Repurposing drugs to address the crisis of antimicrobial resistance

Guest speakers: Freda Jen, Anthony Coates & François Franceschi
Moderator: Jennifer Smart
Host: Victor Kouassi

22 July 2025

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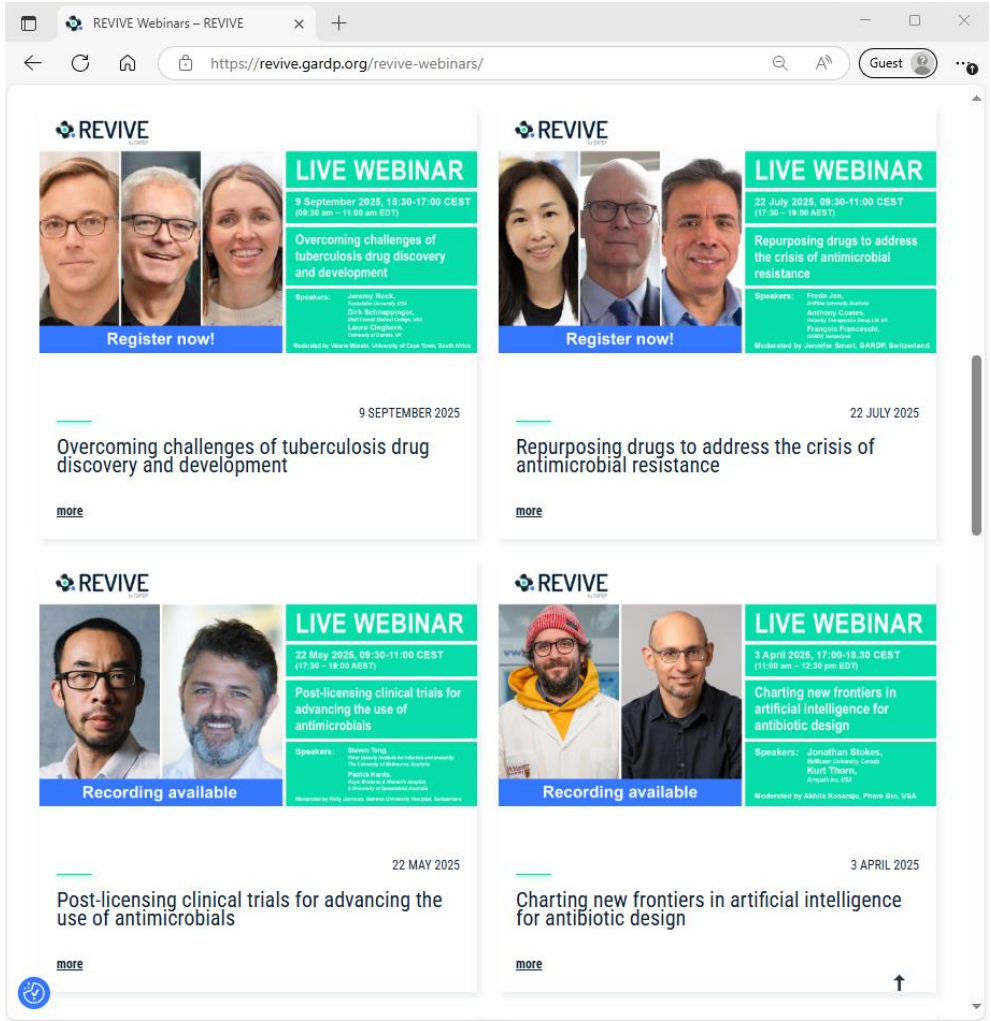

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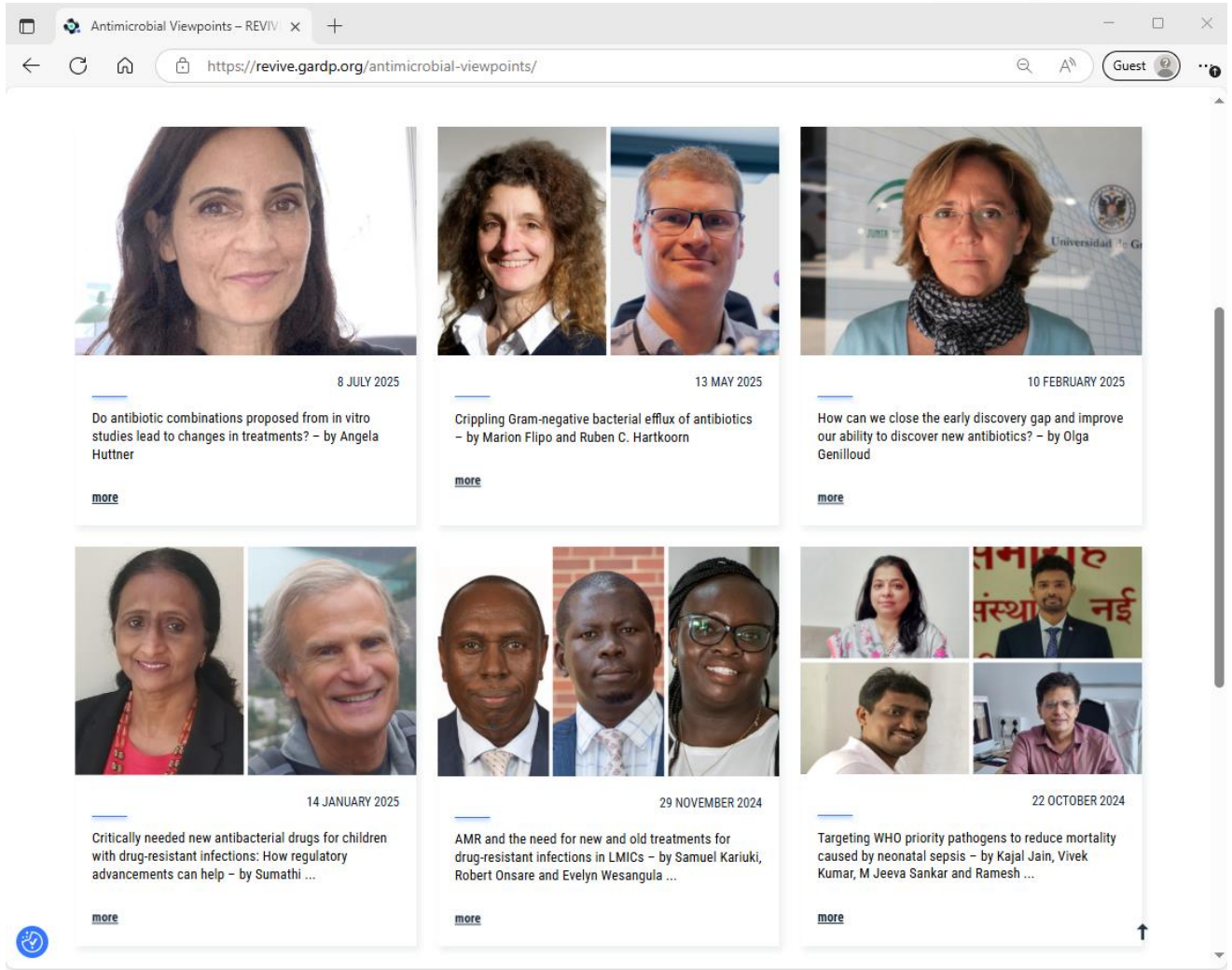

