2005).
- 121 McLean, T. C., Hoskisson, P. A. & Seipke, R. F. Coordinate regulation of antimycin and candicidin biosynthesis. *mSphere* **1**, e00305-16 (2016).
- 122 Liu, G., Chater, K. F., Chandra, G., Niu, G. & Tan, H. Molecular regulation of antibiotic biosynthesis in *Streptomyces*. *Microbiol Mol Biol Rev* **77**, 112-143 (2013).
- 123 Wietzorrek, A. & Bibb, M. A novel family of proteins that regulates antibiotic production in streptomycetes appears to contain an OmpR-like DNA-binding fold. *Mol Microbiol* **25**, 1181-1184. (1997).
- 124 Autret, S., Nair, R. & Errington, J. Genetic analysis of the chromosome segregation protein Spo0J of *Bacillus subtilis*: evidence for separate domains involved in DNA binding and interactions with Soj protein. *Mol Microbiol* **41**, 743-755 (2001).
- 125 Gramajo, H. C., Takano, E. & Bibb, M. J. Stationary-phase production of the antibiotic actinorhodin in *Streptomyces coelicolor* A3(2) is transcriptionally regulated. *Mol Microbiol* **7**, 837-845 (1993).
- 126 Tomono, A., Tsai, Y., Yamazaki, H., Ohnishi, Y. & Horinouchi, S. Transcriptional control by A-factor of *strR*, the pathway-specific transcriptional activator for streptomycin biosynthesis in *Streptomyces griseus*. *J Bacteriol* **187**, 5595-5604 (2005).
- 127 Lawlor, E. J., Baylis, H. A. & Chater, K. F. Pleiotropic morphological and antibiotic deficiencies result from mutations in a gene encoding a tRNA-like product in *Streptomyces coelicolor* A3(2). *Genes Dev* **1**, 1305-1310 (1987).

- 128 Fernandez-Moreno, M. A., Caballero, J. L., Hopwood, D. A. & Malpartida, F. The act cluster contains regulatory and antibiotic export genes, direct targets for translational control by the *bldA* tRNA gene of *Streptomyces*. *Cell* **66**, 769-780 (1991).
- 129 Willey, J. M. & Gaskell, A. A. Morphogenetic signaling molecules of the streptomycetes. *Chem Rev* **111**, 174-187 (2011).
- 130 Tahlan, K. *et al.* Initiation of actinorhodin export in *Streptomyces coelicolor*. *Mol Microbiol* **63**, 951-961 (2007).
- 131 Wang, L. *et al.* Autoregulation of antibiotic biosynthesis by binding of the end product to an atypical response regulator. *Proc Natl Acad Sci U S A* **106**, 8617-8622 (2009).
- 132 Willems, A. R. *et al.* Crystal structures of the *Streptomyces coelicolor* TetR-like protein ActR alone and in complex with actinorhodin or the actinorhodin biosynthetic precursor (S)-DNPA. *J Mol Biol* **376**, 1377-1387 (2008).
- 133 Francis, I. M., Jourdan, S., Fanara, S., Loria, R. & Rigali, S. The cellobiose sensor CebR is the gatekeeper of *Streptomyces scabies* pathogenicity. *MBio* **6**, e02018 (2015).
- 134 Nazari, B. *et al.* Chitin-induced gene expression involved in secondary metabolic pathways in *Streptomyces coelicolor* A3(2) grown in soil. *Appl Environ Microbiol* **79**, 707-713 (2012).
- 135 Craig, M. *et al.* Unsuspected control of siderophore production by N-acetylglucosamine in streptomycetes. *Environ Microbiol Rep* **4**, 512-521 (2012).
- 136 Świątek-Polatyńska, M. A. *et al.* Genome-wide analysis of *in vivo* binding of the master regulator DasR in *Streptomyces coelicolor* identifies novel non-canonical targets. *PLoS One* **10**, e0122479 (2015).
- 137 Urem, M., Swiatek-Polatynska, M. A., Rigali, S. & van Wezel, G. P. Intertwining nutrient-sensory networks and the control of antibiotic production in *Streptomyces*. *Mol Microbiol* **102**, 183-195 (2016).
- 138 Zhu, H. *et al.* Eliciting antibiotics active against the ESKAPE pathogens in a collection of actinomycetes isolated from mountain soils. *Microbiology* **160**, 1714-1725 (2014).
- 139 Hosaka, T. *et al.* Antibacterial discovery in actinomycetes strains with mutations in RNA polymerase or ribosomal protein S12. *Nat Biotechnol* **27**, 462-464 (2009).
- 140 Tanaka, Y. *et al.* Antibiotic overproduction by *rpsL* and *rsmG* mutants of various actinomycetes. *Appl Environ Microbiol* **75**, 4919-4922 (2009).
- 141 Bertrand, S. *et al.* Metabolite induction via microorganism co-culture: a potential way to enhance chemical diversity for drug discovery. *Biotechnol Adv* **32**, 1180-1204 (2014).
- 142 Hoshino, S., Wakimoto, T., Onaka, H. & Abe, I. Chojalactones A–C, cytotoxic butanolides isolated from *Streptomyces* sp. cultivated with mycolic acid containing bacterium. *Org Lett* **17**, 1501-1504 (2015).
- 143 Sugiyama, R. *et al.* 5-Alkyl-1,2,3,4-tetrahydroquinolines, new membrane-interacting lipophilic metabolites produced by combined culture of *Streptomyces nigrescens* and *Tsukamurella pulmonis*. *Org Lett* **17**, 1918-1921 (2015).
- 144 Hsiao, N. H., Gottelt, M. & Takano, E. Chapter 6. Regulation of antibiotic production by bacterial hormones. *Methods Enzymol* **458**, 143-157 (2009).
- 145 Albright, J. C. *et al.* Large-scale metabolomics reveals a complex response of *Aspergillus nidulans* to epigenetic perturbation. *ACS Chem Biol*, 1535-1541 (2015).
- 146 Craney, A., Ozimok, C., Pimentel-Elardo, S. M., Capretta, A. & Nodwell, J. R. Chemical perturbation of secondary metabolism demonstrates important links to primary metabolism. *Chem Biol* **19**, 1020-1027 (2012).

