UNIVERSITI PUTRA MALAYSIA

ISOLATION, MOLECULAR CHARACTERISATION AND BIOPROSPECTING OF ACTINOBACTERIA FROM GREENWICH ISLAND AND DEE ISLAND, ANTARCTICA

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By

CHU PEK LIM

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

ISOLATION, MOLECULAR CHARACTERISATION AND BIOPROSPECTING OF ACTINOBACTERIA FROM GREENWICH ISLAND AND DEE ISLAND, ANTARCTICA

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December 2014

Chair : Cheah Yoke Kqueen, PhD
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Antarctica is a pristine region on Earth that is well known for its extreme environmental conditions. The limited distribution of microbes shaped by the biogeography of Antarctica might promote the development of endemic microbial populations and evolution of endemic taxa with unique cold-adaptation and survival strategies in the harsh environment. *Actinobacteria* is one of the dominant soil inhabitants in the Antarctic continent. A total of 15 soil samples were collected from different sites of Greenwich Island and Dee Island to investigate the distributions of actinobacteria in the soil and to reveal their biosynthesis potential. Molecular screening for actinobacteria was achieved by amplifying the large insert stretch specifically found in the 23S rRNA gene of *Actinobacteria*. A selective isolation approach enabled 36 actinobacteria isolates of ten different genera to be successfully recovered. The highest diversity and abundance of actinobacteria was harboured in slightly alkaline soil (62.5%), compared to the moderately alkaline soil (26.8%) and extremely alkaline soil (10.7%). The major representatives of *Actinobacteria* belong to the genera *Streptomyces, Micrococcus, Kocuria and Micromonospora*. Phylogenetic analysis revealed that one presumptive new species of *Micromonospora* was isolated (98.8% 16S rRNA gene sequence similarity). Through the PCA analysis, water availability which serves as a dynamic source for the interactions of microbes was examined as the principal factor that shaped the distribution of actinobacteria from Greenwich Island and Dee Island. The presence of the biosynthetic systems polyketide synthase (PKS) and non-ribosomal peptide synthase (NRPS) in the genomes of the actinobacteria isolates indicated their great biosynthesis potential. In the expression analysis, the bioactive compounds recovered in ethyl acetate extracts were showing antibacterial activity against a broad spectrum of Gram-positive and Gram-negative pathogenic bacterial strains. The best group of antibacterial producers was the actinobacteria isolated from highly alkaline soil (>pH8.5), which exhibited 19.5% higher antibacterial activity than the next group of isolates from moderately alkaline soil (pH 7.9-8.4). The random amplified polymorphic DNA (RAPD) analysis was capable of detecting the intra-specific genetic variations among the 11 *Streptomyces* species and generated a specific cluster of *Streptomyces albidoflavus*. Other than taxonomic classification, RAPD is also capable of segregating the

actinobacteria isolates into clusters having specific antibacterial patterns. Antarctica has emerged as a natural reservoir of actinobacteria with great biosynthesis potential for bioprospecting.

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Sebagai memenuhi keperluan untuk Ijazah Master Sains

PENGASINGAN, PENCIRIAN MOLEKUL DAN BIOPROSPEK ACTINOBACTERIA DARIPADA PULAU GREENWICH DAN PULAU DEE, ANTARTIKA

Oleh

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Antartika merupakan satu kawasan yang asal di Bumi dan terkenal dengan keadaan persekitaran yang ekstrim. Taburan mikrob yang dihadkan oleh biogeografi Antartika mungkin menggalakkan pembentukan populasi mikrob yang endemik dalam alam sekitar yang sukar. *Actinobacteria* merupakan salah satu penghuni dominan dalam tanah benua Antartika. Sebanyak 15 sampel tanah telah dikumpulkan dari tempat-tempat yang berlainan di Pulau Greenwich dan Pulau Dee untuk menyiasat penaburan actinobacteria di dalam tanah dan mendedahkan potensi biosintesis actinobacteria tersebut. Pemeriksaan molekular untuk *actinobacteria* daripada pencilan bakteria telah dicapai dengan amplifikasi sisip besar khusus yang terdapat dalam gen 23S rRNA filum *Actinobacteria*. Kaedah pengasingan terpilih membolehkan 36 pencilan *actinobacteria* yang terdiri daripada sepuluh jenis genus yang berbeza telah berjaya diperolehi. Actinobacteria yang terbanyak dan berkepelbagaian tinggi adalah daripada tanah beralkali rendah (62.5%), berbanding dengan tanah beralkali sederhana (26.8%) dan beralkali ekstrim (10.7%). Wakil-wakil majoriti *Actinobacteria* adalah genus *Streptomyces*, *Micrococcus*, *Kocuria* dan *Micromonospora*. Analisis filogenetik mendedahkan bahawa satu spesies novel andaian daripada *Micromonospora* telah diasingkan, dengran rujukan kepada persamaan jujukan gen 16S rRNA. Melalui analisis PCA, air yang berfungsi sebagai sumber dinamik untuk interaksi mikrob telah dikaji sebagai faktor utama yang membentuk corak penaburan actinobacteria dari Pulau Greenwich dan Pulau Dee. Kehadiran sistem biosintetik poliketida sintase (PKS) dan Peptida Nonribosom (NRPS) dalam genom pencilan *actinobacteria* mendedahkan potensi biosintesis yang tinggi. Dalam analisis ekspresi, komposisi bioaktif dalam ekstrak etil asetat menunjuk aktiviti antibakteria terhadap patogen-patogen bakteria Gram-positif dan Gram-negatif yang berspektrum luas. Kumpulan terbaik penghasilan antibakteria adalah *actinobacteria* daripada tanah beralkali tinggi (> pH 8.5), dengan menunjukkan aktiviti antibakteria sebanyak 19.5% lebih tinggi daripada kumpulan yang berikutnya, iaitu actinobacteria daripada tanah beralkali sederhana (pH 7,9-8,4). Analisis *Random Amplification of Polymorphic DNA* (*RAPD*) dapat mengesan variasi genetik intra-spesifik antara 11 spesies *Streptomyces* dan menjana kelompok tertentu *Streptomyces albidoflavus*. Selain daripada pengelasan taksonomi, *RAPD* juga mampu

mengasingkan pencilan *actinobacteria* ke dalam kelompok corak antibakteria tertentu. Antartika muncul sebagai takungan semula jadi *actinobacteria* yang memiliki potensi tinggi dalam biosintesis bagi tujuan bioprospek.

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The thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master. The members of the Supervisory Committee were as follows:

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LIST OF SYMBOLS, UNITS, ABBREVIATIONS AND TERMS

%	percentage
℃	degree Celcius
rpm	revolution per minute
w/v	weight/volume
RNA	ribonucleic acid
DNA	deoxyribonucleic acid
rRNA	ribosomal RNA
PCR	polymerase chain reaction
RFLP	restriction fragment length polymorphism
RAPD	Random Amplification of Polymorphic DNA
CLPP	community level physiological profile
PLFA	phospholipid fatty acid analysis
PCA	Principal Component Analysis
NGS	Next-Generation Sequencing
MRSA	methicillin-resistant *Staphylococcus aureus*
LGT	lateral gene transfer
BLAST	Basic Local Alignment Search Tool
SDS	sodium dodecyl sulphate
dNTP	dinucleotide triphosphate
pH	potential of hydrogen
PKS	polyketide synthase
KS	ketosynthase
NRPS	non-ribosomal peptide synthase
UV	ultraviolet
TE	tris-ethylenediamine tetraacetate
CFCS	cell-free culture supernatant
DMSO	dimethyl sulfoxide
ISP	International *Streptomyces* Project
CFU	colony forming unit
UPGMA	unweighted paired group method with arithmetic mean
PUFA	polyunsaturated fatty acids
AFP	antifreeze protein

CHAPTER 1

INTRODUCTION

Soil is an essential and principal component on Earth, in which it could harbor the most diverse and complicated biological sources. Microbial communities have found to be closely related and perform around 80-90% of the biological events in the soils (Nannipieri & Badalucco, 2003). One gram of soil could harbour 6000 bacterial genomes, reflecting the great diversity of microbes that inhabited and probably can be isolated from the soils (Torsvik et al., 1996). However, the distribution of soil microbes still remains unclear, either they are widely distributed or geographically native. Through the molecular approaches that applied in the study of microbial ecology, somehow the distance and historical and contemporary environmental conditions have found to be some of the conclusive factors that shaped the biogeographic structure of bacteria (Martiny et al., 2006). In this study, the ordination method such as principal component analysis (PCA) is used to access the environmental factors that underlie the distribution of actinobacteria from Greenwich Island and Dee Island, Antarctica.

Secondary metabolites are low molecular weight organic substances produced by various living things, included microbes (Davies & Ryan, 2012). The interest of study has gained on the potential biological activities of these natural products secreted by microbes, included bacteria and fungi. Nevertheless, these microbial metabolites are only being synthesised upon certain stage of growth. Therefore, actinobacteria of this study are grown on solid agar (primary screening) and culture media broth (secondary screening) to access their secondary metabolites production in different growth conditions.

Actinobacteria is one of the dominant soil inhabitants. Presently, the phylum *Actinobacteria* comprised of more than 300 genera, representing one of the largest phyla within the domain *Bacteria* (Gao & Gupta, 2012). In line with this, the genus *Streptomyces* is the most studied group and also recognised as the most prolific producer of bioactive secondary metabolites (Berdy, 2005). Low discriminatory power of phenotypic morphological and chemotaxonomic profiles up-to-date has make it difficult for us to understand the taxonomy and evolutionary of *Actinobacteria* (Embley & Stackebrandt, 1994). On the basis of ribosomal RNA (rRNA) sequences comparisons as advocated by Woese, the evolution of *Actinobacteria* had been studied extensively to uncover their interrelationship. The 16S rRNA gene is commonly presented in prokaryotes and is highly conserved. This gene serves as a molecular signature for the classification of actinobacteria isolates.

Over the past decades, polymerase chain reaction (PCR) has become more accessible and widely applied in laboratory research (Erlich, 1989). With the advance development in molecular biology techniques, many useful genome mapping assays have been developed by implementing the PCR technique, such as random amplified polymorphism DNA (RAPD) (Welsh & McClelland, 1990). DNA polymorphism analysis by RAPD methods enables the differentiation of closely related bacterial strains within species level. Apart from that, RAPD is capable of revealing the relationships

between actinobacteria isolates, such as antibacterial profile, in accordance to their genetic diversity.

Recently, the increased emergence of multiple-drug resistance pathogens has brought to a serious impact on the therapeutic of pathogen-causing infections and diseases (Demain & Sanchez, 2009). Antibiotic resistance was declared by World Health Organisation (WHO) as a rapidly evolving health issue and a threat to global health security in May2013. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin or multidrug-resistant enterococci Gram-negative bacteria (Annual report on the antibiotic resistance monitoring/surveillance network, 2008). This, followed by the rapid declined effectiveness of the existing antibiotics, applied for the treatment of pathogen infections. During the search for bioactive compounds, the situation become even worse when well-known compounds are being produced by different microbes that are isolated from various environments (Bredholt et al., 2007). Notably, the search and discovery of novel and new generations or classes of drugs from microbes, especially actinobacteria from poorly explored area, the Antarctica, has seemed to be the potent alternative of relieving the current crisis.