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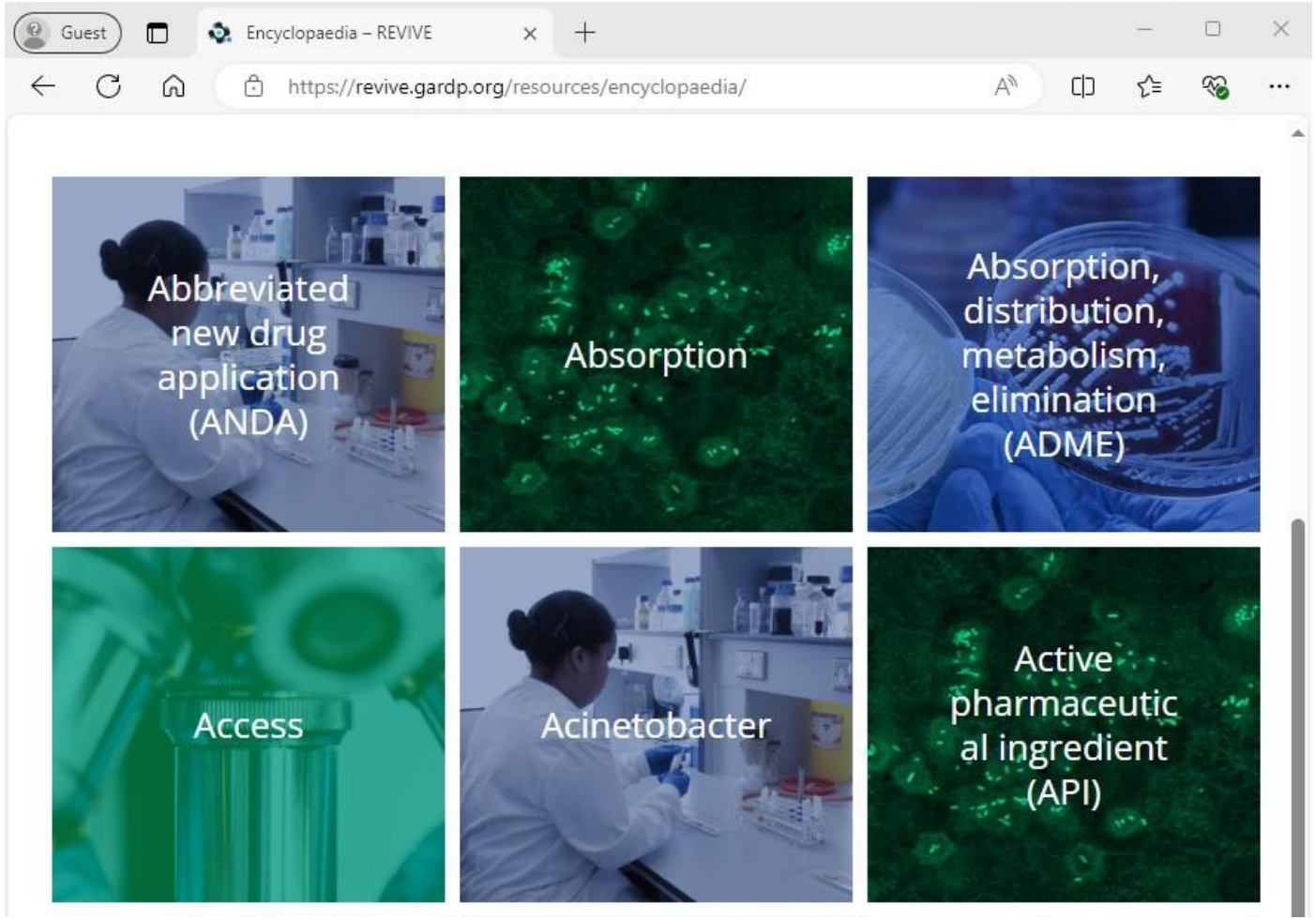

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How to submit your questions

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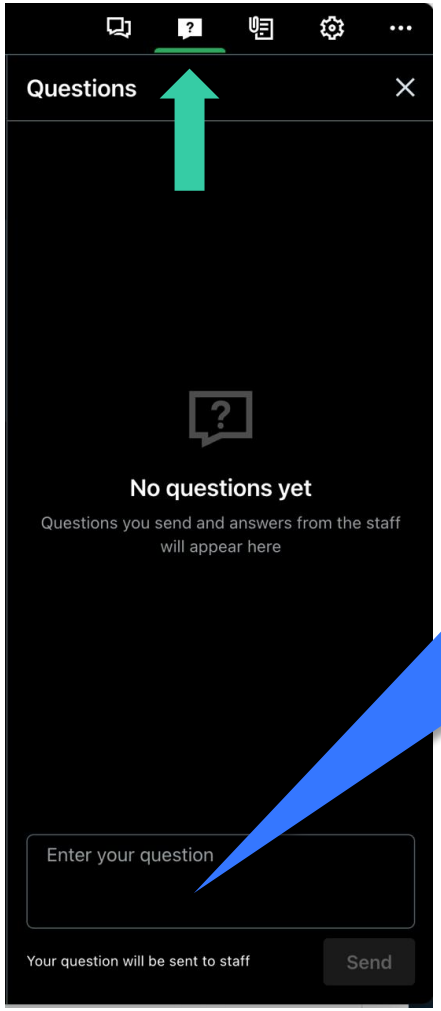
If your question is addressed to a specific speaker, please include their name when submitting the question.



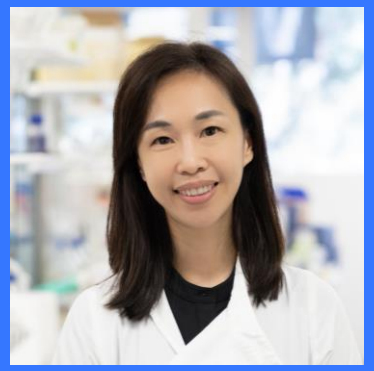
Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

