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*review*

# Biosynthesis of Oxytetracycline by *Streptomyces rimosus*: Past, Present and Future Directions in the Development of Tetracycline Antibiotics

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**Summary**

Natural tetracycline (TC) antibiotics were the first major class of therapeutics to earn the distinction of 'broad-spectrum antibiotics' and they have been used since the 1940s against a wide range of both Gram-positive and Gram-negative pathogens, mycoplasmas, intracellular chlamydiae, rickettsiae and protozoan parasites. The second generation of semisynthetic tetracyclines, such as minocycline and doxycycline, with improved antimicrobial potency, were introduced during the 1960s. Despite emerging resistance to TCs erupting during the 1980s, it was not until 2006, more than four decades later, that a third-generation TC, named tigecycline, was launched. In addition, two TC analogues, omadacycline and eravacycline, developed *via* (semi)synthetic and fully synthetic routes, respectively, are at present under clinical evaluation. Interestingly, despite very productive early work on the isolation of a *Streptomyces aureofaciens* mutant strain that produced 6-demethyl-7-chlortetracycline, the key intermediate in the production of second- and third-generation TCs, biosynthetic approaches in TC development have not been productive for more than 50 years. Relatively slow and tedious molecular biology approaches for the genetic manipulation of TC-producing actinobacteria, as well as an insufficient understanding of the enzymatic mechanisms involved in TC biosynthesis have significantly contributed to the low success of such biosynthetic engineering efforts. However, new opportunities in TC drug development have arisen thanks to a significant progress in the development of affordable and versatile biosynthetic engineering and synthetic biology approaches, and, importantly, to a much deeper understanding of TC biosynthesis, mostly gained over the last two decades.

*Key words:* antibiotics, biosynthesis, polyketides, polyketide synthase, tetracyclines, oxytetracycline, chlortetracycline, *Streptomyces*, *Streptomyces rimosus*, *Streptomyces aureofaciens*

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