Antarctica, one of the polar regions, and also a poorly explored area on Earth by humans, now emerged as a new hope for the discovery of novel bacterial species and isolation of novel bioactive secondary metabolites (Smith et al., 2006; Teixeira et al., 2010; Li et al., 2011; Muñoz et al., 2011; Wong et al., 2011; Gesheva & Negoita, 2012; Lee et al., 2012). The harsh environment and extreme conditions on this pristine continent have contributed to the evolution of bacteria by acquiring unique cold-adaptation and survival strategies (Teixeira et al., 2010). By taking the initiative of isolating rare species of *Actinobacteria* from this continent, it will greatly improve our understanding regarding their distribution, ecological and evolutionary relationship in Antarctica and their unique biosynthesis potential.

Objectives of the study

The study was undertaken with the following objectives:

1. To isolate and identify the different genera of *Actinobacteria* from soil samples from Greenwich Island and Dee Island, Antarctica.
2. To characterise the selected actinobacteria isolates through DNA profile by using RAPD fingerprinting method.
3. To investigate the biosynthesis potential of actinobacteria isolates by using PCR method and expression-based method.

REFERENCES

Aislabie, J.M., Lau, A., Dsouza, M., Shepherd, C., Rhodes, P. and Turner, S.J. (2013). Bacterial composition of soils of the Lake Wellman area, Darwin Mountains, Antarctica. *Extremophiles*, 17: 775-786.

Atlas, R.M. (1993). *Handbook of Microbiological Media*. ed. Parks, L.C.. Boca Raton, FL.: CRC Press.

Altas, R. (1997). *Principles of Microbiology*. New York: WCB McGrill-Hill.

Arasu, M.V., Al-Dhabi, N.A., Saritha, V., Duraipandiyan, V., Muthukumar, C. and Kim, S.J. (2013). Antifeedant, larvicidal and growth inhibitory bioactivities of novel polyketide metabolite isolated from *Streptomyces* sp. AP-123 against *Helicoverpa armigera* and *Spodoptera litura*. *BMC Microbiology*, 13(1): 105.

Arenas, F.A., Pugin, B., Henríquez, N.A., Arenas-Salinas, M.A., Díaz-Vásquez, W.A., Pozo, M.F., Muñoz, C.M., Chasteen, T.G., Pérez-Donoso, J.M. and Vásquez, C.C. (2014). Isolation, identification and characterization of highly telluriteresistant, tellurite-reducing bacteria from Antarctica. *Polar Science*, 8: 40-52.

Ashforth, E.J., Fu, C., Liu, X., Dai, H., Song, F., Guo, H. and Zhang, L. (2010). Bioprospecting for antituberculosis leads from microbial metabolites. *Natural Product Reports*, 27: 1709–1719.

Asolkar, R.N., Jensen, P.R., Kauffman, C.A. and Fenical, W. (2006). Daryamides AC, weakly cytotoxic polyketides from a marine-derived actinomycete of the genus *Streptomyces* strain CNQ-085. *Journal of Natural Products*, 69(12): 1756-1759.

Aspedon, A., Palmer, K. and Whiteley, M. (2006). Microarray analysis of the osmotic stress response in *Pseudomonas aeruginosa*. *Journal of Bacteriology*, 188: 2721–2725.

Atlas, R.M. (1993). *Handbook of Microbiological Media.* Boca Raton: CRC Press.

Ayliffe G.A.J. Recommendations for the Control of Methicillin-Resistant *Staphylococcus aureus* (MRSA). World Health Organization, Division of Emerging and other Communicable Diseases Surveillance Control. Geneva, 1996 (WHO/EMC/LTS/96.1)

Ayuso-Sacido, A. and Genilloud, O. (2005). New PCR primers for the screening of NRPS and PKS-I systems in actinomycetes: detection and distribution of these biosynthetic gene sequences in major taxonomic groups. *Microbial Ecology*, 49(1): 10-24.

Baas-Becking, L.G.M. (1934). Geobiologie of inleiding tot de milieukunde. In: De Wit, R., Bouvier, T. (Eds.), 'Everything is Everywhere, But, the Environment Selects';

What did Baas Becking and Beijerinck Really Says? *Environmental Microbiology*, 8(4): 755-758.

Babalola, O.O., Kirby, B.M., Roes-Hill, L., Cook, A.E., Cary, S.C., Burton, S.G. and Cowan, D.A. (2009). Phylogenetic analysis of actinobacterial populations associated with Antarctic Dry Valley mineral soils. *Environmental Microbiology*, 11(3): 566-576.

Bachmann, B.O., Van Lanen, S.G. and Baltz, R.H. (2014). Microbial genome mining for accelerated natural products discovery: is a renaissance in the making? *Journal of Industrial Microbiology and Biotechnology*, 41(2): 175-184.

Baltz, R.H. (2006) Marcel Faber Roundtable: is our antibiotic pipeline unproductive because of starvation, constipation or lack of inspiration? *Journal of Industrial Microbiology and Biotechnology*, 33(7): 507–513.

Bardakci, F. (2001). Random amplified polymorphic DNA (RAPD) markers. *Turkish Journal of Biology*, 25(1): 2185-2196.

Bardakci, F. and Skibinski, D.O.F. (1994). Applications of the RAPD technique in tilapia fish: species and subspecies identification. *Heredity*, 73: 117-123.

Basilio, A., González, I., Vicente, M.F., Gorrochategui, J., Cabello, A., González, A. and Genilloud, O. (2003). Patterns of antimicrobial activities from soil actinomycetes isolated under different conditions of pH and salinity. *Journal of Applied Microbiology*, 95: 814–823.

Batist, G., Ramakrishnan, G., Rao, C.S., Chandrasekharan, A. Gutheil, J., Guthrie, T., Shah, P., Khojasteh, A., Nair, M.K., Hoelzer, K., Tkaczuk, K., Park, Y.C. and Lee, L.W. (2001). Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. *Journal of Clinical Oncology*, 19(5): 1444-1454.

Bauer, A.W., Kirby, W.M.M., Sherris, J.C. and Turck, M. (1966). Antibiotic susceptibility testing by a standardized single disc method. *American Journal of Clinical Pathology*, 45: 493-496.

Becerril-Espinosa, A., Freel, K.C., Jensen, P.R. and Soria-Mercado, I.E. (2013). Marine Actinobacteria from the Gulf of California: diversity, abundance and secondary metabolite biosynthetic potential. *Antonie van Leeuwenhoek*, 103: 809-819.

Bentley, S.D., Chater, K.F., Cerdeno-Tarraga, A.M., Challis, G.L., Thomson, N.R., James, K.D., Harris, D.E., Quail, M.A., Kieser, H., Harper, D., Bateman, A., Brown, S., Chandra, G., Chen, C.W., Collins, M., Cronin, A., Fraser, A., Goble, A., Hidalgo, J., Hornsby, T., Howarth, S., Huang, C.H., Kieser, T., Larke, L., Murphy, L., Oliver, K., O'Neil, S., Rabbinowitsch, E., Rajandream, M.A., Rutherford, K.,

Rutter, S., Seeger, K., Saunders, D., Sharp, S., Squares, R., Squares, S., Taylor, K., Warren, T., Wietzorrek, A., Woodward, J., Barrell, B.G., Parkhill, J. and Hopwood, D.A. (2002). Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3(2). *Nature*, 417(6885): 141–147.

Berdy, J. (2005). Bioactive microbial metabolites. *Journal of Antibiotics*, 58: 1-26.

Berlemont, R., Jacquin, O., Delsaute, M., La Salla, M., Georis, J., Vertéé, F., Galleni, M. and Power, P. (2013). Novel cold-adapted esterase MHlip from an Antarctic soil metagenome. *Biology*, 2(1): 177-188.

Bian, J, Li, Y., Wang, J., Song, F.H., Liu, M., Dai, H.Q., Ren, B., Gao, H., Hu, X., Liu, Z.H., Li, W.J. and Zhang, L.X. (2009) Amycolatopsis marina sp. nov., an actinomycete isolated from an ocean sediment. *International Journal of Systematic and Evolutionary Microbiology*, 59: 477–481.

Biondi, N., Tredici, M.R., Taton, A., Wilmotte, A., Hodgson, D.A., Losi, D. and Marinelli, F. (2008). Cyanobacteria from benthic mats of Antarctic lakes as a source of new bioactivities. *Journal of Applied Microbiology*, 105(1): 105-115.

Bister, B., Bischoff, D., Strö bele, M., Riedlinger, J., Reicke, A., Wolter, F., Bull, A.T., Zä hner, H., Fiedler, H.P. and Suessmuth, R.D. (2004). Abyssomicin C—A Polycyclic Antibiotic from a Marine *Verrucosispora* Strain as an Inhibitor of the p-Aminobenzoic Acid/Tetrahydrofolate Biosynthesis Pathway. *Angewandte Chemie International Edition*, 43(19): 2574-2576.

Bochner, B.R. (2009). Global phenotypic characterization of bacteria. *FEMS Microbiology Reviews*, 33(1): 191-205.

Bode, H.B., Bethe, B., Hofs, R. and Zeeck, A. (2002). Big effects from small changes: possible ways to explore nature's chemical diversity. *ChemBioChem*, 3(7): 619–627.

Bode, H.B. and Müller, R. (2005). The impact of bacterial genomics on natural product research. *Angewandte Chemie International Edition*, 44: 6828–6846.

Bossio, D.A., Scow, K.M., Gunapala, N. and Graham, K.J. (1998). Determinants of soil microbial communities: effects of agricultural management, season, and soil type on phospholipid fatty acid profiles. *Microbial Ecology*, 36: 1–12.

Botstein, D., White, R.L., Skolnick, M. and Davis, R.W. (1980). Construction of a genetic linkage map in man using restriction fragment length polymorphisms. The *American Journal of Human Genetics*, 32: 314-331.

Bredholdt, H., Galatenko, O.A., Engelhardt, K., Fjaervik, E., Terekhova, L.P. and Zotchev, S.B. (2007). Rare actinomycete bacteria from the shallow water

sediments of the Trondheim fjord, Norway: isolation, diversity and biological activity. *Environmental Microbiology,* 9(11): 2756-2764.

Bredholt, H., Fjaervik, E., Johnsen, G. and Zotchev, S.B. (2008). Actinomycetes from sediments in the Trondheim fjord, Norway: diversity and biological activity. *Marine Drugs*, 6: 12-24.

Brennan, P.J. and Nikaido, H. (1995). The envelope of mycobacteria. *Annual Review of Biochemistry*, 64(1): 29-63.

Brockmann, H. and Bauer, K. (1950). Rhodomycin, ein rotes Antibioticum aus Actinomyceten. *Naturwissenschaften*, 37(21): 492-493.

