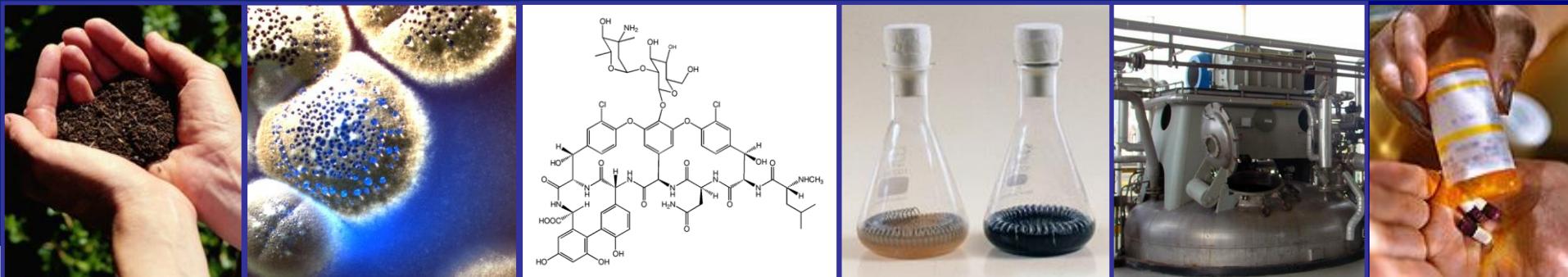


Discovery and development of the novel antibiotic Lugdunomycin



Gilles van Wezel

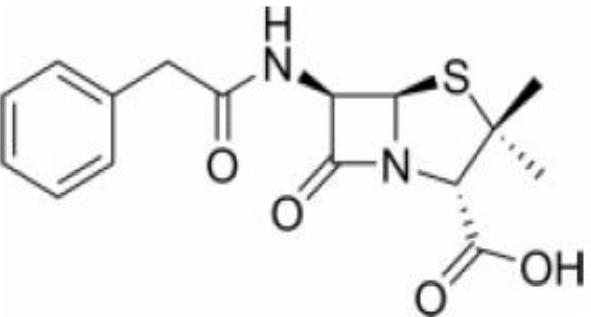
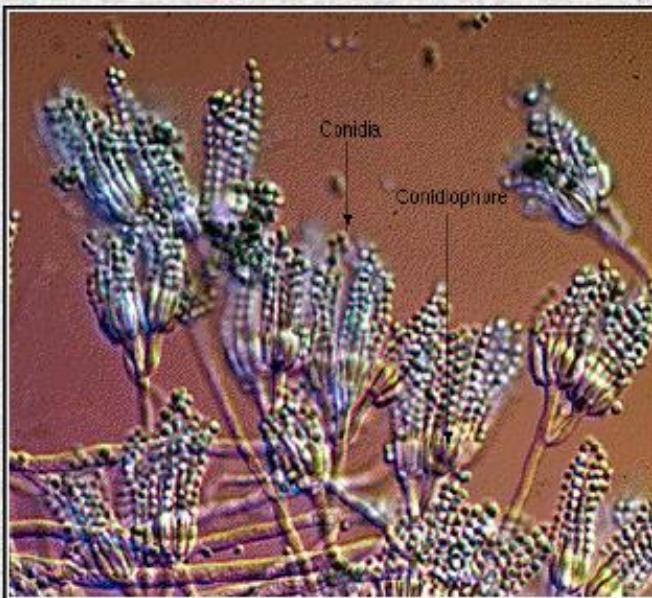
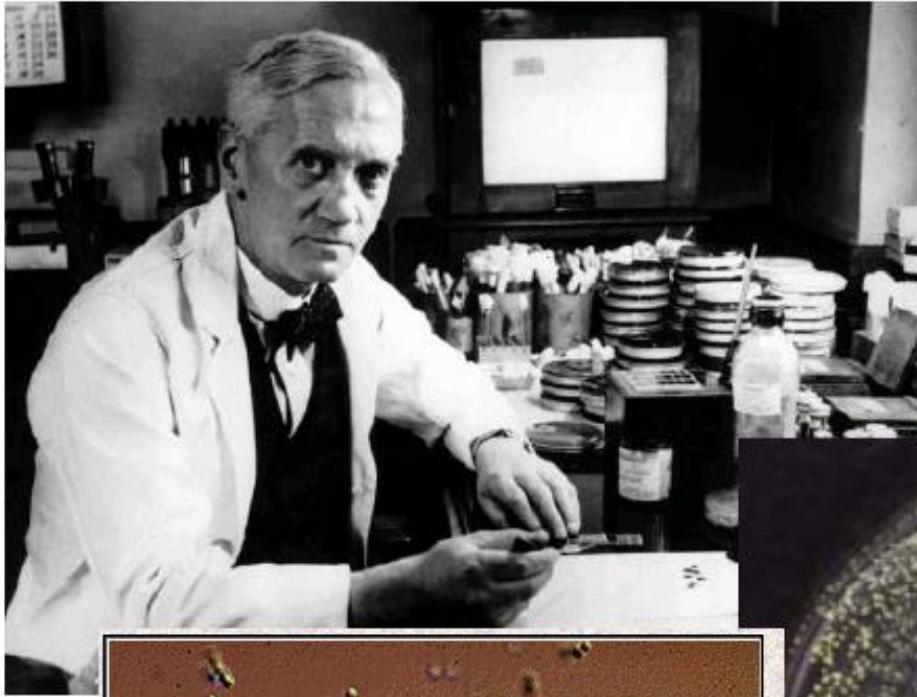


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NACTAR

A decorative graphic element consisting of five colored dots of decreasing size from left to right: red, orange, yellow, orange, and red. To the right of the dots is a capsule-shaped graphic divided horizontally, with the top half being yellow and the bottom half being red.

Discover the world at Leiden University



Penicillin G

Alexander Fleming

Streptomycin: Background, Isolation, Properties, and Utilization¹

Selman A. Waksman²

Institute of Microbiology, Rutgers University, New Brunswick, New Jersey

The Lord hath created medicines out of the earth; and he that is wise will not abhor them. Ecclesiastes XXXVIII, 4.

THE HIGHEST SCIENTIFIC AWARD AND HONOR presented to me today gives me the opportunity to summarize briefly the discovery and utilization of streptomycin for disease control, notably in the treatment of tuberculosis, the "Great White Plague" of man.

HISTORICAL BACKGROUND

Streptomycin belongs to a group of compounds, known as antibiotics, which are produced by microorganisms and which possess the property of inhibiting the growth of, and even of destroying, other microorganisms. Antibiotics vary greatly in their chemical nature, mode of action upon different organisms, and effect upon the animal body. The selective action of antibiotics upon bacteria and other microorganisms is known as the antibiotic spectrum. Some antibiotics are characterized by a very narrow spectrum, whereas others possess a wide range of activity. Some are active only against certain bacteria and not against others, whereas some are active against fungi, and some against viruses. There is not only considerable qualitative variation in the activity of different antibiotics, but also wide quantitative differences. Antibiotics are produced by bacteria, fungi, actinomycetes, and, to a limited extent, by other groups of microorganisms.

It has been known for more than six decades that certain fungi and bacteria are capable of producing chemical substances which have the propensity to inhibit the growth of, and even to destroy, pathogenic organisms. Only within the last twelve or thirteen years, however, have antibiotics begun to find extensive application.

¹Nobel Prize Address, delivered at the Cowdray Institute in Stockholm, Sweden, on December 12, 1952.

