Natural product-inspired antibiotics: Successes and future prospects

Guest speakers: Mark Butler & Christine Beemelmanns
Moderator: Jennifer Herrmann
Host: Victor Kouassi

28 April 2026

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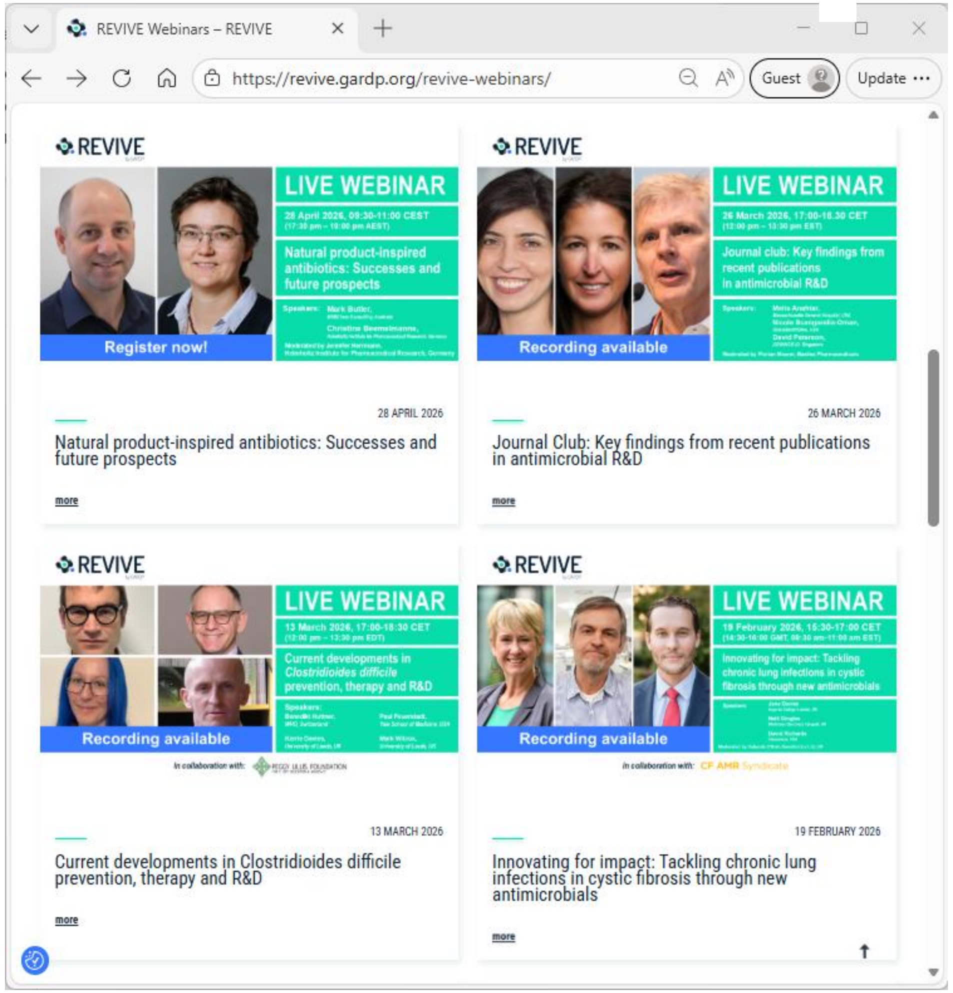

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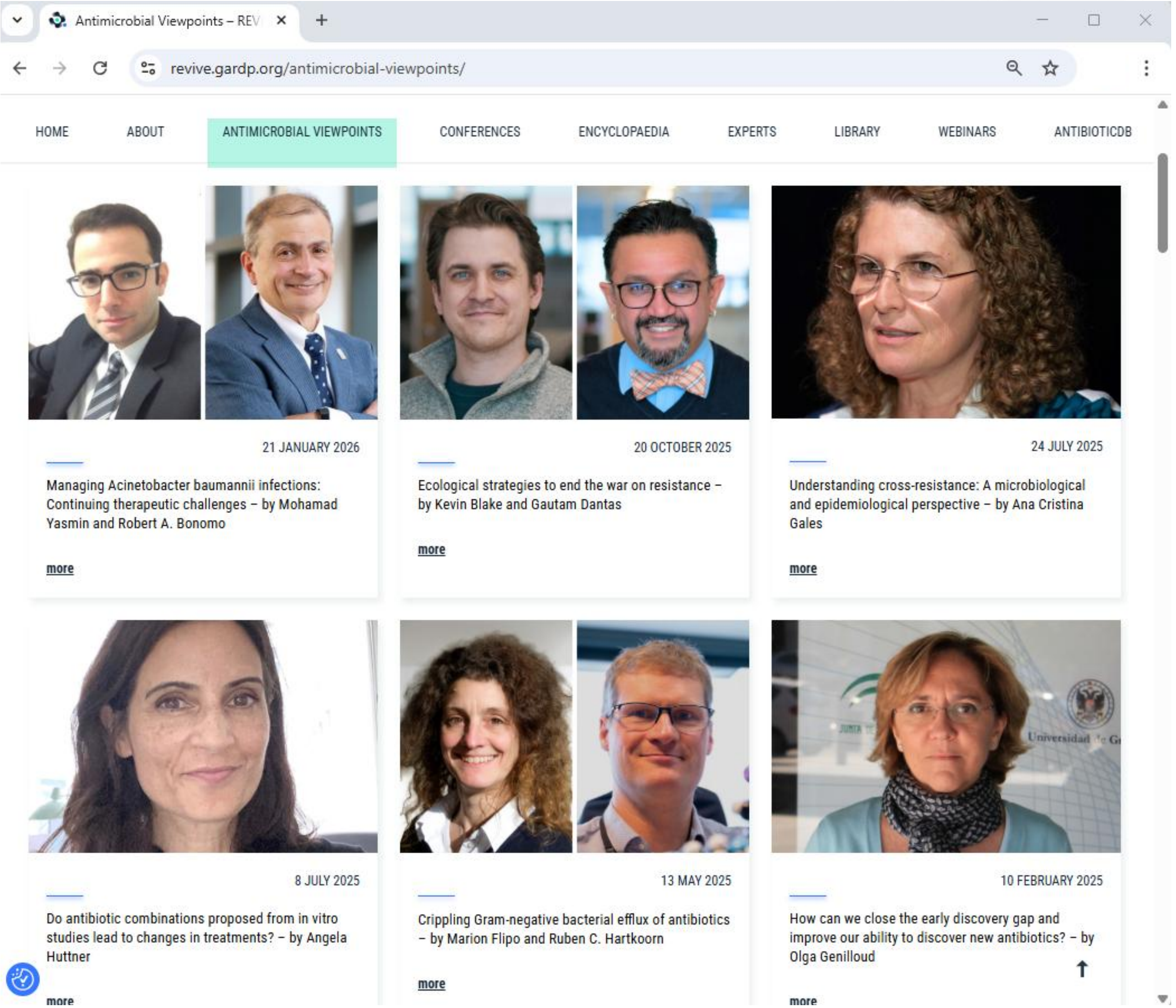

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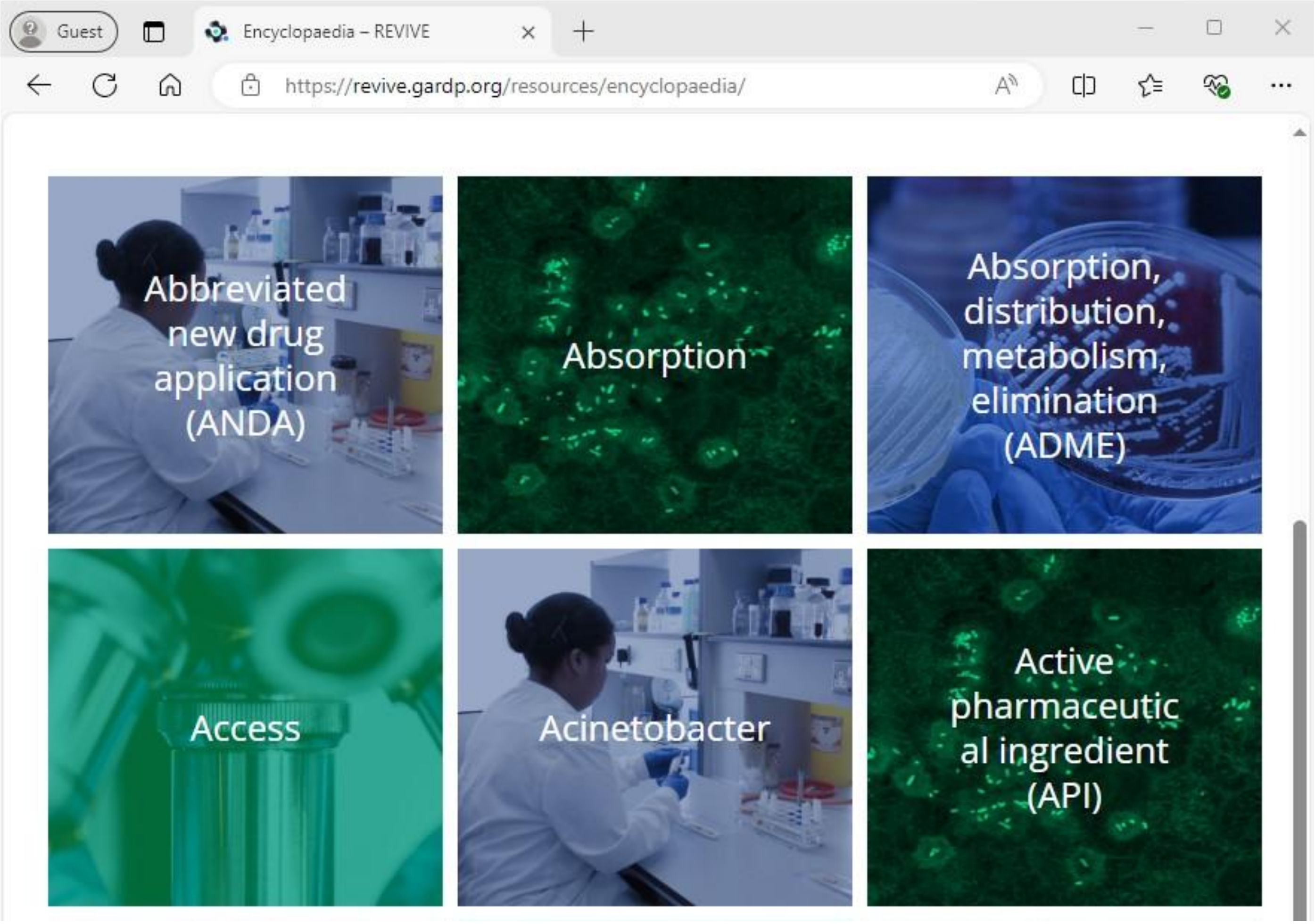

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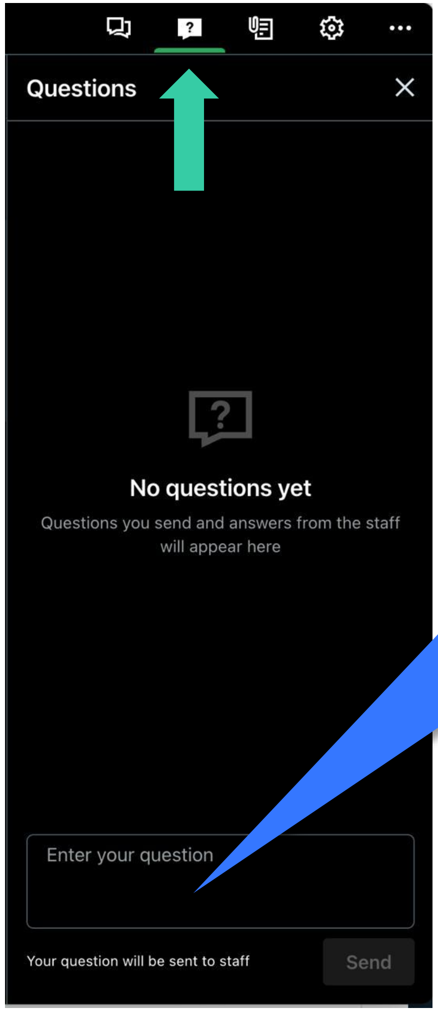
If your question is addressed to a specific speaker, please include their name when submitting the question.



Please submit your questions through the box provided after clicking the 'questions' button. We will review all questions and respond to as many as possible after the presentation.

Today's speakers

REVIVE by GARDP

Natural product-inspired antibiotics: Successes and future prospects

Moderator:
Jennifer Herrmann
Helmoltz Institute for Pharmaceutical Research Saarland

Mark Butler
MSBChem Consulting

Christine Beemelmanns
Helmoltz Institute for Pharmaceutical Research Saarland

Mark Butler

Mark S. Butler is a drug development expert specialising in natural product-inspired therapeutics, with over three decades of experience spanning academia, biotech, and pharmaceutical R&D. He is currently Director of MSBChem Consulting and a Casual Academic at UQ, advising on AMR, drug development strategy, and bioproduct innovation.

He has led and contributed to multiple natural product and anti-infective discovery and development programmes and has worked with the WHO on its Global Action Plan on antimicrobial resistance (AMR).

Mark holds a PhD in Natural Product Chemistry from the University of Melbourne and an MBA from the University of Queensland (UQ), both in Australia. He has authored over 140 scientific publications and is a multiple-year Clarivate Highly Cited Researcher.

GARDP Revive Seminar - 28 April 2026

Natural product-inspired antibiotics: Successes and future prospects

Presentation 1:
The contribution of natural products to antibiotic discovery

Dr Mark Butler

MSBChem Consulting, Brisbane, Australia

Casual academic/consultant, The University of Queensland

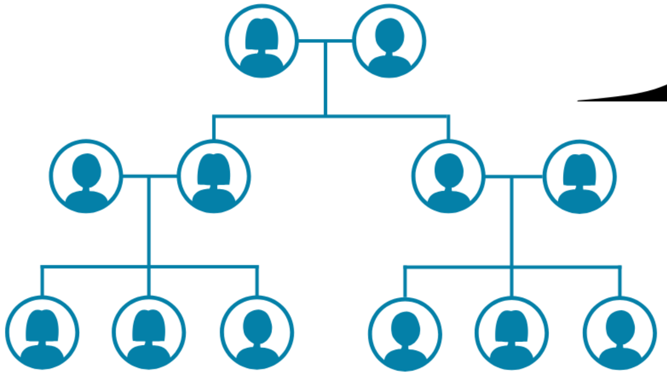
Outline

Talk overview

1. Pre-antibiotic era
2. New antibacterial drugs since 2000
3. Analysis of the 217 natural product (NP)-derived antibacterial drugs
4. Lessons from the vancapticin R&D program
5. Some thoughts on NP antibacterial lead discovery & development

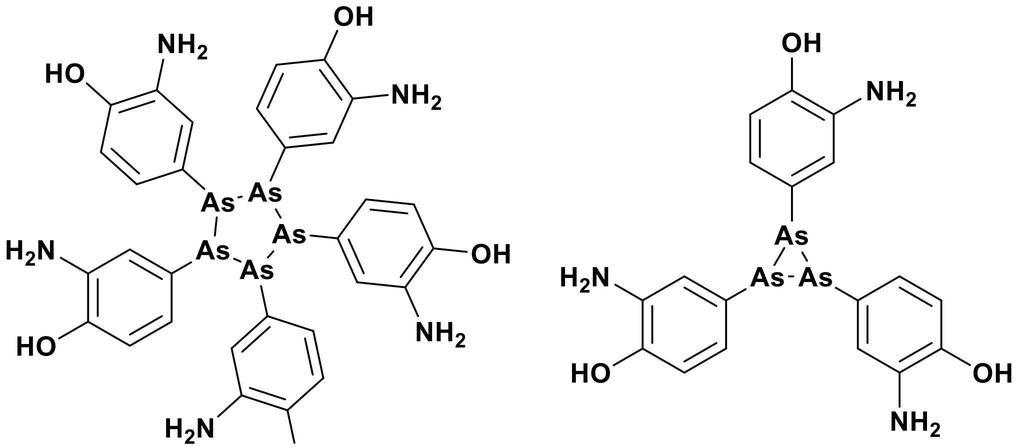
1. Pre-antibiotic era

- Although early societies knew nothing of bacteria, they lived in constant fear of infectious disease
- The following infections could be life-threatening or permanently disabling:
    - Skin and soft tissue infections, sepsis, meningitis and pneumonia
    - Tuberculosis and leprosy
    - Sexually transmitted infections
    - Dysentery
    - Plague
    - Toxin-mediated such as tetanus, botulism, anthrax
    - Zoonotic infections such as leptospirosis



Antibacterial treatments prior to the 1930s

- Topical antiseptics and disinfectants, including phenolics, iodine, and metal-based agents such as mercury and silver
- Selective chemotherapies for specific infections, especially arsphenamine (Salvarsan) and related arsenicals for syphilis
- Surgical source control: drainage, debridement, and amputation
- Early biologic approaches in some settings, including bacteriophage therapy
- Isolation, sanitation, and supportive care in the absence of effective systemic antibacterials

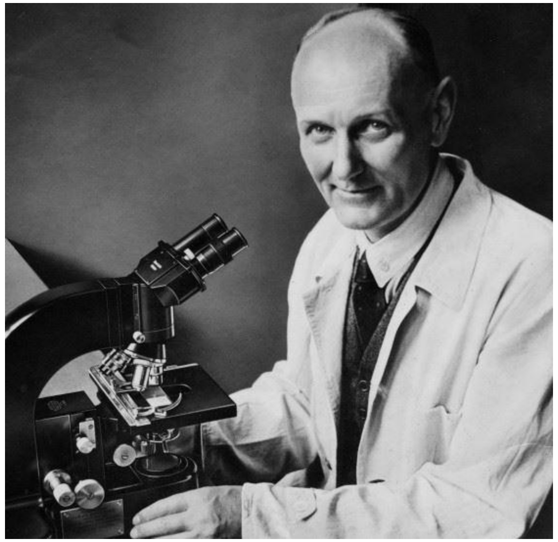


Savarsan

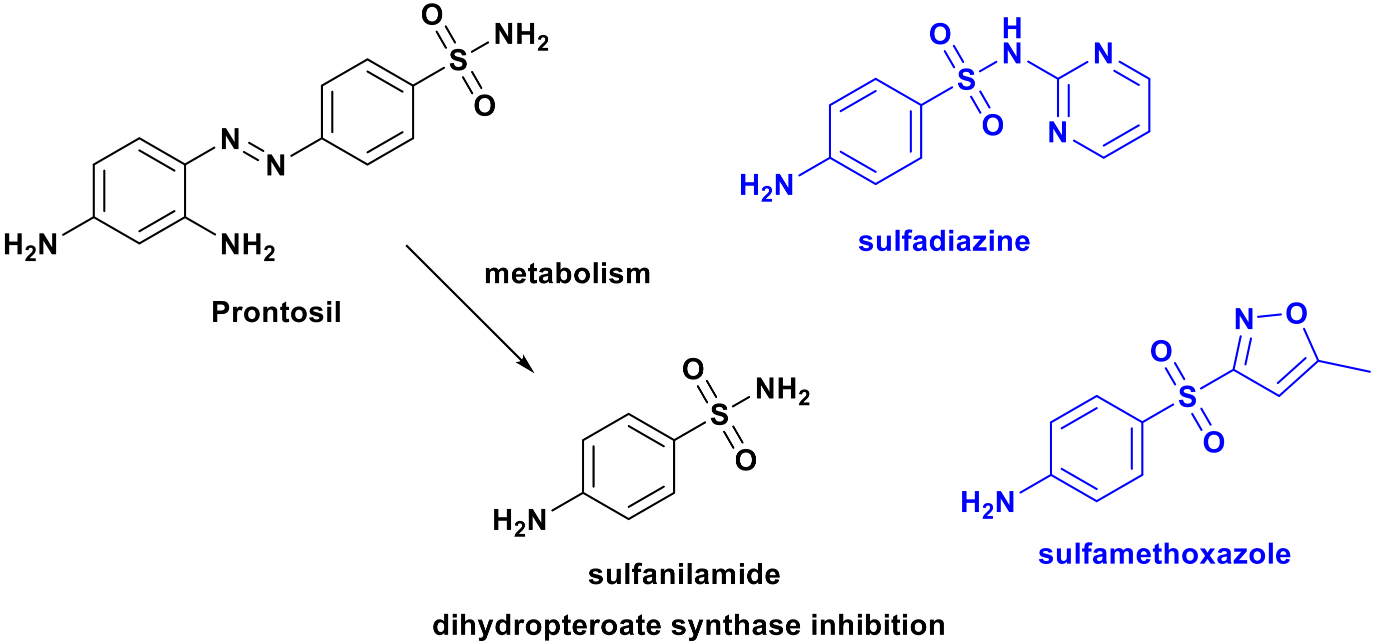
https://www.sciencehistory.org/stories/magazine/early-solution/ *Agnew. Chem. Int. Ed.*, **2005**, *44*, 941–944, DOI: 10.1002/anie.200461471