Bruntner, C., Binder, T., Pathom-aree, W., Goodfellow, M., Bull, A.T., Potterat, O., Puder, C., Hörer, S., Schmid, A., Bolek, W., Wagner, K. and Fiedler, H.P. (2005). Frigocyclinone, a novel angucyclinone antibiotic produced by a *Streptomyces griseus* strain from Antarctica. *The Journal of antibiotics*, 58(5): 346-349.

Bull, A.T., Goodfellow, M. and Slater, J.H. (1992). Biodiversity as a source of innovation in biotechnology. *Annual Review of Microbiology,* 46: 219–252.

Bull, A.T., Ward, A.C. and Goodfellow, M. (2000). Search and discovery strategies for biotechnology: the paradigm shift. *Microbiology and Molecular Biology Reviews,* 64: 573–606.

Bull, A.T. (2004). *Microbial Diversity and Bioprospecting.* Washington: ASM Press.

Bull, A.T. and Stach, J.E.M. (2007). Marine actinobacteria: new opportunities for natural product search and discovery. *Trends in Microbiology,* 15: 491–499.

Bull, A.T. (2011). Actinobacteria of the Extremobiosphere. In *Extremophiles Handbook,* ed. Horikoshi, K., Antranikian, G., Bull, A.T., Robb, F. and Stetter, K.O., pp. 1204-1240. NewYork: Springer.

Burgin, A.B., Parodos, K., Lane, D.J. and Pace, N.R. (1990). The excision of intervening sequences from *Salmonella* 23S ribosomal RNA. *Cell*, 60(3): 405-414.

Busti, E., Monciardini, P., Cavaletti, L., Bamonte, R., Lazzarini, A., Sosio, M. and Donadio, S. (2006). Antibiotic-producing ability by representatives of a newly discovered lineage of actinomycetes. *Microbiology*, 152: 675–683.

Butcher, R.A., Schroeder, F.C., Fischbach, M.A., Straight, P.D., Kolter, R., Walsh, C.T. and Clardy, J. (2007). The identification of bacillaene, the product of the PksX megacomplex in *Bacillus subtilis*. *Proceedings of the National Academy of Sciences of United States of American*, 104(5): 1506–1509.

Butler, M.S. (2008). Natural products to drugs: natural product-derived compounds in clinical trials. *Natural Product Reports,* 25(3): 475-516.

Campbell, I.B. and Claridge, G.G.C. (1987). *Antarctica: Soils, Weathering Processes and Environment.* New York: Elsevier Science Publishers.

Cerda-Olmedo, E. (1994). The genetics of chemical diversity. *Critical Review in Microbiology,* 20(2): 151-160.

Chai, L.C., Kong, B.H., Elemfareji, O.I., Thong, K.L. (2012). Variable carbon catabolism among *Salmonella enterica* serovar typhi isolates. *PLoS ONE,* 7(5): e36201.

Chen, X.H., Vater, J., Piel, J., Franke, P., Scholz, R., Schneider, K., Koumoutsi, A., Hitzeroth, G., Grammel, N., Strittmatter, A.W., Gottschalk, G., Sussmuth, R.D. and Borriss, R. (2006). Structural and functional characterization of three polyketide synthase gene clusters in *Bacillus amyloliquefaciens* FZB42. *Journal of Bacteriology,* 188(11): 4024–4036.

Chong, C.W., Goh, Y.S., Convey, P., Pearce, D. and Tan, I.K.P. (2013). Spatial pattern in Antarctica: what can we learn from Antarctic bacterial isolates? *Extremophiles,* 17: 733–745.

Choulet, F., Aigle, B., Gallois, A., Mangenot, S., Gerbaud, C., Truong, C., Francou F.X., Fourrier, C., Guérineau, M., Decaris, B., Barbe, V., Pernodet J.L. and Leblond, P. (2006). Evolution of the terminal regions of the *Streptomyces* linear chromosome. *Molecular Biology and Evolution*, 23(12): 2361-2369.

Chu, H.Y., Fierer, N., Lauber, C.L., Caporaso, J.G., Knight, R. and Grogan, P. (2010). Soil bacterial diversity in the Arctic is not fundamentally different from that found in other biomes. *Environmental Microbiology,* 12: 2998–3006.

Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Ninth Edition;* Clinical and Laboratory Standards Institute document M2-A9 [ISBN 1-56238-586-0]: USA, 2006.

Cocito, C. (1979). Antibiotics of the virginiamycin family, inhibitors which contain synergistic components. *Microbiological Reviews,* 43(2): 145.

Cole, S., Brosch, R., Parkhill, J., Garnier, T., Churcher, C., Harris, D., Gordon, S.V. Eiglmeier, K., Gas, S., Barry, C.E., Tekaia, F., Badcock, K., Basham, D., Brown, D., Chillingworth, T., Connor, R., Davies, R., Devlin, K., Feltwell, T., Gentles, S., Hamlin, N., Holroyd, S., Hornsby, T., Jagels, K., Krogh, A., McLean, J., Moule, S., Murphy, L., Oliver, K., Osborne, J., Quail, M.A., Rajandream, M.A., Rogers, J., Rutter, S., Seeger, K., Skelton, J., Squares, R., Squares, S., Sulston, J.E., Taylor, K., Whitehead, S. and Barrell, B.G. (1998). Deciphering the biology of

Mycobacterium tuberculosis from the complete genome sequence. *Nature*, 393(6685): 537-544.

Convey P., Gibson J.A.E., Hillenbrand C.D., Hodgson D.A., Pugh P.J.A., Smellie J.L. and Stevens, M.I. (2008). Antarctic terrestrial life—challenging the history of the frozen continent? *Biological Reviews*, 83: 103–117.

Crawford, D.L. (1988). Biodegradation of agricultural and urban wastes. In *Actinobacteria in Biotechnology*, pp. 433-439. United Kingdom: Academic Press, Ltd.

Cremen, P.A. and Zeng, L. (2002). High-throughput analysis of natural product compound libraries by parallel LC–MS evaporative light scattering detection. *Analytical Chemistry*, 74: 5492–5500.

Cross, T. (1982). Actinomycetes: A continuing source of new metabolites. *Developments in Industrial Microbiology*, 23: 1-20.

Das, A. and Khosla, C. (2009). Biosynthesis of aromatic polyketides in bacteria. *Accounts of Chemical Research*, 42(5): 631-639.

Davies, J. and Ryan, K.S. (2012). Introducing the parvome: Bioactive compounds in the microbial world. *ACS Chemical Biology*, 7: 252-259.

De Ley, J., Cattoir, H. and Reynaerts, A. (1970). The quantitative measurement of DNA hybridization from renaturation rates. *European Journal of Biochemistry*, 12: 133-142.

De Souza, M.J., Nair, S., Bharathi, P.L. and Chandramohan, D. (2006). Metal and antibiotic-resistance in psychrotrophic bacteria from Antarctic Marine waters. *Ecotoxicology*, 15(4): 379-384.

Deane, C.D. and Mitchell, D.A. (2014). Lessons learned from the transformation of natural product discovery to a genome-driven endeavor. *Journal of Industrial Microbiology and Biotechnology*, 41(2): 315-331.

Demain, A.L. and Sanchez, S. (2009). Microbial drug discovery: 80 years of progress. *The Journal of Antibiotics*, 62(1): 5-16.

Demain, A.L. (2014). Importance of microbial natural products and the need to revitalize their discovery. *Journal of Industrial Microbiology and Biotechnology*, 41(2): 185-201.

Dieser, M., Greenwood, M. and Foreman, C.M. (2010). Carotenoid pigmentation in Antarctic heterotrophic bacteria as a strategy to withstand environmental stresses. *Arctic, Antarctic, and Alpine Research*, 42(4): 396-405.

Dix, N.J. and Webster, J. (1994). *Fungal Ecology*. London: Chapman and Hall Ltd.

Donadio, S. and Katz, L. (1992). Organization of enzymatic domains in the multifunctional polyketide synthase involved in erythromycin formation in *Saccharopolyspora erythraea. Gene,* 111(1): 51-60.

Donadio, S., Staver, M.J., McAlpine, J.B., Swanson, S.J. and Katz, L. (1991). Modular organization of genes required for complex polyketide biosynthesis. *Science*, 252(5006): 675-679.

Drees, K.P., Neilson, J.W., Betancourt, J.L., Quade, J., Henderson, D.A., Pryor, B.M. and Maier, R.M. (2006). Bacterial community structure in the hyperarid core of the Atacama Desert, Chile. *Applied and Environmental Microbiology*, 72(12): 7902-7908.

Duarte, A.W.F., Dayo-Owoyemi, I., Nobre, F.S., Pagnocca, F.C., Chaud, L.C.S., Pessoa, A., Felipe, M.G.A. and Sette, L.D. (2013). Taxonomic assessment and enzymes production by yeasts isolated from marine and terrestrial Antarctic samples. *Extremophiles*, 17: 1023-1035.

Embley, T.M. and Stackebrandt, E. (1994). The molecular phylogency and systematics of the actinomycetes. *Annual Reviews in Microbiology,* 48(1): 257-289.

Emerson, J.J., Cardoso-Moreira, M., Borevitz, J.O. and Long, M. (2008). Natural selection shapes genome-wide patterns of copy-number polymorphism in Drosophila melanogaster. *Science*, 320(5883): 1629-1631.

Ensign, J.C. (1978). Formation, properties, and germination of actinomycete spores. *Annual Reviews in Microbiology,* 32(1): 185-219.

Erlich, H.A. (1989). Polymerase chain reaction. *Journal of Clinical Immunology*, 9(6): 437-447.

Felsenstein, J. (1985). Confidence limits on phylogeny: an appropriate use of the bootstrap. *Evolution* 39:783–791.

Fernandez, R., Hodgson, D.A., Convey, P. and Wilmotte, A. (2011). Low cyanobacterial diversity in biotopes of the transantarctic mountains and shackleton range (80-82 °S), Antarctica. *FEMS Microbiology Ecology*, 77: 503-517.

Fiedler, H.P., Bruntner, C., Riedlinger, J., Bull, A.T., Knutsen, G., Goodfellow, M., Jones, A., Maldonado, L., Pathom-aree, W., Beil, W., Schneider, K., Keller, S. and Sussmuth, R.D. (2008). Proximicin A, B and C, novel aminofuran antibiotic and anticancer compounds isolated from marine strains of the actinomycete Verrucosispora. *Journal of Antibiotics,* 61(3): 158-163.

Franklin, R.B., Taylor, D.R. and Mills, A.L. (1999). Characterization of microbial communities using randomly amplified polymorphic DNA (RAPD). *Journal of Microbiological Methods,* 35(3): 225-235.

Gabriel, K.R. (1971). The biplot graphic display of matrices with application to principal component analysis. *Biometrika,* 58(3): 453-467.

Gao, B. and Gupta, R.S. (2005). Conserved indels in protein sequences that are characteristic of the phylum *Actinobacteria*. *International Journal of Systemic and Evolutionary Microbiology,* 55: 2401-2412.