Today's speakers

REVIVE by GARDP

Repurposing drugs to address the crisis of antimicrobial resistance

Moderator:
Jennifer Smart
GARDP,
Switzerland



Freda Jen
Griffiths University,
Australia

Anthony Coates
Helperby
Therapeutics, UK

François Franceschi
GARDP,
Switzerland

Repurposing drugs to address the crisis of antimicrobial resistance

Jennifer I. Smart, Ph.D.
Microbiology Consultant

22 July 2025

GARDP
Global Antibiotic Research & Development Partnership

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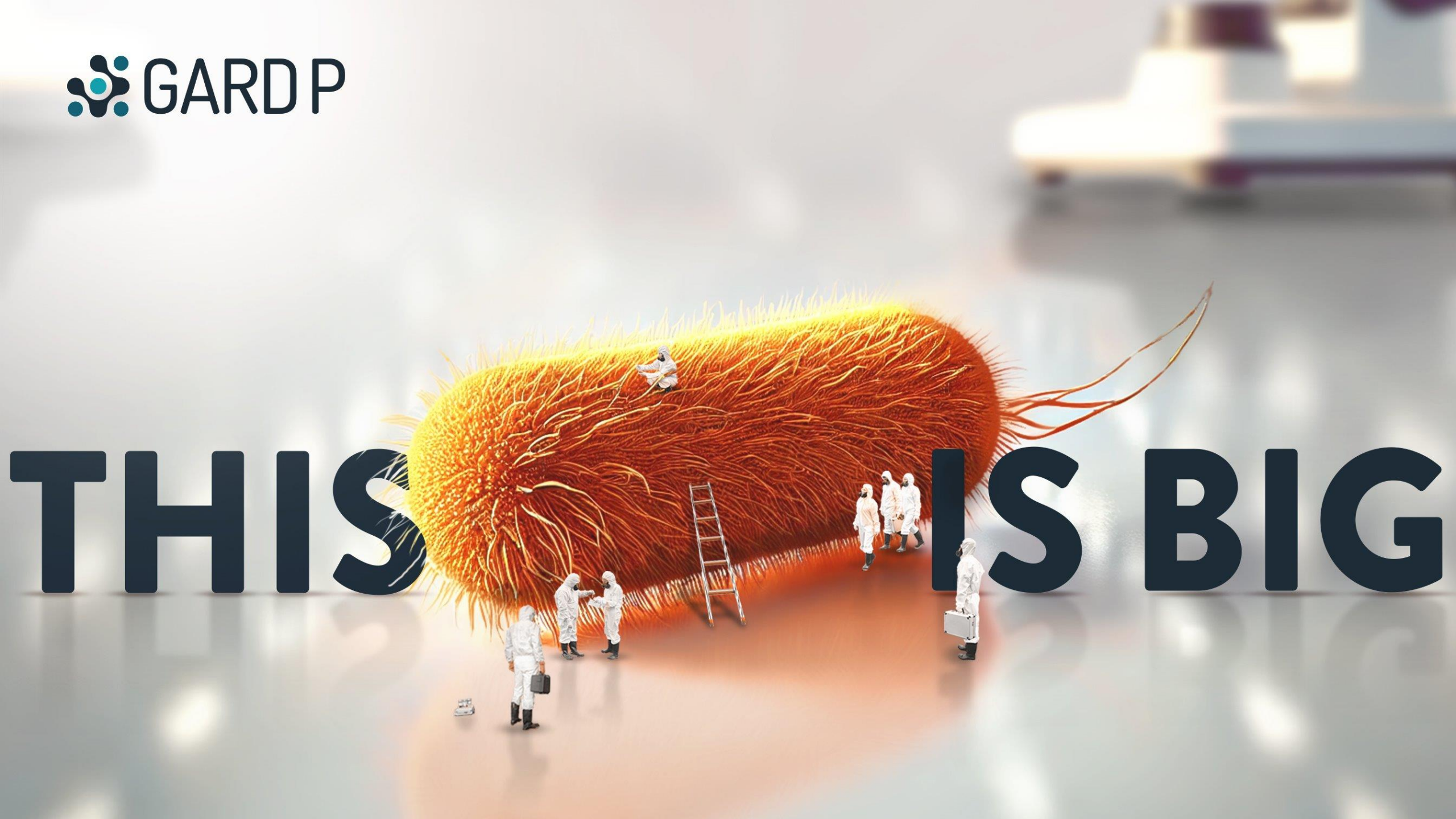


Antibiotic pipeline facing significant challenges

Current antibiotic pipeline not meeting the AMR crisis

Repurposing drugs to address the AMR crisis

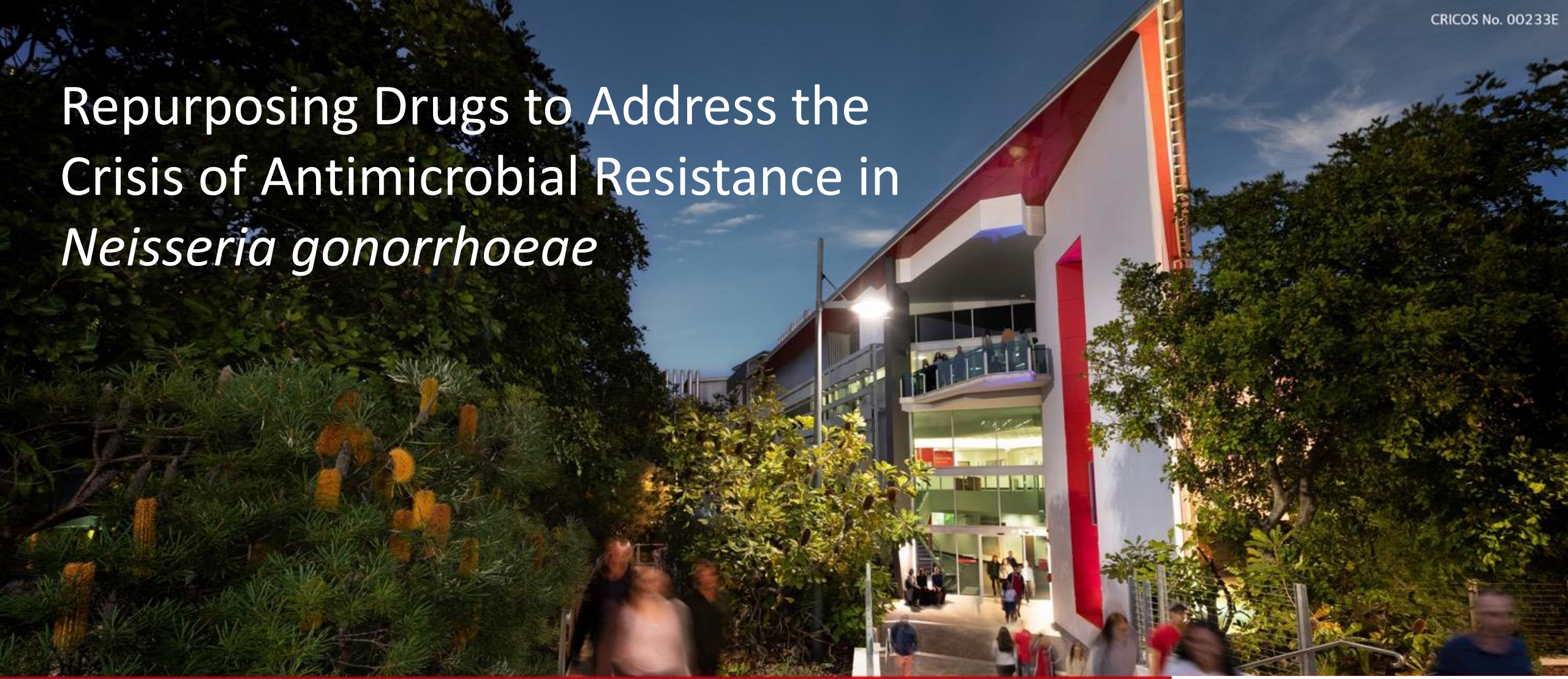
Evaluating existing drugs for priority infections

Freda Jen

Freda Jen is a molecular microbiologist with a PhD focused on pathogenic *Neisseria* species, the bacteria responsible for gonorrhoea and meningitis. Her research focuses on host–pathogen interactions and the molecular mechanisms that drive bacterial virulence, with the ultimate goal of developing new therapeutics and vaccines.