- 147 Niu, G., Chater, K. F., Tian, Y., Zhang, J. & Tan, H. Specialised metabolites regulating antibiotic biosynthesis in *Streptomyces* spp. *FEMS Microbiol Rev* **40**, 554-573 (2016).
- 148 Onaka, H., Mori, Y., Igarashi, Y. & Furumai, T. Mycolic acid-containing bacteria induce natural-product biosynthesis in *Streptomyces* species. *Appl Environ Microbiol* **77**, 400-406 (2011).
- 149 Schroeckh, V. *et al.* Intimate bacterial-fungal interaction triggers biosynthesis of archetypal polyketides in *Aspergillus nidulans*. *Proc Natl Acad Sci U S A* **106**, 14558-14563 (2009).
- 150 Sung, A. A., Gromek, S. M. & Balunas, M. J. Upregulation and identification of antibiotic activity of a marine-derived *Streptomyces* sp. via co-cultures with human pathogens. *Mar Drugs* **15**, 250 (2017).
- 151 Pérez, J. *et al.* *Myxococcus xanthus* induces actinorhodin overproduction and aerial mycelium formation by *Streptomyces coelicolor*. *Microb Biotechnol* **4**, 175-183 (2011).
- 152 Patin, N. V., Floros, D. J., Hughes, C. C., Dorrestein, P. C. & Jensen, P. R. The role of inter-species interactions in *Salinispora* specialized metabolism. *Microbiology* **164**, 946-955 (2018).
- 153 Ezaki, M. *et al.* Biphenomycin A production by a mixed culture. *Appl. Environ. Microbiol.* **58**, 3879-3882 (1992).
- 154 Kurosawa, K. *et al.* Rhodostreptomycins, antibiotics biosynthesized following horizontal gene transfer from *Streptomyces padanus* to *Rhodococcus fascians*. *J Amer Chem Soc* **130**, 1126-1127 (2008).
- 155 Traxler, M. F., Seyedsayamdost, M. R., Clardy, J. & Kolter, R. Interspecies modulation of bacterial development through iron competition and siderophore piracy. *Mol Microbiol* **86**, 628-644 (2012).
- 156 Onaka, H., Tabata, H., Igarashi, Y., Sato, Y. & Furumai, T. Goadsporin, a chemical substance which promotes secondary metabolism and morphogenesis in streptomycetes. I. Purification and characterization. *J Antibiot* **54**, 1036-1044 (2001).
- 157 Yang, Y. L., Xu, Y., Straight, P. & Dorrestein, P. C. Translating metabolic exchange with imaging mass spectrometry. *Nat Chem Biol* **5**, 885-887 (2009).
- 158 Currie, C. R., Scott, J. A., Summerbell, R. C. & Malloch, D. D. Fungus-growing ants use antibiotic-producing bacteria to control garden parasites. *Nature* **398**, 701-704 (1999).
- 159 Heine, D. *et al.* Chemical warfare between leafcutter ant symbionts and a co-evolved pathogen. *Nat Commun* **9**, 2208 (2018).
- 160 Spaepen, S. in *Principles of Plant-Microbe Interactions* (ed B. Lugtenberg), 247-256 (Springer, 2015).
- 161 Badri, D. V. & Vivanco, J. M. Regulation and function of root exudates. *Plant Cell Environ* **32**, 666-681 (2009).
- 162 Badri, D. V., Chaparro, J. M., Zhang, R., Shen, Q. & Vivanco, J. M. Application of natural blends of phytochemicals derived from the root exudates of *Arabidopsis* to the soil reveal that phenolic-related compounds predominantly modulate the soil microbiome. *J Biol Chem* **288**, 4502-4512 (2013).
- 163 Bulgarelli, D. *et al.* Revealing structure and assembly cues for *Arabidopsis* root-inhabiting bacterial microbiota. *Nature* **488**, 91-95 (2012).
- 164 Lebeis, S. L. *et al.* PLANT MICROBIOME. Salicylic acid modulates colonization of the root microbiome by specific bacterial taxa. *Science* **349**, 860-864 (2015).
- 165 Blin, K. *et al.* antiSMASH 5.0: updates to the secondary metabolite genome mining pipeline. *Nucleic Acids Res* **47**, W81-W87 (2019).
- 166 Skinnider, M. A., Merwin, N. J., Johnston, C. W. & Magarvey, N. A. PRISM 3: expanded prediction of natural product chemical structures from microbial genomes. *Nucleic Acids Res* **45**, W49-W54 (2017).