Gao, B. and Gupta, R.S. (2012). Phylogenetic framework and molecular signatures for the main clades of the phylum *Actinobacteria*. *Microbiology and Molecular Biology Reviews,* 76: 66-112.

Genilloud, O., Gonz á lez, I., Salazar, O., Mart ń, J., Tormo, J.R. and Vicente, F. (2011). Current approaches to exploit actinomycetes as a source of novel natural products. *Journal of Industrial Microbiology and Biotechnology,* 38(3): 375-389.

Gesheva, V. and Negoita, T. (2012). Psychrotrophic microorganism communities in soils of Haswell Island, Antarctica, and their biosynthetic potential. *Polar Biology*, 35(2): 291-297.

Giddings, L.A. and Newman, D.J. (2013). Microbial natural products: molecular blueprints for antitumor drugs. *Journal of Industrial Microbiology and Biotechnology,* 40: 1181–1210.

Gilbert, J.A., Hill, P.J., Dodd, C.E., and Laybourn-Parry, J. (2004). Demonstration of antifreeze protein activity in Antarctic lake bacteria. *Microbiology,* 150(1): 171-180.

Giudice, L.A., Bruni, V., and Michaud, L. (2007). Characterization of Antarctic psychrotrophic bacteria with antibacterial activities against terrestrial microorganisms. *Journal of basic microbiology,* 47(6): 496-505.

Goh, E.B., Yim, G., Tsui, W., McClure, J., Surette, M.G. and Davies, J. (2002). Transcriptional modulation of bacterial gene expression by subinhibitory concentrations of antibiotics. *Proceedings of the National Academy of Sciences,* 99(26): 17025–17030.

Goldenberger, D., Kunzli, A., Vogt, P., Zbinden, R. and Altwegg, M. (1997). Molecular diagnosis of bacterial endocarditis by broad-range PCR amplification and direct sequencing. *Journal of Clinical Microbiology*, 35: 2733–2739.

Goodall, D.W. (1954). Objective methods for the classification of vegetation. III. An essay in the use of factor analysis. *Australian Journal of Botany,* 2(3): 304-324.

Goodfellow, M. and Williams, S.T. (1983). Ecology of actinomycetes. *Annual Review of Microbiology,* 37: 189-216.

Goodfellow, M., Williams, S.T. and Mordarski, M. (1988). *Actinobacteria in Biotechnology*. London, United Kingdom: Academic Press Ltd.

Goodfellow, M. and O'Donnell, A.G. (1989). Search and discovery of industrially significant actinomycetes. In *Microbial Products: New Approaches. Society for General Microbiology Symposium No. 44*, ed. Baumberg, S., Hunter, I.S. and Rhodes, P.M., pp. 343-383. Cambridge: Cambridge University Press.

Goodfellow, M. and Fiedler, H.P. (2010). A guide to successful bioprospecting: informed by actinobacterial systematics. *Antonie van Leeuwenhoek,* 98: 119-142.

Goodier, J.L. and Davidson, W.S. (1993). A repetitive element in the genome of Altantic salmon, Salmo salar. *Gene,* 131: 237–242.

Graca, A.P., Bondoso, J., Gaspar, H., Xavier, J.R., Monteiro, M.C., dela Cruz, M., Oves-Costales, D., Vicente, F. and Lage, O.M. (2013). Antimicrobial activity of heterotrophic bacterial communities from the marine sponge Erylus discophorus (astrophorida, geodiidae). *PloS One,* 8(11): e78992.

Gross, F., Luniak, N., Perlova, O., Gaitatzis, N., Jenke-Kodama, H., Gerth, K., Gottschalk, D., Dittmann, E. and Müller, R. (2006). Bacterial type III polyketide synthases: phylogenetic analysis and potential for the production of novel secondary metabolites by heterologous expression in pseudomonads. *Archives of Microbiology,* 185(1): 28-38.

Grossart, H.P., Schlingloff, A., Bernhard, M., Simon, M. and Brinkhoff, T. (2004). Antagonistic activity of bacteria isolated from organic aggregates of the German Wadden Sea. *FEMS Microbiology Ecology,* 47: 387–396.

Grundmann, L.G. and Gourbiere, F. (1999). A micro-sampling approach to improve the inventory of bacterial diversity in soil. *Applied Soil Ecology,* 13(2): 123-126.

Gurtler, V. and Stanisich, V.A. (1996). New approaches to typing and identification of bacteria using the 16S–23S rDNA spacer region. *Microbiology,* 142: 13–16.

Hadrys, H., Balick, M. and Schierwater, B. (1992). Applications of random amplified polymorphic DNA (RAPD) in molecular ecology. *Molecular Ecology,* 1(1): 55-63.

Hara, M., Asano, K., Kawamoto, I., Takiguchi, T., Katsumata, S., Takahashi, K. and Nakano, H. (1989). Leinamycin, a new antitumor antibiotic from *Streptomyces*: producing organism, fermentation and isolation. *The Journal of Antibiotics,* 42(12): 1768-1774.

Harper, J.L. and Hawksworth D.L. (1994) Biodiversity: measurement and estimation. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 345: 5–12.

Hayakawa, M. and Ohara, Y. (1987). Humic acid-vitamin agar, a new medium for the selective isolation of soil actinomycetes. *Journal of Fermentation Technology*, 65: 501-509.

Hayakawa, M. and Nonomura, H. (1989). A new method for the intensive isolation of actinomycetes from soil. *Actinomycetologic*, 3: 95-104.

Hayakawa, M., Momose, Y., Yamazaki, T. and Nonomura, H. (1996). A method for the selective isolation of *Microtetraspora glauca* and related four-spored actinomycetes from soil. Journal of *Applied Bacteriology*, 80: 375–386.

Hayakawa, M., Iino, H., Takeuchi, S. and Yamazaki, T. (1997). Application of a method incorporating treatment with chloramine-T for the selective isolation of *Streptosporangiaceae* from soil. *Journal of Fermentation and Bioengineering*, 84(6): 599-602.

Hayakawa, M., Yoshida, Y. and Limura, Y. (2004). Selective isolation of bioactive soil actinomycetes belonging to the *Streptomyces violaceusniger* phenotypic cluster. *Journal of Applied Microbiology*, 96: 973-981.

Hayakawa, M. (2008). Studies on the isolation and distribution of rare Actinomycetes in soil. *Actinomycetologica*, 22: 12-19.

He, H.Y., Ding, W.D., Bernan, V.S., Richardson, A.D., Ireland, C.M., Greenstein, M., Ellestad, G.A. and Carter, G.T. (2001). Lomaiviticins A and B, Potent Antitumor Antibiotics from *Micromonospora lomaivitiensis*. *Journal of the American Chemical Society*, 123(22): 5362-5363.

He, H.Y., Pan, H.X., Wu, L.F., Zhang, B.B., Chai, H.B., Liu, W. and Tang, G.L. (2012). Quartromicin biosynthesis: two alternative polyketide chains produced by one polyketide synthase assembly line. *Chemistry and Biology*, 19(10): 1313-1323.

Health Protection Agency. *Identification of aerobic Actinomycetes;* UK Standards for Microbiology Investigations. Issue 1.2, 2012. (http://www.hpa.org.uk/SMI)

Heath, C., Hu, X.P., Cary, S.C. and Cowan, D. (2009). Identification of a novel alkaliphilic esterase active at low temperatures by screening a metagenomic library from antarctic desert soil. *Applied and Environmental Microbiology*, 75(13): 4657-4659.

Hedrick, P. (1992). Shooting the RAPDs. *Nature*, 355: 679-680.

Hertweck, C., Luzhetskyy, A., Rebets, Y. and Bechthold, A. (2007). Type II polyketide synthases: gaining a deeper insight into enzymatic teamwork. *Natural Product Reports*, 24(1): 162-190.

Hirsch, P., Mevs, U., Kroppendstedt, R.M., Schumann. P. and Stackebrandt, E. (2004). Cryptoendolithic Actinomycetes from Antarctic Sandstone Rock Samples: *Micromonospora endolithica* sp. nov. and two Isolates Related to *Micromonospora coerulea* Jensen 1932. *Systematic and Applied Microbiology*, 27(2): 166-274.

Hodges, T.W., Slattery, M., and Olson, J.B. (2012). Unique actinomycetes from marine caves and coral reef sediments provide novel PKS and NRPS biosynthetic gene cluster. *Marine Biotechnology*, 14(3): 270-280.

Hong, K., Gao, A.H., Xie, Q.Y., Gao, H., Zhuang, L., Lin, H.P., Yu, H.P., Li, J., Yao, X.S., Goodfellow, M. and Ruan, J.S. (2009). Actinomycetes for marine drug discovery isolated from mangrove soils and plants in China. *Marine Drugs*, 7: 24-44.

Hopwood, D.A. (1997). Genetic contributions to understanding polyketide synthases. *Chemical Reviews*, 97(7): 2465-2498.

Hopwood, D.A. (2003). The *Streptomyces* genome-be prepared! *Nature Biotechnology*, 21(5): 505-506.

Horikoshi, K. (1999). Alkaliphiles: some applications of their products for biotechnology. *Microbiology and Molecular Biology Reviews*, 63(4): 735-750.

Hotelling, H. (1933). Analysis of a complex of statistical variables into principal components. *Journal of Educational Psychology*, 24(6): 417.

Huck, T.A., Porter, N. and Bushell, M.E. (1991). Positive selection of antibiotic-producing soil isolates. *Journal of General Microbiology*, 137(10): 2321-2329.

Heuer, O.E., Grave, K., Beloeil, G.-A., Goossens, H. and Wegener, H.C. Surveillance of antimicrobial resistance and antimicrobial use in humans and animals. International Society for Infectious Diseases, European Centre for Disease Prevention and Control: Vienna. 5 February 2011.

Huss, V.A.R., Festl, H. and Schleifer, K.H. (1983). Studies on the spectrophotometric determination of DNA hybridization from renaturation rates. *Systematic and Applied Microbiology*, 4: 184-192.

Ibekwe, A.M. and Kennedy, A. (1998). Phospholipid fatty acid profiles and carbon utilization patterns for analysis of microbial community structure under field and greenhouse conditions. *FEMS Microbiology Ecology*, 26(2): 151-163.

İnceoğlu, Ö., Al-Soud, W.A., Salles, J.F., Semenov, A.V. and van Elsas, J.D. (2011). Comparative analysis of bacterial communities in a potato field as determined by pyrosequencing. *PLoS One*, 6(8): e23321.

Ivanov, L.L. (2009). Antarctica: Livingston Island and Greenwich, Robert, Snow and Smith Islands. Scale 1:120000 topographic map. Troyan: Manfred Wörner Foundation. ISBN 978-954-92032-6-4

Ivantiskaya, L.P., Singal, S.M., Bibikova, M.V. and Vostrov, S.N. (1978). Direct isolation of *Micromonospora* on selective media with gentamicin. *Antibiotiki*, 23: 690-692.