Sulfonamides

- In 1932, scientists at Bayer in Germany found that the azo-dye Prontosil had *in vivo* activity in infected mice
- In 1935, researchers at the Pasteur Institute in Paris found that Prontosil was a prodrug that metabolised to the antibacterial sulfanilamide
- In 1939, Gerhard Domagk from Bayer received the 1939 Nobel Prize in Physiology or Medicine
- Roughly 40 antibacterial sulfonamides were developed; most are no longer in use
- Notable exceptions include sulfamethoxazole–trimethoprim combinations (co-trimoxazole) and sulfadiazine



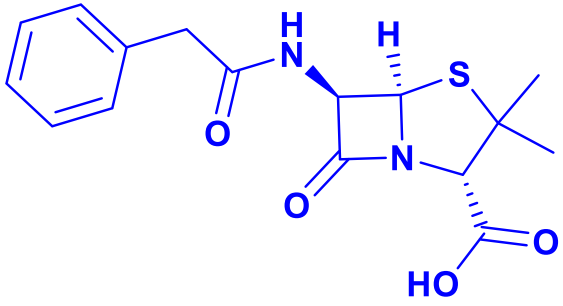
Gerhard Domagk



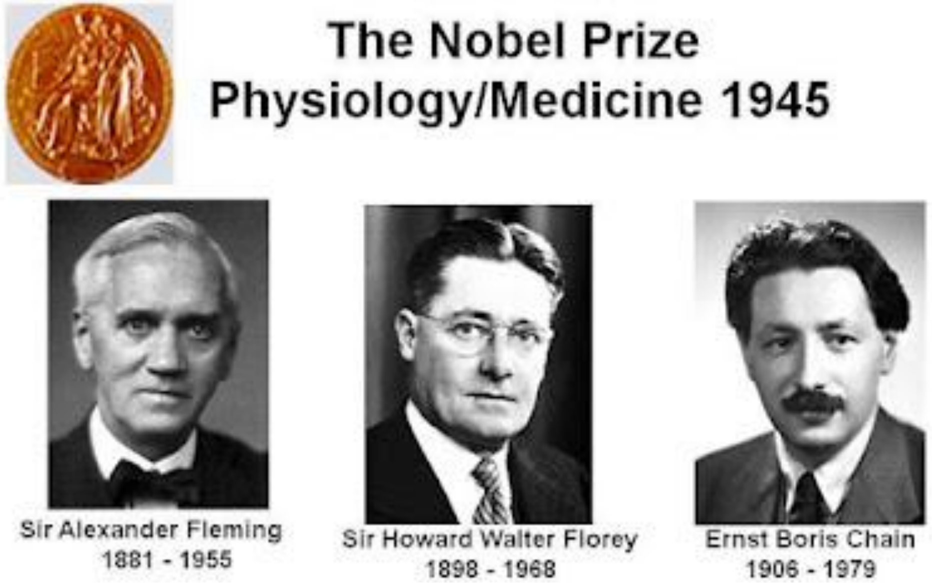
Penicillin

- In 1928, Alexander Fleming (St. Mary's Hospital in London) noticed that bacteria failed to grow on an agar plate near mould contamination
- In 1929, Fleming reported that 'penicillin' could kill certain G+ve pathogens, including *S. aureus*, *S. pneumoniae*, and *S. pyogenes*, and was non-toxic in animal models
- In 1938, Oxford University's Chain, Heatley and Florey started to investigate penicillin
- In 1941, the first patients were successfully treated and by 1943 it was used World War II
- Structure proposed in 1943 and confirmed by X-ray crystallography in 1945

https://blog.sciencemuseum.org.uk/keeping-history-alive/



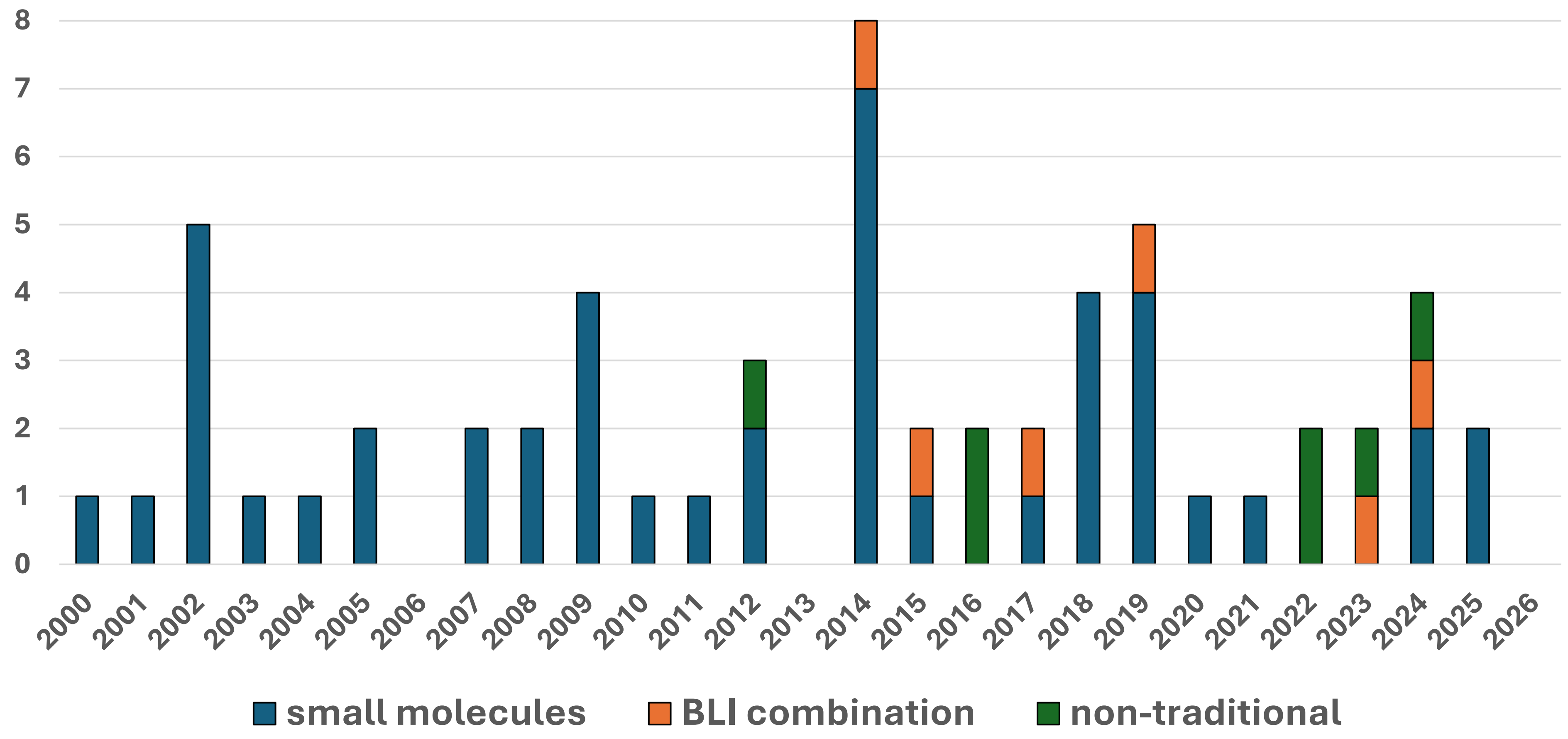
penicillin G



https://www.nobelprize.org/prizes/medicine/1945

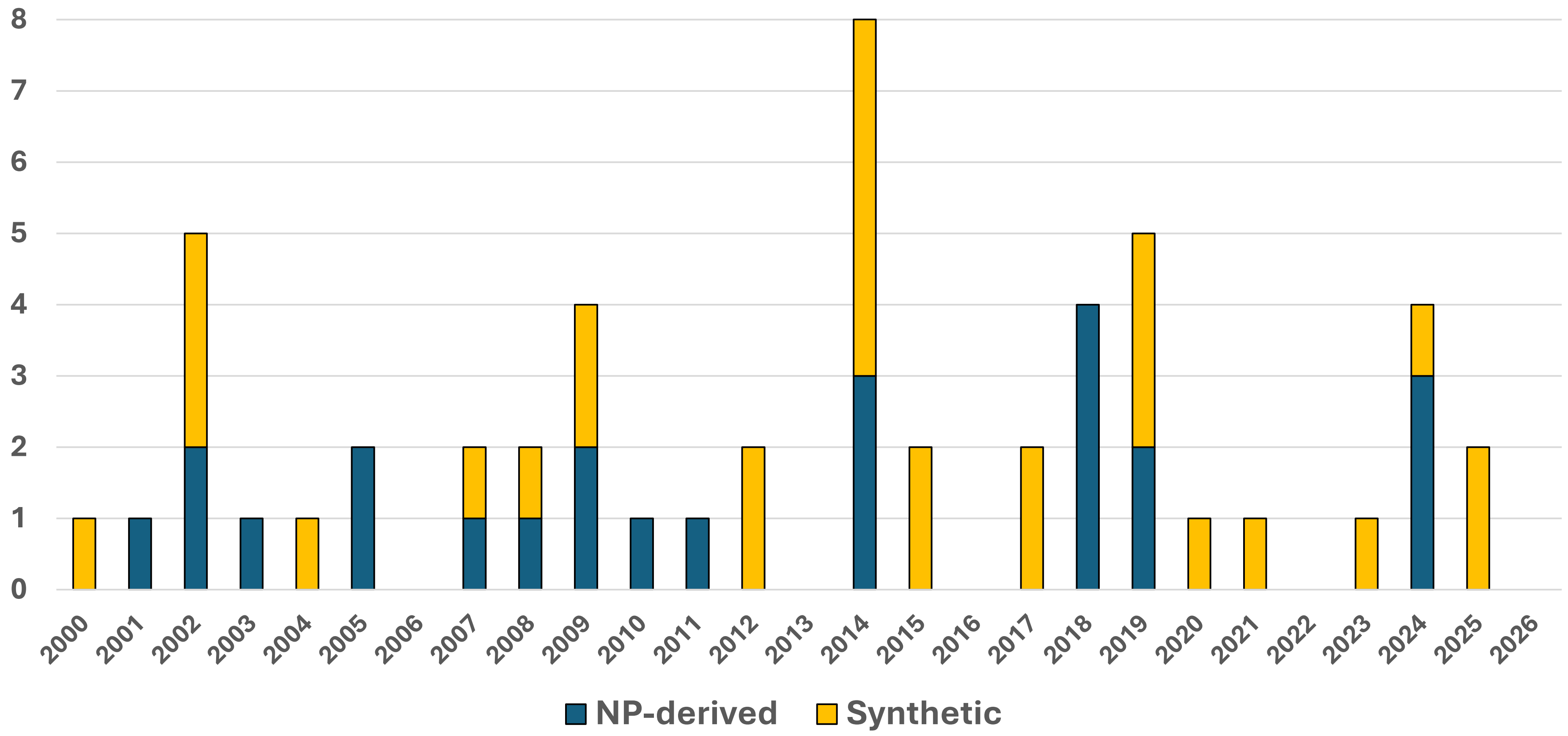
2. New (NCE and NBE) antibacterial drugs launched since 2000

- **46 Small molecules, 6 β-lactam & β-lactamase inhibitor (BLI) combinations and 7 non-traditional antibacterials**
  - Non-traditional = 3 monoclonal antibodies (mAbs) antibacterials; 3 microbiome-related; 1 anti-virulence small molecule



NP-D NCE antibacterial drugs launched since 2000

- **46 Small molecules, 6 BLI combinations and 1 non-traditional antibacterials**
  - 24/53 (45%) of new antibacterial NCE drugs were NP-derived



New antibacterial small molecule classes launched since 2000

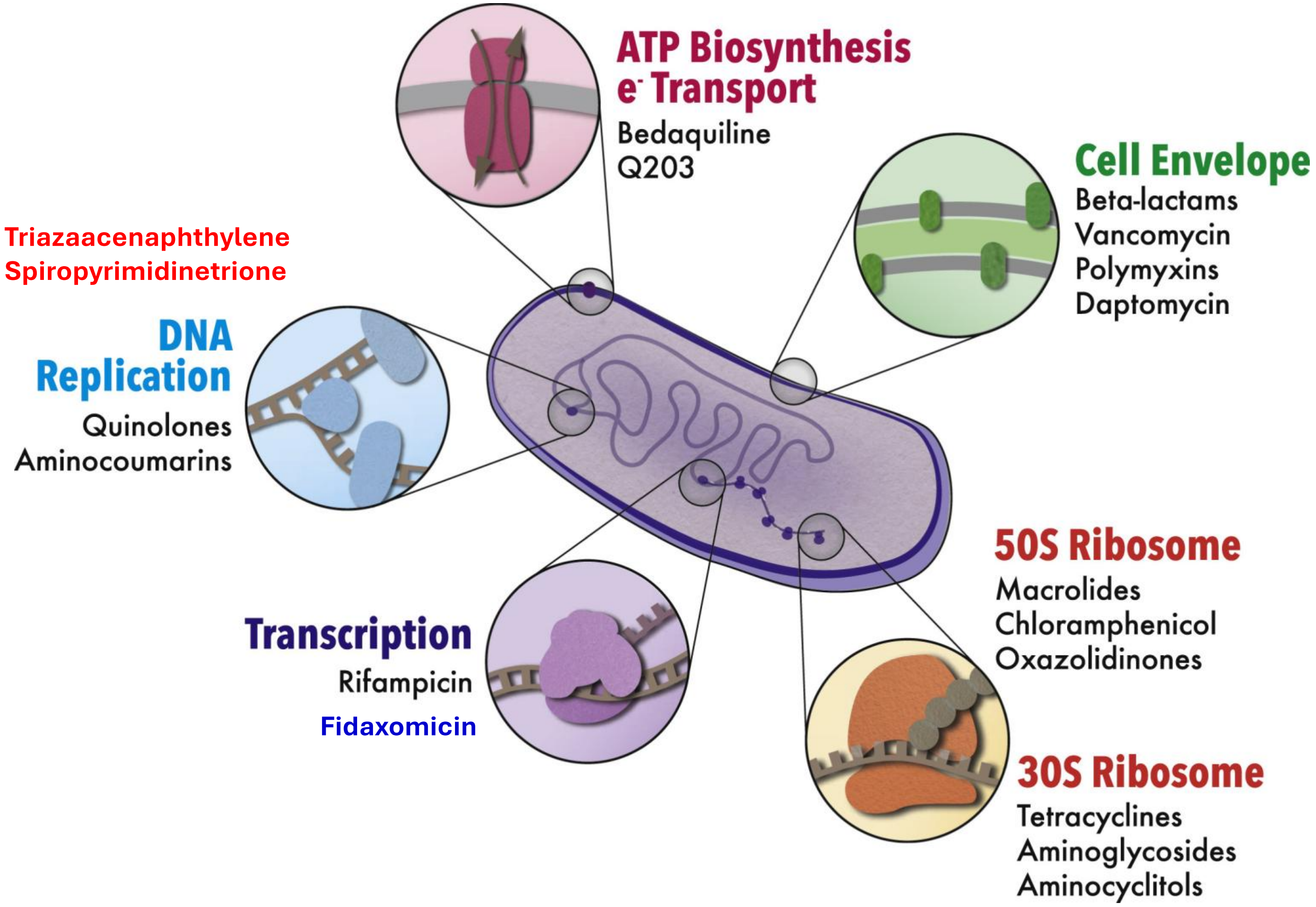
From 47 small molecules, 6 BLI combinations and 1 non-traditional antibacterial

- Seven first-in-class direct acting small molecules
  - Linezolid (oxazolidinone, 2000 USA) – iv/oral, G+ve
  - Daptomycin (lipopeptide, 2003 USA) – iv, G+ve **[Natural product]**
  - Retapamulin (pleuromutilin, 2007 USA) – topical, G+ve **[Natural product-derived]**
  - Fidaxomicin (tiacumicin, 2011 USA) – oral non-systemic, G+ve **[Natural product]**
  - Bedaquiline (diarylquinoline, 2012 USA) – oral, TB
  - Gepotidacin (triazaacenaphthylene, 2025 USA) – oral, gonorrhea and UTI
  - Zoliflodacin (spiropyrimidinetrione, 2025 USA) – oral, gonorrhea
- Two first-in-class BLIs
  - Avibactam (diazabicyclooctane (DBO), 2015 USA) – iv, G-ve
  - Vaborbactam (boronate, 2017 USA) – iv, G-ve
- One first-in-class antivirulence
  - Ftortiazinon + cefepime (fluorothiazinone, 2024 Russia) – iv/oral, G-ve

Antibacterial Modes of Action (MoA)

- **Four predominant MoAs**
  - Cell wall
  - Protein synthesis
  - DNA synthesis
  - RNA synthesis

- **Others**
  - Respiration system
  - Folic acid pathway
  - Nitroimidazoles
  - Antivirulence
  - …



Stokes, Lopatkin, Lobritz & Collins, *Cell Metab.*, **2019**, *30*, 251

3. Analysis of 217 NP-derived antibacterial drugs

Natural Product Reports

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Cite this: DOI: 10.1039/d5np00067j

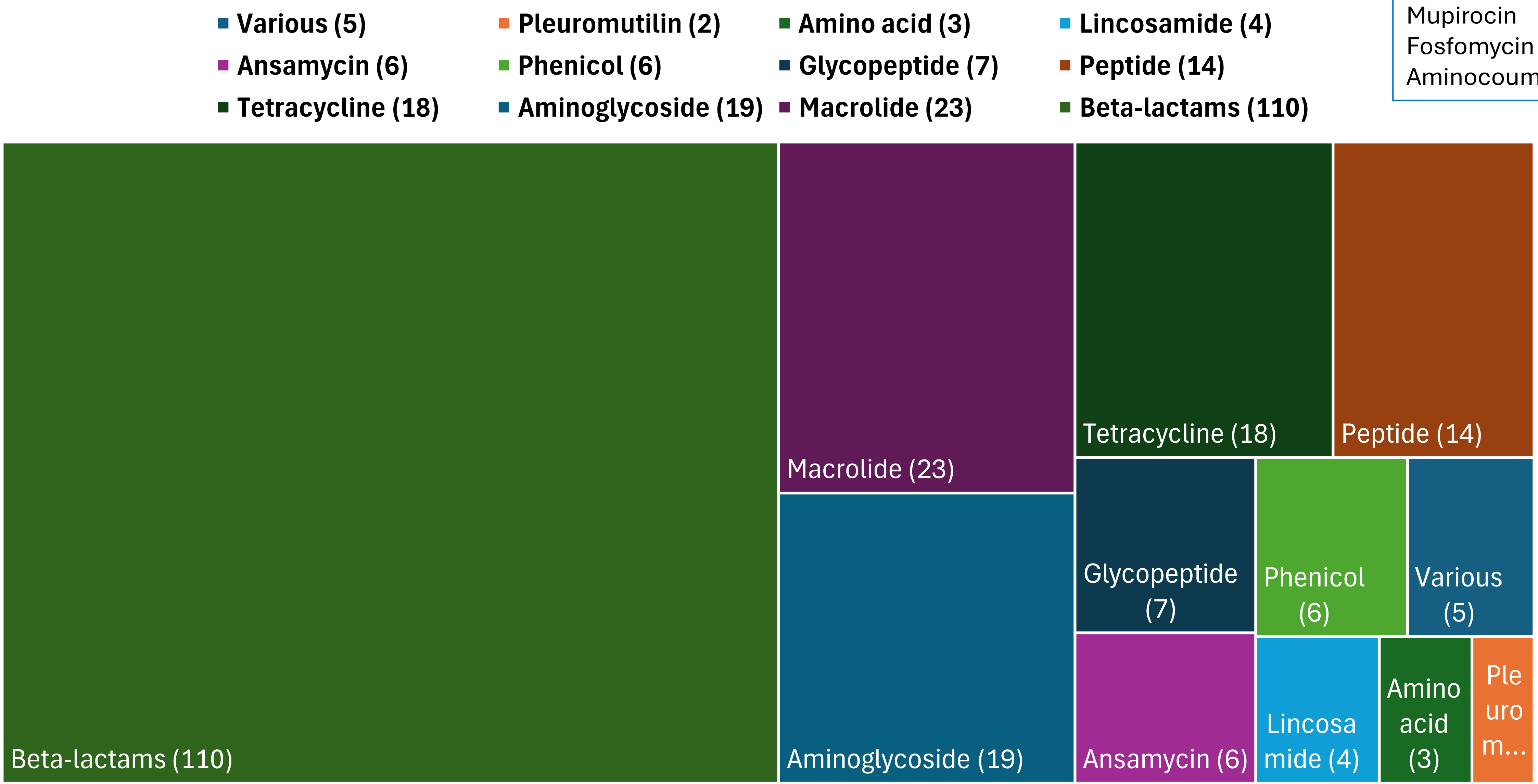
Natural product inspired antibiotics approved for human use – 1943 to 2025