²I wish to take this opportunity to thank all my colleagues, associates, and graduate students who have participated in the investigations necessary in the development of our broad antibiotic program. Special thanks are due to the following colleagues and graduate students: Misses Elizabeth S. Horwitz, Elizabeth Bagle, Doris Jones, Dr. H. H. Johnson, H. C. Bellry and Dorothy G. Smith; Drs. M. Waksman, W. George, E. Goracci and E. A. Sweet; and Messrs. H. B. Woodruff, Albert Schatz, H. Leichberger, K. E. Green, J. J. Harris, W. P. Iverson, D. Reynolds, H. E. Robinson, and Otto Grunberg; to the chemists, pharmacologists, bacteriologists, and many others of Merck & Co.; to Drs. W. B. Peacock and H. C. Blodow of the Mayo Clinic; to Dr. C. S. Kooser of the Committee on Medical Research; and to numerous clinical investigators who have helped to make streptomycin the important chemotherapeutic agent it is today.

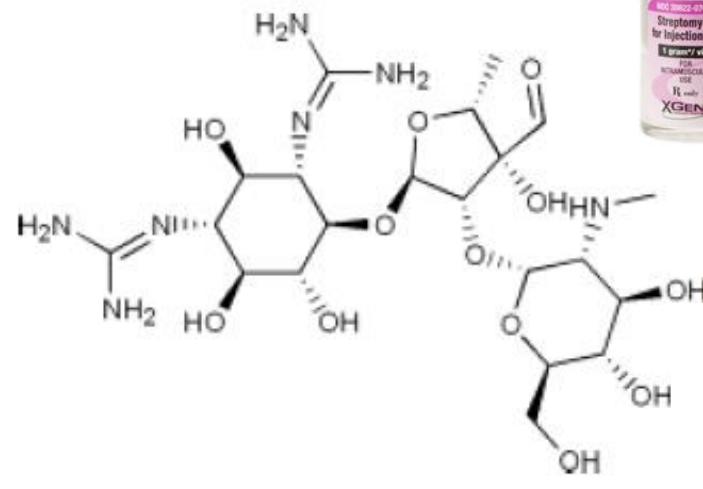


FIG. 1. SELMAN A. WAKSMAN, Nobel Prize laureate for Physiology and Medicine in 1952.

application as chemotherapeutic agents. Among these, penicillin and streptomycin have occupied a prominent place. Penicillin is largely active against gram-positive bacteria, gram-negative cocci, anaerobic bacteria, spirochetes and actinomycetes; streptomycin is active against a variety of gram-negative and acid-fast bacteria, as well as against gram-positive organisms which have become resistant to penicillin. Neither of these antibiotics is active upon rickettsias, viruses, and fungi. They differ too in their physical and chemical properties and in their toxicity to animals.

Since the discovery of streptomycin, the production and clinical application of this antibiotic have had a

Selman Waksman



streptomycin



MAY 21ST–27TH 2016

Do recoveries die, or are they killed?
Pinstriped greens take on Big Oil
Boss of the UN: worst job in the world
Win or lose, dark days for Cameron
How gangs suck El Salvador dry

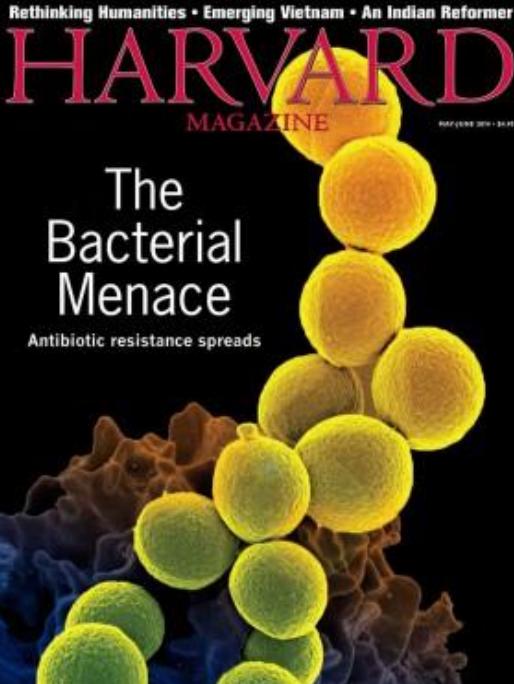
When the drugs don't work

The rise of antibiotic resistance



2017 Could Be A Terrible Tipping Point for Antibiotic Resistance

Food and Animals Food and Health Take Action January 12, 2017



Antibiotic Resistance Will Soon Hit the Tipping Point, Unless We Act

the guardian

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Antibiotics

Disease resistance to antibiotics at tipping point, expert warns

Prof Jeremy Farrar says evolution of diseases will 'creep up on us insidiously' and begin to affect patients in UK

If we fail to effectively respond to the global threat of AMR, an increasing number of bacterial infections will become untreatable.