Jadoon, W.A., Nakai, R. and Naganuma, T. (2013). Biogeographical note on Antarctic microflorae: Endenism and cosmopolitanism. *Geoscience Frontiers*, 4: 633-646.

Jenke-Kodama, H., Sandmann, A., Müller, R. and Dittmann, E. (2005). Evolutionary implications of bacterial polyketide synthases. *Molecular Biology and Evolution*, 22(10): 2027-2039.

Jensen, P.R. and Fenical, W. (1996). Marine bacterial diversity as a resource for novel microbial products. *Journal of Industrial Microbiology and Biotechnology*, 17: 346–351.

Jiang, C.L. and Xu, L.H. (1996). Diversity of aquatic actinomycetes in Lakes of the Middle Plateau, Yunnan, China. *Applied and Environmental Microbiology*, 62(1): 249–253.

Jiang, Y., Cao, Y.R., Wiese, J., Tang, S.K., Xu, L.H., Imhoff, J.F. and Jiang, C.L. (2011). *Streptomyces sparsus* sp. nov., isolated from a saline and alkaline soil. *International Journal of Systematic and Evolutionary Microbiology*, 61: 1601-1605.

Johnson, S.L., Midson, C.N., Ballinger, E.W. and Postlethwait, J.H. (1994). Identification of RAPD primers that reveal extensive polymorphisms between laboratory strains of zebrafish. *Genomics*, 19: 152-156.

Kalakoutskii, L.V. and Agre, N.S. (1976). Comparative aspects of development and differentiation in actinomycetes. *Bacteriological Reviews*, 40(2): 469.

Kambhampati, S., Blavk, W.C. and Rai, K.S. (1992). Random Amplified Polymorphic DNA of mosquito species and populations (Diptera: Culicidae): techniques, statistical analysis, and applications. *Journal of Medical Entomology*, 29: 939-945.

Katsuyama, Y. and Ohnishi, Y. (2012) Type III polyketide synthases in microorganisms. *Methods in Enzymology*, 515: 359-377.

Kelly, J.J., Häggblom, M. and Tate III, R.L. (1999). Changes in soil microbial communities over time resulting from one time application of zinc: a laboratory microcosm study. *Soil Biology and Biochemistry*, 31(10): 1455-1465.

Khamna, S., Yokota, A. and Lumyong, S. (2009). Actinomycetes isolated from medicinal plant rhizosphere soils: diversity and screening of antifungal compounds, indole-3-acetic acid and siderophore production. *World Journal of Microbiology and Biotechnology*, 25: 649–655.

Khosla, C. (1997). Harnessing the biosynthetic potential of modular polyketide synthases. *Chemical Reviews*, 97(7): 2577-2590.

Kim, O.S., Cho, Y.J., Lee, K., Yoon, S.H., Kim, M., Na, H., Park, S.C., Jeon, Y.S., Lee, J.H., Yi, H., Won, S. and Chun, J. (2012). Introducing EzTaxon: a prokaryotic 16S rRNA Gene sequence database with phylotypes that represent uncultured species. *International Journal of Systematic and Evolutionary Microbiology*, 62: 716–721.

Kirk, J.L., Beaudette, L.A., Hart, M., Moutoglis, P., Klironomos, J.N., Lee, H. and Trevors, J.T. (2004). Methods of studying soil microbial diversity. *Journal of Microbiological Methods*, 58(2): 169-188.

Kochi, A. (1991). The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle*, 72(1): 1-6.

Konstantinidis, K.T. and Tiedje, J.M. (2004). Trends between gene content and genome size in prokaryotic species with larger genomes. *Proceedings of the National Academy of Sciences of the United States of America*, 101: 3160 –3165.

Küster, E and Williams, S.T. (1964). Media for the isolation of streptomycetes: starch casein medium. *Nature*, 202: 928-929.

Labeda, D.P. and Shearer M.C. (1990). Isolation of actinomycetes for biotechnological applications. In *Isolation of Biotechnological Organisms From Nature*, ed. Labeda, D.P., pp. 1-19. New York: McGraw-Hill Publishing Co.

Lane, D.J. (1991). 16S/23S rRNA sequencing. In *Nucleic Acid Techniques in Bacterial Systematics*, ed. Stackebrandt, E. and Goodfellow, M., pp. 115-175. New York: John Wiley and Sons.

Laskaris. P., Sekine, T. and Wellington, E.M.H. (2012). Diversity analysis of *Streptomycetes* and associated phosphotranspherase genes in soil. *PLoS ONE*, 7(4): e35756.

Lauber, C.L., Hamady, M., Knight, R. and Fierer, N. (2009). Pyrosequencing-based assessment of soil pH as a predictor of soil bacterial community structure at the continental scale. *Applied and Environmental Microbiology*, 75: 5111–5120.

Lautru, S., Deeth, R.J., Bailey, L.M. and Challis, G.L. (2005). Discovery of a new peptide natural product by *Streptomyces coelicolor* genome mining. *Nature Chemical Biology*, 1(5): 265–269.

Lawrence, C. H. (1956). A method of isolating actinomycetes from scabby potato tissue and soil with minimal contamination. *Canadian Journal of Botany*, 34(1): 44-47.

Laybourn-Parry, J. and Pearce, D.A. (2007). The biodiversity and ecology of Antarctic lakes: models for evolution. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 362: 2273-2289.

Learn-Han, L., Yoke-Kqueen, C., Shiran, M.S., Vui-Ling, C.M.W., Nurul-Syakima, A.M., Son, R. and Andrade, H.M. (2012). Identification of actinomycete communities in Antarctic soil from Barrientos Island using PCR-denaturing gradient gel electrophoresis. *Genetics and Molecular Research*, 11(1): 277-291.

Lederberg, J. (2000). Pathways of discovery: infectious history. *Science*, 288: 287–293.

Lee, K.E. (1991). The diversity of soil organisms. In *The Biodiversity of Microorganisms and Invertebrates: Its Role in Sustainable Agriculture,* ed. Hawksworth, D.L., pp. 73–87. Wallingford, UK: CAB International.

Lee, L.H., Cheah, Y.K., Syakima, A.N., Shiran, M.S., Tang, Y.L., Lin, H.P., and Hong, K. (2012). Analysis of Antarctic proteobacteria by PCR fingerprinting and screening for antimicrobial secondary metabolites. *Genetics and Molecular Research*, 11(2): 1627-1641.

Lee, L.H., Cheah, Y.K., Sidik, S.M., Xie, Q.Y., Tang, Y.L., Lin, H.P., Ab Mutalib, N.S. and Hong, K. (2013). *Barrientosiimonas humi* gen. nov., sp. nov., anactinobacterium of the family Dermacoccaceae. *International Journal of Systematic and Evolutionary Microbiology*, 63(1): 241-248.

Li, F., Maskey, R.P., Qin, S., Sattler, I., Fiebig, H.H., Maier, A., Zeeck, A. and Laatsch, H. (2005). Chinikomycins A and B: isolation, structure elucidation, and biological activity of novel antibiotics from a marine *Streptomyces* sp. isolate M045. *Journal of Natural Products*, 68: 349-353.

Li, J., Tian, X.P., Zhu, T.J., Yang, L.L. and Li, W.J. (2011). *Streptomyces fildesensis* sp. nov., a novel streptomycete isolated from Antarctic soil. *Antonie van Leeuwenhoek*, 100: 537-543.

Li, J., Zhao, G.Z., Huang, H.Y., Qin, S., Zhu, W.Y., Zhao, L.X., Xu, L.H., Zhang, S., Li, W.J. and Strobel, G. (2012). Isolation and characterization of culturable endophytic actinobacteria associated with *Artemisia annua* L. *Antonie van Leeuwenhoek,* 101: 515-527.

Liu, X., Bolla, K., Ashforth, E.J., Zhuo, Y., Gao, H., Huang, P., Stanley S.A., Hung, D.T. and Zhang, L. (2012). Systematics-guided bioprospecting for bioactive microbial natural products. *Antonie van Leeuwenhoek*, 101(1): 55-66.

Lo Giudice, A., Brilli, M., Bruni, V., De Domenico, M., Fani, R. and Michaud, L. (2007). Bacterium-bacterium inhibitory interactions among psychrotrophic bacteria isolated from Antarctic seawater (Terra Nova Bay, Ross Sea). *FEMS Microbiology Ecology*, 60: 383–396.

Lynch, M. and Milligan, B.G. (1994). Analysis of population genetic structure with RAPD markers. *Molecular Ecology*, 3: 91-99.

Maldonado, L.A., Fenical, W., Jensen, P.R., Kauffman, C.A., Mincer, T.J., Ward, A.C., bull, A.T. and Goodfellow, M. (2005). *Salinispora arenicola* gen. nov., sp. nov. and *Salinispora tropica* sp. nov., obligate marine actinomycetes belonging to the family *Micromonosporaceae*. *International Journal of Systematic and Evolutionary Microbiology*, 55(5): 1759-1766.

Malpartida, F., Hallam, S.E., Kieser, H.M., Motamedi, H., Hutchinson, C.R., Butler, M.J., Sudgen, D.A., Warren, M., McKillop, C., Bailey, C.R., Humphreys, G.O. and Hopwood, D.A. (1987). Homology between *Streptomyces* genes coding for synthesis of different polyketides used to clone antibiotic biosynthetic genes. *Nature*, 325(6107): 818-821.

Mao, J., Wang, J., Dai, H.Q., Zhang, Z.D., Tang, Q.Y., Ren, B., Yang, N., Goodfellow, M., Zhang, L.X. and Liu, Z.H. (2010). *Yuhushiella deserti* gen. nov., sp. nov., a new genus of the suborder *Pseudonocardineae*. *International Journal of Systematic and Evolutionary Microbiology*, 61: 621–630.

Margesin, R. and Miteva, V. (2011). Diversity and ecology of psychrophilic microorganisms. *Research in Microbiology*, 162: 346–361.

Margesin, R. and Schinner, F. (1999). Biological decontamination of oil spills in cold environments. *Journal of Chemical Technology and Biotechnology*, 74: 381–389.

Martiny, J.B.H., Bohannan, B.J.M., Brown, J.H., Colwell, R.K., Fuhrman, J.A., Green, J.L., Horner-Devine, M.C., Kane, M., Krumins, J.A., Kuske, C.R., Morin, P.J., Naeem, S., Øvreås, L., Reysenbach, A.L., Smith, V.H. and Staley, J.T. (2006). Microbial biogeography: putting microorganisms on the map. *Nature Reviews Microbiology*, 4: 102–112.

Maskos, U. and Southern, E.M. (1992). Oligonucleotide hybridisations on glass supports: a novel linker for oligonucleotide synthesis and hybridization properties of oligonucleotides synthesised in situ. *Nucleic Acids Research*, 20(7): 1679-1684.

Mast, Y., Weber, T., Gölz, M., Ort-Winklbauer, R., Gondran, A., Wohlleben, W. and Schinko, E. (2011). Characterization of the 'pristinamycin supercluster'of *Streptomyces pristinaespiralis*. *Microbial Biotechnology*, 4(2): 192-206.