Mark S. Butler and Robert J. Capon *

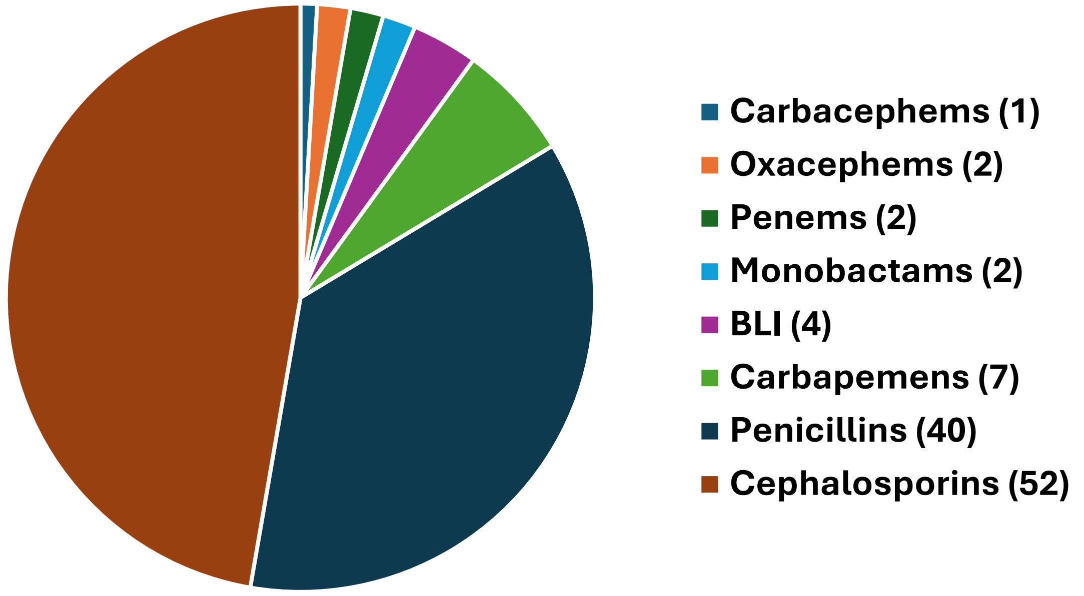
- Supporting information has SMILEs for all structures

217 NP-derived antibiotics by class

Various x 1
Fusidane
Fidaxomicin
Mupirocin
Fosfomycin
Aminocoumarin



Breakdown of β-lactam class into subclasses

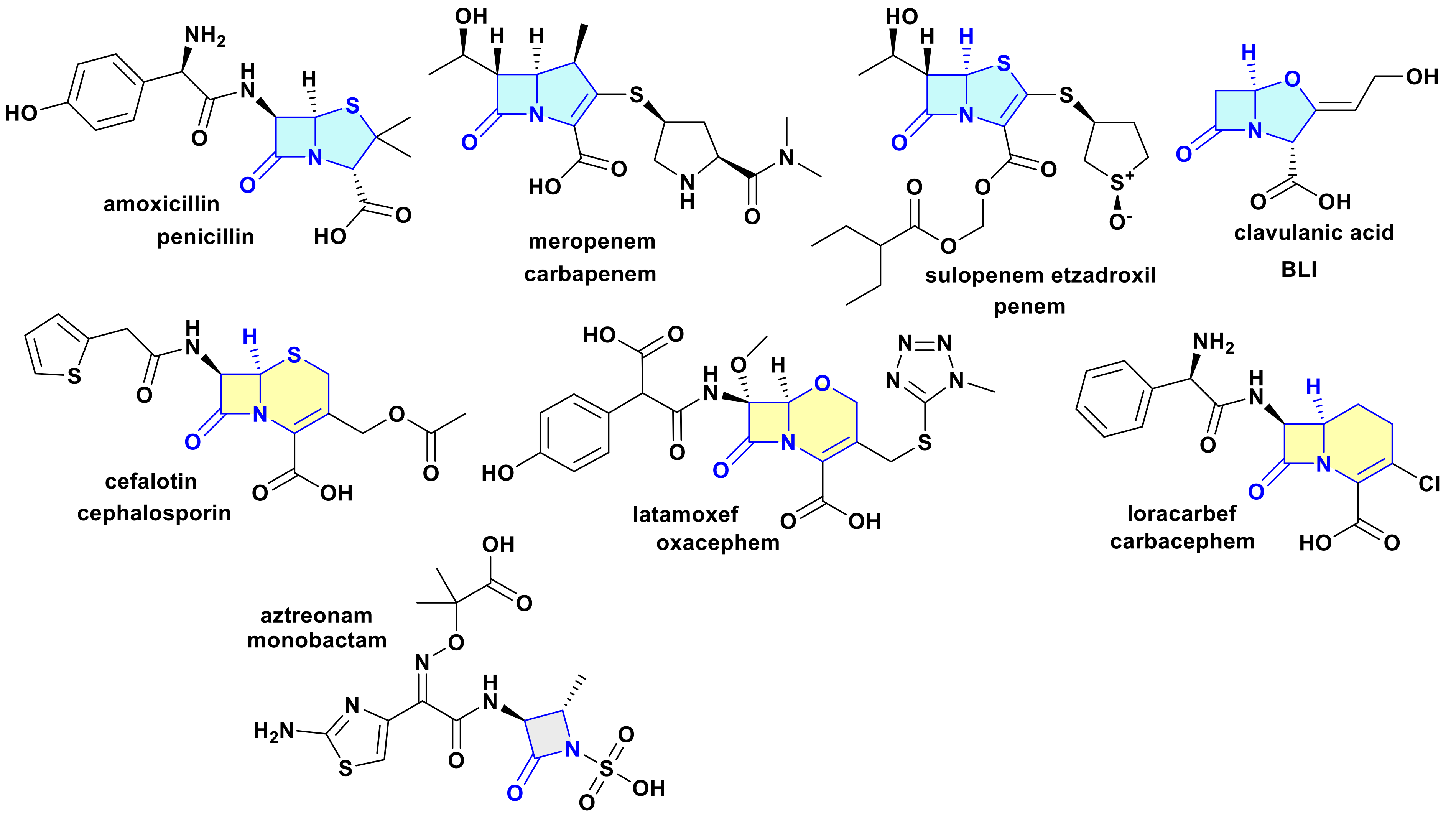


- Cephalosporins 52/217 (~24%) and penicillins 40/217 (~18%)

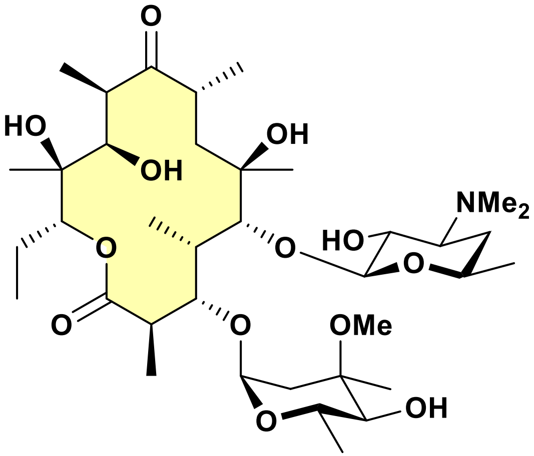
- β-Lactams110 (51%), macrolides 23 (~11%), aminoglycosides 19 (~9%) and tetracyclines 14 (~6%)
- These classes account for 166/217 (~76%) of total NP-derived antibiotics

Butler and Capon, *Nat. Prod. Rep.*, **2026**, DOI: 10.1039/D5NP00067

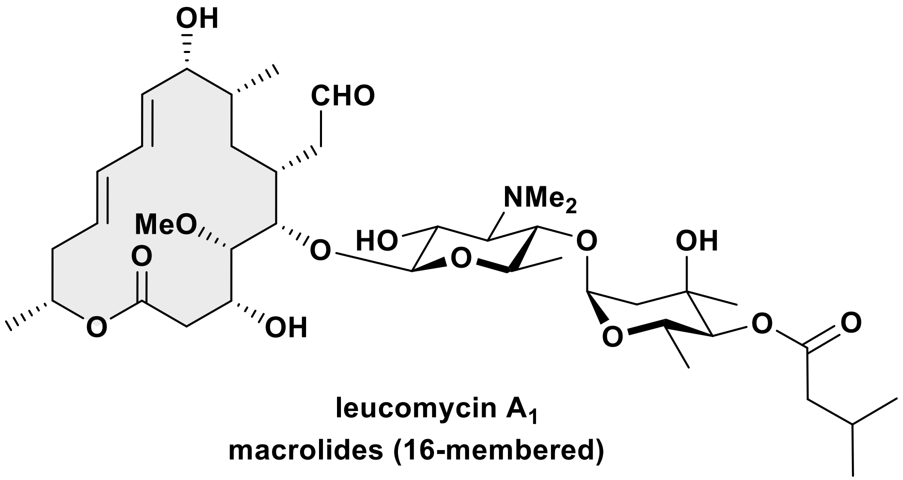
NP-derived antibiotic classes: β-lactams (110)



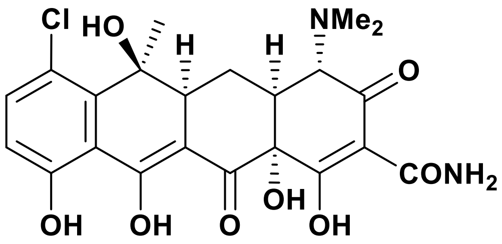
Macrolides (23), aminoglycosides (19) and tetracyclines (18)



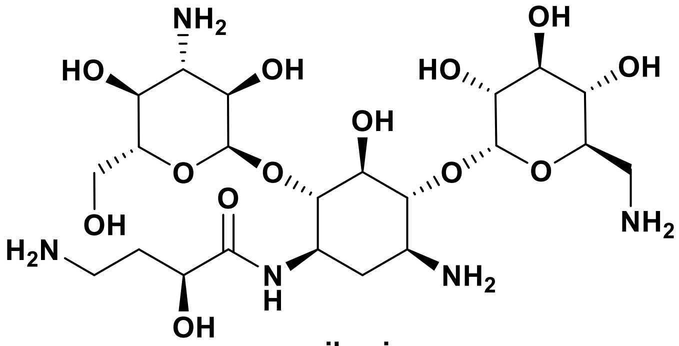
erythromycin
macrolides (14-membered)



leucomycin A_1
macrolides (16-membered)

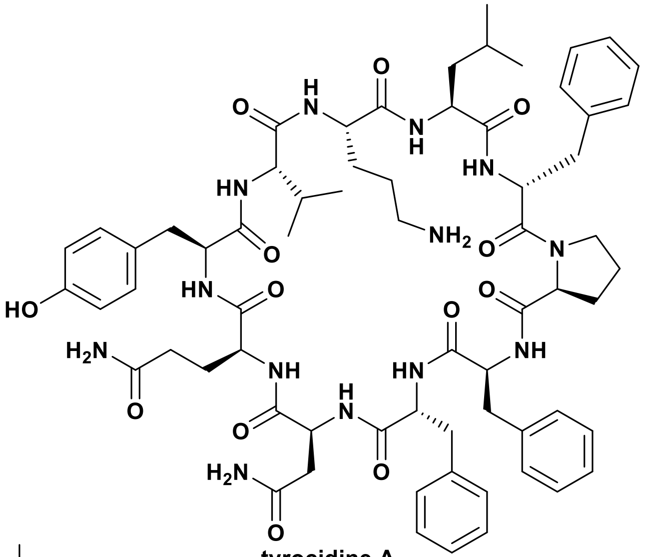


chlortetracycline
tetracyclines

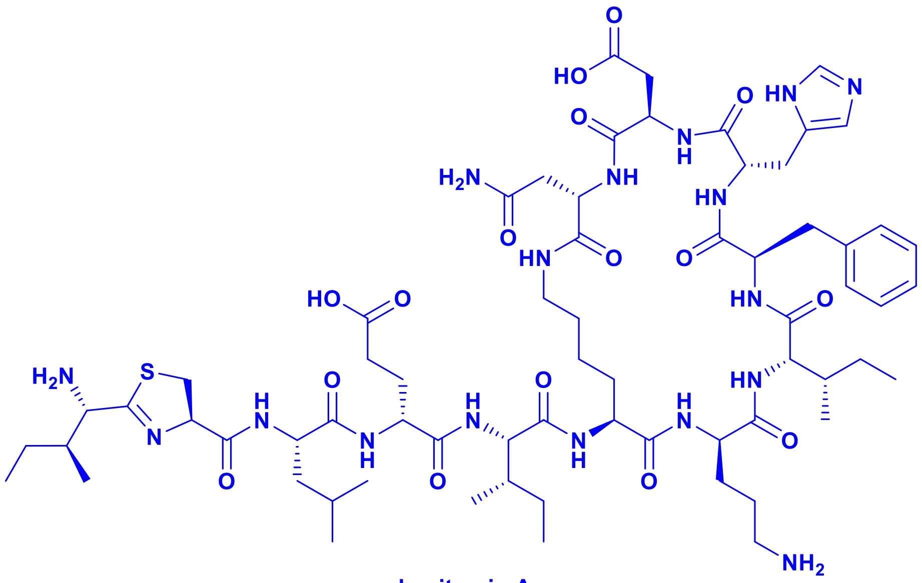


amikacin
aminoglycosides

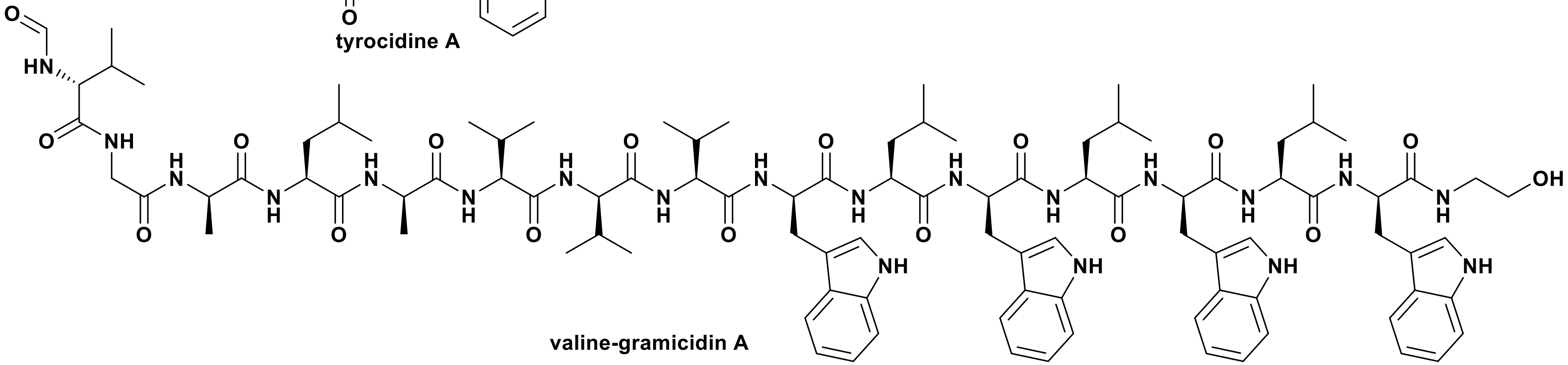
Peptides (14) – part 1



tyrocidine A

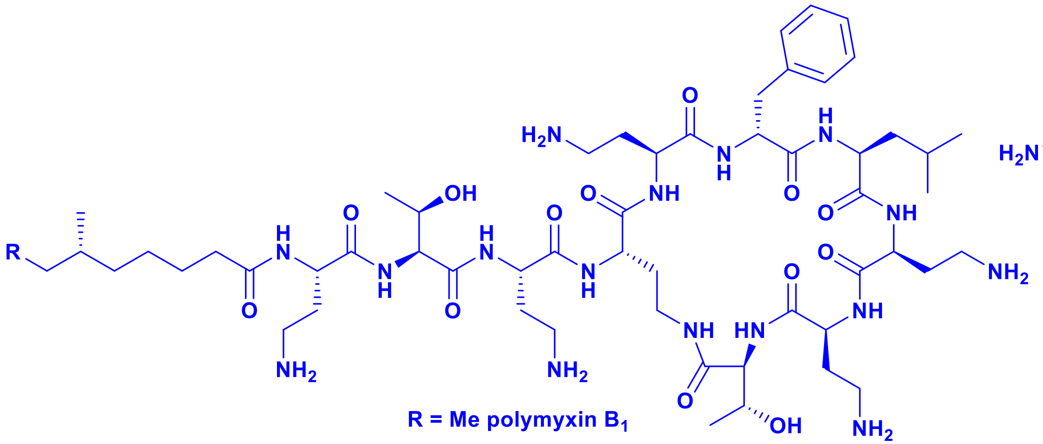


bacitracin A



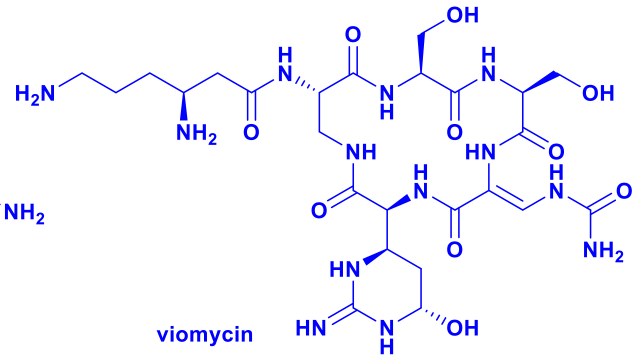
valine-gramicidin A

Peptides (14) – part 2

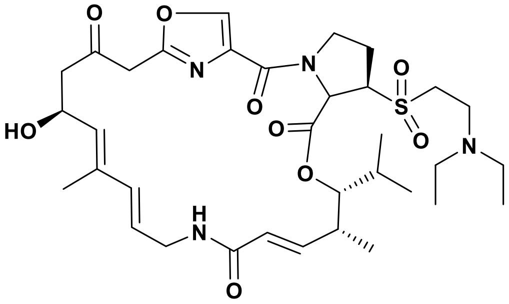


R = Me polymyxin B_1

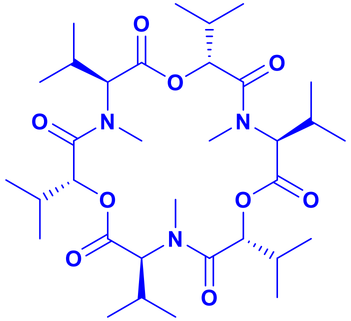
R = H polymyxin B_2



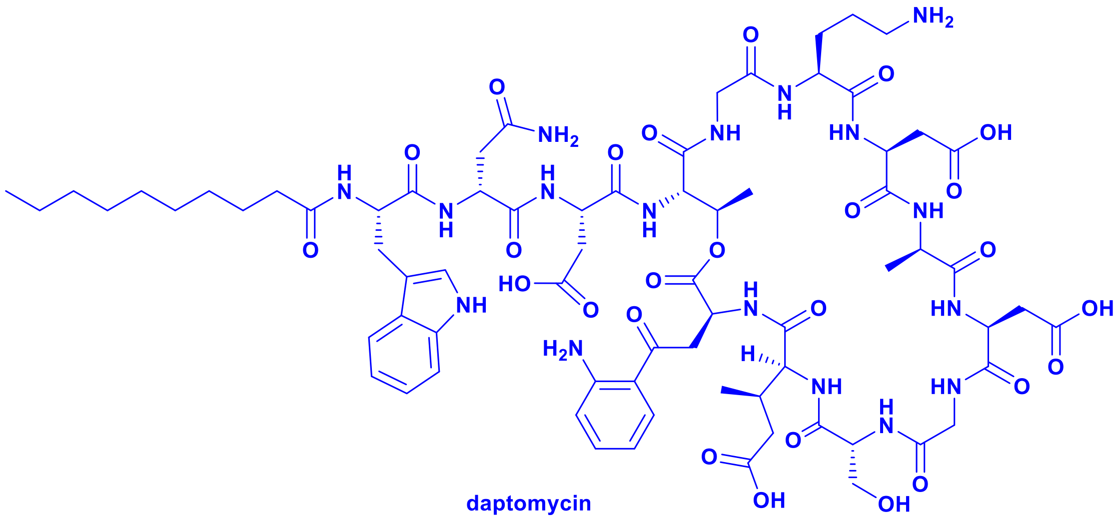
viomycin



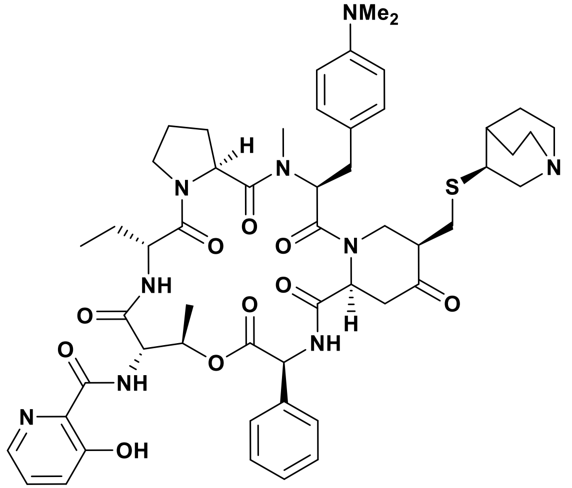
dalfopristin



fusafungine (enniatin mixture)