NCOH Strategic Research Themes

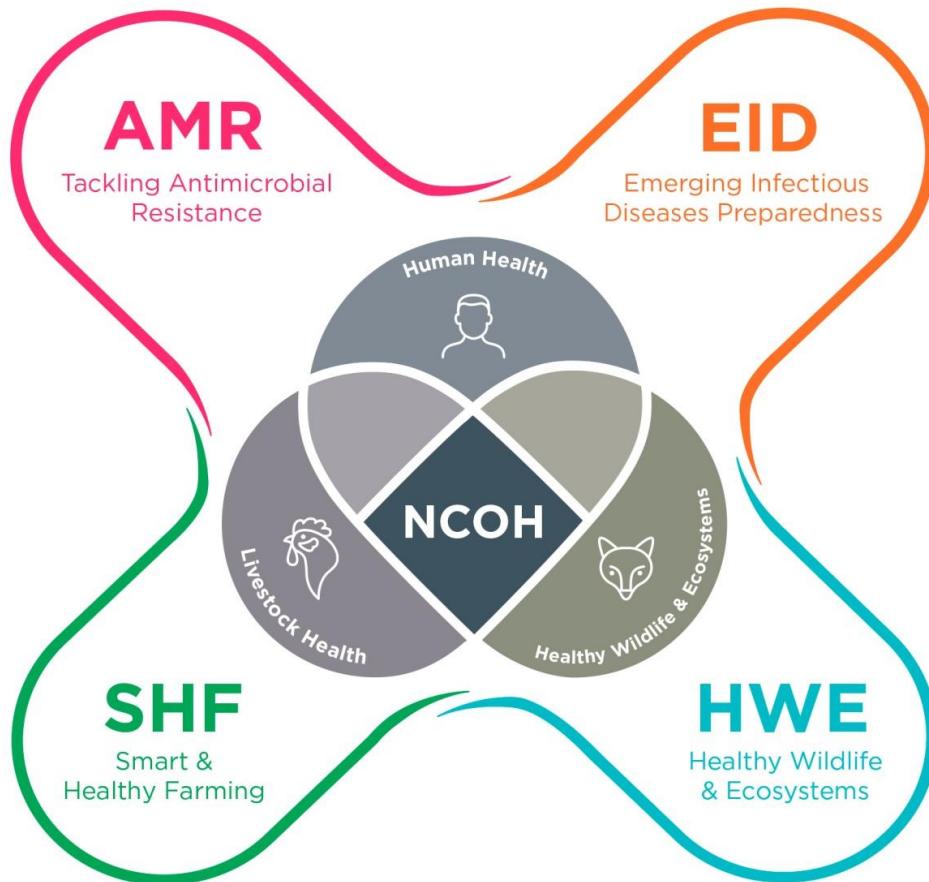
Universities

UL
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UMCU

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Associated partners

RIVM
TNO
MUMC



netherlands
centre for
one health

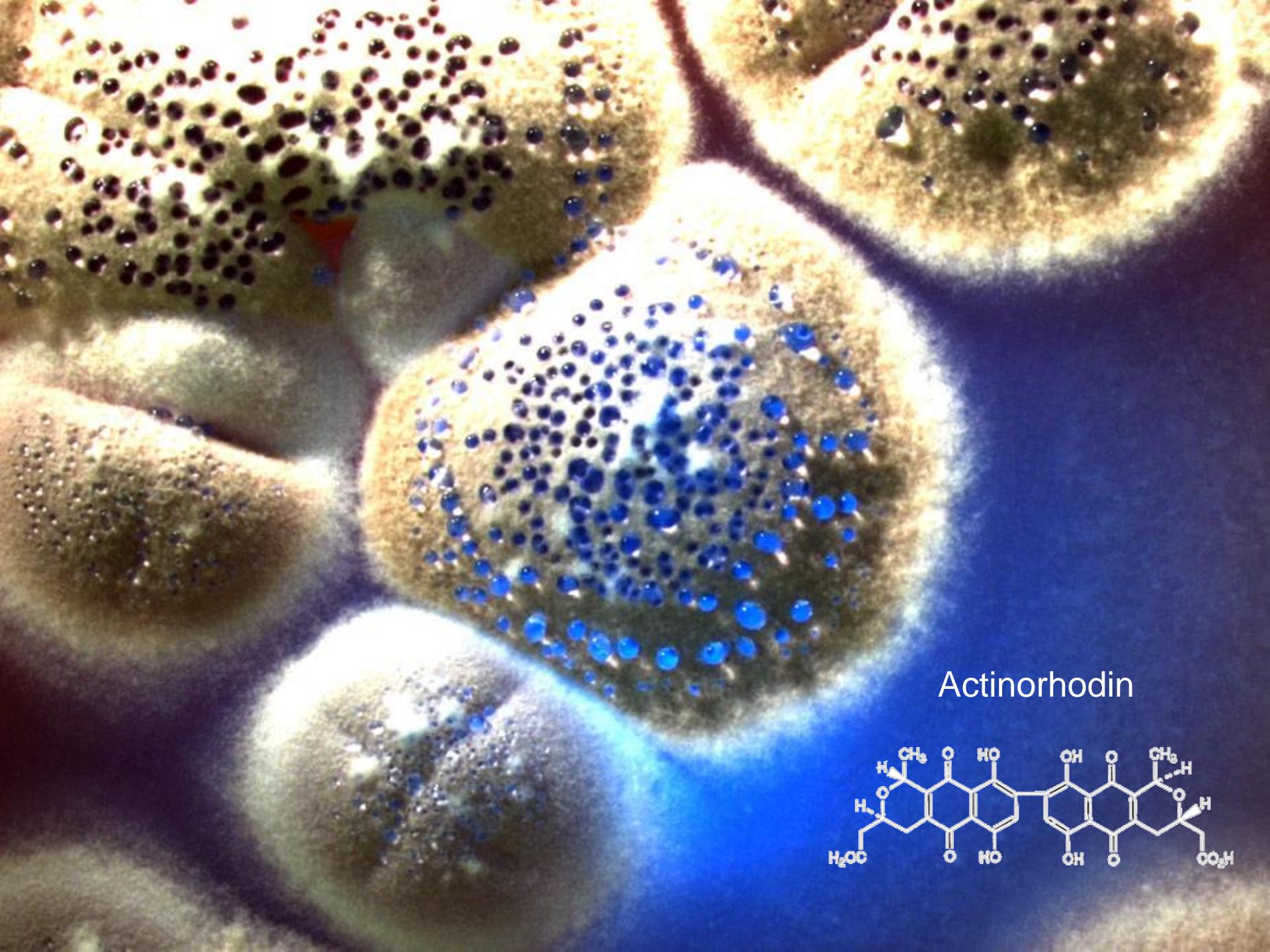


REVIEWS

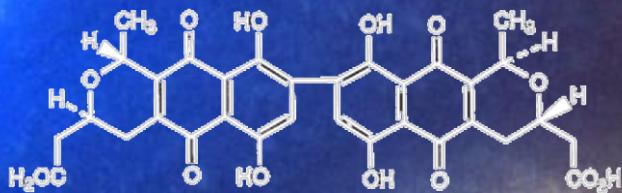
Drugs for bad bugs: confronting the challenges of antibacterial discovery

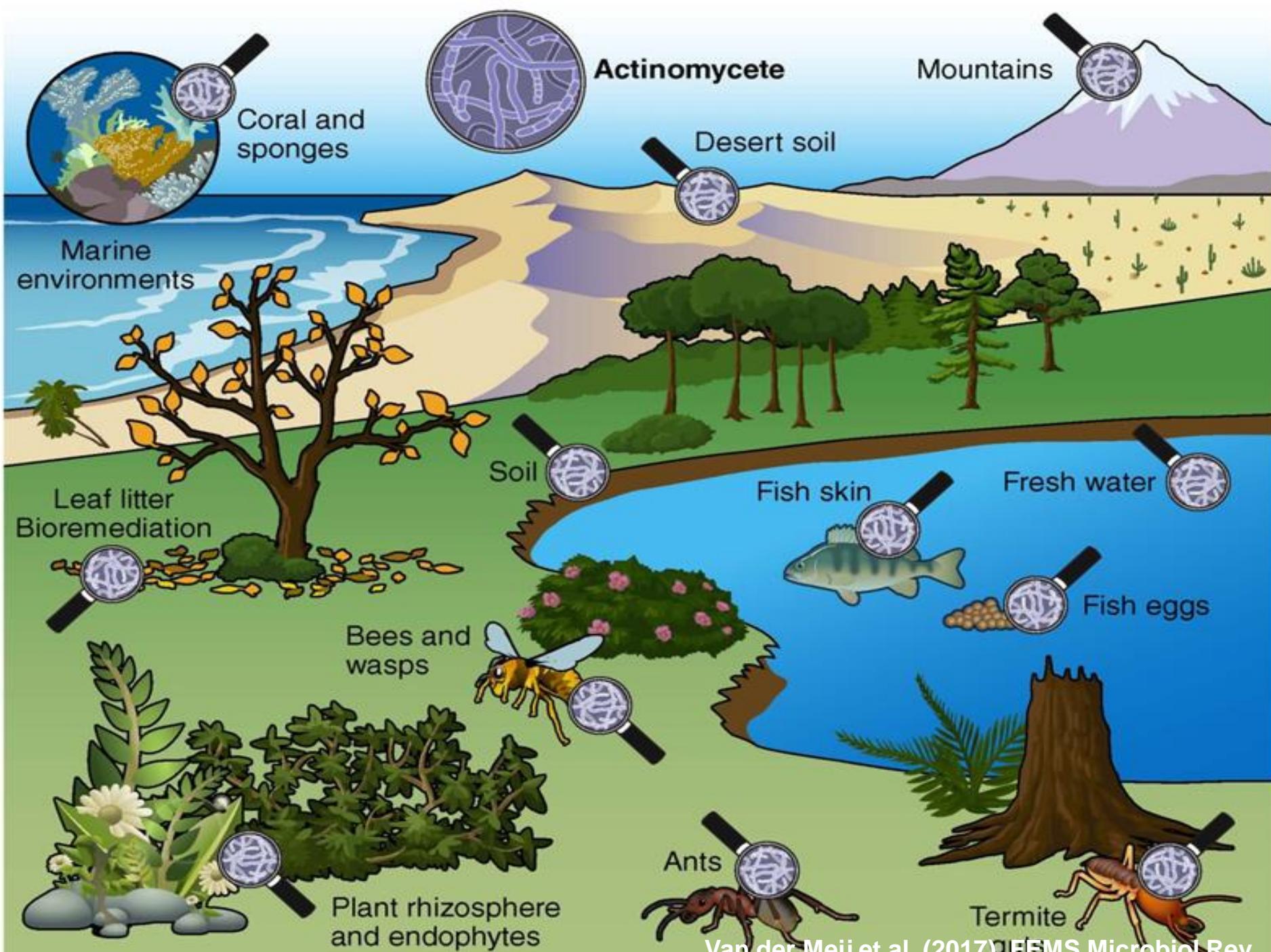
David J. Payne, Michael N. Gwynn, David J. Holmes and David L. Pompliano

Abstract | The sequencing of the first complete bacterial genome in 1995 heralded a new era of hope for antibacterial drug discoverers, who now had the tools to search entire genomes for new antibacterial targets. Several companies, including GlaxoSmithKline, moved back into the antibacterials area and embraced a genomics-derived, target-based approach to screen for new classes of drugs with novel modes of action. Here, we share our experience of evaluating more than 300 genes and 70 high-throughput screening campaigns over a period of 7 years, and look at what we learned and how that has influenced GlaxoSmithKline's antibacterials strategy going forward.