McAlpine, J.B., Bachmann, B.O., Piraee, M., Tremblay, S., Alarco, A.M., Zazopoulos, E. and Farnet, C.M. (2005). Microbial genomics as a guide to drug discovery and structural elucidation: ECO-02301, a novel antifungal agent, as an example. *Journal of Natural Products*, 68: 493–496.

McDougald, D., Rice, S.A., Weichart, D. and Kjelleberg, S. (1998). Nonculturability: adaptation or debilitation. *FEMS Microbiology Ecology*, 25: 1–9.

McLeod, M.P., Warren, R.L., Hsiao, W.W., Araki, N., Myhre, M., Fernandes C., Miyazawa, D., Wong, W., Lillquist, A.L., Wang, D., Dosanjh, M., Hara, H., Petrescu, A., Morin, R.D., Yang, G., Stott, J.M., Schein, J.E., Shin, H., Smailus, D., Siddiqui, A.S., Marra, MA, Jones, S.J., Holt, R., Brinkman, F.S., Miyauchi, K., Fukuda, M., Davies, J.E., Mohn, W.W. and Eltis, L.D. (2006). The complete genome of *Rhodococcus* sp. RHA1 provides insights into a catabolic powerhouse. *Proceedings of the National Academy of Sciences*, 103(42): 15582-15587.

Megnegneau, B., Debets, F. and Hoekstra, R.F. (1993). Genetic variability and relatedness in the complex group of black *Aspergilli* based on random amplified polymorphic DNA. *Current Genetics*, 23: 323-329.

Melo, I.S., Santos, S.N., Rosa, L.H., Parma, M.M., Silva, L.J., Queiroz, S.C.N. and Pellizari, V.H. (2014). Isolation and biological activities of an endophytic *Mortierella alpine* strain from the Antarctic moss *Schistidium antarctici*. *Extremophiles*, 18: 15-23.

Millar, B.C. and Moore, J.E. (2004). Molecular diagnostics. In *Methods in Molecular Biology, vol. 266: Genomics, Proteomics, and Clinical Bacteriology: Methods and Reviews*, ed. Woodford, N. and Johnson, A. pp. 139-165. Totowa, NJ: Humana Press.

Millière, J.B., Abidi, F.Z. and Lefebvre, G. (1996), Taxonomic characterization of *Lactobacillus delbrueckii* subsp. *bulgaricus* isolates from a Cameroonian zebu's fermented raw milk. *Journal of Applied Bacteriology*, 80: 583–588.

Miteva, V.I., Sheridan, P.P. and Brenchley, J.E. (2004). Phylogenetic and physiological diversity of microorganisms isolated from a deep Greenland glacier ice core. *Applied and Environmental Microbiology*, 70(1): 202-213.

Mitsui, R., Hirota, M., Tsuno, T. and Tanaka, M. (2010). Purification and characterization of vanillin dehydrogenases fromalkaliphile *Micrococcus* sp.TA1and neutrophile *Burkholderia cepacia*TM1. *FEMS Microbiology Letters*, 303: 41–47.

Miyadoh, S. (1993). Research on antibiotic screening in Japan over the last decade: a producing microorganisms approach. *Actinomycetol*, 7: 100-106.

Moreira, D., Rodríguez-Valera, F. and López-García, P. (2006). Metagenomic analysis of mesopelagic Antarctic plankton reveals a novel deltaproteobacterial group. *Microbiology*, 152(2): 505-517.

Morón, R., González, I. and Genilloud, O. (1999). New genus-specific primers for the PCR identification of members of the genera *Pseudonocardia* and *Saccharopolyspora*. *International Journal of Systematic Bacteriology*, 49(1): 149-162.

Muñoz, P.A., Flores, P.A., Boehmwald, F.A. and Blamey, J.M.. (2011). Thermophilic bacteria present in a sample from Fumarole Bay, Deception Island. Antarctic *Science*, 23: 549-555.

Nacke, H., Engelhaupt, M., Brady, S., Fischer, C., Tautzt, J. and Daniel, R. (2012). Identification and characterization of novel cellulolytic and hemicellulolytic genes and enzymes derived from German grassland soil metagenomes. *Biotechnology Letters*, 34(4): 663-675.

Naish, K.A., Warren, M., Bardakci, F., Skibinski, D.O.F., Carvalho, G.R. and Mair, G.C. (1995). Multilocus DNA fingerprinting and RAPD reveal similar genetic relationships between strains of *Oreochromis niloticus* (Pisces: Cichlidae). *Molecular Ecology*, 4: 271-274.

Nannipieri, P. and Badalucco, L. (2003). Biological processes. In *Processes in the Soil–Plant System: Modelling Concepts and Applications*, ed. Bembi, D.K. and Nieder, R. Binghamton, New York: The Haworth Press.

Nannipieri, P., Ascher, J., Ceccherini, M., Landi, L., Pietramellara, G. and Renella, G. (2003). Microbial diversity and soil functions. *European Journal of Soil Science*, 54(4): 655-670.

Nathan, C. (2004). Antibiotics at the crossroads. *Nature*, 431: 899–902.

Newman, D.J. and Cragg, G.M. (2007). Natural products as sources of new drugs over the last 25 years. *Journal of Natural Products*, 70: 461–477.

Newman, D.J., Cragg, G.M. and Snader, K.M. (2003). Natural products as sources of new drugs over the period 1981–2002. *Journal of Natural Products*, 66: 1022–1037.

Nichols, D., Bowman, J., Sanderson, K., Nichols, C., Lewis, T., Mcmeekin, T. and Nichols, P.D. (1999). Development with Antarctic microorganisms: culture collections, bioactivity screening, taxonomy, PUFA production and cold-adapted enzymes. *Current Opinion in Biotechnology*, 10(3): 240-246.

Nimnoi, P., Pongsilp, N., and Lumyong, S. (2010). Endophytic actinomycetes isolated from *Aquilaria crassna* Pierre ex Lec and screening of plant growth promoters production. *World Journal of Microbiology and Biotechnology*, 26(2): 193-203.

Nonomura, H. and Ohara, Y. (1971). Distribution of actinomycetes in soil. VIII. Green spore group of *Microtetraspora*, its preferential isolation and taxonomic characteristics. *Journal of Fermentation Technology*, 49: 1-7.

Norse, E. A., Rosenbaum, K.L., Wilcove, D.S., Wilcox, B.A., Romme, W.H., Johnston, D.W. and Stout, M.L. (1986). *Conserving Biological Diversity in Our National Forests*. Washington, DC: The Wilderness Society.

O'Brien, A., Sharp, R., Russell, N.J. and Roller, S. (2004). Antarctic bacteria inhibit growth of food-borne microorganisms at low temperatures. *FEMS Microbiology Ecology*, 48(2): 157-167.

Ohta, Y., Ito, T., Mori, K., Nishi, S., Shimane, Y., Mikuni, K. and Hatada, Y. (2013). *Microbacterium saccharophilum* sp. nov., isolated from a sucrose-refining factory. *International Journal of Systematic and Evolutionary Microbiology*, *63*(8): 2765-2769.

Okami, Y. and Hotta, K. (1988). Search and discovery of new antibiotics. In *Actinomycetes in Biotechnology*, ed. Goodfellow, M., Williams, S.T. and Mordarski, M., pp. 33-67. San Diego: Academic Press, Inc.

Okoro, C.K., Brown, R., Jones, A.L., Andrews, B.A., Asenjo, J.A., Goodfellow, M. and Bull, A.T. (2009). Diversity of culturable actinomycetes in hyper-arid soils of the Atacama Desert, Chile. *Antonie van Leeuwenhoek*, 95(2): 121-133.

Olano, C., Méndez, C. and Salas, J.A. (2009). Antitumor compounds from marine actinomycetes. *Marine Drugs*, 7(2): 210-248.

Olsen, G.J., Lane, D.J., Giovannoni, S.J., Pace, N.R. and Stahl, D.A. (1986). Microbial ecology and evolution: a ribosomal RNA approach. *Annual Reviews in Microbiology*, 40(1): 337-365.

Ōmura, S., Ikeda, H., Ishikawa, J., Hanamoto, A., Takahashi, C., Shinose, M., Takahashi, Y., Horikawa, H., Nakazawa, H., Osonoe, T., Kikuchi, H., Shiba, T., Sakaki, Y. and Hattori, M. (2001). Genome sequence of an industrial microorganism *Streptomyces avermitilis*: deducing the ability of producing secondary metabolites. *Proceedings of the National Academy of Sciences*, 98(21): 12215-12220.

Ongley, S.E., Bian, X., Neilan, B.A. and Müller, R. (2013). Recent advances in the heterologous expression of microbial natural product biosynthetic pathways. *Natural Product Reports*, 30(8): 1121-1138.

Onofri, S., Selbmann, L., Hoog, G.S., Grube, M., Barreca, D., Ruisi, S. and Zucconi, L. (2007). Evolution and adaptation of fungi at boundaries of life. *Advances in Space Research,* 40: 1657–1664.

Oren, A. (2010). Microbial systematics. In *Environmental biotechnology*, ed. Wang, L.K., Tay, J.H., Ivanov, V., and Hung, Y.T., pp. 783-814. Totowa, NJ: Humana Press.

Pine, L. and Watson, S.J. (1959). Evaluation of an isolation and maintenance medium for Actinomyces species and related organisms. *The Journal of laboratory and clinical medicine,* 54(1): 107-114.

Pace, N.R. (1997). A molecular view of microbial diversity and the biosphere. *Science,* 276(5313): 734-740.

Padan, E., Bibi, E., Ito, M. and Krulwich, T.A. (2005). Alkaline pH homeostasis in bacteria: New insights. *Biochimica et Biophysica Acta*, 1717: 67-88.

Paitan, Y., Orr, E., Ron, E.Z. and Rosenberg, E. (1999). Genetic and functional analysis of genes required for the post-modification of the polyketide antibiotic TA of *Myxococcus xanthus*. *Microbiology,* 145(11): 3059-3067.

Pan, S.Y., Tan, G.Y.A., Convey, P., Pearce, D.A. and Tan, I.K.P. (2013) Diversity and bioactivity of actinomycetes from Signy Island terrestrial soils, maritime Antarctic. *Advances in Polar Science,* 24(4): 208-212.

Pang, M.F., Tan, G.Y.A., Abdullah, N., Lee, C.W. and Ng, C.C. (2008). Phylogenetic analysis of type I and type II polyketide synthase from tropical forest coil. *Biotechnology*, 7(4): 660-668.

Papaleo, M.C., Romoli, R., Bartolucci, G., Maida, I., Perrin, R., Fondi, M., Orlandini, V., Mengoni, A., Emiliani, G., Tutino, M.L., Parrilli, E., de Pascale, D., Michaud, L., Lo Giudice, A. and Fani, R. (2013). Bioactive volatile organic compounds from Antarctic (sponges) bacteria. *New Biotechnology,* 30(6): 824-838.