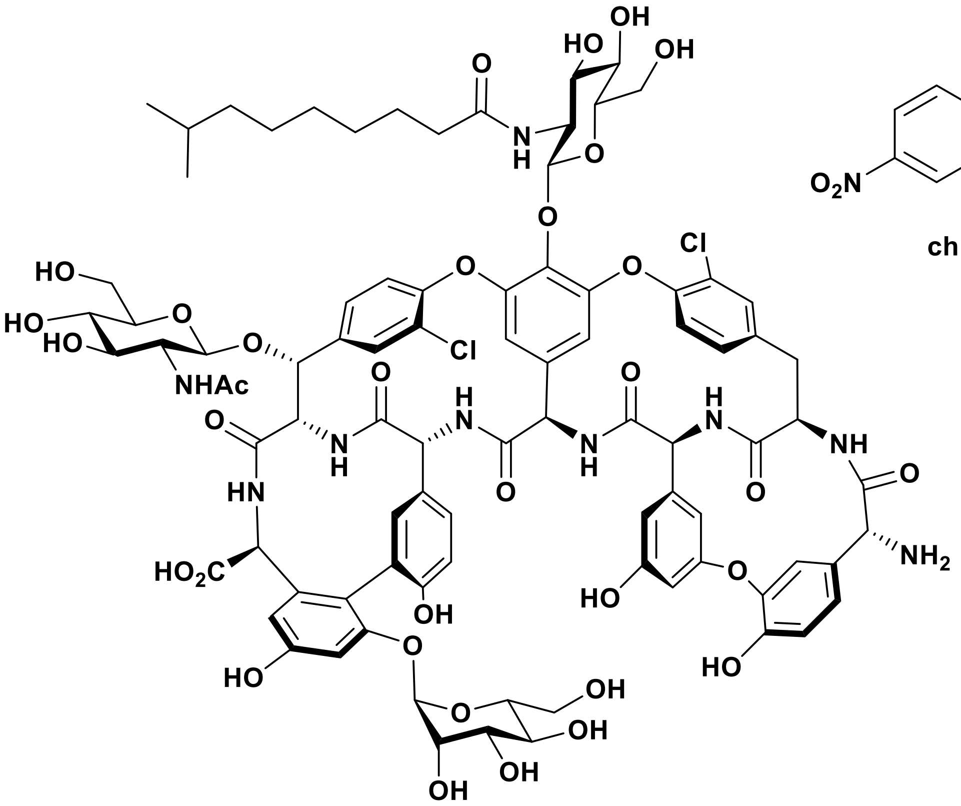


daptomycin

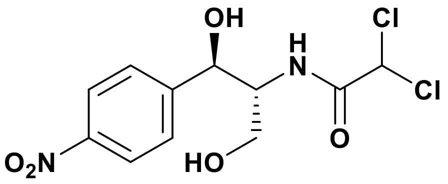


quinupristin

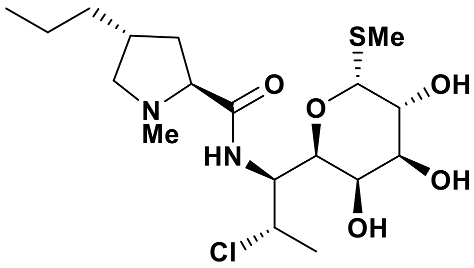
Glycopeptides (7), phenicols (6), ansamycin (6), lincosamide (4)



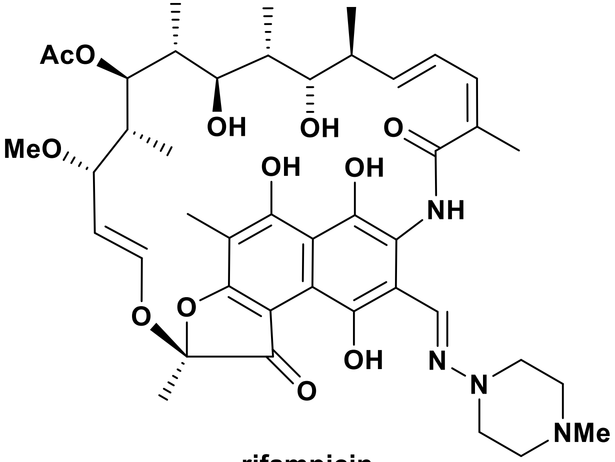
teicoplanin A$_2$-2 (teicoplanin complex)
glycopeptides



chloramphenicol
phenicols

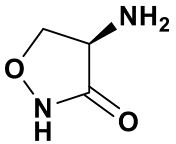


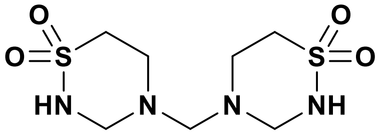
clindamycin
lincosamides



rifampicin
ansamycins

Amino acids (3), pleuromutilin (2) and various (5 x 1)

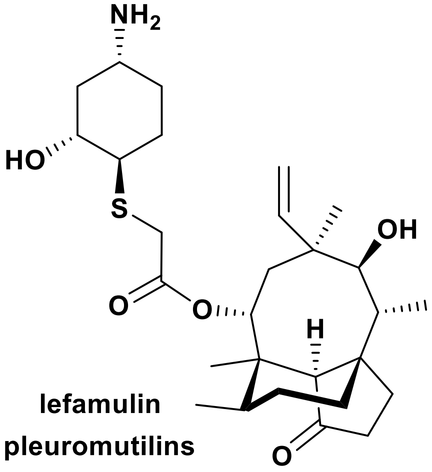




D-cycloserine

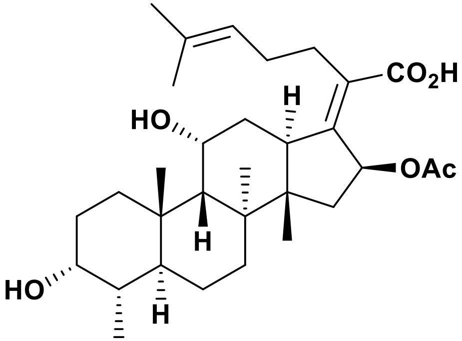
taurolidine

amino acids



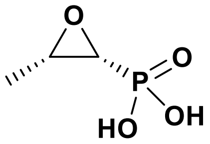
lefamulin

pleuromutilins



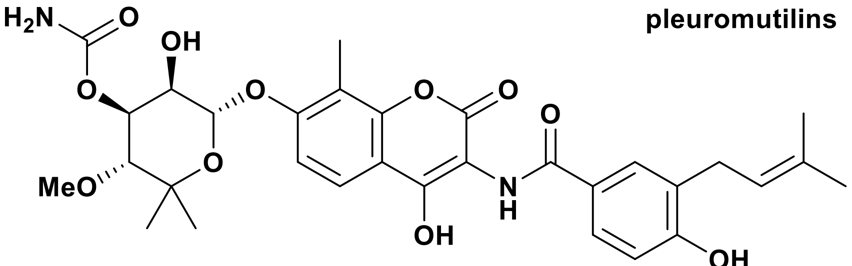
fusidic acid

fusidane



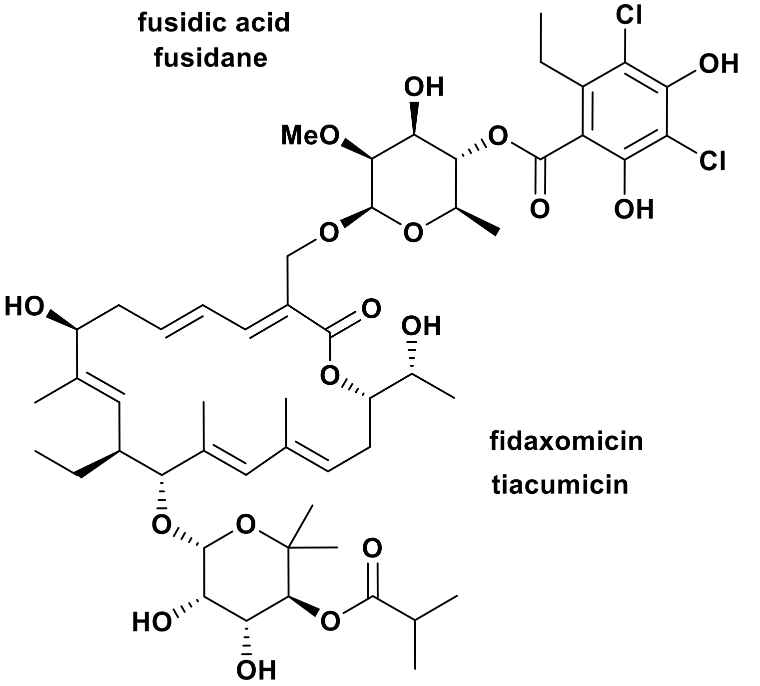
fosfomycin

fosfomycin



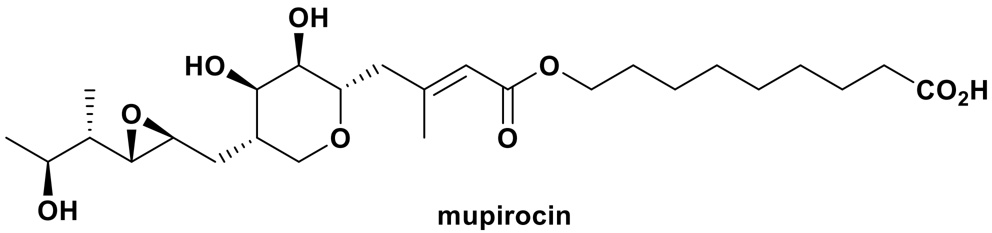
novobiocin

aminocoumarin



fidaxomicin

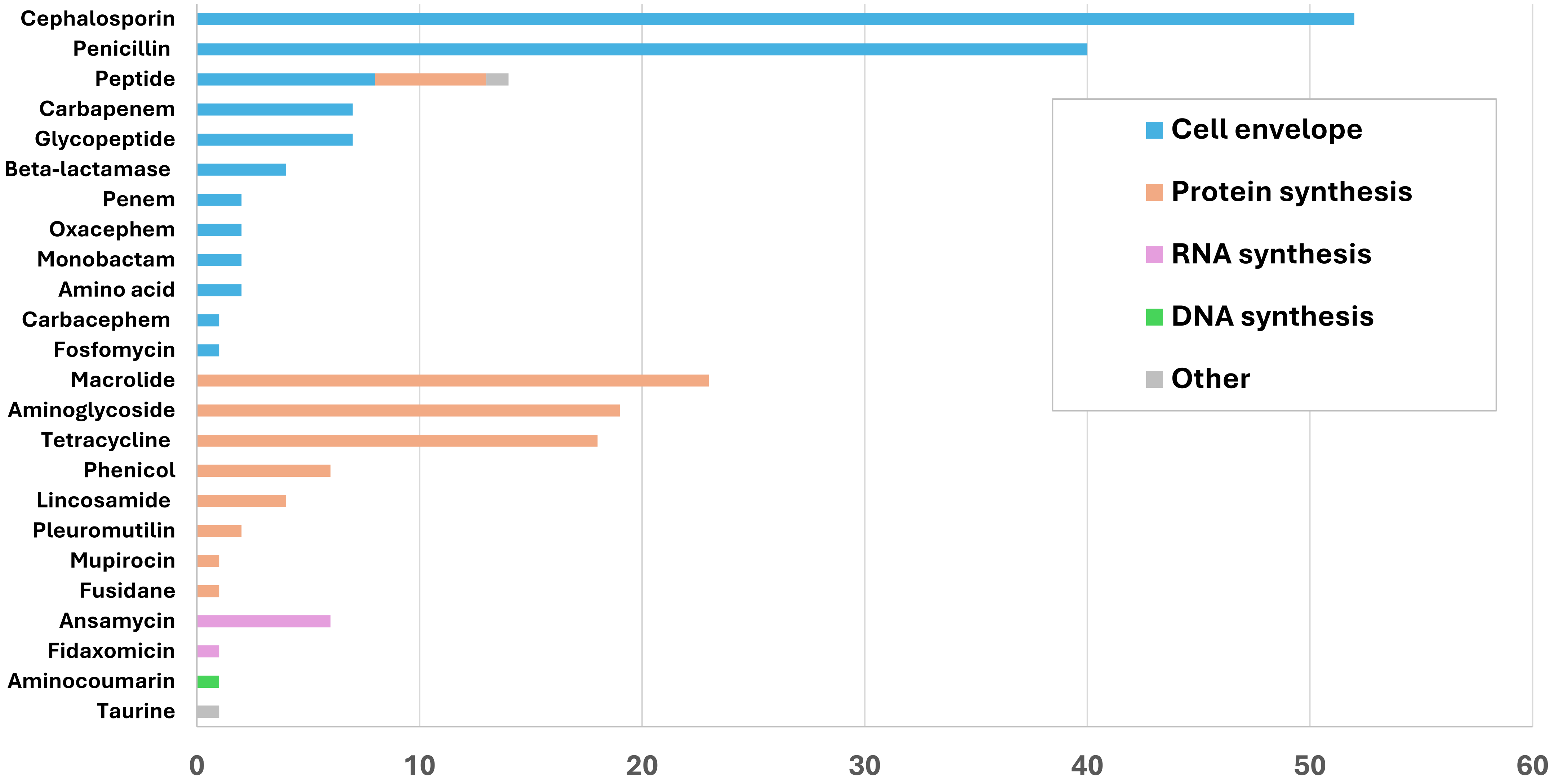
tiacumicin



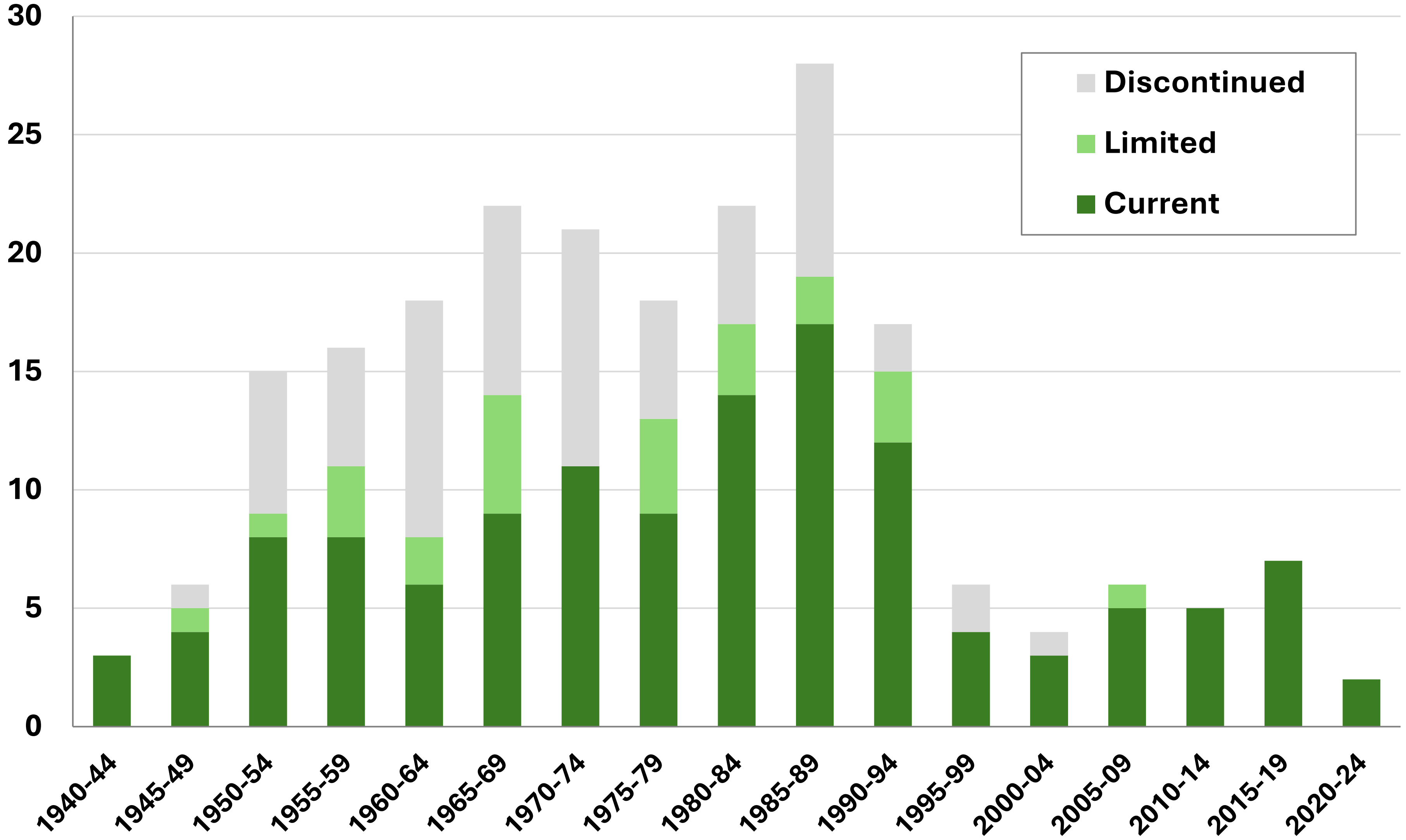
mupirocin

mupirocin

Antibiotics by class and mechanism

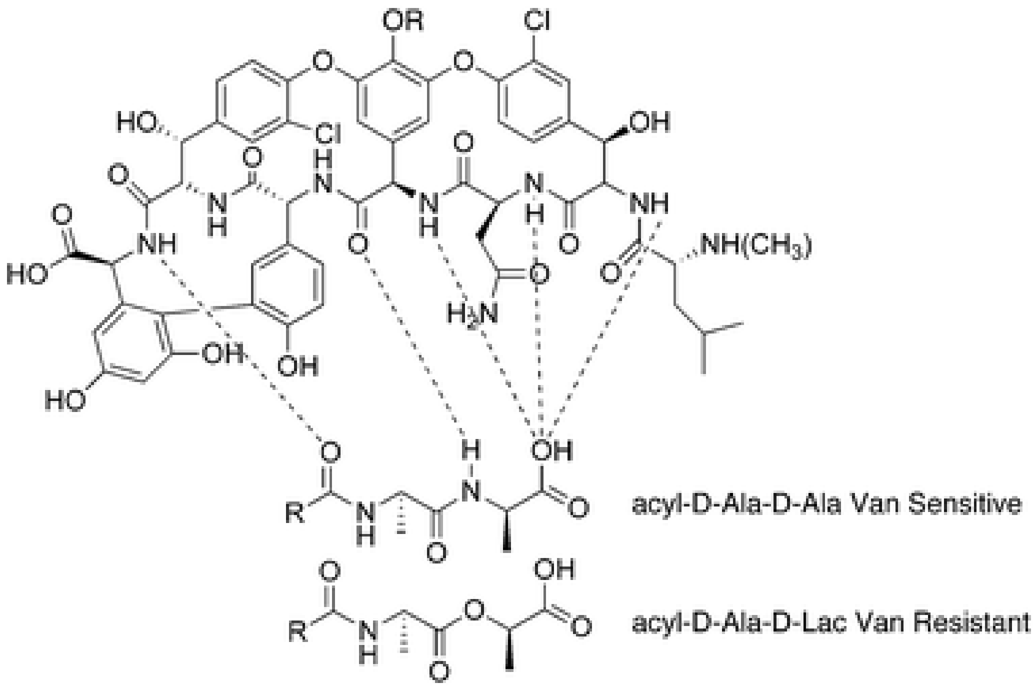


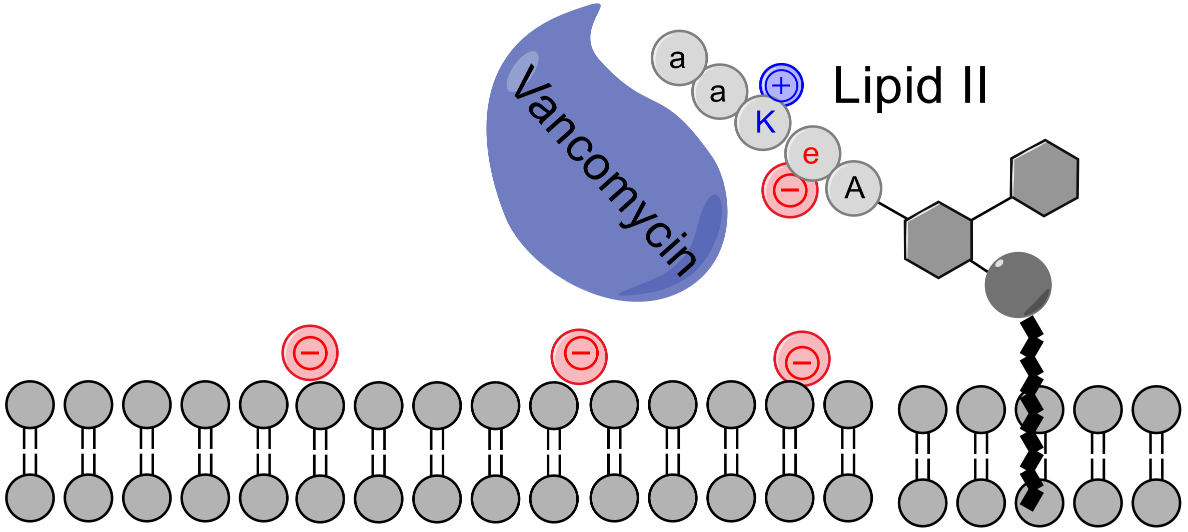
Approved antibiotics (current usage) over time (1940–2024)



4. Lessons from the vancapticin R&D program

- Glycopeptides bind to D-Ala-D-Ala component of peptidoglycan
- Could we design vancomycin derivatives that also bound the lipid layer?