- 167 Kautsar, S. A. *et al.* MIBiG 2.0: a repository for biosynthetic gene clusters of known function. *Nucleic Acids Res* **48**, D454-D458 (2019).
- 168 Doroghazi, J. R. *et al.* A roadmap for natural product discovery based on large-scale genomics and metabolomics. *Nat Chem Biol* **10**, 963-968 (2014).
- 169 Alanjary, M. *et al.* The Antibiotic Resistant Target Seeker (ARTS), an exploration engine for antibiotic cluster prioritization and novel drug target discovery. *Nucleic Acids Res* **45**, W42-W48 (2017).
- 170 Culp, E. J. *et al.* Evolution-guided discovery of antibiotics that inhibit peptidoglycan remodelling. *Nature* **578**, 582-587 (2020).
- 171 van Heel, A. J. *et al.* BAGEL4: a user-friendly web server to thoroughly mine RiPPs and bacteriocins. *Nucleic Acids Res* **46**, W278-W281 (2018).
- 172 Du, C. & van Wezel, G. P. Mining for microbial gems: integrating proteomics in the postgenomic natural product discovery pipeline. *Proteomics* **18**, e1700332 (2018).
- 173 Goering, A. W. *et al.* Metabologenomics: correlation of microbial gene clusters with metabolites drives discovery of a nonribosomal peptide with an unusual amino acid monomer. *ACS Cent Sci* **2**, 99-108 (2016).
- 174 Soldatou, S., Eldjarn, G. H., Huerta-Urbe, A., Rogers, S. & Duncan, K. R. Linking biosynthetic and chemical space to accelerate microbial secondary metabolite discovery. *FEMS Microbiol Lett* **366** (2019).
- 175 Stokes, J. M. *et al.* A deep learning approach to antibiotic discovery. *Cell* **180**, 688-702.e13 (2020).
- 176 van der Hooft, J. J., Wandy, J., Barrett, M. P., Burgess, K. E. & Rogers, S. Topic modeling for untargted substructure exploration in metabolomics. *Proc Natl Acad Sci U S A* **113**, 13738-13743 (2016).
- 177 Schorn, M. A. *et al.* Sequencing rare marine actinomycete genomes reveals high density of unique natural product biosynthetic gene clusters. *Microbiology* **162**, 2075-2086 (2016).
- 178 Charlop-Powers, Z. *et al.* Global biogeographic sampling of bacterial secondary metabolism. *Elife* **4**, e05048 (2015).
- 179 Charlop-Powers, Z. *et al.* Urban park soil microbiomes are a rich reservoir of natural product biosynthetic diversity. *Proc Natl Acad Sci U S A* **113**, 14811-14816 (2016).
- 180 Tiwari, K. & Gupta, R. K. Rare actinomycetes: a potential storehouse for novel antibiotics. *Crit Rev Biotechnol* **32**, 108-132 (2012).
- 181 Donia, M. S. *et al.* A systematic analysis of biosynthetic gene clusters in the human microbiome reveals a common family of antibiotics. *Cell* **158**, 1402-1414 (2014).
- 182 Culp, E. J. *et al.* Hidden antibiotics in actinomycetes can be identified by inactivation of gene clusters for common antibiotics. *Nat Biotechnol* **37**, 1149-1154 (2019).
- 183 Hiard, S. *et al.* PREDetector: a new tool to identify regulatory elements in bacterial genomes. *Biochem Biophys Res Commun* **357**, 861-864 (2007).
- 184 Tan, K., Moreno-Hagelsieb, G., Collado-Vides, J. & Stormo, G. D. A comparative genomics approach to prediction of new members of regulons. *Genome Res* **11**, 566-584 (2001).
- 185 Rigali, S., Anderssen, S., Naome, A. & van Wezel, G. P. Cracking the regulatory code of biosynthetic gene clusters as a strategy for natural product discovery. *Biochem Pharmacol* **153**, 24-34 (2018).
- 186 Carrion, V. J. *et al.* Pathogen-induced activation of disease-suppressive functions in the endophytic root microbiome. *Science* **366**, 606-612 (2019).
- 187 Duhrkop, K., Shen, H., Meusel, M., Rousu, J. & Bocker, S. Searching molecular structure databases with tandem mass spectra using CSI:FingerID. *Proc Natl Acad Sci U S A* **112**, 12580-12585 (2015).

- 188 Mohimani, H. *et al.* Dereplication of peptidic natural products through database search of mass spectra. *Nat Chem Biol* **13**, 30-37 (2017).
- 189 Mohimani, H. *et al.* Dereplication of microbial metabolites through database search of mass spectra. *Nat Commun* **9**, 4035 (2018).
- 190 Ernst, M. *et al.* MolNetEnhancer: enhanced molecular networks by integrating metabolome mining and annotation tools. *Metabolites*, **9**, 144 (2019).
- 191 Wilson, M. C. & Piel, J. Metagenomic approaches for exploiting uncultivated bacteria as a resource for novel biosynthetic enzymology. *Chem Biol* **20**, 636-647 (2013).
- 192 Smanski, M. J. *et al.* Synthetic biology to access and expand nature's chemical diversity. *Nat Rev Microbiol* **14**, 135-149 (2016).
- 193 Sugimoto, Y. *et al.* A metagenomic strategy for harnessing the chemical repertoire of the human microbiome. *Science* **366** (2019).
- 194 Smanski, M. J. *et al.* Functional optimization of gene clusters by combinatorial design and assembly. *Nat Biotechnol* **32**, 1241-1249 (2014).
- 195 Shomar, H. *et al.* Metabolic engineering of a carbapenem antibiotic synthesis pathway in *Escherichia coli*. *Nat Chem Biol* **14**, 794-800 (2018).
- 196 Kuypers, M. M. M., Marchant, H. K. & Kartal, B. The microbial nitrogen-cycling network. *Nat Rev Microbiol* **16**, 263-276 (2018).
- 197 Stursova, M., Zifcakova, L., Leigh, M. B., Burgess, R. & Baldrian, P. Cellulose utilization in forest litter and soil: identification of bacterial and fungal decomposers. *FEMS Microbiol Ecol* **80**, 735-746 (2012).
- 198 Tremaroli, V. & Backhed, F. Functional interactions between the gut microbiota and host metabolism. *Nature* **489**, 242-249 (2012).
- 199 Mendes, R., Garbeva, P. & Raaijmakers, J. M. The rhizosphere microbiome: significance of plant beneficial, plant pathogenic, and human pathogenic microorganisms. *FEMS Microbiol Rev* **37**, 634-663 (2013).
- 200 Lloyd, K. G., Steen, A. D., Ladau, J., Yin, J. & Crosby, L. Phylogenetically novel uncultured microbial cells dominate earth microbiomes. *mSystems* **3**, e00055-18 (2018).
- 201 Wibowo, M. C. *et al.* Reconstruction of ancient microbial genomes from the human gut. *Nature* **594**, 234-239 (2021).
- 202 D'Costa, V. M. *et al.* Antibiotic resistance is ancient. *Nature* **477**, 457-461 (2011).
- 203 Soldatou, S. *et al.* Comparative metabologenomics analysis of polar actinomycetes. *Mar Drugs* **19**, 103 (2021).
- 204 Millan-Aguinaga, N. *et al.* Awakening ancient polar Actinobacteria: diversity, evolution and specialized metabolite potential. *Microbiology (Reading)* **165**, 1169-1180 (2019).
- 205 Wetterich, S. *et al.* Ice Complex formation on Bol'shoy Lyakhovsky Island (New Siberian Archipelago, East Siberian Arctic) since about 200 ka. *Quaternary Research* **92**, 530-548 (2019).
- 206 Nikolskiy, P. A., Sulerzhitsky, L. D. & Pitulko, V. V. Last straw versus Blitzkrieg overkill: Climate-driven changes in the Arctic Siberian mammoth population and the Late Pleistocene extinction problem. *Quaternary Science Reviews* **30**, 2309-2328 (2011).
- 207 Grigoriev, S. E. *et al.* A woolly mammoth (*Mammuthus primigenius*) carcass from Maly Lyakhovsky Island (New Siberian Islands, Russian Federation). *Quaternary International* **445**, 89-103 (2017).
- 208 Kornienko, I. V. *et al.* Complete mitochondrial genome of a woolly mammoth (*Mammuthus primigenius*) from Maly Lyakhovsky Island (New Siberian Islands, Russia) and its phylogenetic assessment. *Mitochondrial DNA B Resour* **3**, 596-598 (2018).