A microscopic image showing several dark, rod-shaped bacteria. Some cells contain bright blue, granular inclusions, while others are clear or contain smaller, darker inclusions. A small red triangular marker is visible on one of the bacteria.

Actinorhodin



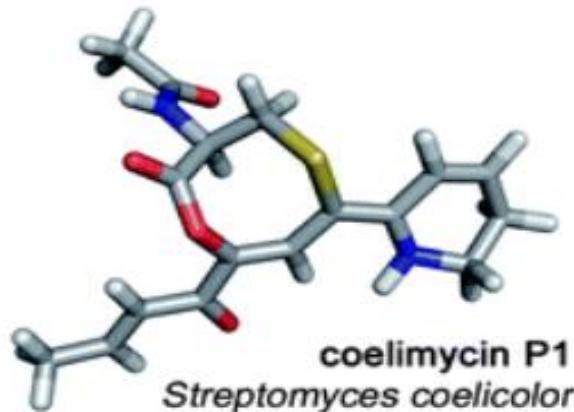


9 May 2002

International weekly journal of science

nature

£7.00



Genome of an antibiotics factory

Semiconductor lasers

Turned on to terahertz

Plant development

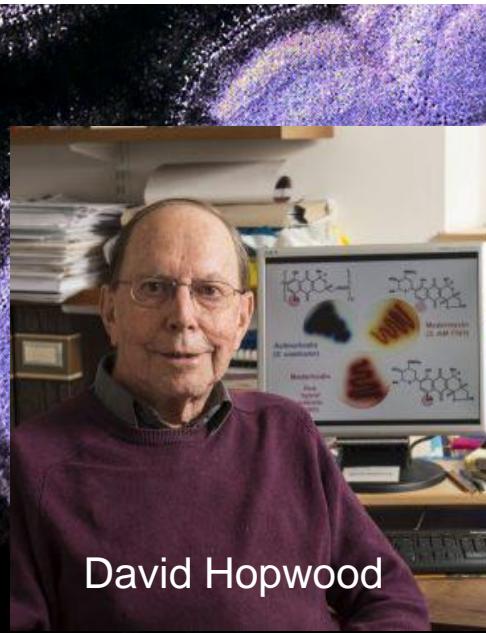
Tubulin makes a left

Bose-Einstein condensates

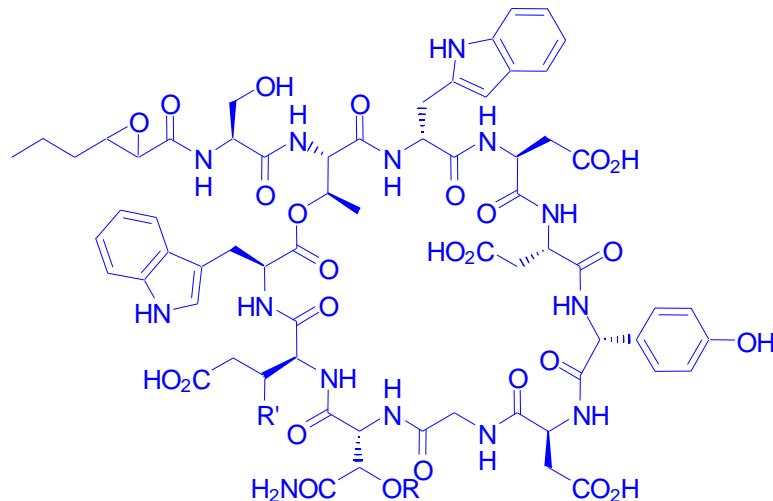
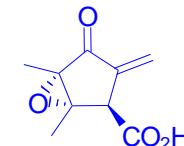
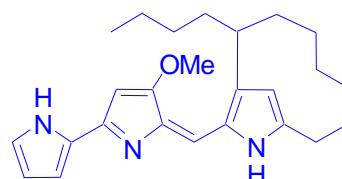
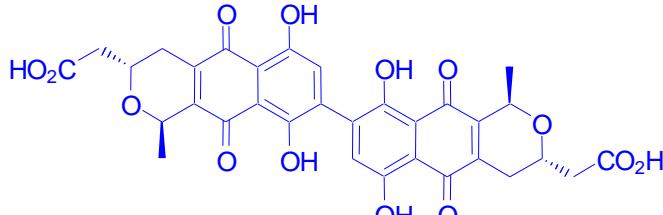
Solitons make their move