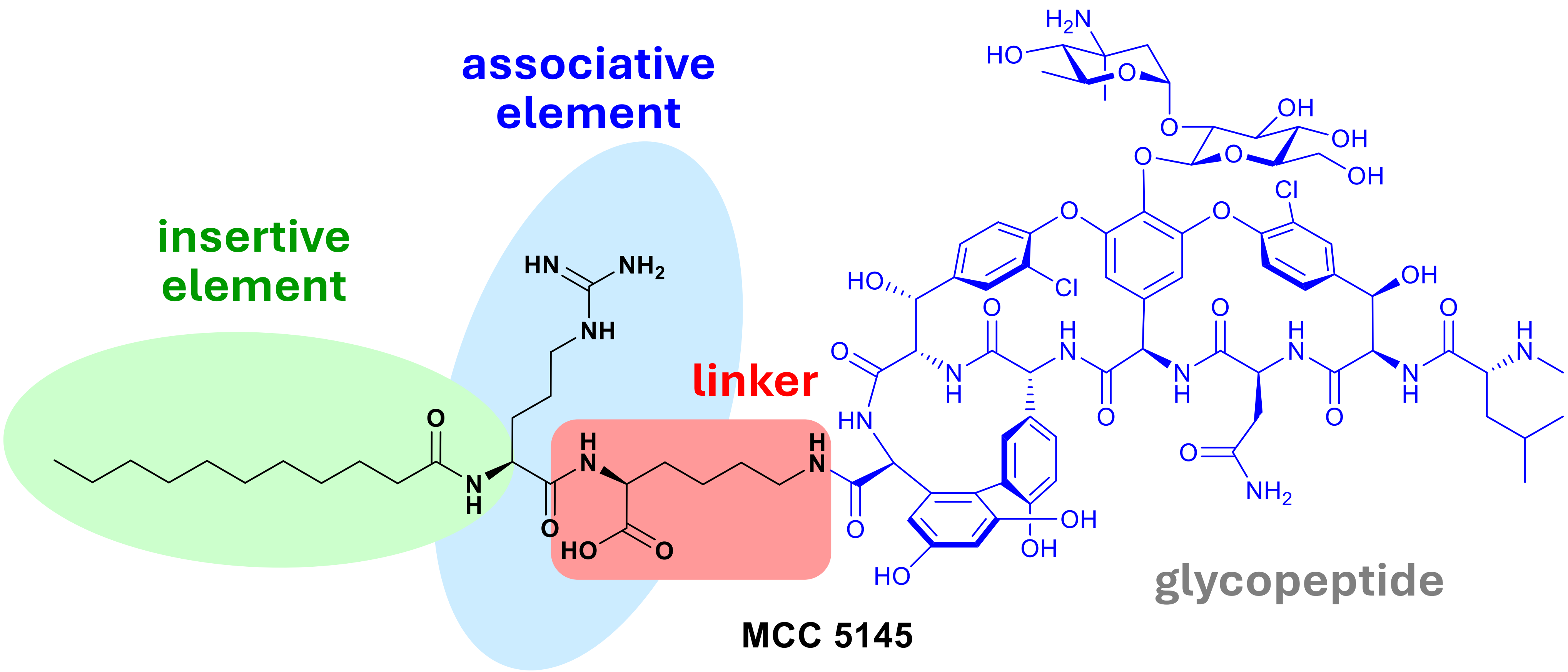




Cytoplasmic membrane of Gram+ve bacteria

Vancapticin MCC 5145 structure

- Over 300 combinations were prepared
- MCC 5145 selected for preclinical evaluation



MCC 5145

MCC5145 biological activity and properties

- **Potency, spectrum and resistance**
  - MIC_{90} ≤ 0.06 μg/mL against hundreds of MRSA and other key Gram-positive pathogens
  - Active vs VISA/VRSA and VanA VRE at MICs 4–>8 μg/mL, better than vancomycin/dalbavancin
  - Also active against biofilm and periprosthetic joint infection (PJI)-associated MRSA
  - Retains sub-μg/mL MICs in 50% human serum and lung surfactant
  - >1000-fold window over mammalian cell cytotoxicity
  - Low propensity for resistance selection *in vitro*

- ***In vivo* efficacy and safety**
  - Efficacious in multiple murine models (MRSA thigh infection, *S. pneumoniae* septicaemia, oral *C. difficile* model, foreign-body infection model), with PK consistent with once-daily dosing
  - Reduced nephrotoxicity versus vancomycin at microbiologically active doses
  - Good solubility and workable IV/oral formulations

Science Translational Medicine **2022**, *14*, doi: 10.1126/scitranslmed.abj2381
Antimicrobial Agents and Chemotherapy **2021**, *65*, e02443-20, doi: 10.1128/AAC.02443-20
Microbiology Spectrum **2023**, *11*, doi: 10.1128/spectrum.04459-22

Vancapticin epilogue

Clinical need and market in early stages of the project

- Vancomycin still used in hospitals; teicoplanin outside USA
- Semi-synthetic telavancin approved in 2009 but has issues
- Funded by the Wellcome Trust and Australian NHMRC from 2009 to 2017
- 10 g synthesis and late-stage pre-clinical toxicity successfully completed

Clinical need and market in 2017

- Approval of semi-synthetic glycopeptides oritavancin and dalbavancin in 2014
- Funding was halted as it was perceived that there was 'no market' for an IV administered Gram-positive only or a non-selective *C. difficile* treatment

Science Translational Medicine **2022**, *14*, doi: 10.1126/scitranslmed.abj2381
Antimicrobial Agents and Chemotherapy **2021**, *65*, e02443-20, doi: 10.1128/AAC.02443-20.
Microbiology Spectrum **2023**, *11*, doi: 10.1128/spectrum.04459-22
Nature Communications, **2018**, *9*, 22, doi: 10.1038/s41467-017-02123-w.
Antimicrobial Agents and Chemotherapy **2018**, *63*, e01760-18, doi: 10.1128/AAC.01760-18

5. Thoughts on NP antibacterial lead discovery & development

- **There is a still a medical unmet need**
    - Orally bioavailable agents active against MDR G-ve pathogens
    - Safer and more effective treatments for MDR *P. aeruginosa* and *A. baumannii*
    - Agents that retain activity against metallo-β-lactamase-producing organisms

- **How can NPs continue to have an impact on antibacterial drug discovery?**
    - There are diminishing opportunities for “me too” antibacterial drugs
    - Use of bioassay-guided isolation, focus on new targets, innovative whole-cell assays
    - However, need sophisticated dereplication for whole-cell screening
    - Focus on new chemistry and new organisms (or new BSGs)

Thoughts on NP antibacterial lead discovery & development

- **Data sharing (after projects are completed)**
  - Why did the project fail? What needs to be improved?
  - There are only finite resources (and opportunities)

- **"The Broken Antibiotics Business Model – Part V: The Scorecard", Aleks Engel (Novo Holdings), LinkedIn post, 31 March 2026**
  - From 15 public companies initially analysed in 2018
    - 7 have gone bankrupt, been delisted, or entered liquidation proceedings
    - 3 were acquired or taken private at depressed/moderate valuations
    - 2 have pivoted from the antibiotics space entirely
    - 1 achieved a remarkable exit only after pivoting away from antibiotics
    - 2 remain independently active with anti-infectives franchises
  - Medium to Big Pharma: Merck, GSK, Pfizer, Roche, Shionogi and Wockhardt still involved, several emerging companies in China
  - How to best move forward?

Acknowledgments

- **PhD studies**
  - Antarctic sponge that contained Cd and Zn – crystals of $KCdCl_3$
- **Singapore, IMCB and MerLion Pharmaceuticals (1999 – 2009)**
  - HTS antibacterial targets, preclinical development and clinical trials
- **University of Queensland**
  - 2009 – 2017 @ IMB with Prof Matt Cooper – included vancapticin project
  - 2018 – 2019 @ UQCCR with Prof David Paterson (now in Singapore)
  - 2022 – 2026 @ IMB (casual) with Profs Rob Capon, Ian Henderson and Mark Blaskovich
- **WHO Advisory Group on the "Analysis of the clinical development pipeline of antibacterial treatments" (2017–2019; consultant 2020–2022)**

Contact: LinkedIn or mark@msbchem.com

MSBChem CONSULTING

Christine Beemelmanns

Christine Beemelmanns is Professor of medicinal-Pharmaceutical Microbiota Research at Saarland University, together with the HIPS in Germany. Her research combines different aspects of applied microbiology and organic and natural product chemistry and aims to chemically and to functionally characterize microbial signaling and defense molecules in different model systems. The analysis of ancient and evolved microbial interactions allows her to discover unprecedented chemical core structures with pharmaceutical potential.

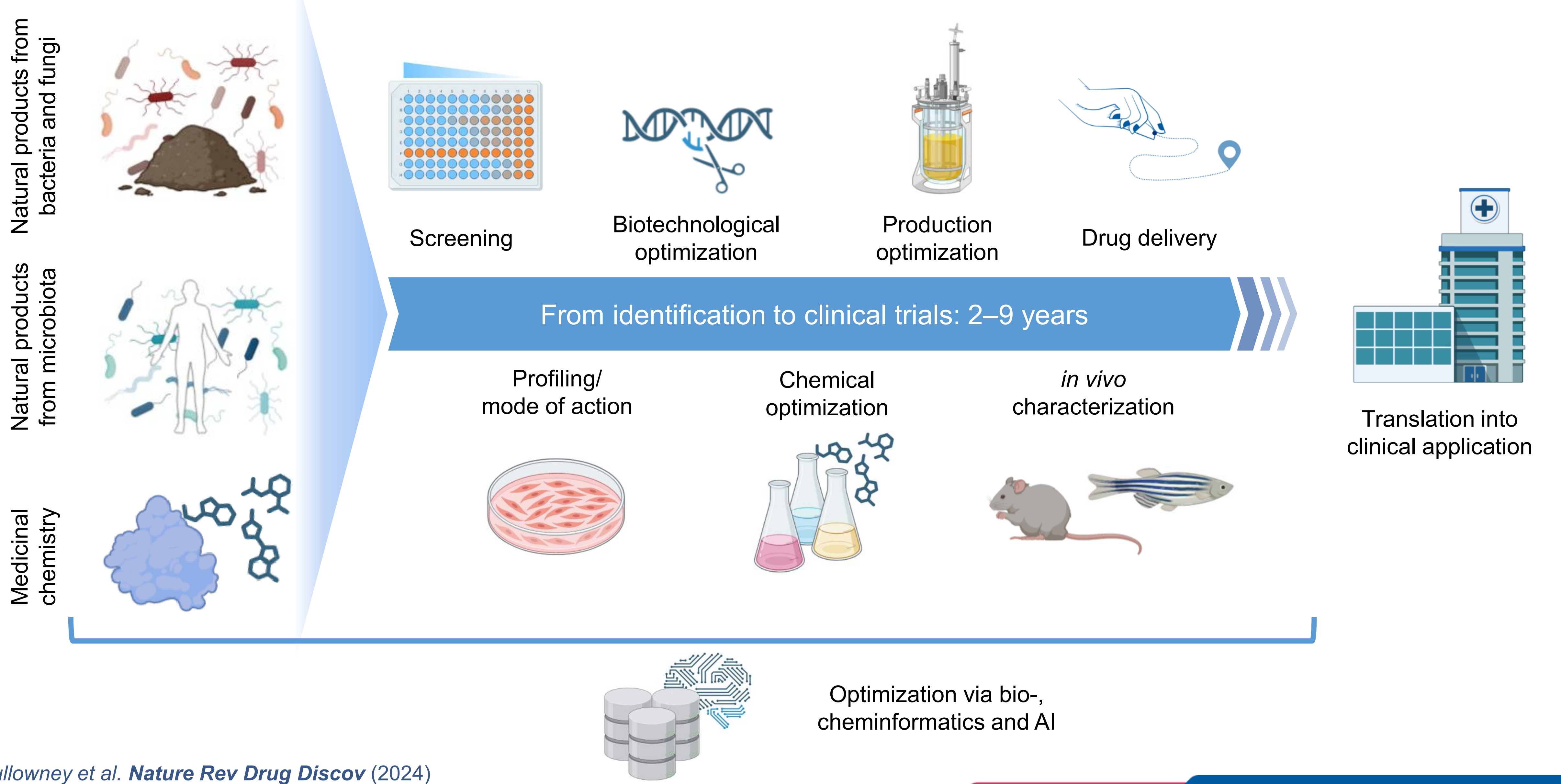
Christine has previously worked as a Junior Research Group leader in the field of Natural Products Chemistry and Chemical Biology at Hans-Knöll Institute (HKI), Germany and as a Margaret L. and Harlan L. Goering Visiting Professor in Organic Chemistry at UW Madison, USA and as a Professor for Biochemistry of Microbial Metabolism at the Leipzig University. She received her PhD in Organic Chemistry after working at FU Berlin with Hans-Ulrich Reissig.

Chemistry of Microbe-Host Interactions

Schmidt et al. ***Nat Prod Rep*** (2022)
Beemelmanns et al. ***Beilstein J Org Che***
Guo et al. ***Nat. Prod. Rep*** (2019)

, Beemelmanns, ***J. Chem. Ecol***. (2018)
Leichnitz et al. ***Soc. Rev***. (2017)

HZI/HIPS Integrated Strategy and Approach

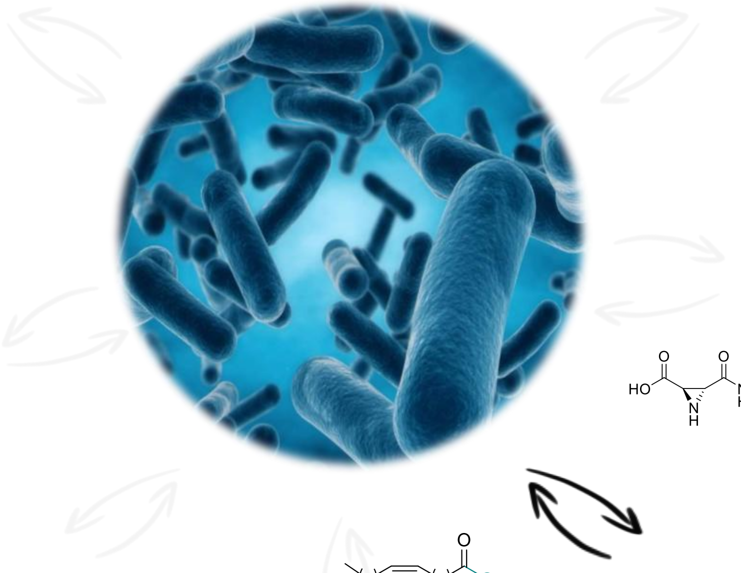


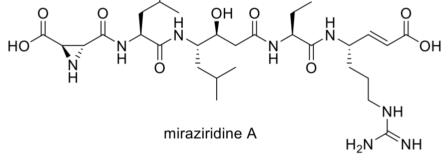
Mullowney et al. ***Nature Rev Drug Discov*** (2024)

HZI HELMHOLTZ Centre for Infection Research

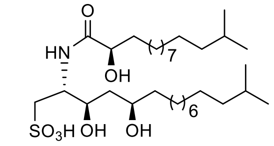
Chemistry of Microbe-Host Interactions

Beemelmanns et al., ***JACS*** (2014)
Raguz et al., ***Angew Chem Int Ed Engl***. (2022)

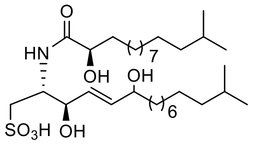




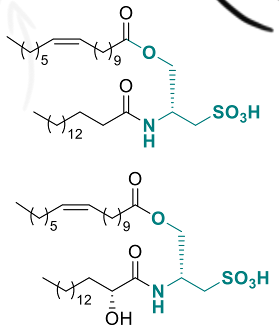
miraziridine A



RIF-1



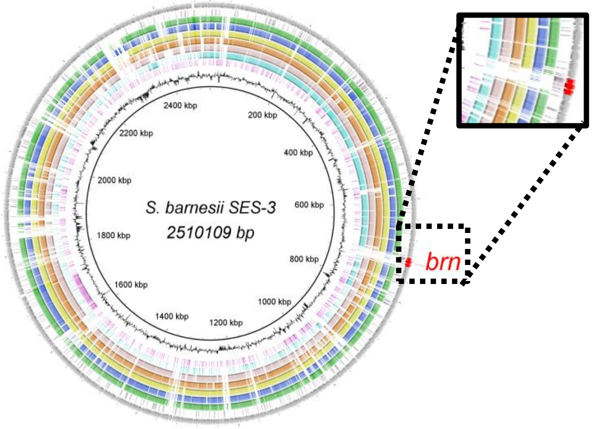
RIF-2



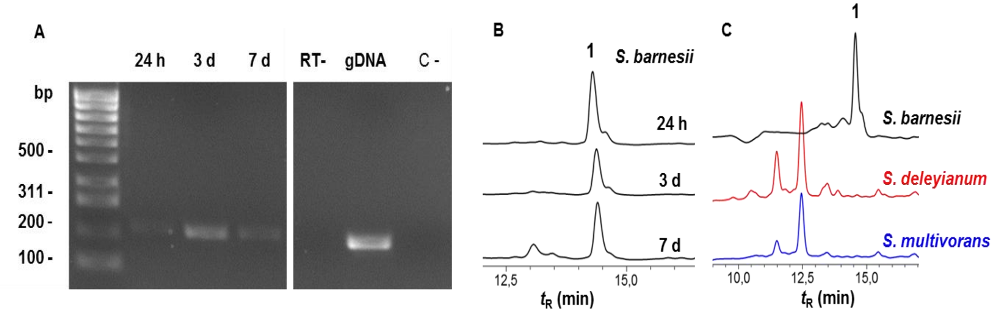
Roman et al., ***Angew Chem Int Ed Engl***. (2024)
Sauer et al., ***Angew Chem Int Ed Engl***. (2024)

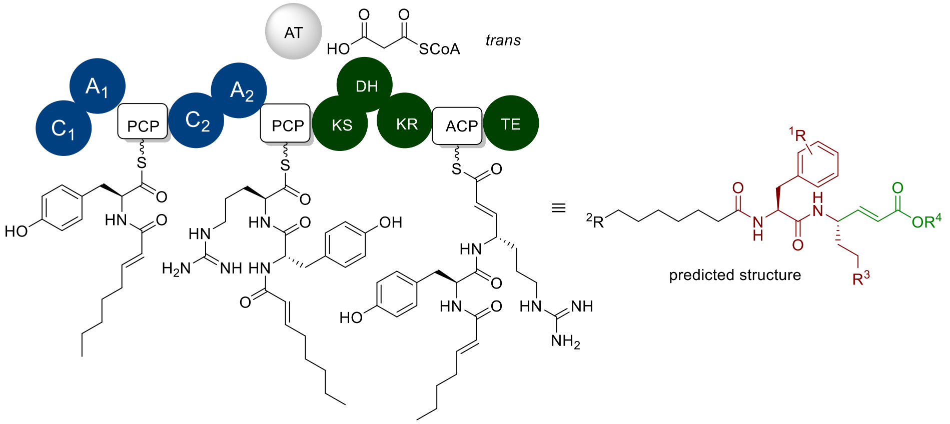
Genome-Driven Explorations - Example from Microaerophiles

Genome mining



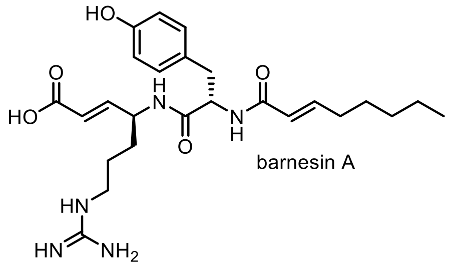
Comparative Metabolomics





Predicted Pathway and Natural Product

Isolation



barnesin A

IC_{50}
papain: 15.96 µM (± 5.8)
cathepsin B: 91.72 nM (± 3.3)

~ 1 mg /80 L (native host)
~ 1 mg/10 L (heterologous expression)

Rischer et al., ***ACS Chem Biol*** *(2018).*
Roman et al., ***Org Lett.*** *(2020)*

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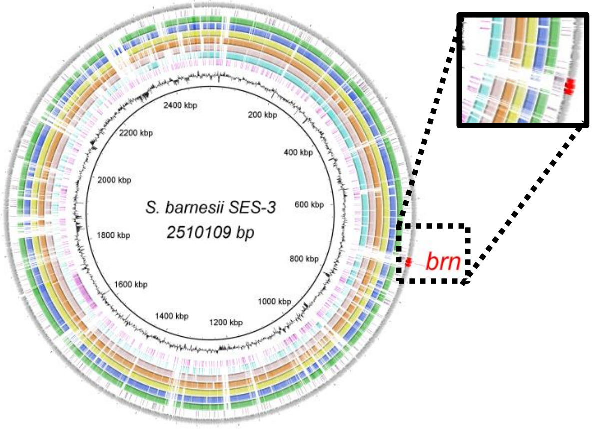
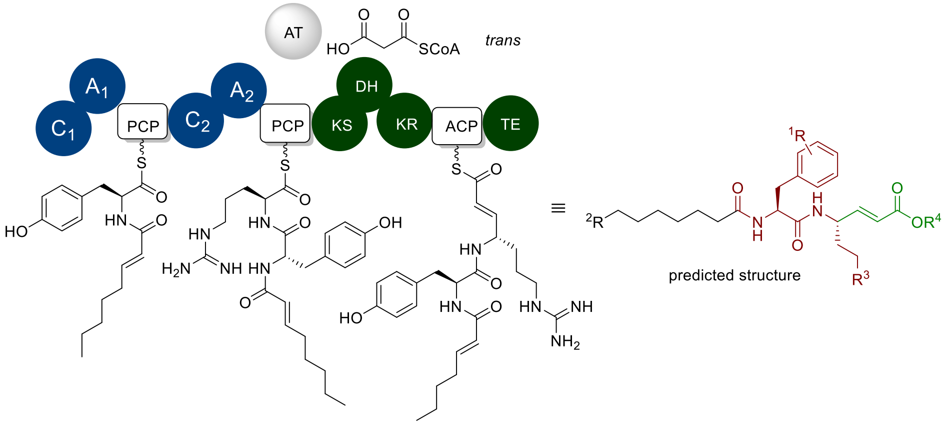
Genome-Driven Explorations - Example from Microaerophiles