- 209 Goncharov, A. *et al.* Draft Genome Sequence of *Enterococcus faecium* Strain 58m, Isolated from Intestinal Tract Content of a Woolly Mammoth, *Mammuthus primigenius*. *Genome Announc* **4** (2016).
- 210 Battistuzzi, F. U., Feijao, A. & Hedges, S. B. A genomic timescale of prokaryote evolution: insights into the origin of methanogenesis, phototrophy, and the colonization of land. *BMC Evol Biol* **4**, 44 (2004).
- 211 Barco, R. A. *et al.* A genus definition for bacteria and archaea based on a standard genome relatedness index. *mBio* **11**, e02475-19 (2020).
- 212 Hohmann, C. *et al.* Caboxamycin, a new antibiotic of the benzoxazole family produced by the deep-sea strain *Streptomyces* sp. NTK 937. *J Antibiot (Tokyo)* **62**, 99-104 (2009).
- 213 Ma, L. *et al.* Complete genome sequence of *Streptomyces* sp. SCSIO 03032 isolated from Indian Ocean sediment, producing diverse bioactive natural products. *Mar Genomics* **55**, 100803 (2021).
- 214 Rottig, A. *et al.* *Streptomyces jeddahensis* sp. nov., an oleaginous bacterium isolated from desert soil. *Int J Syst Evol Microbiol* **67**, 1676-1682 (2017).
- 215 Cornell, C. R., Marasini, D. & Fakhr, M. K. Draft Genome Sequences of Megaplasmid-Bearing *Streptomyces* sp. Strains BF-3 and 4F, Isolated from the Great Salt Plains of Oklahoma. *Genome Announc* **6**, e00208-18 (2018).
- 216 Zhang, Z. *et al.* Antibiotic production in *Streptomyces* is organized by a division of labor through terminal genomic differentiation. *Sci Adv* **6**, eaay5781 (2020).
- 217 Blin, K. *et al.* antiSMASH 6.0: improving cluster detection and comparison capabilities. *Nucleic Acids Res* **49**, W29-W35 (2021).
- 218 Avalos, M., Garbeva, P., Raaijmakers, J. M. & van Wezel, G. P. Production of ammonia as a low-cost and long-distance antibiotic strategy by *Streptomyces* species. *ISME J* **14**, 569-583 (2020).
- 219 Avalos, M., van Wezel, G. P., Raaijmakers, J. M. & Garbeva, P. Healthy scents: microbial volatiles as new frontier in antibiotic research? *Curr Opin Microbiol* **45**, 84-91 (2018).
- 220 Wang, M. *et al.* Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking. *Nat Biotechnol* **34**, 828-837 (2016).
- 221 Sunagawa, S. *et al.* Ocean plankton. Structure and function of the global ocean microbiome. *Science* **348**, 1261359 (2015).
- 222 Ferrari, G. *et al.* Assessing metagenomic signals recovered from Lyuba, a 42,000-year-old permafrost-preserved Woolly Mammoth calf. *Genes (Basel)* **9** (2018).
- 223 Czech, L. *et al.* Role of the extremolytes ectoine and hydroxyectoine as stress protectants and nutrients: genetics, phylogenomics, biochemistry, and structural analysis. *Genes (basel)* **9**, 177 (2018).
- 224 Belknap, K. C., Park, C. J., Barth, B. M. & Andam, C. P. Genome mining of biosynthetic and chemotherapeutic gene clusters in *Streptomyces* bacteria. *Sci Rep* **10**, 2003 (2020).
- 225 Joynt, R. & Seipke, R. F. A phylogenetic and evolutionary analysis of antimycin biosynthesis. *Microbiology (Reading)* **164**, 28-39 (2018).
- 226 Hayakawa, M. & Nonomura, H. Humic acid-vitamin agar, a new medium for the selective isolation of soil actinomycetes. *Journal of Fermentation Technology* **65**, 501-509 (1987).
- 227 Kieser, T., Bibb, M. J., Buttner, M. J., Chater, K. F. & Hopwood, D. A. *Practical Streptomyces Genetics*. (John Innes Foundation, 2000).
- 228 Kuester, E. & Williams, S. T. Selection of Media for Isolation of Streptomycetes. *Nature* **202**, 928-929 (1964).
- 229 Wick, R. R., Judd, L. M., Gorrie, C. L. & Holt, K. E. Unicycler: Resolving bacterial genome assemblies from short and long sequencing reads. *PLoS Comput Biol* **13**, e1005595 (2017).