Patel, P.S., Huang, S., Fisher, S., Pirnik, D., Aklonis, C., Dean, L., Meyers, E., Fernandes, P. and Mayerl, F. (1995). Bacillaene, a novel inhibitor of procaryotic protein synthesis produced by *Bacillus subtilis*: production, taxonomy, isolation, physico-chemical characterization and biological activity. *Journal of Antibiotics,* 48(9): 997–1003.

Patel, J.B. (2001). 16S rRNA gene sequencing for bacterial pathogen identification in the clinical laboratory. *Journal of Molecular Diagnostics,* 6: 313–321.

Pearce, D.A., Newsham, K.K., Thorne, M.A.S., Calvo-Bado, L., Krsek, M., Laskaris, P., Hodson, A., Wellington, E.M. (2012). Metagenomic analysis of a southern maritime Antarctic soil. *Frontiers in Microbiology,* 3(403):1-13.

Pearson, K. (1901). LIII. On lines and planes of closest fit to systems of points in space. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science*, 2(11): 559-572.

Penner, G.A., Bush, A., Wise, R., Kim, W., Domier, L., Kasha, K., Laroche, A., Scoles, G., Molner, S.J. and Fedak, G. (1993). Reproducibility of random amplified polymorphic DNA (RAPD) analysis among laboratories. *PCR Methods and Applications*, 2: 341–345.

Pisano, M.A., Sommer, M.J. and Lopez, M.M. (1986). Application of pretreatments for the isolation of bioactive actinomycetes from marine sediments. *Applied Microbiology and Biotechnology*, 25: 285-288.

Pisano, M.A., Sommer, M.J. and Brancaccio, L. (1989). Isolation of bioactive actinomycetes from marine sediments using rifampicin. *Applied Microbiology and Biotechnology*, 31: 609-612.

Prosser, J.I. (2002). Molecular and functional diversity in soil micro-organisms. *Plant and Soil*, 244(1-2): 9-17.

Ramasamy, K., Lim, S. M., Bakar, H. A., Ismail, N., Ismail, M. S., Ali, M. F., Weber, J-F. F. and Cole, A. L. (2010). Antimicrobial and cytotoxic activities of Malaysian endophytes. *Phytotherapy Research*, 24(5), 640-643.

Riedlinger, J., Reicke, A., Zähner, H., Krismer, B., Bull, A.T., Maldonado, L.A., Ward, A.C., Goodfellow, M., Bister, B., Bischoff, D., Süssmuth, R.D. and Fiedler H.P. (2004). Abyssomicins, inhibitors of the para-aminobenzoic acid pathway produced by the marine Verrucosispra strain AB-18-032. *The Journal of Antibiotics*, 57(4): 271-279.

Roller, C., Ludwig, W. and Schleifer, K.H. (1992). Gram-positive bacteria with a high DNA G+C content are characterized by a common insertion within their 23S rRNA genes. *Journal of General Microbiology*, 138: 167-175.

Saiki, R.K., Gelfand, D.H., Stoffel, S., Scharf, S.J., Higuchi, R., Horn, G.T., Mullis K.B. and Erlich, H.A. (1988). Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science*, 239(4839): 487-491.

Saitou, N. and Nei, M. (1987). The neighbor-joining method: a new method for constructing phylogenetic trees. *Molecular Biology and Evolution*, 4: 406–425.

Salazar. O., Morón, R. and Genilloud, O. (2000). New genus-specific primers for the PCR identification of members of the genus *Saccharomonospora* and evaluation of the diversity of wild-type isolates of *Saccharomonospora* detected from soil DNAs. *International Journal of Systematic and Evolutionary Microbiology*, 50: 2043–2053.

Salazar, O., Gonz á lez, I. and Genilloud, O. (2002). New genus-specific primers for the PCR identification of novel isolates of the genera *Nocardiopsis* and *Saccharothrix*. *International Journal of Systematic and Evolutionary Microbiology,* 52(4): 1411-1421.

Salt, M., Hugenholz, P. and Janssen, P.H. (2002). Cultivation of globally distributed soil bacteria phylogenetic lineages previously only detected in cultivation-independent surveys. *Environmental Microbiology,* 4: 654-656.

Salton, M.R.J. and Kim, K.S. (1996). Structure. In *Medical Microbiology 4th Edition*, ed. Baron, S. and Galveston, T.X. Galveston: University of Texas Medical Branch.

Saul, D.J., Aislabie, J.M., Brown, C.E., Harris, L. and Foght, J.M. (2005). Hydrocarbon contamination changes the bacterial diversity of soil from around Scott Base, Antarctica. *FEMS Microbiology Ecology,* 53(1): 141-155.

Savic, M. and Vasiljevic, B. (2006). Targeting polyketide synthase gene pool within actinomycetes: new degenerate primers. *Journal of Industrial Microbiology and Biotechnology,* 33(6): 423-430.

Sehgal, S.N., Blazekovic, T.M., and Vezina, C. (1975). "Rapamycin and process of preparation." U.S. Patent No. 3,929,992. Washington, DC: U.S. Patent and Trademark Office.

Seidel, V. (2005). Initial and bulk extraction. In *Methods in Biotechnology*, Vol. 20, *Natural Products Isolation 2nd edition*, ed. Sarker S.D., Latif Z. and Gray A.I., pp. 27-46. Totowa, NJ: Humana Press Inc.

Shang, S., Fu, J., Dong, G., Hong, W., Du, L. and Yu, X. (2003). Establishment and analysis of specific DNA patterns in 16S–23S rRNA gene spacer regions for differentiating different bacteria. *Chinese Medical Journal (English)*, 116: 129–133.

Shen, F.T. and Young, C.C. (2005). Rapid detection and identification of the metabolically diverse genus *Gordonia* by 16S rRNA-gene-targeted genus-specific primers. *FEMS Microbiology Letters,* 250: 221–227.

Shen, B., Du, L., Sanchez, C., Edwards, D.J., Chen, M. and Murrell, J.M. (2001). The biosynthetic gene cluster for anticancer drug bleomycin from *Streptomyces* verticillus ATCC15003 as a model for hybrid peptide-polyketide natural product biosynthesis. *Journal of Industrial Microbiology and Biotechnology,* 27(6): 378-385.

Shirling, E.T. and Gottlieb, D. (1966). Methods for characterization of *Streptomyces* species. *International Journal of Systematic Bacteriology,* 16(3): 313-340.

Shivaji, S., Rao, N.S., Saisree, L., Sheth, V., Reddy, G.S. and Bhargava, P.M. (1989). Isolation and identification of *Pseudomonas* spp. from Schirmacher Oasis, Antarctica. *Applied and Environmental Microbiology*, 55(3): 767-770.

Shivaji, S., Ray, M.K., Rao, N.S., Saisree, L., Jagannadham, M.V., Kumar, G.S., Reddy, G.S.N. and Bhargava, P.M. (1992). *Sphingobacterium antarcticus* sp. nov., a psychrotrophic bacterium from the soils of Schirmacher Oasis, Antarctica. *International Journal of Systematic Bacteriology*, 42(1): 102-106.

Shivaji, S., Chattopadhyay, M.K. and Ray, M.K. (1994). Bacteria and yeasts of Schirmacher Oasis, Antarctica: Taxonomy, biochemistry and molecular biology. *Proceedings of the NIPR Symposium on Polar Biology*, 7: 173-184.

Sieber, S.A. and Marahiel, M.A. (2005). Molecular mechanisms underlying nonribosomal peptide synthesis: approaches to new antibiotics. *Chemical Reviews*, 105: 715-738.

Siebert, J., Hirsch, P., Hoffmann, B., Gliesche, C.G., Peissl, K. and Jendrach, M. (1996). Cryptoendolithic microorganisms from Antarctic sandstone of Linnaeus Terrace (Asgard Range): diversity, properties and interactions. *Biodiversity and Conservation*, 5(11): 1337-1363.

Simões, J.C., Arigony Neto, J. and Bremer, U.F. (2004). O uso de mapas antárticos em publicações. *Pesq Antart Brasil*, 4: 191–197.

Smith, J.J., Tow, L.A., Stafford, W., Cary, C. and Cowan, D.A. (2006). Bacterial diversity in three different Antarctic cold desert mineral soils. *Microbial Ecology*, 51: 413-421.

Sogin, M.L., Morrison, H.G., Huber, J.A., Welch, D.M., Huse, S.M., Neal P.R., Arrieta, J.M. and Herndl, G.J. (2006). Microbial diversity in the deep sea and the underexplored "rare biosphere". *Proceedings of the National Academy of Sciences*, 103(32): 12115-12120.

Srivatsan, A., Han, Y., Peng, J., Tehranchi, A.K., Gibbs, R., Wang, J.D. and Chen, R. (2008). High-Precision, Whole-Genome Sequencing of Laboratory Strains Facilitates Genetic Studies. *PLoS Genet*, 4(8): e1000139.

Stackebrandt, E., Frederiksen, W., Garrity, G.M., Grimont, P., Kampfer, P., Maiden, M., Nesme, X., Rossello-Mora, R., Swings. J., Truper, H.G., Vauterin, L., Ward, A.C., Whitman, W.B. (2002). Report of the ad hoc committee for the re-evaluation of the species definition in bacteriology. *International Journal of Systematic and Evolutionary Microbiology*, 152: 1043-1047.

Stackebrandt, E., Koch, C., Gvozdiak, O. and Schumann, P. (1995). Taxonomic dissection of the genus *Micrococcus*: *Kocuria* gen. nov., *Nesterenkonia* gen. nov.,

Kytococcus gen. nov., *Dermacoccus* gen. nov., and *Micrococcus* Cohn 1872 gen. emend. *International Journal of Systematic Bacteriology,* 45: 682–692.

Stackebrandt, E., Rainey, F.A. and Ward-Rainey, N.L. (1997). Proposal for a new hierarchic classification system, Actinobacteria classis nov. *International Journal of Systematic Bacteriology,* 47(2): 479-491.

Stingl, U., Cho, J.C., Foo, W., Vergin, K.L., Lanoil, B. and Giovannoni, S.J. (2008). Dilution-to-extinction culturing of psychrotolerant planktonic bacteria from permanently ice-covered lakes in the McMurdo Dry Valleys, Antarctica. *Microbial Ecology,* 55: 395–405.

Stotzky, G. (1985). Mechanisms of adhesion to clays, with reference to soil systems. In *Bacterial Adhesion,* pp. 195-253. US: Springer.

Sun, W., Peng, C., Zhao, Y. and Li, Z. (2012). Functional gene-guided discovery of type II polyketides from culturable actinomycetes associated with soft coral Scleronephthya sp. *PloS One,* 7(8): e42847.

Sunaryanto, R. and Marwoto, B. (2010). Marine actinomycetes screening of Banten West Coast and their antibiotics purification. *Biodiversitas* 11: 176-181.

Takahashi, Y. and Omura, S. (2003). Isolation of new actinomycete strains for the screening of new bioactive compounds. *Journal of General and Applied Microbiology,* 49: 141–154.