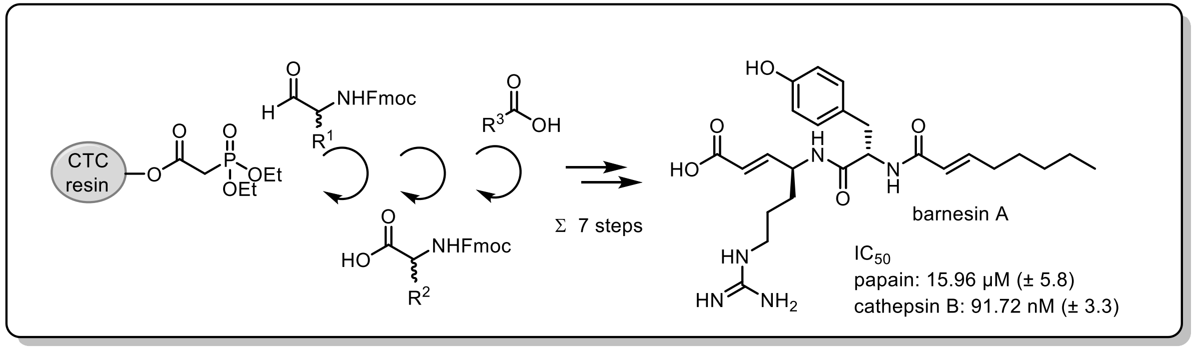
Genome mining



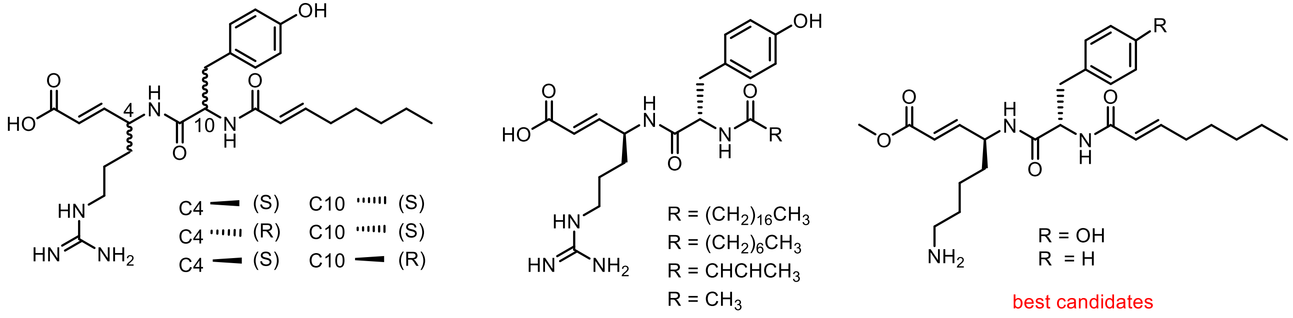


Predicted Pathway and Natural Product

Total Synthesis



14 derivatives

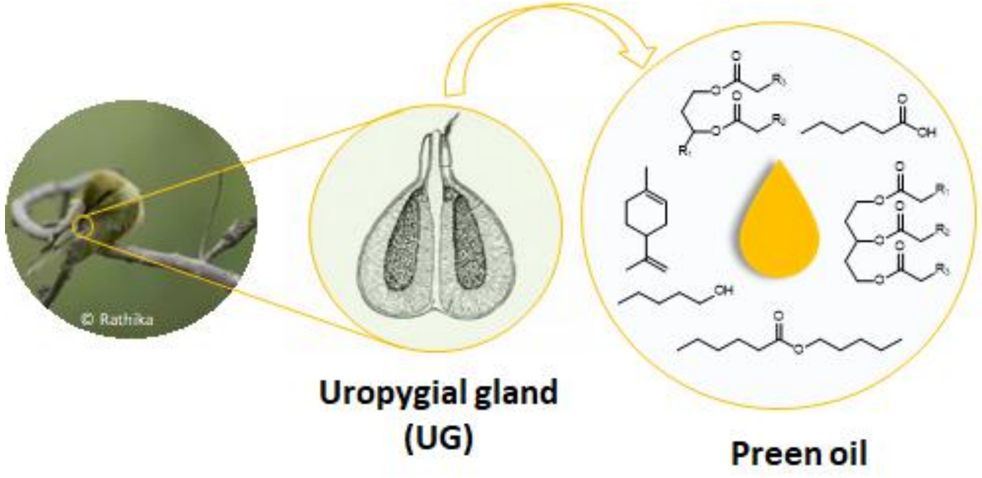


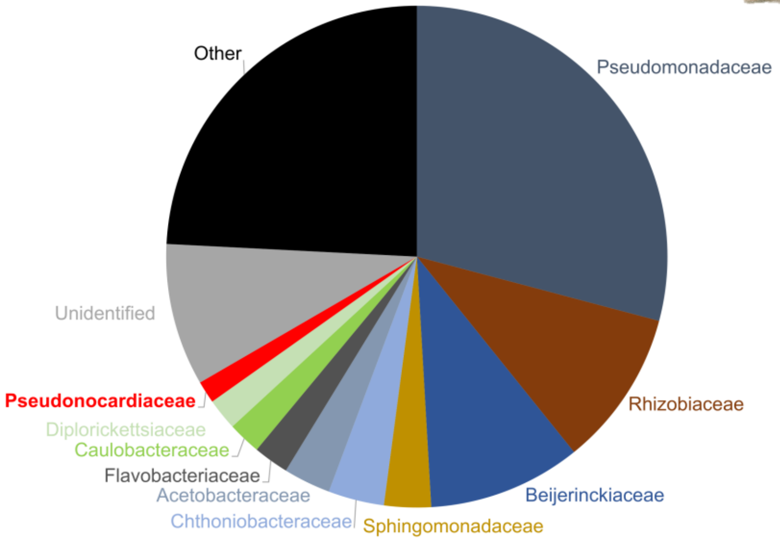
Lessons Learned:

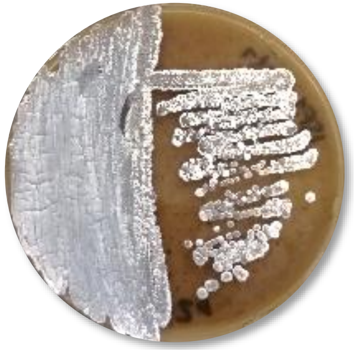
- Genome Mining of unique taxa is worthwhile
- Cultivation can become tedious for follow-up studies
- Synthetic approaches are highly valuable

Rischer et al., ***ACS Chem Biol*** *(2018).*
Roman et al., ***Org Lett.*** *(2020)*

Mining the Birds Microbiome For Antifunagls



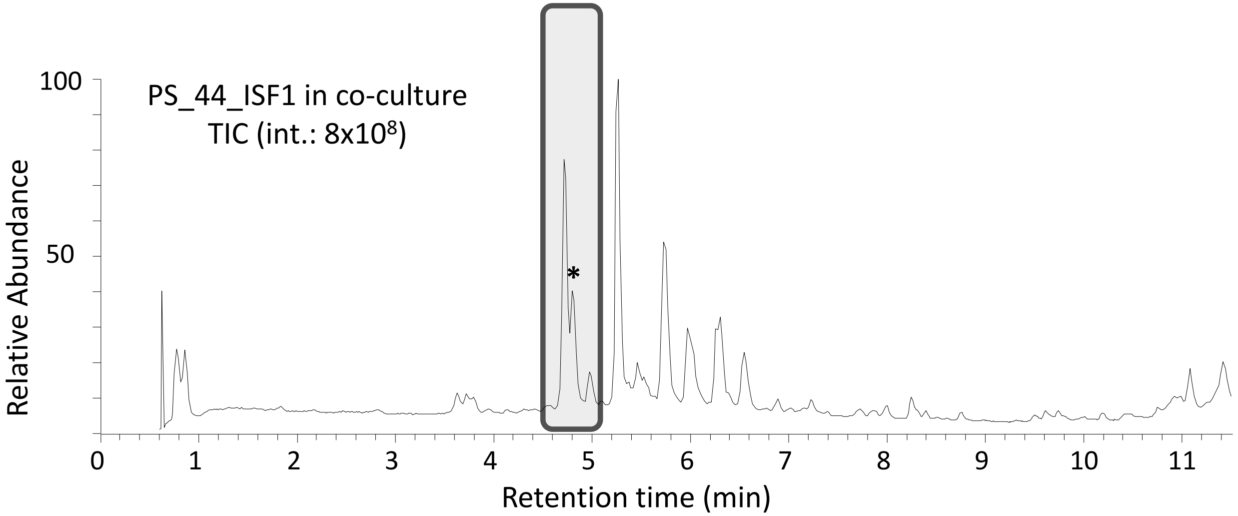


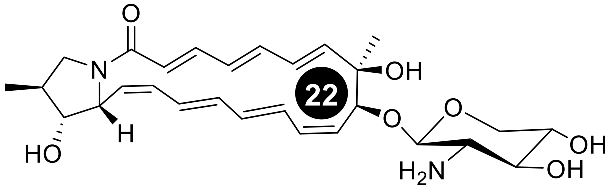


Amycolatopis sp. PS_44_ISF1

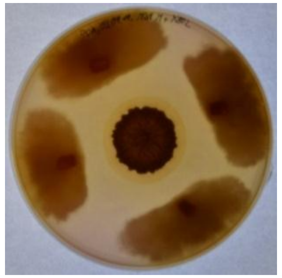
Seibel et al., ***Nat Commun*** *(2024)*
Seibel et al., ***Commun Chem*** *(2023)*

Microbial Symbiont Produces Protective Metabolites



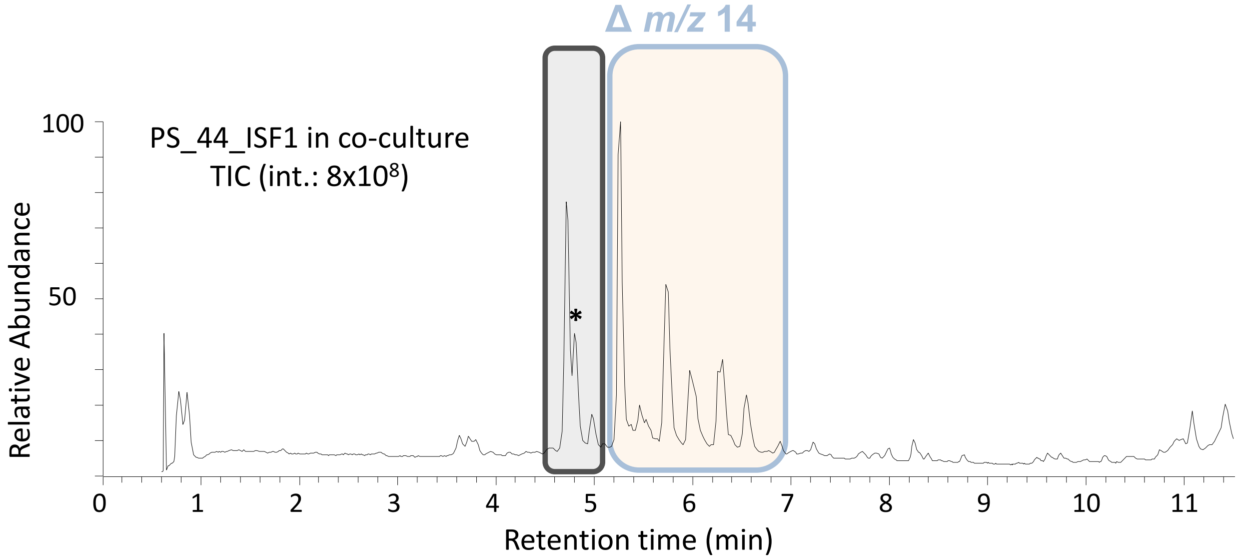


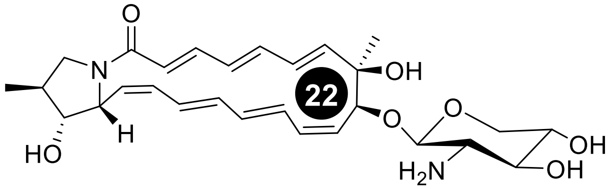
ciromicin A
(antifungal activity, cellular toxcicity)



Seibel et al., ***Nat Commun*** *(2024)*
Seibel et al., ***Commun Chem*** *(2023)*

Microbial Symbionts Produces Protective Metabolites





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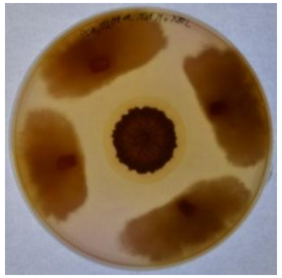
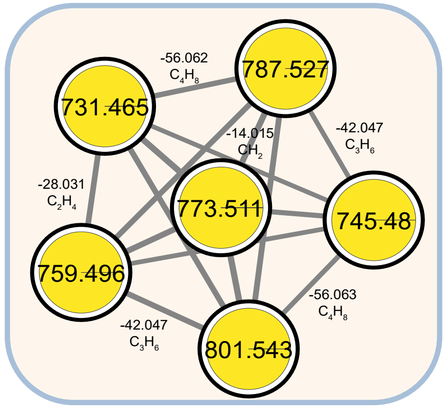
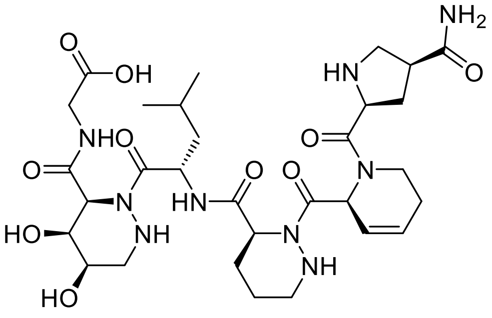
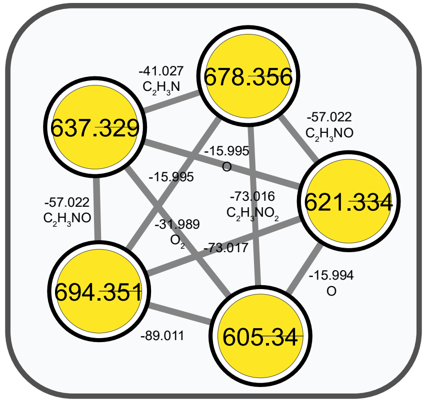
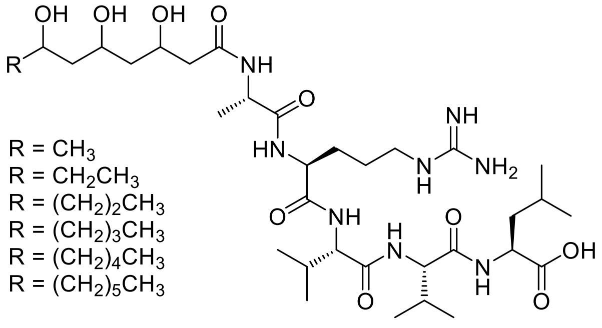






demiguisin
(derivatives exhibit moderate Mtb activty)





pachycephalamide A-F
(tensioactive properties)

Lessons Learned:
- co-secretion of highly bioactive metabolites
- Context-specific activation of transcription/metabolite production
- Combined bioactivities likely important for ecological context

Seibel et al., ***Nat Commun*** *(2024)*
Seibel et al., ***Commun Chem*** *(2023)*

HZI HELMHOLTZ Centre for Infection Research

Soil Microbiomes – Vast Taxonomic and Chemical Space

Gram+ Gram-

parasites

Schmidt et al ***Nat Prod Rep*** *(2022)*
Beemelmanns et al. ***Beilstein J Org Chem*** *(2016)*
Guo et. al. ***Nat. Prod. Rep*** *(2019)*
Götze et al. ***Nat. Prod. Rep (****2026) in press.*

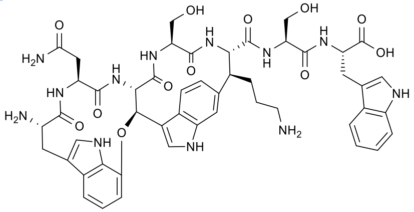
Wichard, Beemelmanns, ***J. Chem. Ecol****.* (**2018**)
Leichnitz et al. ***Soc. Rev****.* (**2017**)

Preclinical projects: Novel anti-infectives from soil bacteria

Gram+ Gram- parasites

Darobactin

New Gram-negative antibiotic

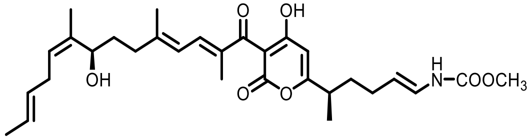


Clinical CRAB isolates:
D22: MIC 0.0625 – 0.5 µg/mL

- Active against **Gram-** in **low µM range**
- **No *in vitro* cytotoxicity** detected
- **Heterologous production platform** established
- optimized versions with **significantly improved bioactivity**
- ***in vivo* activity against *E. coli*** in murine infection model

Corallopyronin

Novel antiparasitic agent



Corallopyronin A

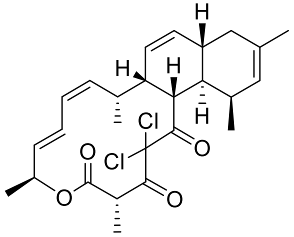
- Development as **treatment of river blindness**
- **Improved oral bioavailability**
- Successful industrial upscaling
- Else Kröner Fresenius Stiftung **funds production** for phase I
- to enter **clinical phase I 2024/25**

Chlorotonil

Unique scaffold & superb activity

VRE MIC 0.025 µg/mL

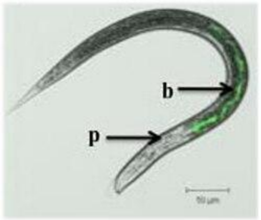
P. falciparum IC_{50} **14 nM**

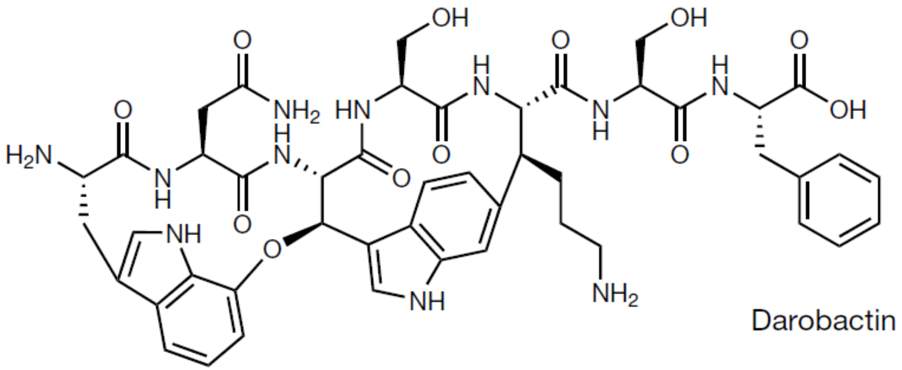


Chlorotonil A

- Active against **MRSA, VRE,** and ***Plasmodium falciparum***
- **Semi-synthetic** approach established
- Promising results in **murine infection models**
- new frontrunner in preclinical development
- **INCATE** funding in 2023

Darobactins from the Nematode Microbiome





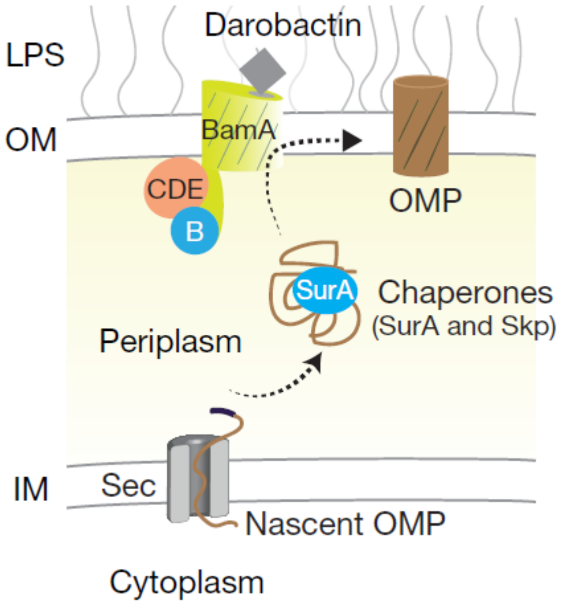
Imai et al, Nature 2019

- **First report by the Lewis Lab 2019**
- reported from entomopathogenic nematode microbiome

  isolates => *Photorhabdus* and *Xenorhabdus* species.
- Ribosomally Synthesized and Post-translationally Modified Peptide (RiPP) antibiotic.
- produced from a nearly silent BGC; only expressed at very low levels under typical laboratory growth conditions.

