From Actinomycin onwards: Actinomycete success stories

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The discovery, development and exploitation of antibiotics was one of the most significant advances in medicine in the 20th century. In a golden era lasting from the 1940s to the late 1960s, antibiotic research provided mankind with a wide range of structurally diverse and effective agents for the treatment of microbial infections[1,2]. Since then, the members of the order *Actinomycetales,* most notably the genus *Streptomyces* have proved to be a particularly rich source of antibiotics (Table 1) with extensive therapeutic applications, possibly because of the extra-large DNA complement of these bacteria[3,4].

When George W. Merck established a research laboratory for his company Merck & Co. Inc. to cooperate with the leading academics of the era, Selman Waksman was at the Department Soil Microbiology, Rutgers University. He turned his research interests towards the discovery of new broad-spectrum antibacterial agents from actinomycetes using soil enrichment techniques with his graduate student H. Boyd Woodruff and their efforts led to the discovery of **Actinomycin**[5,6]. Due to its toxicity, actinomycin was dropped from consideration as an antibiotic; however, years later it was found to be effective against Wilm's disease of children and became the Merck product Cosmogen®. The second antibiotic from Waksman's laboratory was **Streptothricin,** which proved to be unacceptable for commercialisation due to its severe kidney toxicity[5,7]. Finally, the third product called **Streptomycin** isolated by Waksman's graduate student Albert Schatz[5,8] from *Streptomyces griseus* became the first natural product produced on a major scale at Merck by fermentation[5].

In 1945, *Streptomyces aureofaciens* demonstrated strong antibacterial activity and after successful yield increase studies in 1947 at Lederle, **Chlortetracyline** proved to be a "wonder drug" for treatment of numerous diseases including typhoid fever, typhus, invasive infections by *Streptococcus pneumonia* and beta-haemolytic streptococci[9].

Later in the 1950s, Merck & Co. Inc. commenced in-house screening which resulted in the discovery of **Oxamycin** from *Streptomyces garyphalus*[5,10] and **Novobiocin** (Cathomycin), a narrow-spectrum antibiotic from *Streptomyces sphaeroides*, with activity against penicillin-resistant microorganisms[5,11]. Meanwhile Pfizer launched oxytetracycline in 1950 under the trade name of Terramycin[9].

From 1954 onwards, Merck & Co. Inc. started utilising established facilities with qualified staff in other countries to pursue new antibiotic discovery ventures (for example, Prof. Satoshi Omura at the Kitasatoa Institute in Japan)[5]. CEPA in Spain became an important institute for soil-derived actinomycete screening and led to the discovery of **Fosfomycin** from *Streptomycin fradiae*[5,12] and **Cephamycin** from *Nocardia lactamdurans*[5,13]**. Cefoxitin**® a semi-synthetic and broad-spectrum cephamycin resistant to penicillinase and cephalosporinase enzymes became for several years one of the leading antibiotics for hospital use in the world[5]. Another potent antibiotic **Erythromycin** was discovered at Lily in 1952 from also a streptomycete species, *Streptomyces erythreus*[14].

In the late 1970s and early 1980s **Avermectin** produced by *Streptomyces avermitilis* was one of the most potent antiparasitic agent[5,15] and subsequent chemical modification products such as Ivomec (round worm elimination in farm animals) and Mectizan (river blindness treatment) have successfully become established products[5].

Global search for new and potent compounds from streptomycetes resulted in the establishment of the "*International Streptomyces Project* (ISP)", with collaboration of over 40 laboratories from 18 different countries resulting in the description of over 400 streptomycete species[16].

Meanwhile in Europe search and discovery efforts were also advancing with the discovery of important antibiotics such as **Rifamycins** in Lepetit S.p.A. (1957) in Milan, Italy from *Streptomyces mediterranei* strain[17].

By 1961 high rates of rediscovery of known compounds started presenting a major hurdle[17] which is still a major obstacle in biodiscovery programs. Targeting isolation of bioactive rare actinomycetes proved fruitful with discovery of new antibiotics such as **Gentamicin** from *Micromonospora* species at Schering in the USA[17]. In East Germany, the then (Z)IMET/HKI has also played a significant role in the description of bioactive and rare actinomycetes such as *Actinomadura, Amycolatopsis* and *Nocardiotopsis*[18].

Table 1. Actinomycete antibiotics since discovery of Streptomycin.

Discovery/ production years	Name of antibiotics
1940–1950	Streptomycin Streptothricin Actinomycin
1950–1960	Neomycin Chlorotetracycline Candicidin Chloramphenicol Spiramycin Tetracycline Erythromycin Oxytetracyline Nystatin Kanamycin
1960–1970	Mitomycin Novobiocin Amphotericin Vancomycin Virginiamycin Gentamicin Tylosin Pristinamycin Polyoxin Rifamycin Bleomycin
1970–1980	Monensin Adriamycin Avoparcin Kasugamycin Fosfomycin Bialaphos Lincomycin Teicoplanin
1980–1990	Thienamycin Rapamycin Avermectin Nikkomycin
1990–2000	Spinosyn Tacrolimus

Adapted from reference 2.