- 230 Walker, B. J. *et al.* Pilon: an integrated tool for comprehensive microbial variant detection and genome assembly improvement. *PLoS One* **9**, e112963 (2014).
- 231 Asnicar, F. *et al.* Precise phylogenetic analysis of microbial isolates and genomes from metagenomes using PhyloPhlAn 3.0. *Nat Commun* **11**, 2500 (2020).
- 232 Jain, C., Rodriguez, R. L., Phillippy, A. M., Konstantinidis, K. T. & Aluru, S. High throughput ANI analysis of 90K prokaryotic genomes reveals clear species boundaries. *Nat Commun* **9**, 5114 (2018).
- 233 Seemann, T. Prokka: rapid prokaryotic genome annotation. *Bioinformatics* **30**, 2068-2069 (2014).
- 234 Kanz, C. *et al.* The EMBL Nucleotide Sequence Database. *Nucleic Acids Res* **33**, D29-33 (2005).
- 235 Wang, Y. *et al.* MCSanX: a toolkit for detection and evolutionary analysis of gene synteny and collinearity. *Nucleic Acids Res* **40**, e49 (2012).
- 236 Krzywinski, M. *et al.* Circos: an information aesthetic for comparative genomics. *Genome Res* **19**, 1639-1645 (2009).
- 237 Liu, M. & Douthwaite, S. Activity of the ketolide telithromycin is refractory to Erm monomethylation of bacterial rRNA. *Antimicrob Agents Chemother* **46**, 1629-1633 (2002).
- 238 Shannon, P. *et al.* Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* **13**, 2498-2504 (2003).
- 239 Kolter, R. & van Wezel, G. P. Goodbye to brute force in antibiotic discovery? *Nat Microbiol* **1**, 15020 (2016).
- 240 Lewis, K. Platforms for antibiotic discovery. *Nat Rev Drug Discov* **12**, 371-387 (2013).
- 241 van der Aart, L. T. *et al.* Polyphasic classification of the gifted natural product producer *Streptomyces roseifaciens* sp. nov. *Int J Syst Evol Microbiol* **69**, 899-908 (2019).
- 242 Zaborina, O. *et al.* Dynorphin activates quorum sensing quinolone signaling in *Pseudomonas aeruginosa*. *PLoS Pathog* **3**, e35 (2007).
- 243 Lyte, M. & Ernst, S. Catecholamine induced growth of Gram negative bacteria. *Life Sci* **50**, 203-212 (1992).
- 244 Belay, T., Aviles, H., Vance, M., Fountain, K. & Sonnenfeld, G. Catecholamines and in vitro growth of pathogenic bacteria: enhancement of growth varies greatly among bacterial species. *Life Sci* **73**, 1527-1535 (2003).
- 245 Sandrini, S., Alghofaili, F., Freestone, P. & Yesilkaya, H. Host stress hormone norepinephrine stimulates pneumococcal growth, biofilm formation and virulence gene expression. *BMC Microbiol* **14**, 180 (2014).
- 246 Peterson, G., Kumar, A., Gart, E. & Narayanan, S. Catecholamines increase conjugative gene transfer between enteric bacteria. *Microb Pathog* **51**, 1-8 (2011).
- 247 Bernatoniene, J. & Kopustinskiene, D. M. The role of catechins in cellular responses to oxidative stress. *Molecules* **23**, 965 (2018).
- 248 Gubbens, J. *et al.* Intertwined precursor supply during biosynthesis of the catecholate-hydroxamate siderophores qinichelins in *Streptomyces* sp. MBT76. *ACS Chem Biol* **12**, 2756-2766 (2017).
- 249 Gubbens, J. *et al.* Natural product proteomining, a quantitative proteomics platform, allows rapid discovery of biosynthetic gene clusters for different classes of natural products. *Chem Biol* **21**, 707-718 (2014).
- 250 Li, B. & Walsh, C. T. Identification of the gene cluster for the dithiolopyrrolone antibiotic holomycin in *Streptomyces clavuligerus*. *Proc Natl Acad Sci U S A* **107**, 19731-19735 (2010).
- 251 Jones, S. E. *et al.* *Streptomyces* volatile compounds influence exploration and microbial community dynamics by altering iron availability. *mBio* **10**, e00171-19 (2019).

- 252 Lee, N. *et al.* Iron competition triggers antibiotic biosynthesis in *Streptomyces coelicolor* during coculture with *Myxococcus xanthus*. *ISME J* **14**, 1111-1124 (2020).
- 253 Perraud, Q. *et al.* Opportunistic use of catecholamine neurotransmitters as siderophores to access iron by *Pseudomonas aeruginosa*. *Environ Microbiol* (2020).
- 254 Beasley, F. C., Marolda, C. L., Cheung, J., Buac, S. & Heinrichs, D. E. *Staphylococcus aureus* transporters Hts, Sir, and Sst capture iron liberated from human transferrin by Staphyloferrin A, Staphyloferrin B, and catecholamine stress hormones, respectively, and contribute to virulence. *Infect Immun* **79**, 2345-2355 (2011).
- 255 Dichtl, S. *et al.* Dopamine is a siderophore-like iron chelator that promotes *Salmonella enterica* Serovar Typhimurium virulence in mice. *mBio* **10**, e02624-18 (2019).
- 256 Li, W. *et al.* Norepinephrine represses the expression of *toxA* and the siderophore genes in *Pseudomonas aeruginosa*. *FEMS Microbiol Lett* **299**, 100-109 (2009).
- 257 Kloepper, J. W., Leong, J., Teintze, M. & Schroth, M. N. Enhanced plant growth by siderophores produced by plant growth-promoting rhizobacteria. *Nature* **286**, 885-886 (1980).
- 258 Chan, A. N. *et al.* Role for dithiolopyrrolones in disrupting bacterial metal homeostasis. *Proc Natl Acad Sci U S A* **114**, 2717-2722 (2017).
- 259 Li, B., Wever, W. J., Walsh, C. T. & Bowers, A. A. Dithiolopyrrolones: biosynthesis, synthesis, and activity of a unique class of disulfide-containing antibiotics. *Nat Prod Rep* **31**, 905-923 (2014).
- 260 Schwyn, B. & Neilands, J. B. Universal chemical assay for the detection and determination of siderophores. *Anal Biochem* **160**, 47-56 (1987).
- 261 Kolmogorov, M., Yuan, J., Lin, Y. & Pevzner, P. A. Assembly of long, error-prone reads using repeat graphs. *Nat Biotechnol* **37**, 540-546 (2019).
- 262 Wessel, D. & Flugge, U. I. A method for the quantitative recovery of protein in dilute solution in the presence of detergents and lipids. *Anal Biochem* **138**, 141-143 (1984).
- 263 Rappsilber, J., Mann, M. & Ishihama, Y. Protocol for micro-purification, enrichment, pre-fractionation and storage of peptides for proteomics using StageTips. *Nat Protoc* **2**, 1896-1906 (2007).
- 264 Cox, J. & Mann, M. MaxQuant enables high peptide identification rates, individualized p.p.b.-range mass accuracies and proteome-wide protein quantification. *Nat Biotechnol* **26**, 1367-1372 (2008).
- 265 Perez-Riverol, Y. *et al.* The PRIDE database and related tools and resources in 2019: improving support for quantification data. *Nucleic Acids Res* **47**, D442-D450 (2019).
- 266 Nett, M., Ikeda, H. & Moore, B. S. Genomic basis for natural product biosynthetic diversity in the actinomycetes. *Nat Prod Rep* **26**, 1362-1384 (2009).
- 267 Covington, B. C., Xu, F. & Seyedsayamdost, M. R. A natural product chemist's guide to unlocking silent biosynthetic gene clusters. *Annu Rev Biochem* **90**, 763-788 (2021).
- 268 Westhoff, S., Kloosterman, A. M., van Hoesel, S. F. A., van Wezel, G. P. & Rozen, D. E. Competition sensing changes antibiotic production in *Streptomyces*. *mBio* **12**, e02729-20 (2021).
- 269 Soares, A. R. *et al.* The role of L-DOPA in plants. *Plant Signal Behav* **9**, e28275 (2014).
- 270 Ladino-Orjuela, G., Gomes, E., da Silva, R., Salt, C. & Parsons, J. R. Metabolic pathways for degradation of aromatic hydrocarbons by bacteria. *Rev Environ Contam Toxicol* **237**, 105-121 (2016).
- 271 Xia, J., Psychogios, N., Young, N. & Wishart, D. S. MetaboAnalyst: a web server for metabolomic data analysis and interpretation. *Nucleic Acids Res* **37**, W652-660 (2009).
- 272 Mladic, M. *et al.* Detection and identification of antibacterial proteins in snake venoms using at-line nanofractionation coupled to LC-MS. *Toxicon* **155**, 66-74 (2018).