Building on her expertise working on bacterial protein post-translational modifications, she contributed to the development of two gonococcal vaccine candidates, which are soon expected to enter human trials. Her work also focuses on repurposing existing drugs and designing new antibiotics to combat multidrug-resistant *Neisseria gonorrhoeae* and other antimicrobial-resistant Gram-negative bacteria.

experts.griffith.edu.au/8156-freda-jen



Repurposing Drugs to Address the Crisis of Antimicrobial Resistance in *Neisseria gonorrhoeae*

Freda Jen

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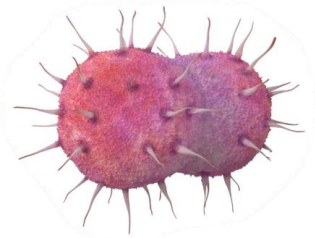
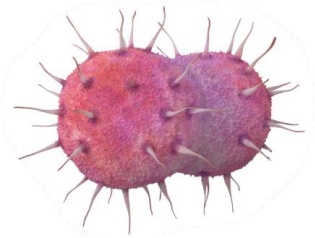


Neisseria gonorrhoeae

- *Neisseria gonorrhoeae* was first discovered by Albert Ludwig Sigesmund Neisser in 1879.



Neisseria gonorrhoeae

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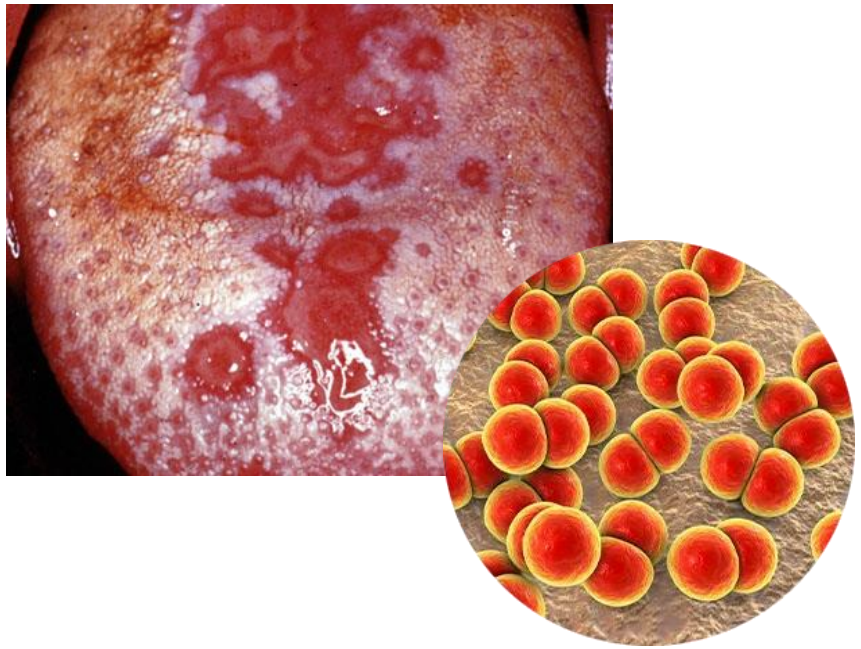

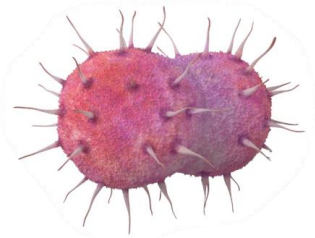

Neisseria gonorrhoeae

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- *Neisseria gonorrhoeae* was first discovered by Albert Ludwig Sigesmund Neisser in 1879.
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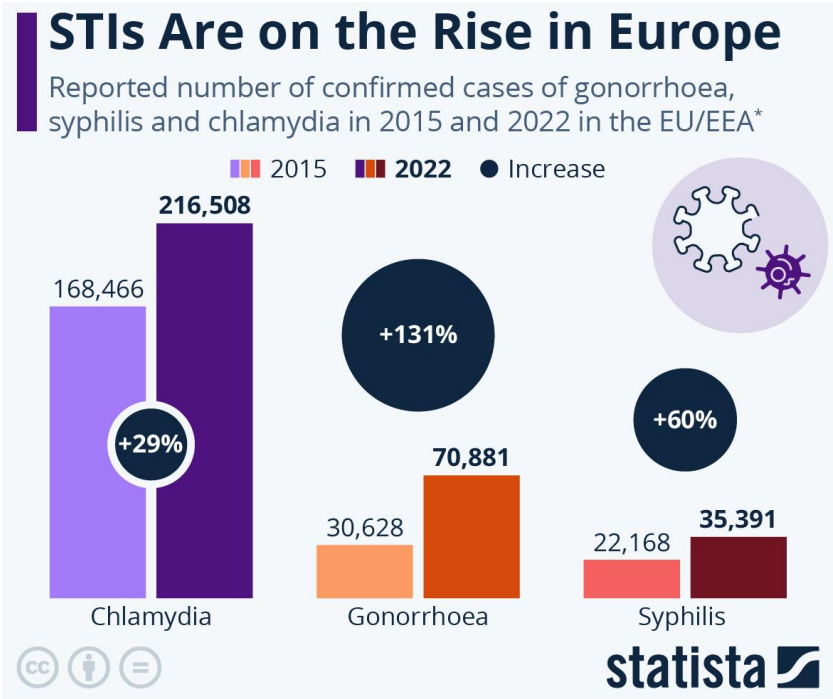
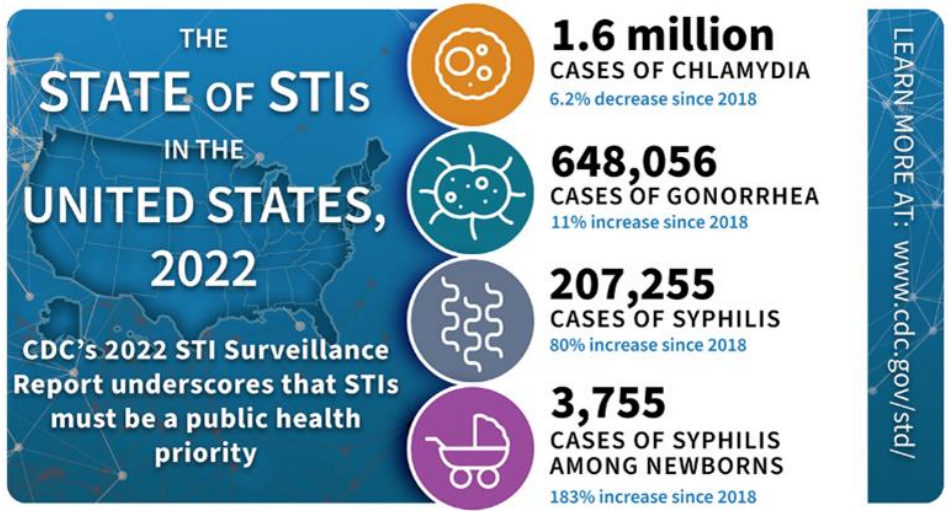
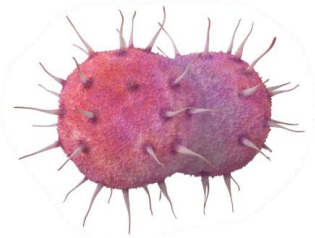
- Gonorrhoea is the **second most commonly reported STI** worldwide.