Photorhabdus sp.	# Strains in screen	Source	*Xenorhabdus sp.*	# Strains in screen	Source
P. akhurstii	1	DSMZ*	*X. beddingii*	1	HGB
P. caribbeanensis	1	DSMZ	*X. bovienii*	12	HGB
P. cinerea	1	DSMZ	*X. doucetiae*	1	HGB
P. hainanensis	1	DSMZ	*X. indica*	5	DSMZ
P. heterorhabditis	2	DSMZ	*X. innexi*	3	HGB and DSMZ
P. kayaii	1	DSMZ	*X. ishibashi*	1	DMZ
P. khanii	2	HGB† and DSMZ	*X. japonica*	2	HGB and DSMZ
P. kleinii	1	DSMZ	*X. japonicus*	1	HGB
P. laumondii subsp. laumondii	1	DSMZ	*X. khoisanae*	4	DSMZ
P. luminescens	3	HGB	*X. miraniensis*	2	HGB
P. noenieputensis	1	DSMZ	*X. nematophila*	2	HGB
P. stackebrandtii	1	DSMZ	*X. poinarii*	3	HGB
P. tasmaniensis	1	DSMZ	*X. szentirmaii*	1	HGB
P. temperata	6	HGB and DSMZ			
P. thracensis	1	DSMZ			
Photorhabdus sp.	5	HGB			

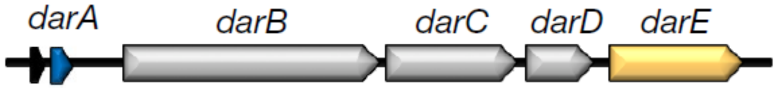
Imai et al. ***NATURE*** (2019)



Darobactin disables target BamA (translocator & chaperone for folding OM proteins) leading to cell lysis!

HZI HELMHOLTZ Centre for Infection Research

Darobactin: a Novel Antibiotic Acting on a Novel Target

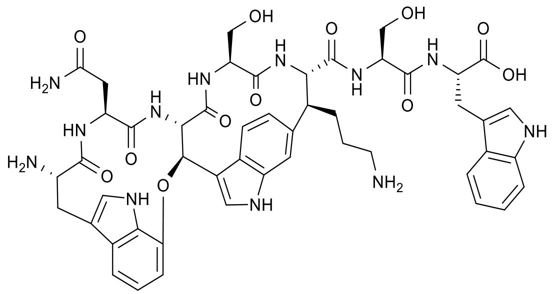


Hirsch

Kazmaier

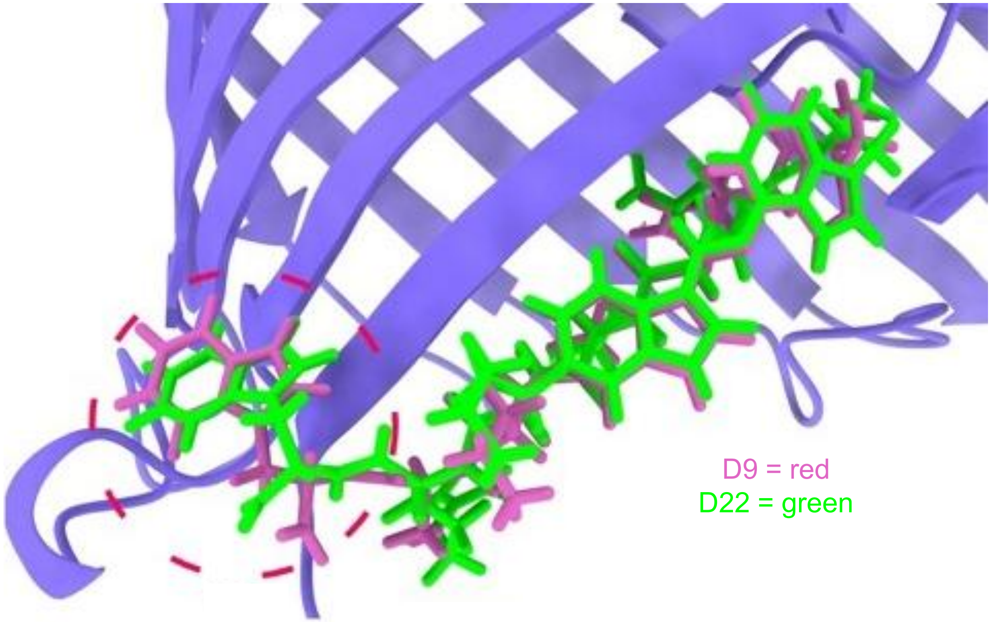
*Target **BamA:** translocator & chaperone for folding OM proteins*

Natural Products

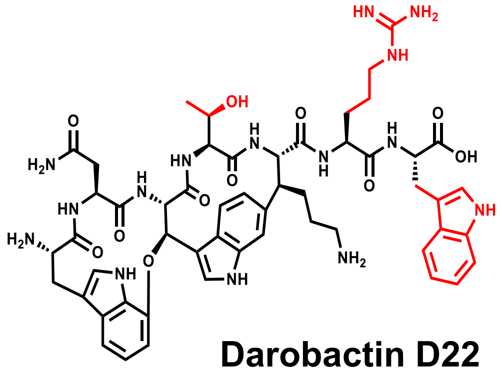


Darobactins

Heterologous production of biosynthetic derivatives



Semisynthesis



Darobactin D22

Semisynthesis → non-natural darobactins

Müller

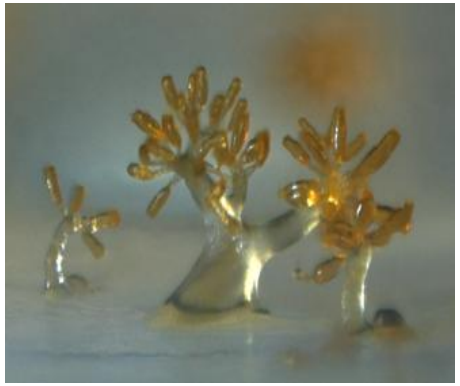
Lead **optimization** towards **novel treatment** for pneumonia

HELMHOLTZ
RESEARCH FOR GRAND CHALLENGES

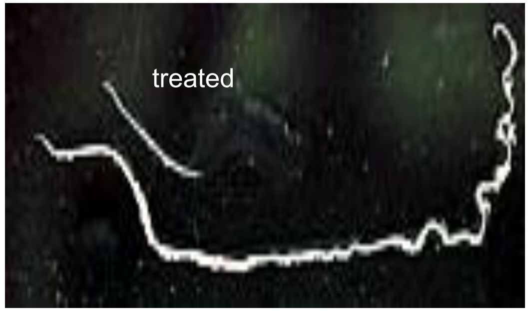
Groß et al. ***Chem Sci*** (2021); *Seyfert et al.* ***J Med Chem*** (2023);
Seyfert et al. ***Angew Chem Int Ed*** (2023); *Seyfert et al. WO2022/175443A1*

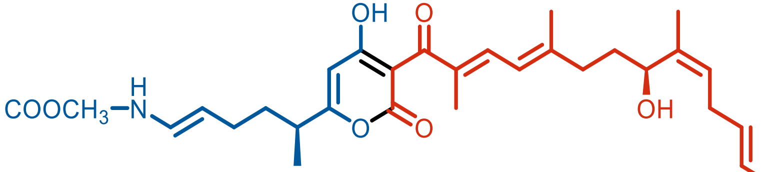
Corallopyronin as Novel Antiparasitic Agent

Müller



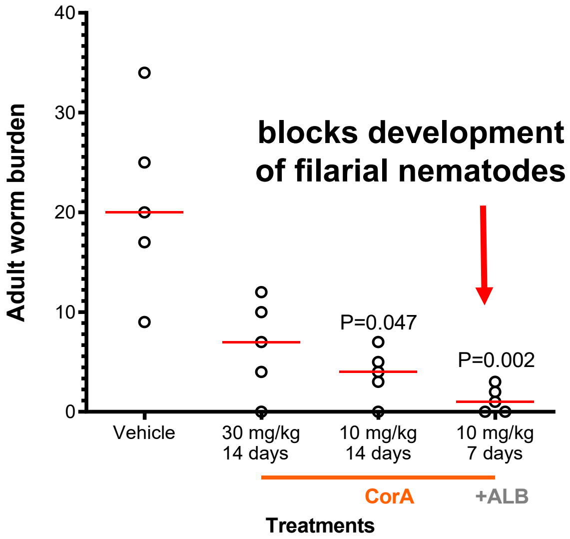
nematodicidal





Corallopyronin A

Initial yields: <1 mg/L



Filariasis

- Lymphatic filariasis (elephantiasis): 120 million infected
- Onchocerciasis (river blindness): 40 million infected

universitäts klinikumbonn

DZIF

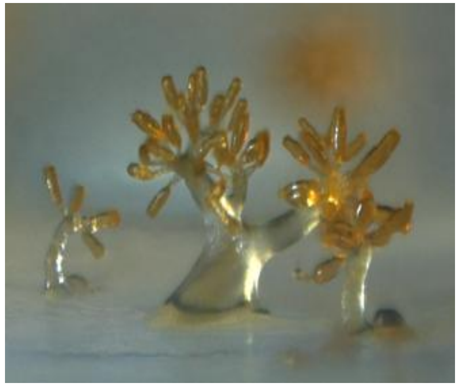
Eisai Global

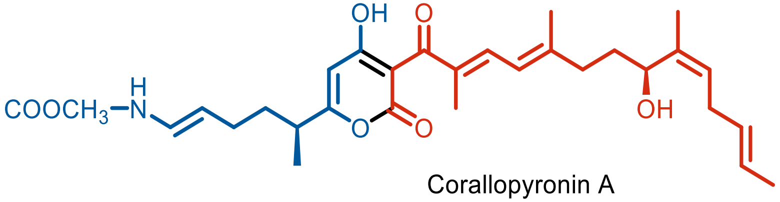
Else Kröner Fresenius Stiftung

Ehrens et al. ***Front Trop Dis*** (2022)
Schiefer et al. ***PLoS Negl Trop Dis*** (2020)
Pogorevc et al. ***Metab Eng*** (2019)
Erol et al. ***ChemBioChem*** (2013)

Corallopyronin as Novel Antiparasitic Agent

Müller

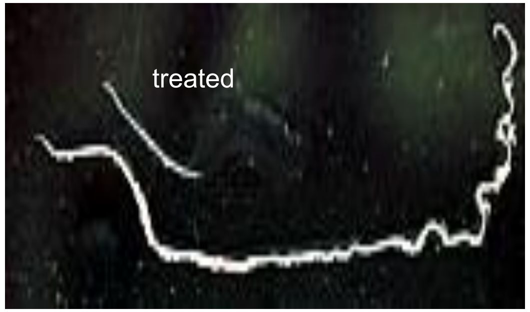


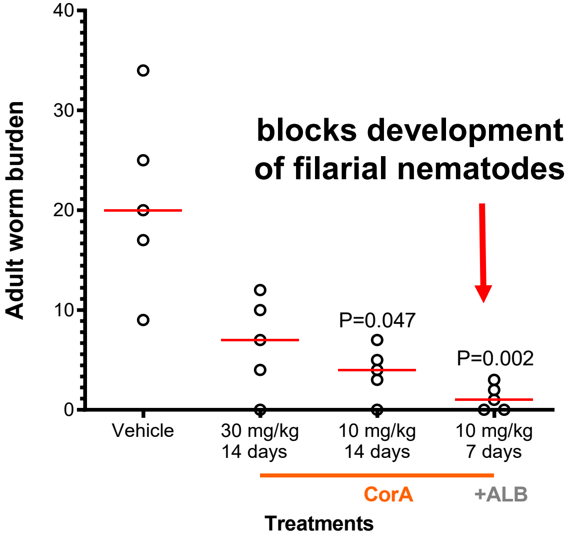


Corallopyronin A

Initial yields: <1 mg/L

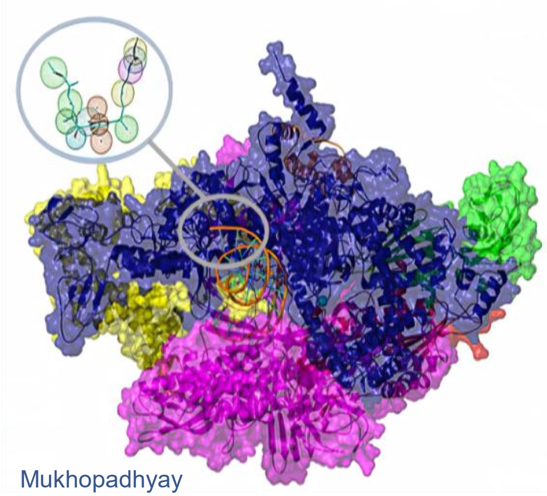
nematodicidal





filarial nematodes depend on endosymbiont ***Wolbachia***

Target: RNA polymerase



Mukhopadhyay *et al.* ***Cell*** (2008)

universitäts klinikumbonn

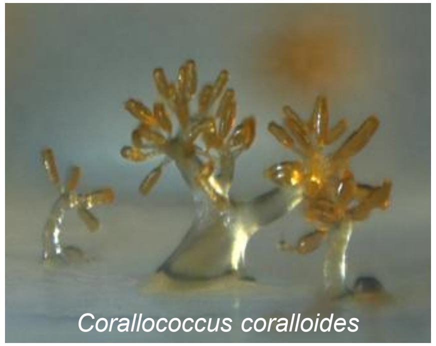
DZIF

Eisai Global

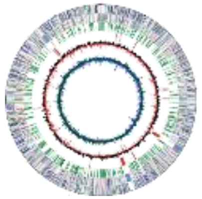
Else Kröner Fresenius Stiftung

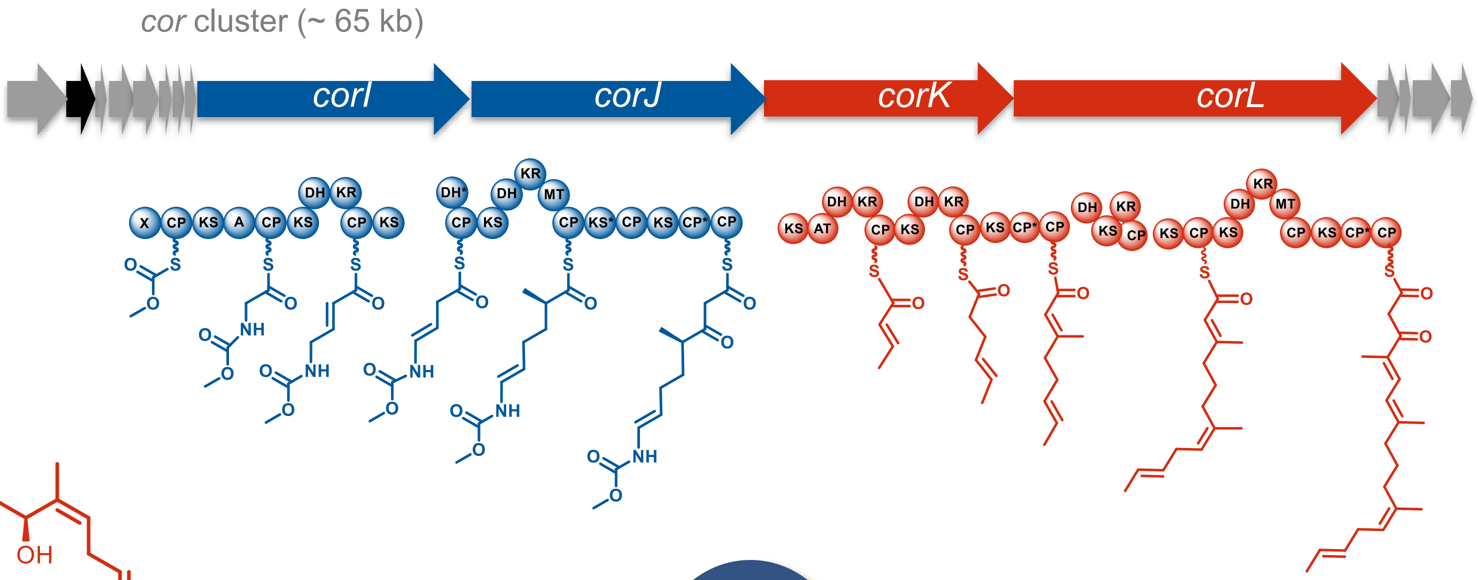
Ehrens et al. ***Front Trop Dis*** (2022)
Schiefer et al. ***PLoS Negl Trop Dis*** (2020)
Pogorevc et al. ***Metab Eng*** (2019)
Erol et al. ***ChemBioChem*** (2013)

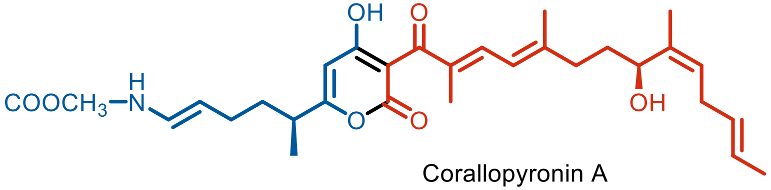
Biotechnological Production of Corralopyronin



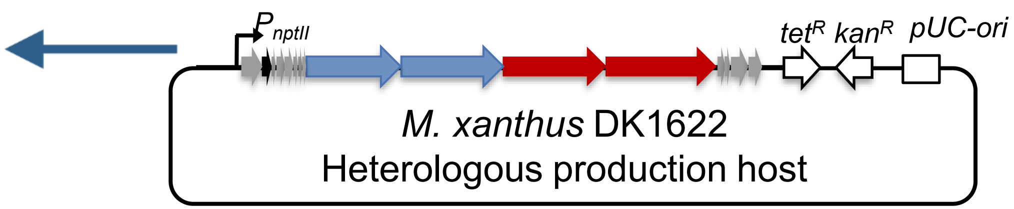
Initial yields:
<1 mg/L

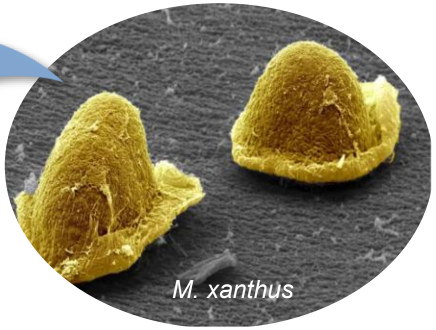


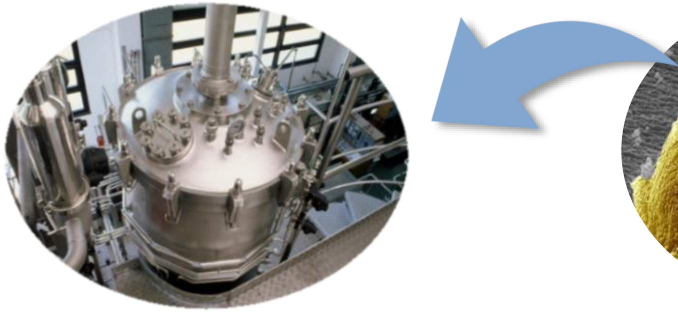




Corallopyronin A







>200 mg/L

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DZIF

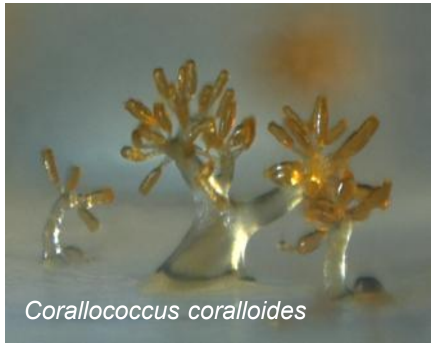
Eisai Global

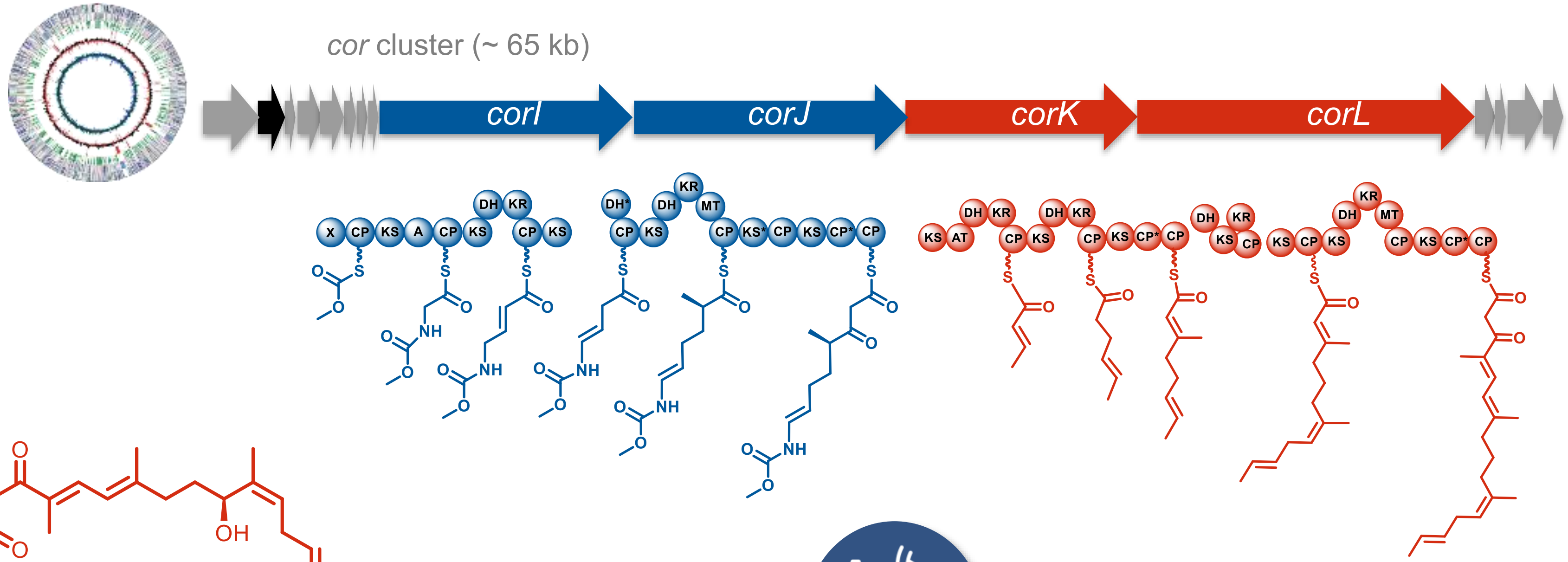
Else Kröner Fresenius Stiftung

Stadler

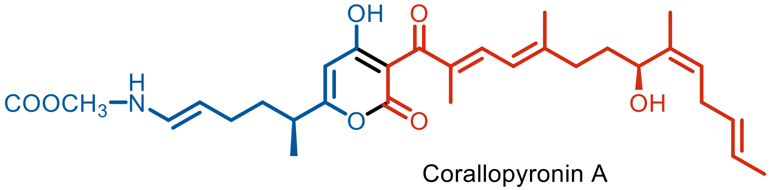
HZI HELMHOLTZ Centre for Infection Research