- 273 Frank, A. M. *et al.* Clustering millions of tandem mass spectra. *J Proteome Res* **7**, 113-122 (2008).
- 274 Peng, A. *et al.* Angucycline glycosides from an intertidal sediments strain *Streptomyces* sp. and their cytotoxic activity against hepatoma carcinoma cells. *Mar Drugs* **16**, 470 (2018).
- 275 Kharel, M. K. *et al.* Angucyclines: biosynthesis, mode-of-action, new natural products, and synthesis. *Nat Prod Rep* **29**, 264-325 (2012).
- 276 Qi, L. S. *et al.* Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. *Cell* **152**, 1173-1183 (2013).
- 277 Tong, Y., Charusanti, P., Zhang, L., Weber, T. & Lee, S. Y. CRISPR-Cas9 based engineering of actinomycetal genomes. *ACS Synth Biol* **4**, 1020-1029 (2015).
- 278 Ingram, C., Brawner, M., Youngman, P. & Westpheling, J. xylE functions as an efficient reporter gene in *Streptomyces* spp.: use for the study of galP1, a catabolite-controlled promoter. *J Bacteriol* **171**, 6617-6624 (1989).
- 279 Labes, G., Bibb, M. & Wohlleben, W. Isolation and characterization of a strong promoter element from the *Streptomyces ghanaensis* phage I19 using the gentamicin resistance gene (aacC1) of Tn 1696 as reporter. *Microbiology (Reading)* **143** (Pt 5), 1503-1512 (1997).
- 280 Xu, F., Nazari, B., Moon, K., Bushin, L. B. & Seyedsayamdost, M. R. Discovery of a cryptic antifungal compound from *Streptomyces albus* J1074 using high-throughput elicitor screens. *J Am Chem Soc* **139**, 9203-9212 (2017).
- 281 Pluskal, T., Castillo, S., Villar-Briones, A. & Oresic, M. MZmine 2: modular framework for processing, visualizing, and analyzing mass spectrometry-based molecular profile data. *BMC Bioinformatics* **11**, 395 (2010).
- 282 Myers, O. D., Sumner, S. J., Li, S., Barnes, S. & Du, X. One step forward for reducing false positive and false negative compound identifications from mass spectrometry metabolomics data: new algorithms for constructing extracted ion chromatograms and detecting chromatographic peaks. *Anal Chem* **89**, 8696-8703 (2017).
- 283 Distler, U. *et al.* Drift time-specific collision energies enable deep-coverage data-independent acquisition proteomics. *Nat Methods* **11**, 167-170 (2014).
- 284 Tong, Y., Charusanti, P., Zhang, L., Weber, T. & Lee, S. Y. CRISPR-Cas9 Based Engineering of Actinomycetal Genomes. *ACS Synth Biol* **4**, 1020-1029 (2015).
- 285 Ultee, E. *et al.* Teichoic acids anchor distinct cell wall lamellae in an apically growing bacterium. *Commun Biol* **3**, 314 (2020).
- 286 Zhang, L. *et al.* An alternative and conserved cell wall enzyme that can substitute for the lipid II synthase MurG. *mBio* **12**, e03381-20 (2021).
- 287 Vara, J., Lewandowska-Skarbek, M., Wang, Y. G., Donadio, S. & Hutchinson, C. R. Cloning of genes governing the deoxysugar portion of the erythromycin biosynthesis pathway in *Saccharopolyspora erythraea* (*Streptomyces erythreus*). *J Bacteriol* **171**, 5872-5881 (1989).
- 288 Currie, C. R., Bot, A. N. M. & Boomsma, J. J. Experimental evidence of a tripartite mutualism: bacteria protect ant fungus gardens from specialized parasites. *Oikos* **101**, 91-102 (2003).
- 289 Oh, D. C., Poulsen, M., Currie, C. R. & Clardy, J. Dentigerumycin: a bacterial mediator of an ant-fungus symbiosis. *Nat Chem Biol* **5**, 391-393 (2009).
- 290 Bruner-Montero, G. *et al.* Symbiont-mediated protection of *Acromyrmex* leaf-cutter ants from the entomopathogenic fungus *Metarhizium anisopliae*. *mBio* **12**, e0188521 (2021).
- 291 Chevrette, M. G. & Currie, C. R. Emerging evolutionary paradigms in antibiotic discovery. *J Ind Microbiol Biotechnol* **46**, 257-271 (2019).