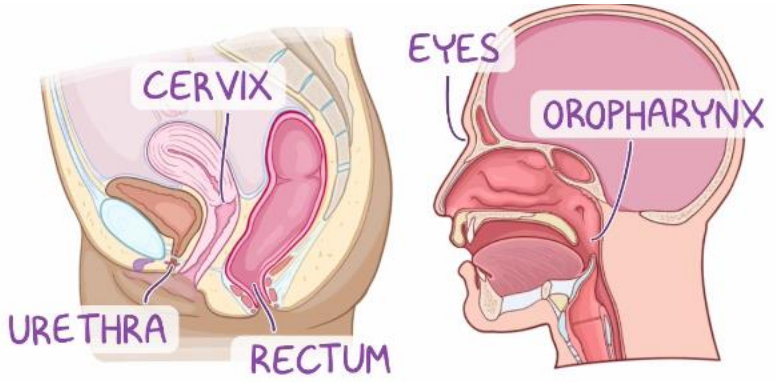


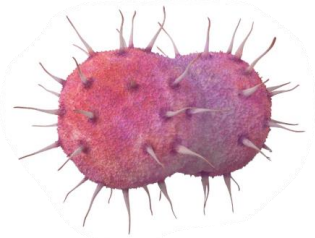




Gonorrhea

- Common sites of infection include the urethra, cervix, rectum, pharynx, and conjunctiva.





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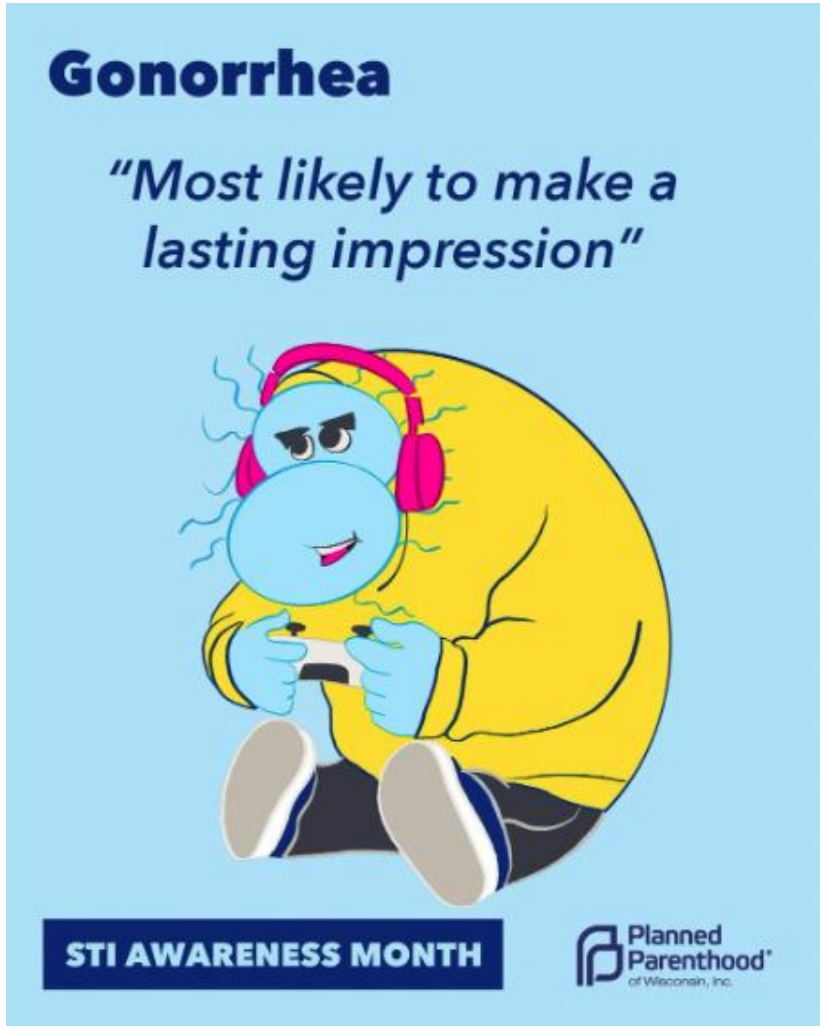
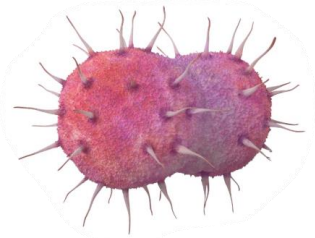
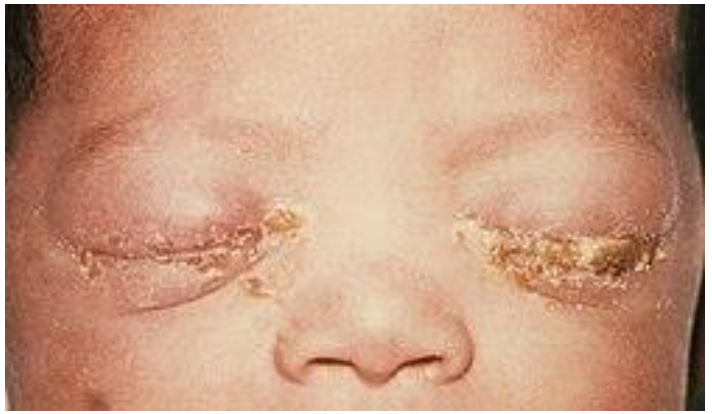
- Common sites of infection include the urethra, cervix, rectum, pharynx, and conjunctiva.
- Many infections are **asymptomatic**, especially in women.