naturejobs

special report: international postdocs

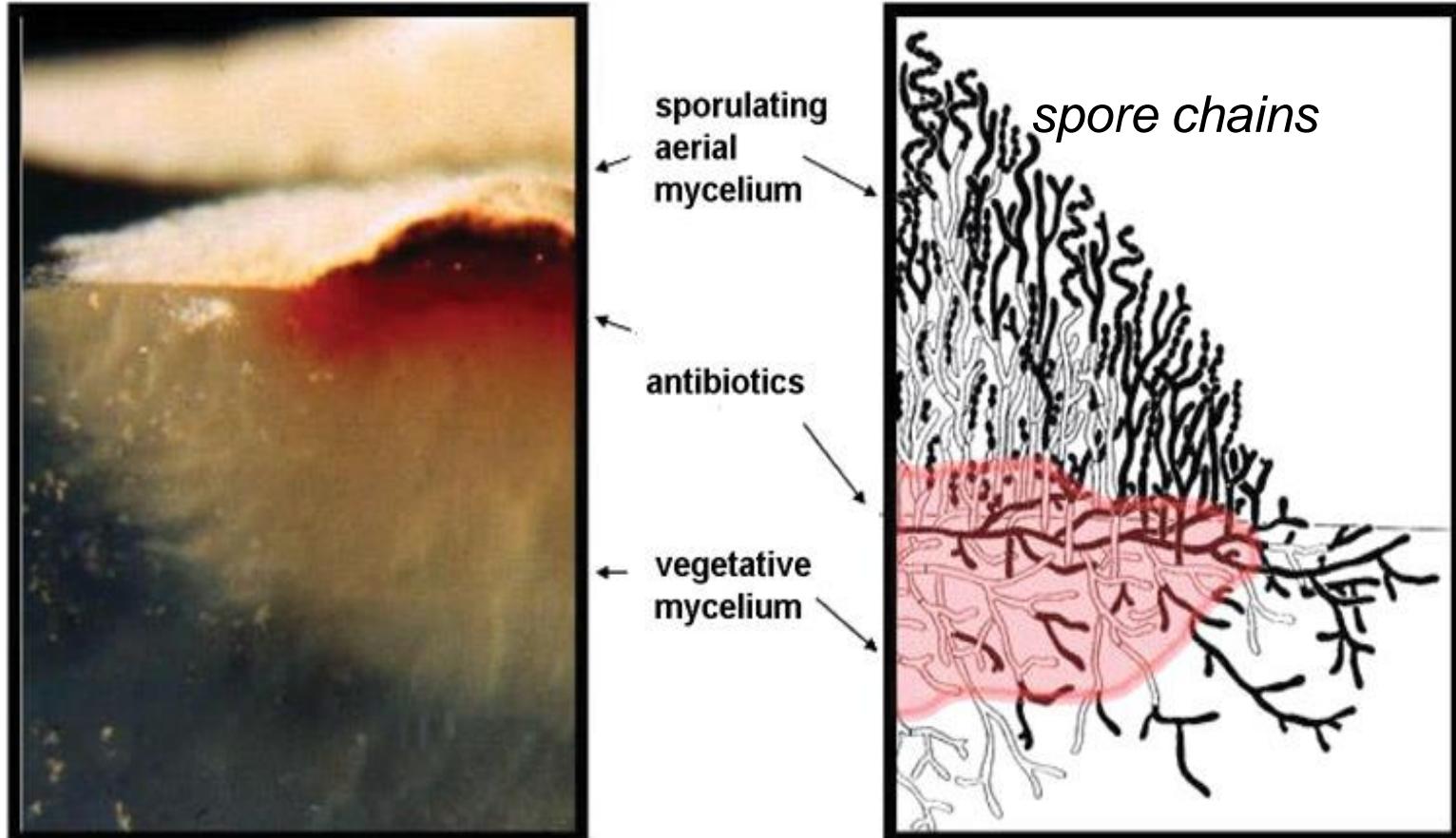


David Hopwood



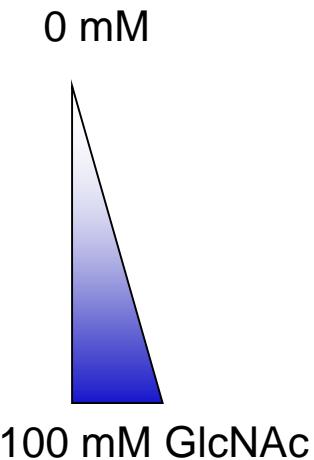
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The *Streptomyces* colony



Jamie Ryding, Keith Chater

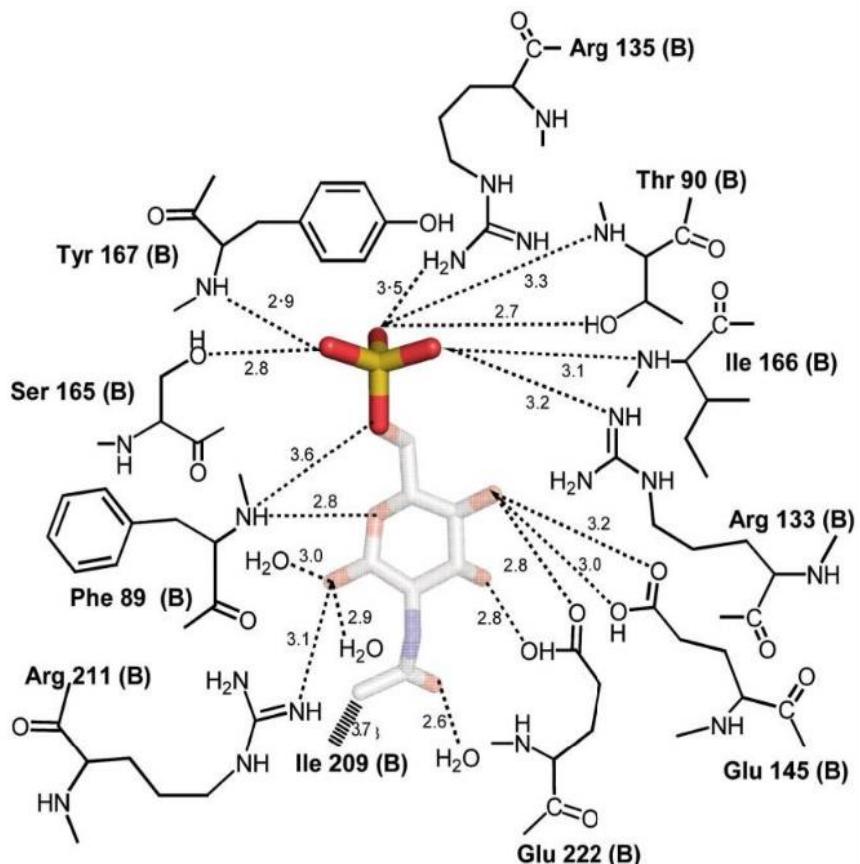
Cell wall N-acetylglucosamine (GlcNAc) activates antibiotic production



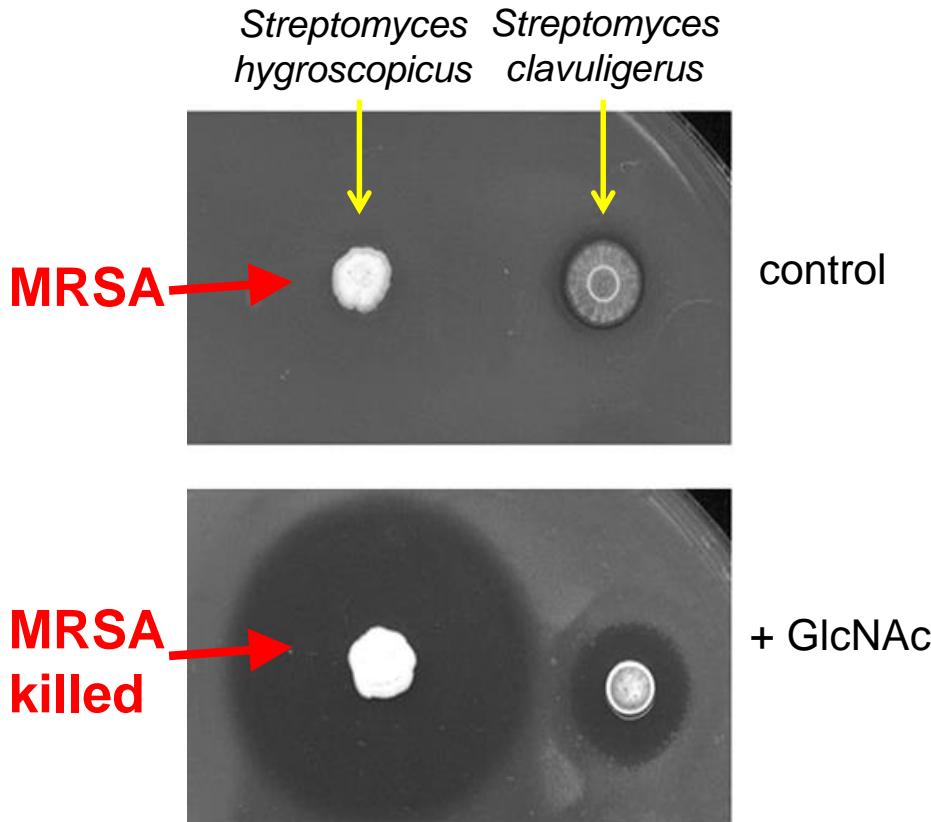
M145 Δ dasR

Rigali et al., EMBO Rep 2008, 9: 670-675

Cell wall-derived GlcNAc elicits antibiotics



GlcNAc-6P bound to DasR
(Yves Müller)