This issue coincides with my 30th anniversary in the field of actinomycetology. Gentamicin was the start of my postgraduate experience with these fascinating microorganisms in 1982 at Eczacibasi Ilac A/S in Istanbul, Turkey, where large-scale production of Gentamicin was in progress. Studies on soil actinomycete screening for discovery of new antibiotics were also under way in the company and resulted in the discovery of a novel compound Egemycin, named after the Aegean Sea. My subsequent research was at the University of Milan (1983–1986), where linked research activities with a number of leading Italian pharmaceutical companies were being undertaken with Prof. Elio Baldacci and Prof. Romano Locci[19]. Years later, an electron micrograph of a bioactive streptomycete species produced at the time, became the cover page of *Microbiology Australia* (Figure 1)[20,21]. After I focused on the isolation of rare actinomycetes at Prof. Stan Williams' laboratory at the University of Liverpool, UK[22] (1986-1990), I continued to work with bioactive actinomycetes since my arrival in Australia in 1990 and the most recent outcome is a large actinomycete library at the University of the Sunshine Coast[23], which is also part of the *Australian Microbial Resources Information Network* http://amrin.org/.

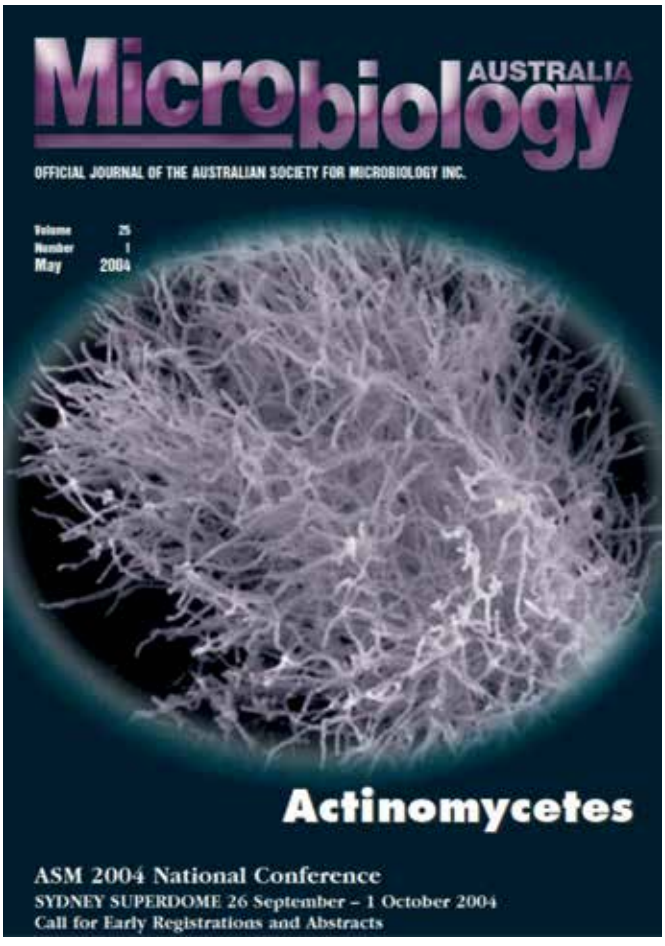

Figure 1. Cover page of *Microbiology Australia* (2004), 25, 1. Aerial mycelium of a *Streptomyces* species (Kurtböke and Locci, 1984)[20]

Metabolites to be discovered from the members of the order *Actinomycetales* have not been exhausted and predictive modelling by Watve *et al*. (2001) suggests that over 150,000 bioactive metabolites are still waiting to be discovered from the members of the genus *Streptomyces* alone[24]. Australian actinofloral diversity will undoubtedly contribute towards new discoveries; examples include Kakadumycins produced from *Streptomyces* sp. (NRRL 30566) an endophyte of *Grevillea pteridifolia* isolated from Kakadu National Park in the Northern Territory in 2003[25]. Novel approaches and use of selective isolation techniques[26] to culture the previously uncultured actinomycetes will also facilitate their detection and isolation such as the discovery of novel bioactive streptomycete species from near shore marine environments[27].

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Biography

Dr Kurtböke is currently the Vice-President of the World Federation of Culture Collections (WFCC). She has been working in the field of biodiscovery and has been an active member of the international actinomycete research community since 1982. She is engaged with studies related to actinomycete diversity and taxonomy, particularly uses of actinophages to define suborder boundaries of the order Actinomycetales. She currently conducts research and teaches in the field of applied microbiology and biotechnology and is senior lecturer at the University of the Sunshine Coast, Queensland.

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