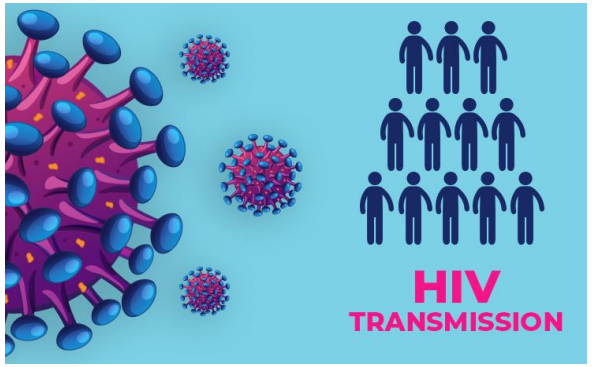


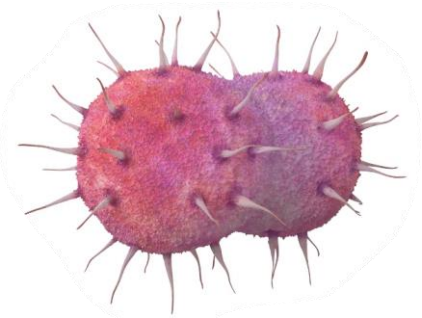


Gonorrhea

- Common sites of infection include the urethra, cervix, rectum, pharynx, and conjunctiva.
- Many infections are **asymptomatic**, especially in women.
- **Symptomatic** infections may include urethritis in men, cervicitis in women, and pharyngeal soreness or burning.
- Untreated or undetected infections lead to: Pelvic inflammatory disease (PID), infertility, neonatal blindness and associated with increased HIV transmission.







Treatment of *Neisseria gonorrhoeae*

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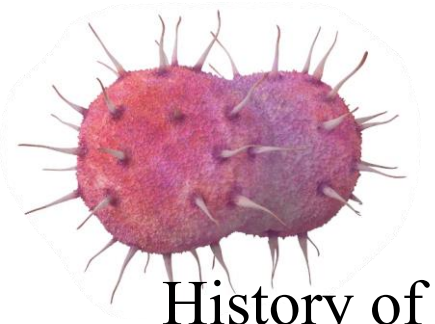
~1944

A poster attached to a kerbside mailbox

"**Penicillin cures gonorrhea in 4 hours**"



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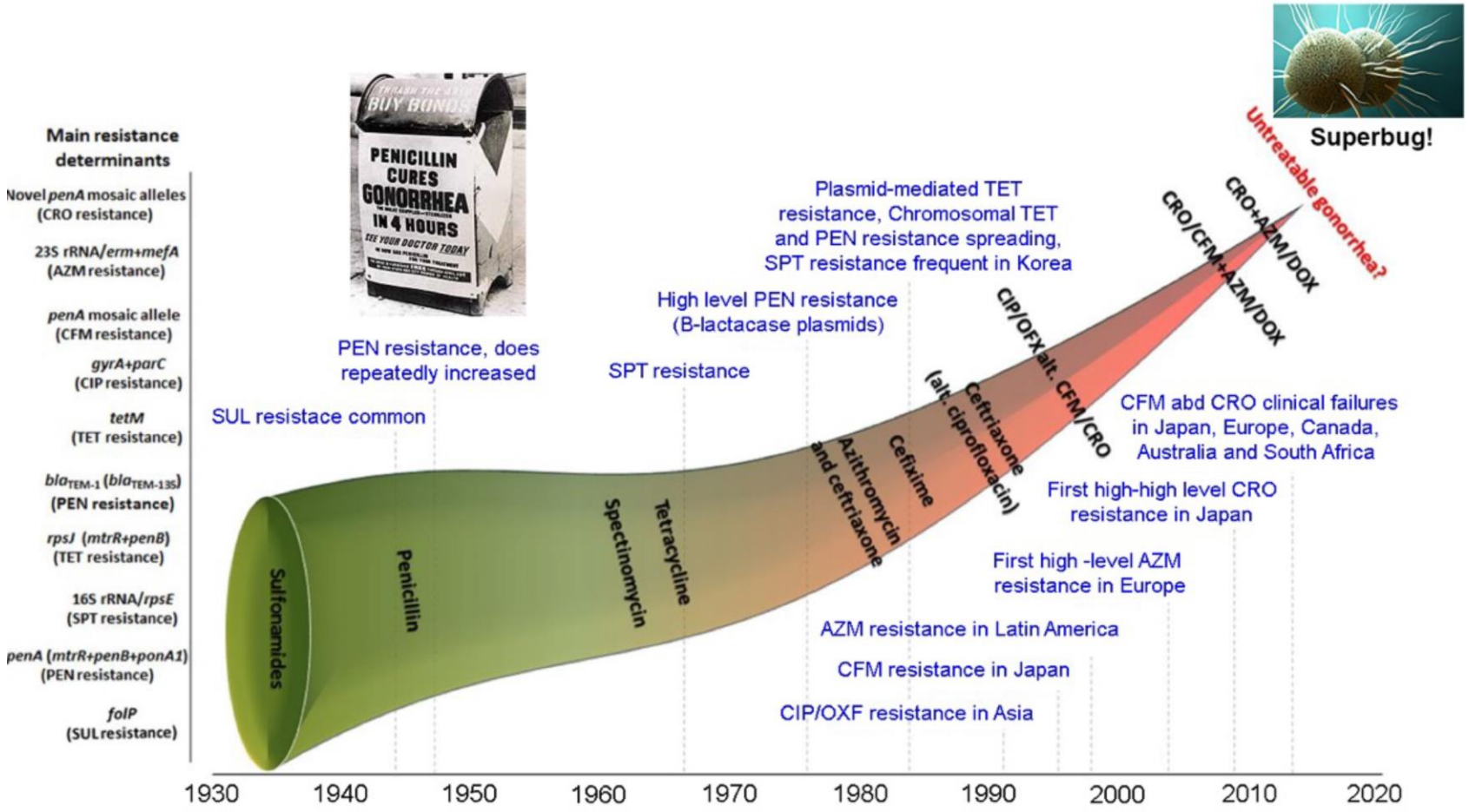
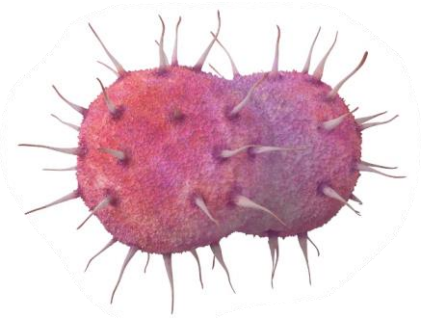
Multidrug resistance of *Neisseria gonorrhoeae*

History of discovered and recommended antimicrobials and evolution of resistance in *N. gonorrhoeae*.