Collection of rare actinomycetes



Deep sea mud



Atacama desert



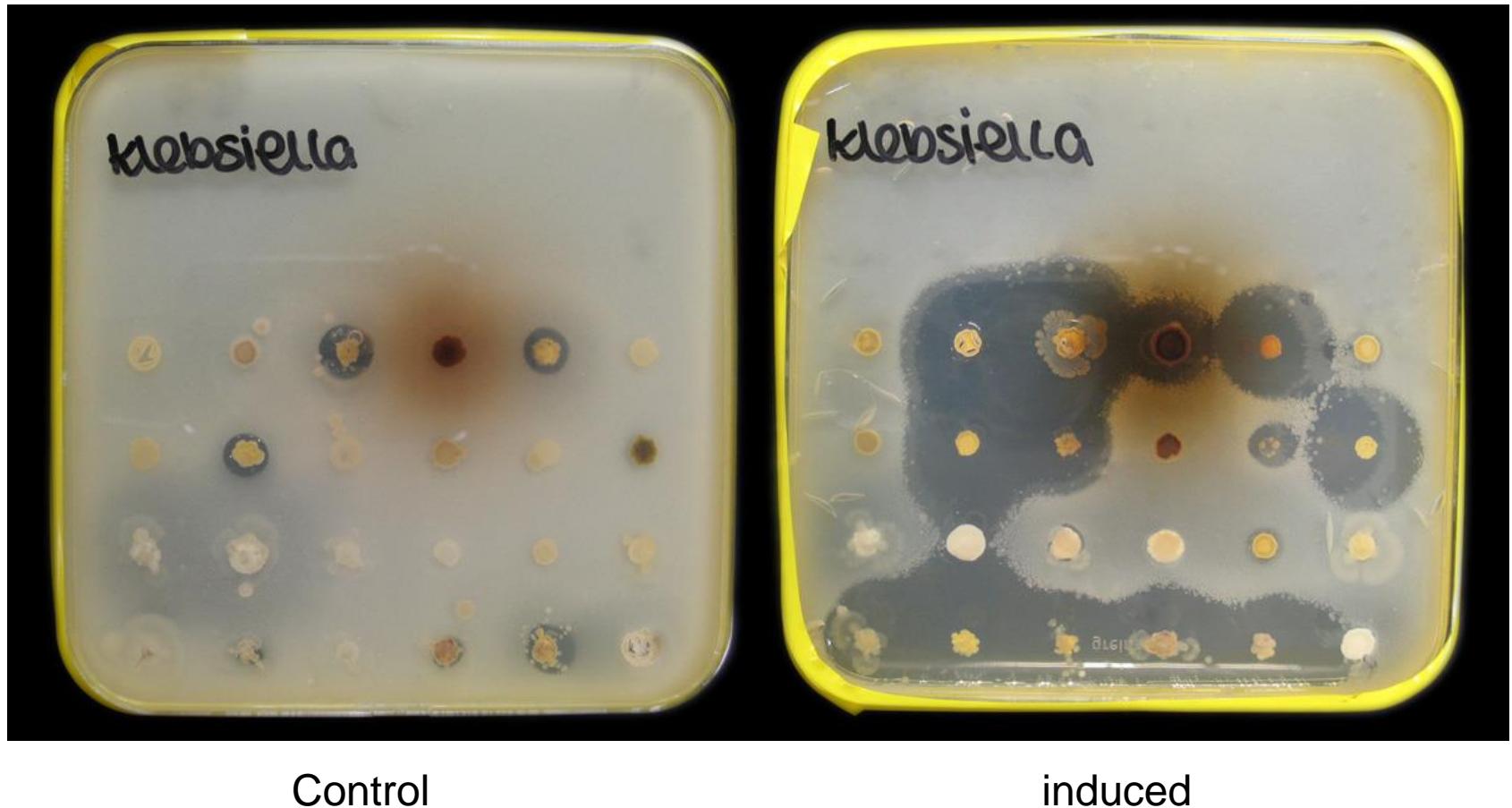
Himalaya mountains



Hua Zhu



Inducing antibiotic production

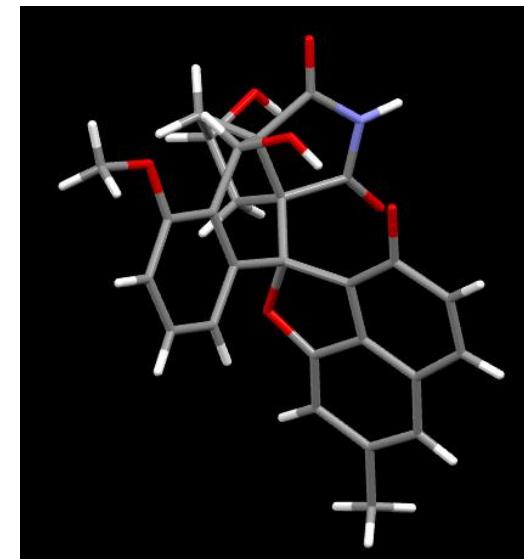
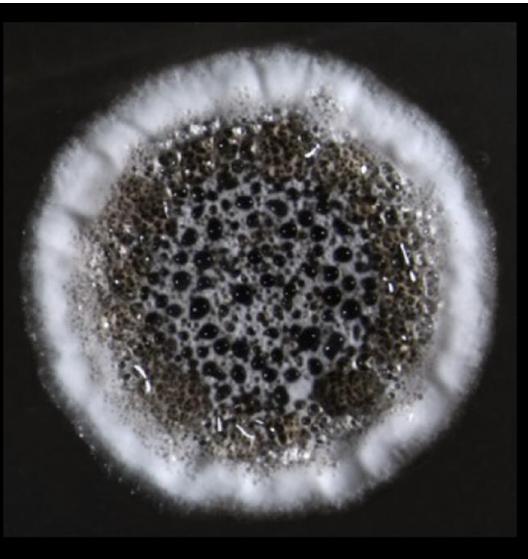


Zhu et al. (2014), *Microbiology* 160: 1714

Lugdunomycins as proof of concept



Streptomyces sp. QL37

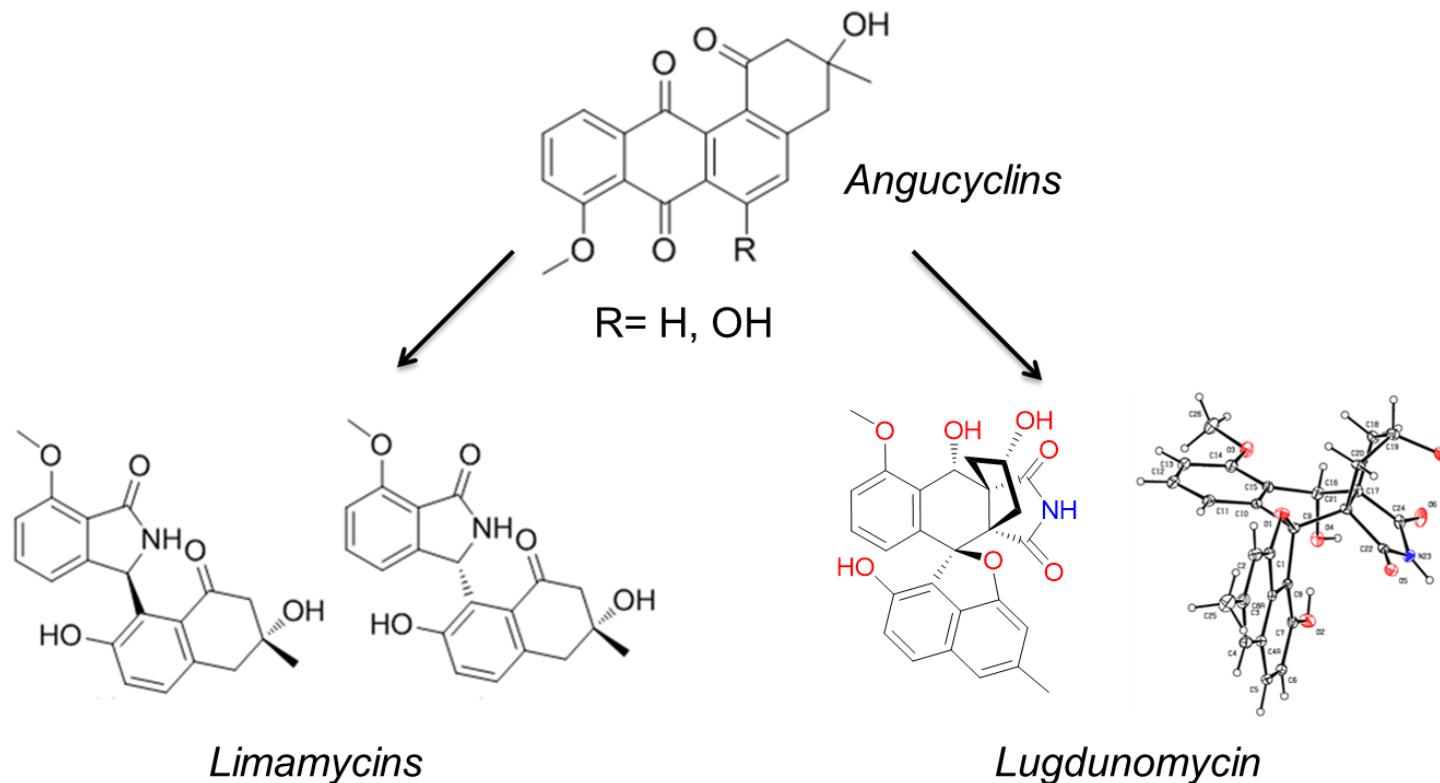
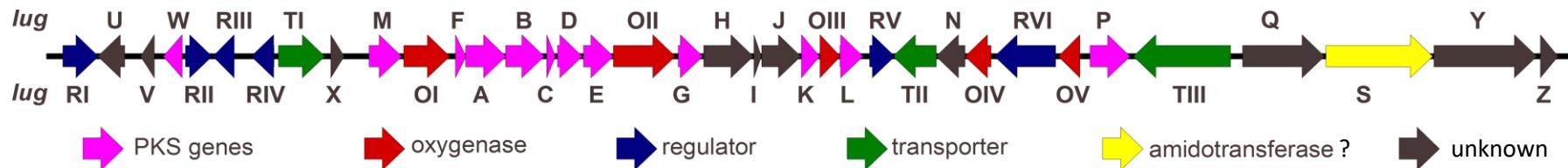