- 292 Adnani, N. *et al.* Coculture of marine invertebrate-associated bacteria and interdisciplinary technologies enable biosynthesis and discovery of a new antibiotic, keyicin. *ACS Chem Biol* **12**, 3093-3102 (2017).
- 293 Cho, I. & Blaser, M. J. The human microbiome: at the interface of health and disease. *Nat Rev Genet* **13**, 260-270 (2012).
- 294 Fukuda, S. *et al.* Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* **469**, 543-547 (2011).
- 295 Henrick, B. M. *et al.* Bifidobacteria-mediated immune system imprinting early in life. *Cell* **184**, 3884-3898 e3811 (2021).
- 296 Zhalnina, K. *et al.* Dynamic root exudate chemistry and microbial substrate preferences drive patterns in rhizosphere microbial community assembly. *Nat Microbiol* **3**, 470-480 (2018).
- 297 Bulgarelli, D. *et al.* Revealing structure and assembly cues for *Arabidopsis* root-inhabiting bacterial microbiota. *Nature* **488**, 91-95 (2012).
- 298 Badri, D. V., Chaparro, J. M., Zhang, R., Shen, Q. & Vivanco, J. M. Application of natural blends of phytochemicals derived from the root exudates of *Arabidopsis* to the soil reveal that phenolic-related compounds predominantly modulate the soil microbiome. *J Biol Chem* **288**, 4502-4512 (2013).
- 299 Kaltenpoth, M. *et al.* Partner choice and fidelity stabilize coevolution in a Cretaceous-age defensive symbiosis. *Proc Natl Acad Sci U S A* **111**, 6359-6364 (2014).
- 300 Zhang, M. M., Poulsen, M. & Currie, C. R. Symbiont recognition of mutualistic bacteria by *Acromyrmex* leaf-cutting ants. *ISME J* **1**, 313-320 (2007).
- 301 van Bergeijk, D. A. *et al.* The ubiquitous catechol moiety elicits siderophore and angucycline production in *Streptomyces*. *Commun Chem* **5**, 14 (2022).
- 302 Burns, A. R. & Guillemin, K. The scales of the zebrafish: host-microbiota interactions from proteins to populations. *Curr Opin Microbiol* **38**, 137-141 (2017).
- 303 Douglas, A. E. Simple animal models for microbiome research. *Nat Rev Microbiol* **17**, 764-775 (2019).
- 304 Flores, E. M., Nguyen, A. T., Odem, M. A., Eisenhoffer, G. T. & Krachler, A. M. The zebrafish as a model for gastrointestinal tract-microbe interactions. *Cell Microbiol* **22**, e13152 (2020).
- 305 Stagaman, K., Sharpton, T. J. & Guillemin, K. Zebrafish microbiome studies make waves. *Lab Anim (NY)* **49**, 201-207 (2020).
- 306 Alanjary, M., Steinke, K. & Ziemert, N. AutoMLST: an automated web server for generating multi-locus species trees highlighting natural product potential. *Nucleic Acids Res* **47**, W276-W282 (2019).
- 307 Grumaz, C. *et al.* Draft genome sequence of *Pseudonocardia autotrophica* strain DSM 43083, an efficient producer of peroxidases for lignin modification. *Genome Announc* **5** (2017).
- 308 Grant, J. R. & Stothard, P. The CGView Server: a comparative genomics tool for circular genomes. *Nucleic Acids Res* **36**, W181-184 (2008).
- 309 Gilchrist, C. L. M. *et al.* cblaster: a remote search tool for rapid identification and visualization of homologous gene clusters. *Bioinformatics Advances* **1**, vbab016 (2021).
- 310 Rajilic-Stojanovic, M. & de Vos, W. M. The first 1000 cultured species of the human gastrointestinal microbiota. *FEMS Microbiol Rev* **38**, 996-1047 (2014).
- 311 Gaiser, R. F., M. et al. A mammalian commensal of the oropharyngeal cavity produces antibiotic and antiviral valinomycin *in vivo* (preprint). *Research square* (2021).
- 312 Goldstein, S. L. & Klassen, J. L. *Pseudonocardia* symbionts of fungus-growing ants and the evolution of defensive secondary metabolism. *Front Microbiol* **11**, 621041 (2020).