Unemo and Shafer 2014
Clin Microbiol Rev



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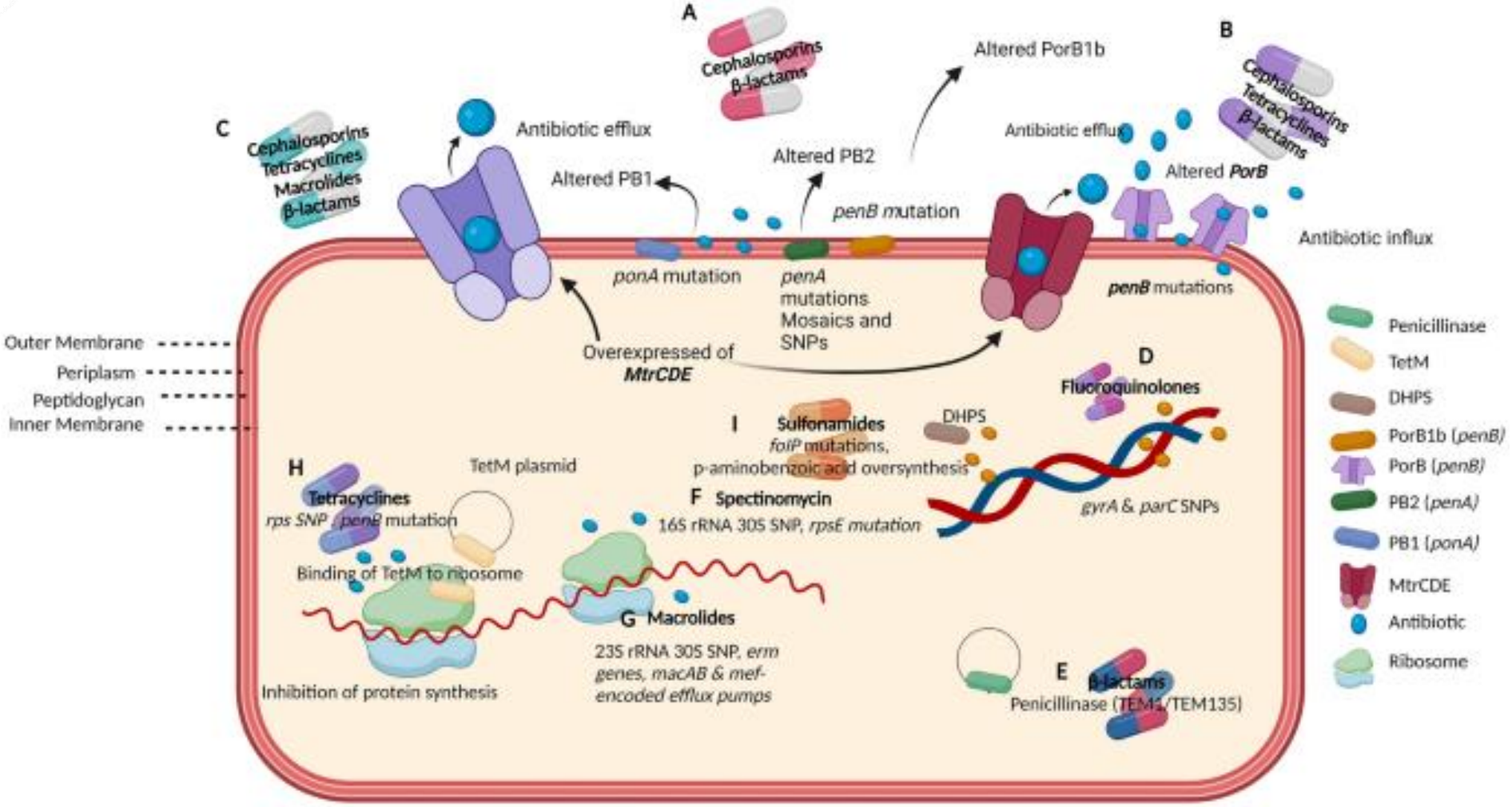
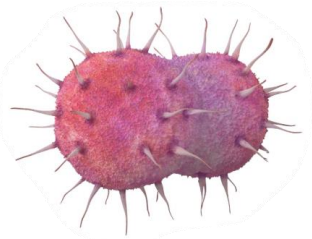
Multidrug resistance of *Neisseria gonorrhoeae*



Omeershfudin *et al*, 2023, Archives of Microbiology



Neisseria gonorrhoeae Is Evolving Faster Than Our Antibiotics

- Global cases of *N. gonorrhoeae* are rising
- XDR and MDR strains challenge current treatments
- Resistance to ceftriaxone, azithromycin, and others increasing (WHO/CDC)
- Treatment failures reported in Europe & Southeast Asia
- No vaccine currently available

Drug Repurposing for Antimicrobial Discovery – PBT2

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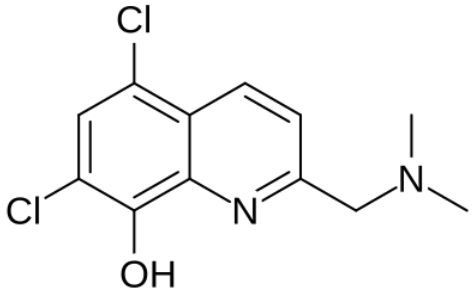
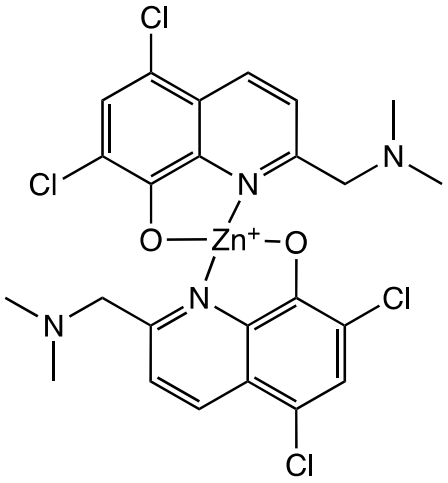


PBT2



PBT2-Zn complex

- PBT2 is a zinc ionophore (although it also interacts with copper).
- Was designed to target zinc and copper dysregulation to reduce brain toxicity as a potential treatment for Alzheimer's disease and Huntington's disease.
- Passed Phase I but discontinued after phase II human trials due to ineffectiveness.
- In clinical trials, an oral dose of PTB2 250 mg/day was safe and well tolerated in Alzheimer's patients.

PBT2 can synergise with antibiotics to reverse antimicrobial resistance.