Lugdunomycin
(1 mg/1000 agar plates)

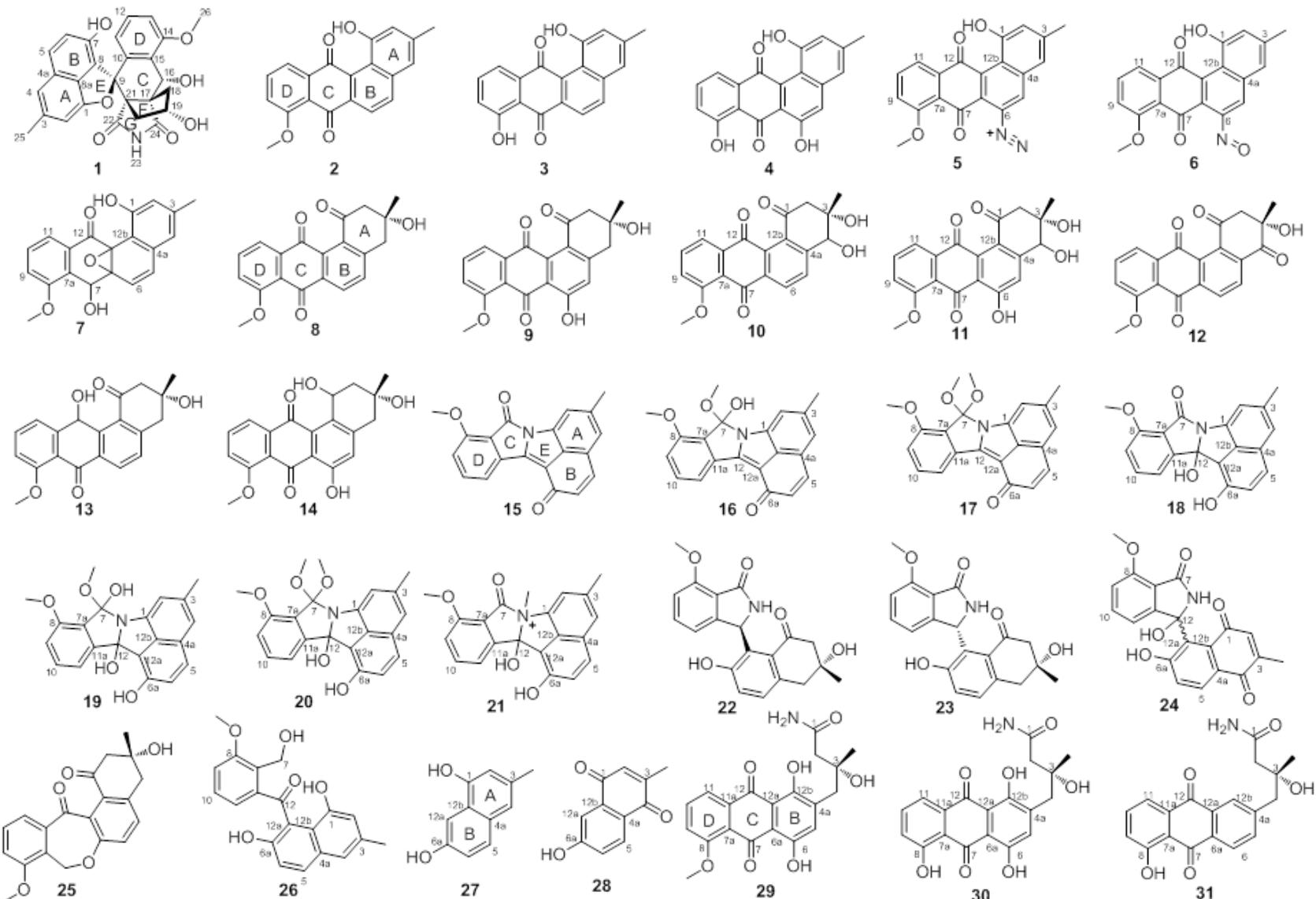
novel class of polyketide-derived compounds with new enzymology

Wu et al. (2019), *Angewandte Chemie Intl. Ed.* 58: 2809-2814; patent application.