Tamura, K., Stecher, G., Peterson, D., Filipski, A. and Kumar, S. (2013). MEGA6: Molecular Evolutionary Genetics Analysis Version 6.0. *Molecular Biology and Evolution,* 30: 2725-2729.

Teixeira, L.C., Peixoto, R.S., Cury, J.C., Sul, W.J., Pellizari, V.H., Tiedje, J. and Rosado, A.S. (2010). Bacterial diversity in rhizosphere soil from Antarctic vascular plants of Admiralty Bay, maritime Antarctica. *ISME Journal,* 4(8): 989-1001.

Tejero-Sariñena, S., Barlow, J., Costabile, A., Gibson, G.R. and Rowland, I. (2012). *In vitro* evaluation of the antimicrobial activity of a range of probiotics against pathogens: Evidence for the effects of organic acids. *Anaerobe,* 18(5): 530-538.

Teo, J.K.C. and Wong, C.M.V.L. (2014). Analyses of soil bacterial diversity of the Schirmacher Oasis, Antarctica. *Polar Biology,* 37(5): 631-640.

Thalib, L., Kitching, R.L. and Bhatti, M.I. (1999). Principal component analysis for grouped data—a case study. *Environmetrics,* 10: 565–574.

Torsvik, V., Goksøyr, J. and Daae, F.L. (1990). High diversity in DNA of soil bacteria. Appl. *Environmental Microbiology,* 56: 782-787.

Torsvik, V.L., Sørheim, R. and Goksoyr, J. (1996). Total bacterial diversity in soil and sediment communities – a review. *Journal of Industrial Microbiology,* 17: 170–178.

Trenozhnikova, L.P., Khasenova, A.K., Balgimbaeva, A.S., Fedorova, G.B., Katrukha, G.S., Tokareva, N.L., Kwa, B.H. and Azizan, A. (2012). Characterization of the antibiotic compound no. 70 produced by *Streptomyces* sp. IMV-70. *Scientific World Journal,* 2012: 594231.

Trevors, J.T. (1998). Molecular evolution in bacteria: cell division. *Annual Review of Microbiology,* 29: 237– 245.

Udwary, D.W., Zeigler, L., Asolkar, R.N., Singan, V., Lapidus, A., Fenical, W., Jensen, P.R. and Moore, B.S. (2007). Genome sequencing reveals complex secondary metabolome in the marine actinomycete Salinispora tropica. *Proceedings of the National Academy of Sciences,* 104(25): 10376-10381.

Ugolini, F.C. and Bockheim, J.G. (2008). Antarctic soils and soil formation in a changing environment: a review. *Geoderma,* 144: 1–8.

Umezawa, H., Maeda, K., Takeuchi, T. and Okami, Y. (1966). New antibiotics, bleomycin A and B. *The Journal of Antibiotics*, 19(5): 200.

Vasavada, S.H., Thumar, J.T. and Singh, S.P. (2006). Secretion of a potent antibiotic by salt-tolerant and alkaliphilic actinomycete *Streptomyces sannanensis* strain RJT-1. *Current Science*, 91(10): 1393-1397.

Ventura, M., Canchaya, C., Tauch, A., Chandra, G., Fitzgerald, G.F., Chater, K.F. and van Sinderen, D. (2007). Genomics of *Actinobacteria*: Tracing the evolutionary history of an ancient phylum. *Microbiology and Molecular Biology Reviews,* 71: 495-548.

Vincent, W.F. (2000). Evolutionary origins of Antarctic microbiota: invasion, selection and endemism. *Antarctic Science,* 12(3): 374-385.

Vizcaino, M.I., Guo, X. and Crawford, J.M. (2014). Merging chemical ecology with bacterial genome mining for secondary metabolite discovery. *Journal of Industrial Microbiology and Biotechnology,* 41(2): 285-299.

Volff, J.N. and Altenbuchner, J. (2000). A new beginning with new ends: linearisation of circular chromosomes during bacterial evolution. *FEMS Microbiology Letters*, 186(2): 143-150.

Wagner, M., Gierth, A., Abdel-Mageed, W., Jaspers, M., Goodfellow, M., Bull, A.T., Horikoshi, K. and Fiedler, H.P. (2009, August). Dermacozines: drugs from the abyss. In *15th International Symposium on the Biology of Actinomycetes, Shanghai, China.*

Walsh, C.T. (2004). Polyketide and nonribosomal peptide antibiotics: modularity and versatility. *Science,* 303: 1805-1810.

Wawrik, B., Kutliev, D., Abdivasievna, U.A., Kukor, J.J., Zylstra, G.J. and Kerkhof, L. (2007). Biogeography of actinomycete communities and type II polyketide synthase genes in coils collected in New Jersey and Central Asia. *Applied and Environmental Microbiology,* 73(9): 2982-2989.

Wawrik, B., Kerkhof, L., Zylstra, G.J. and Kukor, J.J. (2005). Identification of unique type II polyketide synthase genes in soil. *Applied and Environmental Microbiology,* 71: 2232–2238.

Wayne, L.G., Brenner, D.J., Colwell, R.R., Grimont, P.A.D., Kandler, O., Krichevsky, M.I., Moore, L.H., Moore, W.E.C., Murray, R.G.E., Stackebrandt, E., Starr, M.P. and Trüper, H.G. (1987). Report of the ad hoc committee on reconciliation of approaches to bacterial systematics. *International Journal of Systematic and Evolutionary Microbiology,* 37: 463–464.

Weatherhead, P.J. and Montgomerie, R.D. (1991). Good news and bad news about DNA fingerprinting. *Trends in Ecology and Evolution,* 6(6): 173-174.

Weisburg, W.G., Barms, S.M., Pelletier, D.A. and Lane, D.J. (1991). 16S ribosomal DNA amplification for phylogenetic study. *Journal of Bacteriology,* 173: 697-703.

Weiss, R.B. (1992, December). The anthracyclines: will we ever find a better doxorubicin? In *Seminars in Oncology* (Vol.19, No. 6, pp. 670-686).

Welsh, J. and McClelland, M. (1990). Fingerprinting genomes using PCR with arbitrary primers. *Nucleic acids research,* 18(24): 7213-7218.

Wessam, M.F., Abiramy, K., Abneuf, M.A. and Alias, S.A. (2011, June). Antimicrobial activity of mesophilic and psychrotrophic microfungi isolates from: King George Island, Greenwich Island, Maritime Antarctica. In *5th Malaysian International Seminar on Antarctica, Kuala Lumpur, Malaysia*.

Williams, S.T. and Davies, F.L. (1965). Use of antibiotics for selective isolation and enumeration of actinomycetes in soil. *Journal of General Microbiology,* 38: 251–261.

Williams, S.T. and Vickers, J.C. (1988). Detection of actinomycetes in the natural environment: problems and perspectives. In *Biology of Actinomycetes,* ed. Okami, Y., Beppu, T. and Ogawara, K., pp 265–270, Tokyo: Japan Scientific Societies Press.

Williams, J.G., Kubelik, A.R., Livak, K.J., Rafalski, J.A. and Tingey, S.V. (1990). DNA polymorphisms amplified by arbitrary primers are useful as genetic markers. *Nucleic Acids Research,* 18(22): 6531-6535.

Wilson, K. (1987). Preparation of genomic DNA from bacteria. *Current Protocols in Molecular Biology*, 2-4.

Woese, C.R. (1987). Bacterial evolution. *Microbiological Reviews*, 51(2): 221-271.

Wong, C.M.V.L., Tam, H.K., Alias, S.A., Gonz áez, M., Gonz áez-Rocha, G. and Dom ínguez-Y évenes, M. (2011). *Pseudomonas* and *Pedobacter* isolates from King George Island inhibited the growth of foodborne pathogens. *Polish Polar Research*, 32: 3-14.

Wright A. and Tipper D.J. (1979). The outer membrane of Gram-negative bacteria. In *The Bacteria Vol 7*, ed. Sokatch, J.R. and Ornston, L.N., pp. 427. San Diego: Academic Press.

Wynn-Williams, D.D. (1996). Antarctic microbial diversity: the basis of polar ecosystem processes. *Biodiversity and Conservation*, 5: 1271–1293.

Yamada, H., Shiomi, K., Xu, Q., Nagai, T., Shirata, M., Oya, I., Takahashi, Y. and Omura, S. (1995). New glycosidases inhibitors, panosialins d and wD produced by *Streptomyces* sp. OH-5186. *Journal of Antibiotics*, 48 (3): 205-210.

Yergeau, E. and Kowalchuk, G.A. (2008). Responses of Antarctic soil microbial communities and associated functions to temperature and freeze–thaw cycle frequency. *Environmental Microbiology*, 10: 2223–2235.

Yu, D., Xu, F., Zeng, J. and Zhan, J. (2012). Type III polyketide synthases in natural product biosynthesis. *IUBMB Life*, 64(4): 285-295.

Zakharova, O.S., Zenova, G.M. and Zvyagintsev, D.G. (2003). Selective isolation of actinomycetes of the genus *Actinomadura* from soil. *Mikrobiologiia*, 72(1): 110-113.

Zhang, D.F., Chen, W., He, J., Zhang, X.M., Xiong, Z.J., Sahu, M.K., Sivakumar, K. and Li, W.J. (2013a). *Saccharomonospora oceani* sp. nov. isolated from marine sediments in Little Andaman, India. *Antonie van Leeuwenhoek*, 103(6): 1377-1384.

Zhang, Y.G., Wang, H.F., Liu, Q., Hozzein, W.N., Wadaan, M.A.M., Cheng, J., Chen, Y.J., Zhang, Y.M. and Li, W.J. (2013b) *Streptomyces fukangensis* sp. nov., a novel alkaliphilic actinomycete isolated from a saline-alkaline soil. *Antonie van Leeuwenhoek*, 104: 1227-1233.

Zhao, G.Z., Li, J., Qin, S., Zhang, Y.Q., Zhu, W.Y., Jiang, C.L., Xu, L.H. and Li, W.J. (2009). *Micrococcus yunnanensis* sp. nov., a novel actinobacterium isolated from surface-sterilized *Polyspora axillaris* roots. *International Journal of Systematic and Evolutionary Microbiology*, 59: 2383-2387.

Zhao, J., Yang, N. and Zeng, R. (2008). Phylogenetic analysis of type I polyketide synthase and nonribosomal peptide synthetase genes in Antarctic sediment. *Extremophiles,* 12(1): 97-105.

Zhi, X.Y., Li, W.J. and Stackebrandt, E. (2009). An update of the structure and 16S rRNA gene sequence-based definition of the higher ranks of the class Actinobacteria, with the proposal of two new suborders and four new families and emended descriptions of the existing higher taxa. *International Journal of Systematic and Evolutionary Microbiology*, 59: 589–608.

Zhu, T., Li, J., Li, L., Ma, H., Che, Q. and Gu, Q. (2009, August). Isolation and bioactive metabolites research of Antarctica actinomycetes. In *15th International symposium on the biology of actinomycetes, Shanghai, China* (pp. 20–25).