Biotechnological Production of Corralopyronin



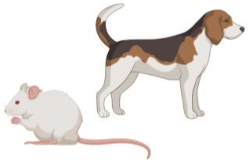


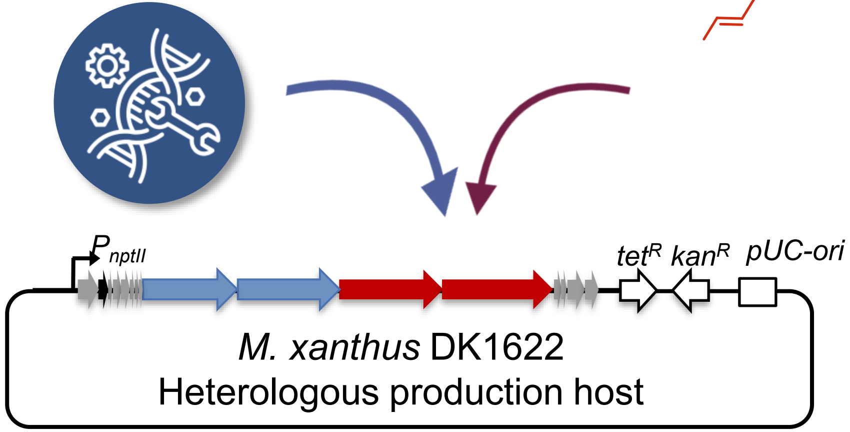
Initial yields:
<1 mg/L



Corallopyronin A

- *In vivo* toxicity
- Improved oral bioavailability
- Finalisation of preclinics





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Lessons Learned
- Understanding of ecology/pathogenicity is essential for drug target identification
- Heterologous expression important for compound supply and translation

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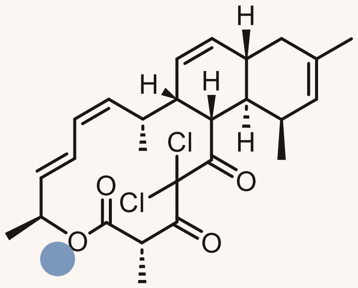
Chlorotonil – Unique Chemical Properties and Pharmacological Profile

Müller

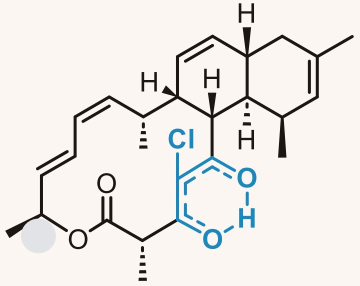
myxobacterial strain

***Sorangium cellulosum* 1525**

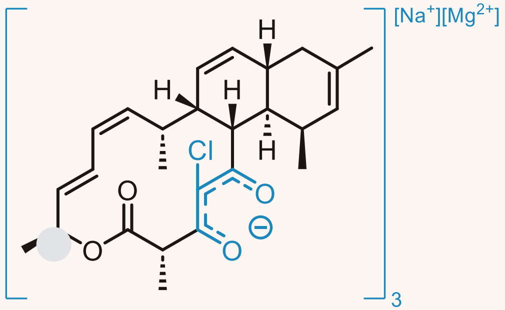
Crude extract



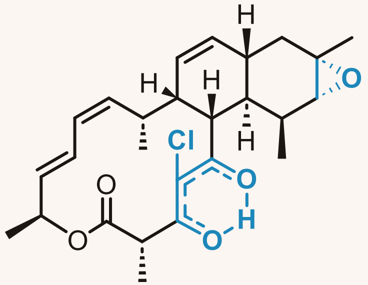
Chlorotonil A



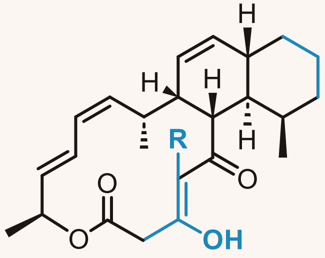
Chlorotonil B1



Chlorotonil B2



ChB1-Epo2



Chlorotonil C1, R = Cl
C2, R = H

The largest isolated

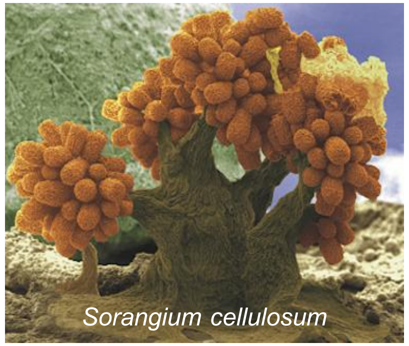
Less abundant

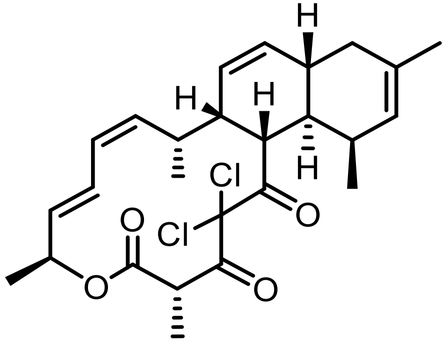
Substance information:

- **Antimalarial** activity and broad **gram positive antibacterial**
- **Highly lipophilic**
- Unique *gem*-dichloro 1,3-dione moiety
- **Total synthesis** known but **not feasible** (25 steps, 1.5% yield)
- Fermentation titer: ~40 mg/ml → **semisynthesis**

Gerth, et al. Angew. ***Chem. Int. Ed.*** (2008)
Jungmann, et al. ***ACS Chem. Biol.*** (2015)

Chlorotonil with favorable anti-infective properties

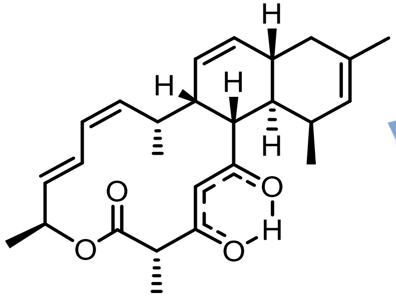




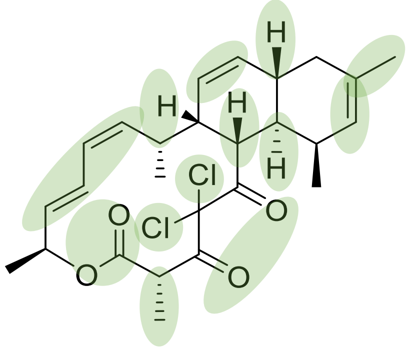
Chlorotonil A

- ✓ MIC (VRE): 0.025 µg/mL
- ✓ IC_{50} (*Plasmodium falciparum*): **14 nM**
- ✓ mouse model (*Plasmodium berghei*)
- ➢ **kinetic solubility pH 7.4: 0.073 µM**

- ✓ MIC (VRE): 0.05 µg/mL
- ✓ IC_{50} (*P. falciparum*): 0.22 µM
- ✓ mouse models
- ✓ **ADMET properties**
- ✓ **kinetic solubility pH 7.4: 16.2 µM**



2^{nd} generation frontrunner



positions addressed by semi-synthesis

Hofer *et al.* ***ACIE*** (2024)
Hofer *et al.* ***ACIE*** (2022)


Müller


Strowig


Faber


Stadler


Hirsch

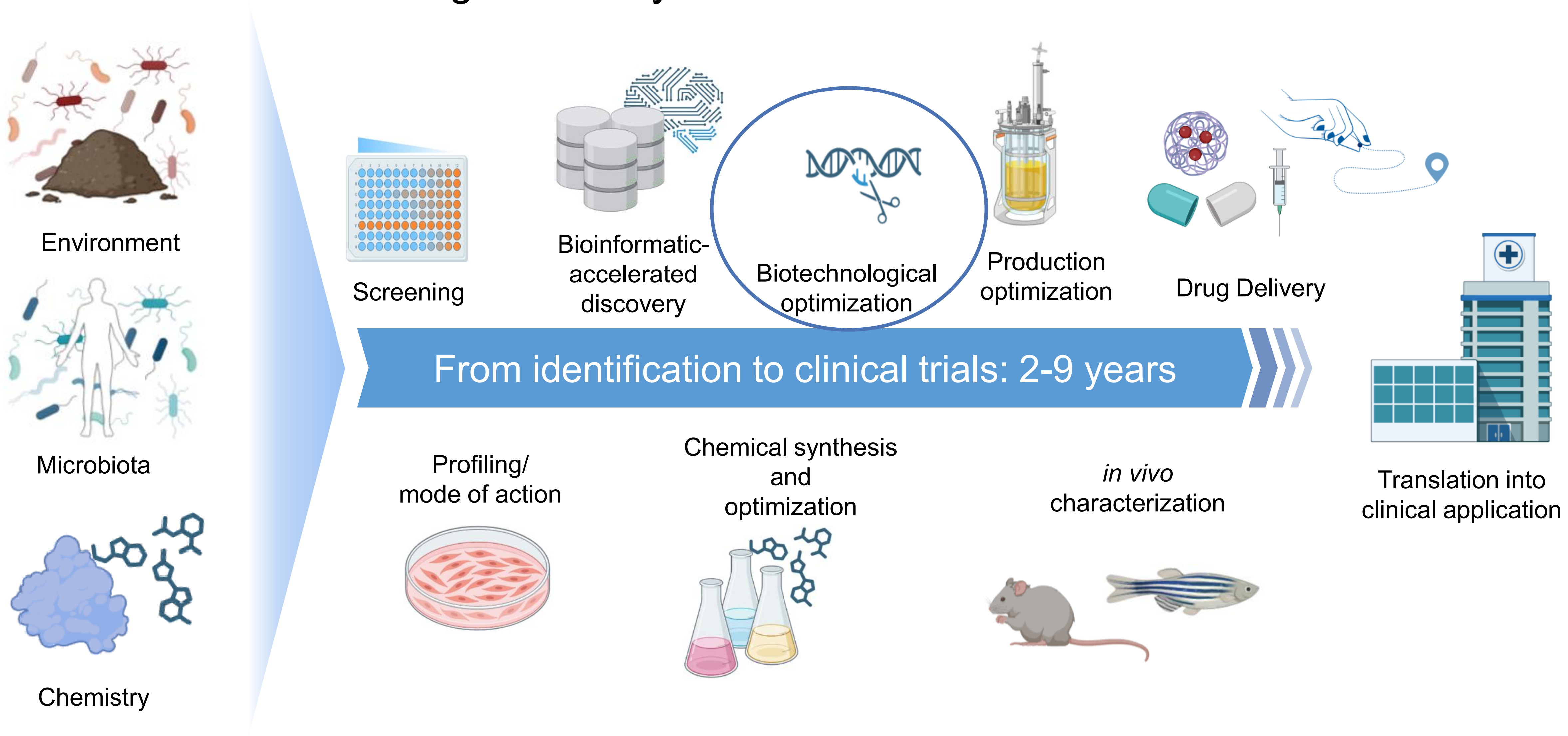
Lessons Learned
- Chemical understanding of compound properties essential for improving pharmacokinetics and bioactivities
- Merging semi-synthesis and fermentation can become alternative to heterologous production or total synthesis

CINCATE | Bundesministerium für Bildung und Forschung | GO-Bio | wellcome centre anti-infectives research | BILL & MELINDA GATES foundation | BIOVERSYS | MYXOBIOMEDICAL breaking resistance | UNIVERSITÄT BONN

HZI HELMHOLTZ Centre for Infection Research

Natural Product Pipeline Highlight

From Microbiota to Drug Discovery of Novel Anti-infectives



HZI HELMHOLTZ Centre for Infection Research

HIPS as a joint institute between HZI and Saarland University since 2009

Aim: Development of novel anti-infectives to combat antimicrobial resistance (AMR)

UNIVERSITÄT DES SAARLANDES

SAARLAND
Großes entsteht immer im Kleinen.

HZI HELMHOLTZ Centre for Infection Research

Pharmaceutical Research

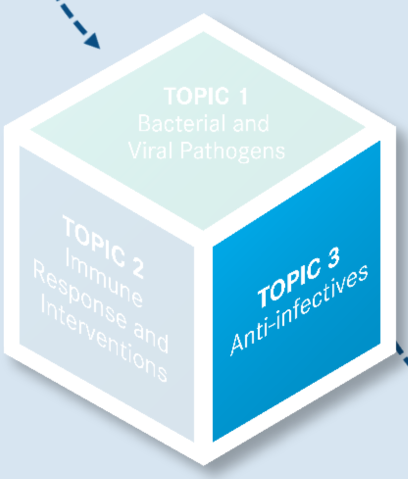
Infection Research

HIPS HELMHOLTZ Institut für Pharmazeutische Forschung Saarland

HIPS/HZI at a glance

***Infection research** at*

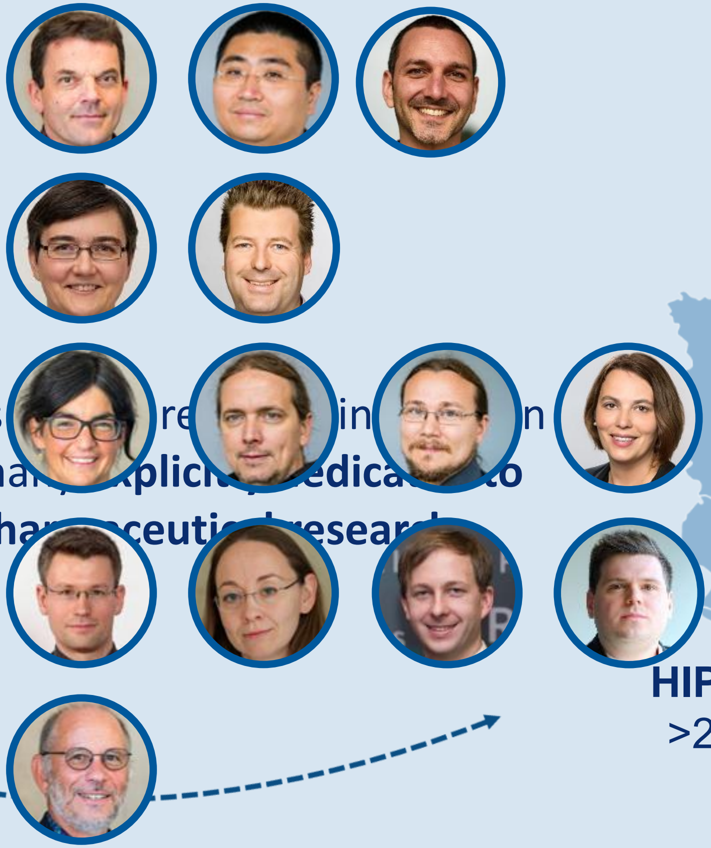
HZI HELMHOLTZ Centre for Infection Research



3 Research topics

PIs in Topic 3

Anti-infectives



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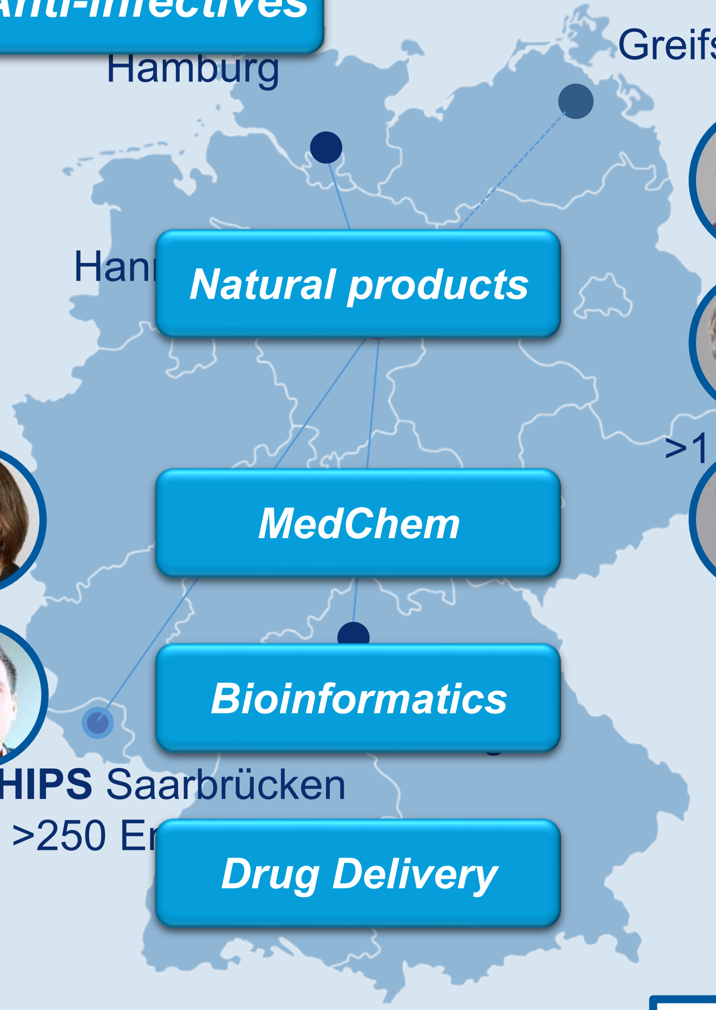


Natural products

MedChem

Bioinformatics

Drug Delivery

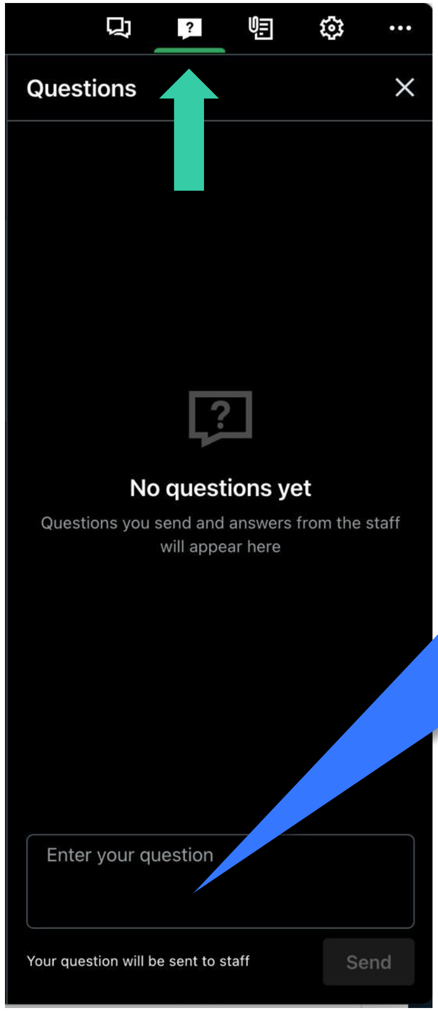
HIPS

HZI

How to submit your questions

REVIVE by GARDP

If your question is addressed to a specific speaker, please include their name when submitting the question.



Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

Today's speakers

Natural product-inspired antibiotics: Successes and future prospects

<u>**Moderator:**</u>
Jennifer Herrmann
Helmoltz Institute for Pharmaceutical Research Saarland

Mark Butler
MSBChem Consulting

Christine Beemelmanns
Helmoltz Institute for Pharmaceutical Research Saarland

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Thank you for joining us