JOURNAL OF NATURAL PRODUCTS

pubs.acs.org/jnp

Review

Amycolatopsis mediterranei: A Sixty-Year Journey from Strain Isolation to Unlocking Its Potential of Rifamycin Analogue Production by Combinatorial Biosynthesis

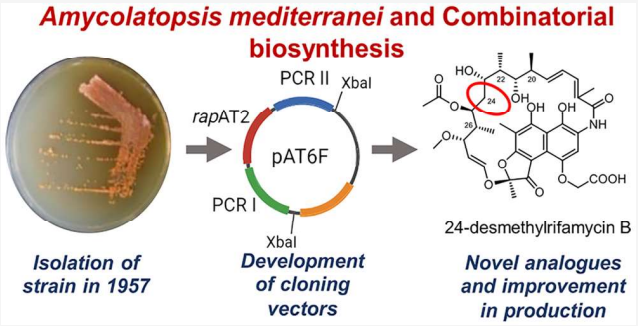
Utkarsh Sood, Moritz Müller, Tian Lan, Gauri Garg, Nirjara Singhvi, Princy Hira, Priya Singh, Aeshna Nigam, Mansi Verma, Pushp Lata, Hardeep Kaur, Abhilash Kumar, Charu Dogra Rawat, Sukanya Lal, Courtney Aldrich,* Andreas Bechthold,* and Rup Lal*

Cite This: https://doi.org/10.1021/acs.jnatprod.3c00686

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Ever since the isolation of *Amycolatopsis mediterranei* in 1957, this strain has been the focus of research worldwide. In the last 60 years or more, our understanding of the taxonomy, development of cloning vectors and conjugation system, physiology, genetics, genomics, and biosynthetic pathway of rifamycin B production in *A. mediterranei* has substantially increased. In particular, the development of cloning vectors, transformation system, characterization of the rifamycin biosynthetic gene cluster, and the regulation of rifamycin B production by the pioneering work of Heinz Floss have made the rifamycin polyketide biosynthetic gene cluster (PKS) an attractive target for extensive genetic manipulations to produce rifamycin B analogues which could be effective against multi-drug-resistant tuberculosis. Additionally, a better understanding of the regulation of rifamycin B production and the application of newer genomics tools, including CRISPR-assisted genome editing systems, might prove useful to overcome the limitations associated with low production of rifamycin analogues.



INTRODUCTION

Species belonging to the genus *Amycolatopsis* are of special importance, as they are known to produce commercially important antibiotics. For instance, *Amycolatopsis mediterranei* produces a broad-spectrum antibiotic (rifamycin) that has been used as the first line of treatment against *Mycobacterium tuberculosis*.[1] *Amycolatopsis* sp. MST-108494 produces amycolatopsins A−C, which show antibacterial activity and cytotoxicity against colon and lung cancer cell lines.[2] *A. teichomyceticus* produces teicoplanin, used to treat infections by multiresistant Gram-positive pathogens such as *Staphylococcus aureus*.[3] *A. alba* produces kigamicins A−E, which show antibacterial activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), and kigamicin D is an anticancer agent.[4,5] Among all these, *A. mediterranei* has been the focus of research the world over.

In fact, *A. mediterranei*, rifamycins, and tuberculosis (TB) have a long history of associations. There was no effective treatment available for TB patients prior to the isolation of rifamycins from *A. mediterranei*. Rifamycins represent an important group of antibiotics that can be chemically transferred into pharmacokinetically improved, more potent, and orally active drugs like rifampicin. Rifampicin played a key role within the therapeutic regimen for curing TB infections caused by *M. tuberculosis*. In the last 60 years or more, there has been ongoing research on rifamycin production, *A. mediterranei*, a strain improvement program, development of cloning vectors and transformation systems, characterization of rifamycin polyketide synthase (PKS) and post-PKS gene clusters, and subsequent manipulation of *rif* PKS.[1,6−11] However, there is no comprehensive review on the subject that unfolds the story of research on *A. mediterranei* and rifamycins. This review will therefore focus on the major contributions of scientists who laid the foundation of research on *A. mediterranei* resulting in the use of modern approaches to manipulate this organism to produce rifamycin analogues.

In the lineup to research in *A. mediterranei* and rifamycins, three milestones (Figure 1) deserve to be mentioned: First is the fundamental contribution in the development of one of the most

Received: August 3, 2023
Revised: November 24, 2023
Accepted: December 27, 2023