- 313 Parra, J., Soldatou, S., Rooney, L. M. & Duncan, K. R. *Pseudonocardia abyssalis* sp. nov. and *Pseudonocardia oceani* sp. nov., two novel actinomycetes isolated from the deep Southern Ocean. *Int J Syst Evol Microbiol* **71** (2021).
- 314 van den Berg, A. H., McLaggan, D., Diéguez-Urbeondo, J. & van West, P. The impact of the water moulds *Saprolegnia diclina* and *Saprolegnia parasitica* on natural ecosystems and the aquaculture industry. *Fungal Biology Reviews* **27**, 33-42 (2013).
- 315 Riahi, H. S., Heidarieh, P. & Fatahi-Bafghi, M. Genus *Pseudonocardia*: What we know about its biological properties, abilities and current application in biotechnology. *J Appl Microbiol* **132**, 890-906 (2022).
- 316 Tyagi, A., Singh, B., Billekallu Thammegowda, N. K. & Singh, N. K. Shotgun metagenomics offers novel insights into taxonomic compositions, metabolic pathways and antibiotic resistance genes in fish gut microbiome. *Arch Microbiol* **201**, 295-303 (2019).
- 317 Sharpton, T. J., Stagaman, K., Sieler, M. J., Jr., Arnold, H. K. & Davis, E. W., 2nd. Phylogenetic integration reveals the zebrafish core microbiome and its sensitivity to environmental exposures. *Toxics* **9** (2021).
- 318 Stephens, W. Z. *et al.* The composition of the zebrafish intestinal microbial community varies across development. *ISME J* **10**, 644-654 (2016).
- 319 Bolyen, E. *et al.* Reproducible, interactive, scalable and extensible microbiome data science using QIIME 2. *Nat Biotechnol* **37**, 852-857 (2019).
- 320 Callahan, B. J. *et al.* DADA2: High-resolution sample inference from Illumina amplicon data. *Nat Methods* **13**, 581-583 (2016).
- 321 Katoh, K., Misawa, K., Kuma, K. & Miyata, T. MAFFT: a novel method for rapid multiple sequence alignment based on fast Fourier transform. *Nucleic Acids Res* **30**, 3059-3066 (2002).
- 322 Price, M. N., Dehal, P. S. & Arkin, A. P. FastTree 2--approximately maximum-likelihood trees for large alignments. *PLoS One* **5**, e9490 (2010).
- 323 Quast, C. *et al.* The SILVA ribosomal RNA gene database project: improved data processing and web-based tools. *Nucleic Acids Res* **41**, D590-596 (2013).
- 324 Jami, M., Ghanbari, M., Kneifel, W. & Domig, K. J. Phylogenetic diversity and biological activity of culturable Actinobacteria isolated from freshwater fish gut microbiota. *Microbiol Res* **175**, 6-15 (2015).
- 325 Maciejewska, M. *et al.* *Streptomyces lunaelactis* sp. nov., a novel ferroverdin A-producing *Streptomyces* species isolated from a moonmilk speleothem. *Antonie Van Leeuwenhoek* **107**, 519-531 (2015).
- 326 Elsayed, S. S. *et al.* Atypical spirotetronate polyketides identified in the underexplored genus *Streptacidiphilus*. *J Org Chem* **85**, 10648-10657 (2020).
- 327 Abdel-Mageed, W. M. *et al.* Dermacozines, a new phenazine family from deep-sea dermacocci isolated from a Mariana Trench sediment. *Org Biomol Chem* **8**, 2352-2362 (2010).
- 328 Coelho, L. P. *et al.* Towards the biogeography of prokaryotic genes. *Nature* **601**, 252-256 (2022).
- 329 Sharrar, A. M. *et al.* Bacterial secondary metabolite biosynthetic potential in soil varies with phylum, depth, and vegetation type. *mBio* **11**, e00416-20 (2020).
- 330 Martiny, J. B. *et al.* Microbial biogeography: putting microorganisms on the map. *Nat Rev Microbiol* **4**, 102-112 (2006).
- 331 D'Onofrio, A. *et al.* Siderophores from neighboring organisms promote the growth of uncultured bacteria. *Chem Biol* **17**, 254-264 (2010).

- 332 Nichols, D. *et al.* Use of ichip for high-throughput in situ cultivation of “uncultivable” microbial species. *Appl Environ Microbiol* **76**, 2445-2450 (2010).
- 333 Gu, S. *et al.* Competition for iron drives phytopathogen control by natural rhizosphere microbiomes. *Nat Microbiol* **5**, 1002-1010 (2020).
- 334 Gu, S. *et al.* Siderophore-mediated interactions determine the disease suppressiveness of microbial consortia. *mSystems* **5**, e00811-19 (2020).
- 335 Radzki, W. *et al.* Bacterial siderophores efficiently provide iron to iron-starved tomato plants in hydroponics culture. *Antonie Van Leeuwenhoek* **104**, 321-330 (2013).
- 336 Lin, L. & Tan, R. X. Cross-kingdom actions of phytohormones: a functional scaffold exploration. *Chem Rev* **111**, 2734-2760 (2011).



Curriculum vitae

Doris Antonia van Bergeijk was born in Hoofddorp, The Netherlands, on the 24th of January, 1992. She attended secondary school at the Haarlemmermeerlyceum in Hoofddorp, during which she followed three years of bilingual education (English-Dutch). After graduating in 2010, she conducted voluntary work in the Philippines and China, and worked and travelled in New Zealand.



In 2011, she continued her studies with the Bachelor Pharmacy at Utrecht University and discovered her passion for microbiology and research. After obtaining her BSc in July 2014, she started the Research Master Drug Innovation at Utrecht University. During her first internship in the pharmaco-epidemiology group of prof. dr. Anke-Hilse Maitland-van der Zee, she collected clinical data for the Children Anticoagulation and Pharmacogenetics Study and extracted DNA from saliva samples for genotyping under supervision of dr. Hedy Maagdenberg. During her second internship, Doris studied the effect of salt exposure on macrophages in zebrafish larvae under supervision of dr. Neeraj Dhaun and dr. Alicja Czopek at the University of Edinburgh. Eager to gain more experience in the lab, she completed an extracurricular internship in the group of dr. ing. Erik Hendriksen, working on the development of a new *in vitro* model to study mast cell-neuron interactions in the brain.

In February 2017, Doris started her PhD project at the Institute of Biology (IBL) at Leiden University, as part of the metagenomics PhD program of the Netherlands Centre for One Health (NCOH), connecting to the NCOH research theme *tackling antimicrobial resistance*. Under the joint supervision of prof. dr. Gilles van Wezel and prof. dr. Herman Spaijk, she worked on different ecological approaches to access the full biosynthetic potential of Actinobacteria. During her PhD, Doris organised several workshops, seminars, and symposia as board member of Young NCOH and as part of the spotlight committee of the IBL. Doris will continue her scientific career as a postdoctoral researcher in the laboratory of prof. dr. Jeroen Raes at KU Leuven, Belgium, to work on intestinal bacteria and their role in health and disease.



List of publications

van Bergeijk, D.A., Elsayed, S.S., Du, C., Nuñez Santiago, I., Roseboom, A.M., Zhang, L., Carrión V.J., Spaink, H.P., van Wezel, G.P. The ubiquitous catechol moiety elicits siderophore and angucycline production in *Streptomyces*. *Commun Chem* **5**, 14 (2022).

van Bergeijk, D.A., Terlouw, B.R., Medema, M.H., van Wezel, G.P. Ecology and genomics of Actinobacteria: new concepts for natural product discovery. *Nat Rev Microbiol.* **18**, 546–558 (2020)

Hendriksen E., **van Bergeijk D.A.**, Oosting R.S. Redegeld F.A. Mast cells in neuroinflammation and brain disorders. *Neurosci Biobehav Rev.* **79**, 119-133. (2017)