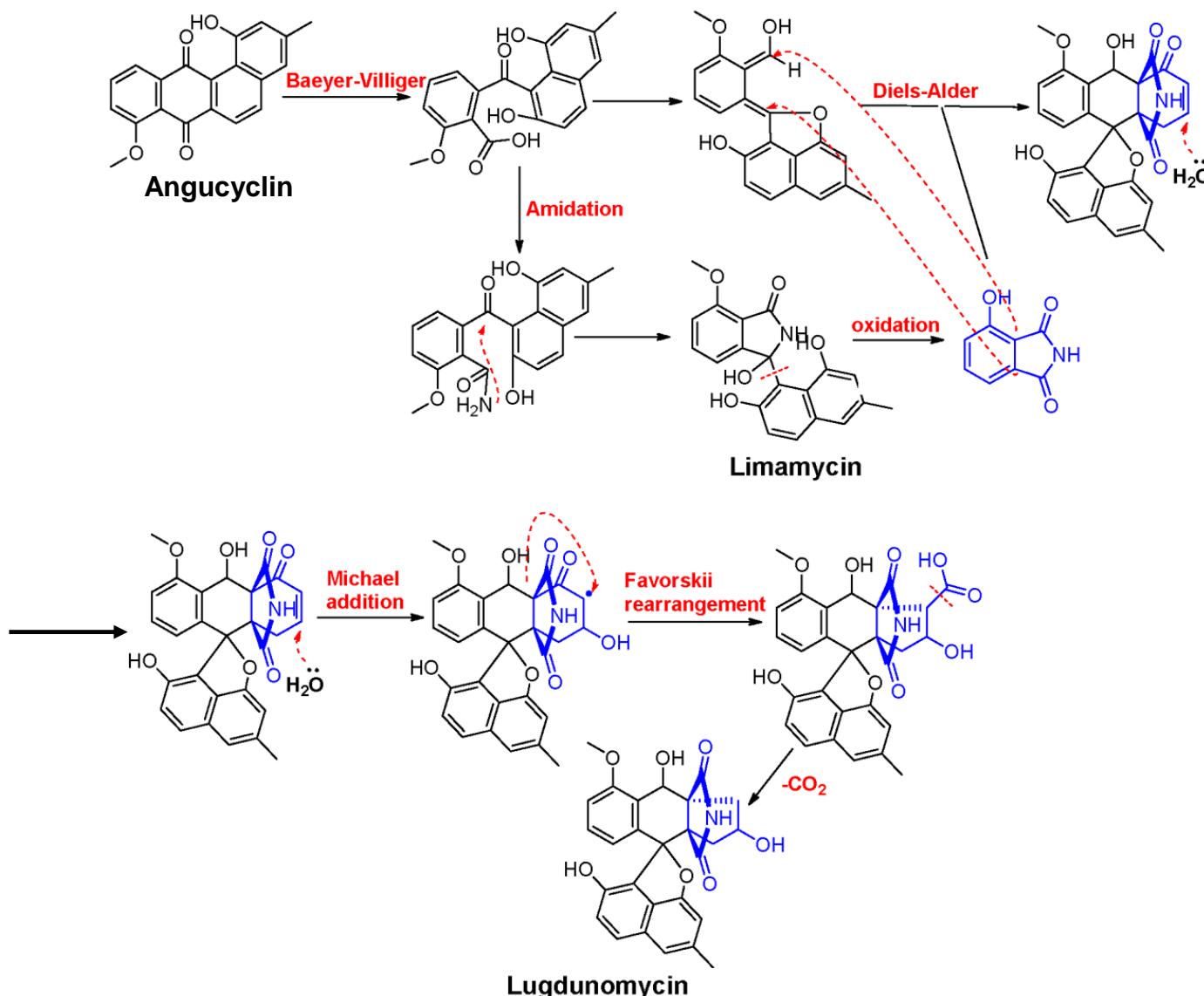
Lugdunomycin: a type II polyketide



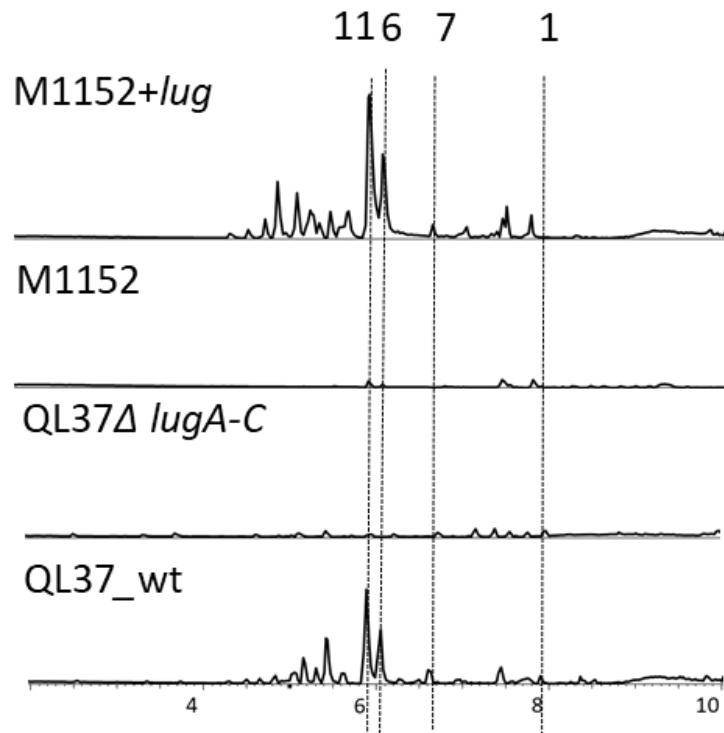
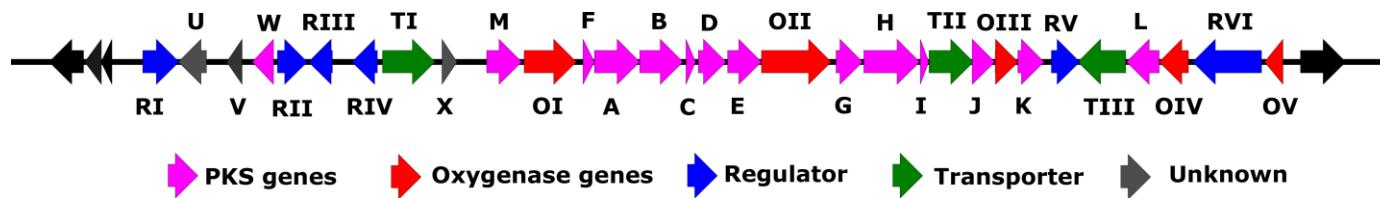
Angucyclines and derivatives from QL37



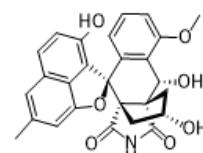
Key steps and questions



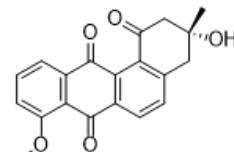
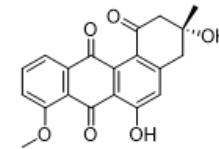
Heterologous expression in *S. coelicolor*



S. coelicolor *S. coelicolor* + lug *Streptomyces* QL37

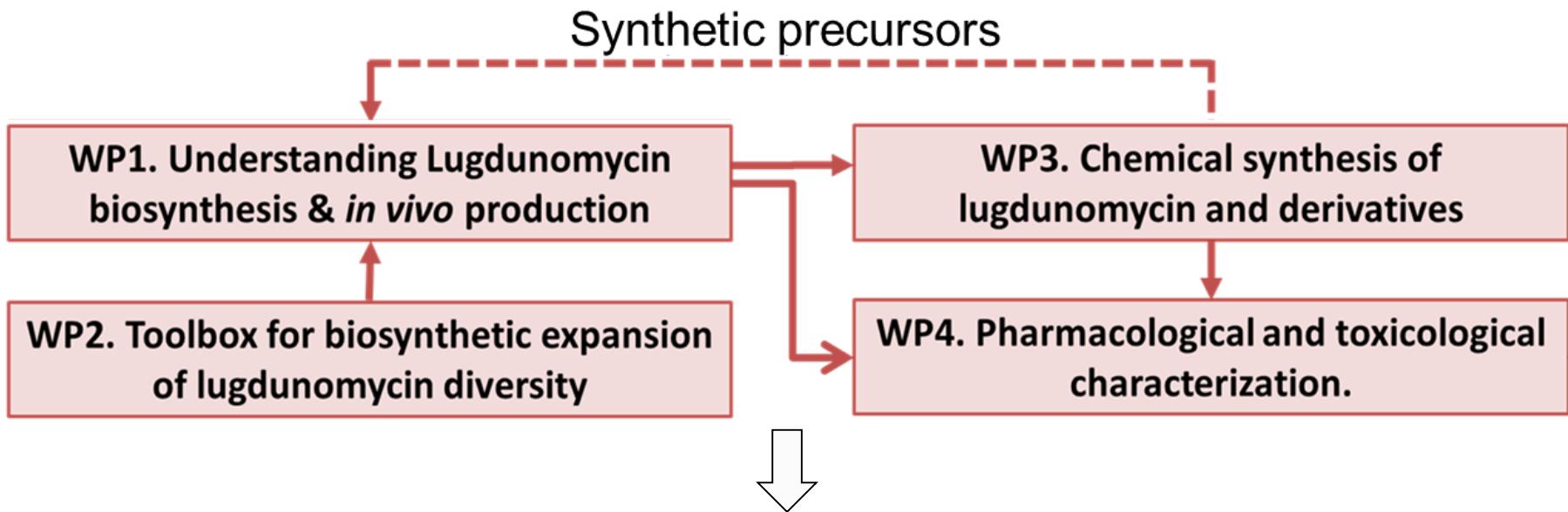


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6 11

Lugdunomycin R&D



Enzymatic toolbox for producing new lugdunomycins

Library of drug candidates and pharmacological characterization



Acknowledgements

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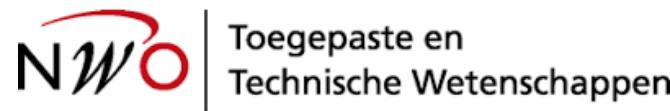
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