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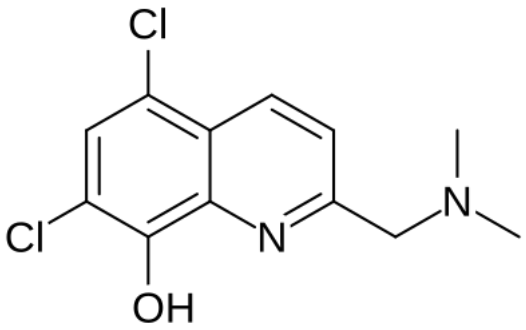
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ANTIBIOTIC RESISTANCE

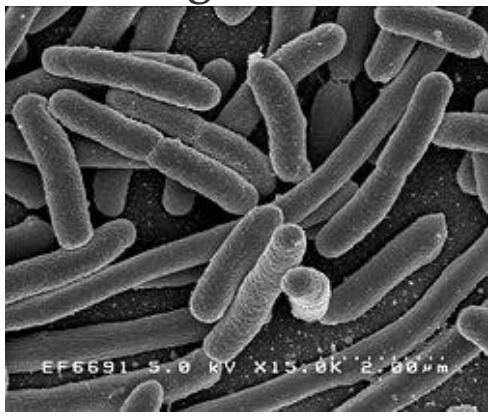
Repurposing a neurodegenerative disease drug to treat Gram-negative antibiotic-resistant bacterial sepsis

David M. P. De Oliveira[1], Lisa Bohlmann[1], Trent Conroy[2], Freda E.-C. Jen[2], Arun Everest-Dass[2], Karl A. Hansford[3], Raghu Bolisetti[3], Ibrahim M. El-Deeb[2], Brian M. Forde[1,4], Minh-Duy Phan[1], Jake A. Lacey[5], Aimee Tan[5], Tania Rivera-Hernandez[1,6], Stephan Brouwer[1], Nadia Keller[1], Timothy J. Kidd[1], Amanda J. Cork[1], Michelle J. Bauer[4], Gregory M. Cook[7], Mark R. Davies[5], Scott A. Beatson[1], David L. Paterson[4], Alastair G. McEwan[1], Jian Li[8], Mark A. Schembri[1], Mark A. T. Blaskovich[3], Michael P. Jennings[2], Christopher A. McDevitt[5]*, Mark von Itzstein[2]*, Mark J. Walker[1]*†



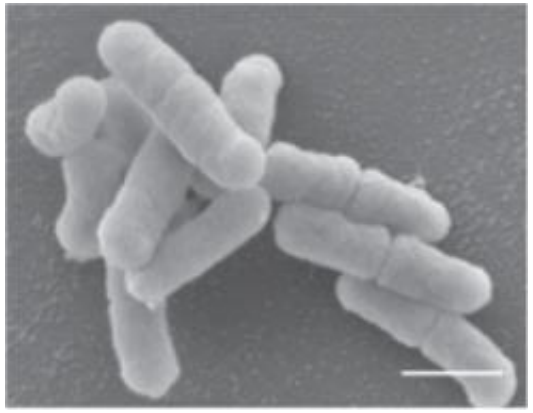
PBT2

Pathogenic *E. coli*



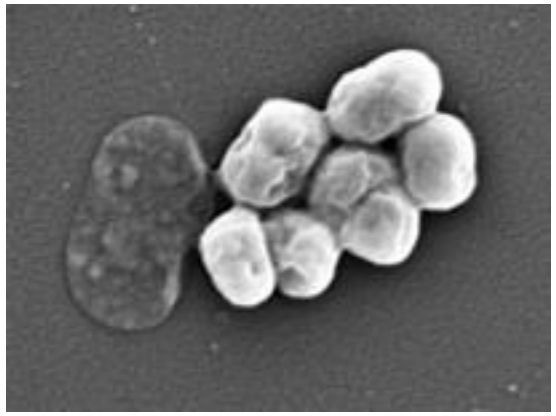
WIKIPEDIA 2024

K. pneumoniae



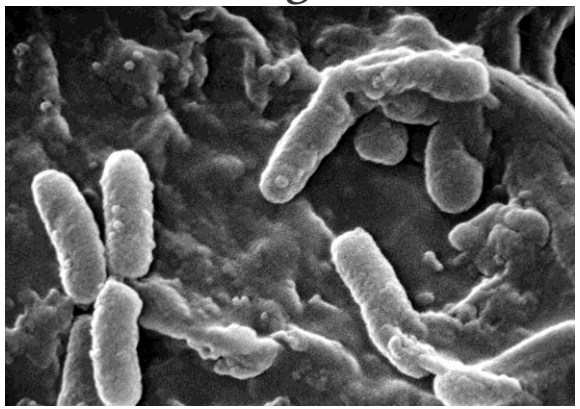
Guilhen et al 2019 npj biofilms and microbiomes

A. baumannii



WIKIPEDIA 2024

P. aeruginosa



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PBT2 can synergise with antibiotics to reverse antimicrobial resistance.

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ACS Infectious Diseases

Letter

Cite This: *ACS Infect. Dis.* 2020, 6, 50−55

pubs.acs.org/journal/aidcbc

Neisseria gonorrhoeae Becomes Susceptible to Polymyxin B and Colistin in the Presence of PBT2

Freda E.-C. Jen,[†] Arun V. Everest-Dass,[†] Ibrahim M. El-Deeb,[†] Sanjesh Singh,[†] Thomas Haselhorst,[†] Mark J. Walker,[‡] Mark von Itzstein,[†] and Michael P. Jennings*[,†]

[†]Institute for Glycomics, Griffith University, Gold Coast Campus, Southport, Queensland 4222, Australia

[‡]School of Chemistry and Molecular Biosciences and Australian Infectious Diseases Research Centre, The University of Queensland, Brisbane, Queensland 4072, Australia

PBT2 can synergise with antibiotics to reverse antimicrobial resistance.

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Table 1: MICs (mg/L) of tetracycline, colistin and polymyxin B in the absence and presence of PBT2/zinc for *N. gonorrhoeae* strains.

Strains	ATCC 49226	MS11	WHO L	WHO M	WHO X	WHO Y	WHO Z
PBT2: 0 µM / Zinc: 0 µM							
Tetracycline ($S \leq 0.5; R > 1$)[#]	0.63(S)	0.63 (S)	2.5 (R)	2.5 (R)	2.5 (R)	5 (R)	5 (R)
Colistin ($S \leq 2; R > 2$)[#]	>200(R)	>200 (R)	>200 (R)	>200 (R)	>200 (R)	>200 (R)	500 (R)
Polymixin B ($S \leq 2; R > 2$)[#]	>1000(R)	1000 (R)	>1000 (R)	1000 (R)	1000 (R)	1000 (R)	1000 (R)
PBT2: 0.5 µM / Zinc: 2.5 µM							
Tetracycline ($S \leq 0.5; R > 1$)[#]	0.31 (S)	0.63 (S)	0.63 (S)	0.63 (S)	0.63 (S)	0.63 (S)	0.31 (S)
Colistin ($S \leq 2; R > 2$)[#]	0.78 (S)	1.56 (S)	1.56 (S)	1.56 (S)	1.56 (S)	1.56 (S)	1.56 (S)
Polymixin B ($S \leq 2; R > 2$)[#]	1.95 (S)	0.98 (S)	1.95 (S)	1.95 (S)	1.95 (S)	1.95 (S)	0.98 (S)

[#]Clinical MIC breakpoints for tetracycline [32] colistin [33] and polymyxin B [34].

PBT2 can synergise with antibiotics to reverse antimicrobial resistance.

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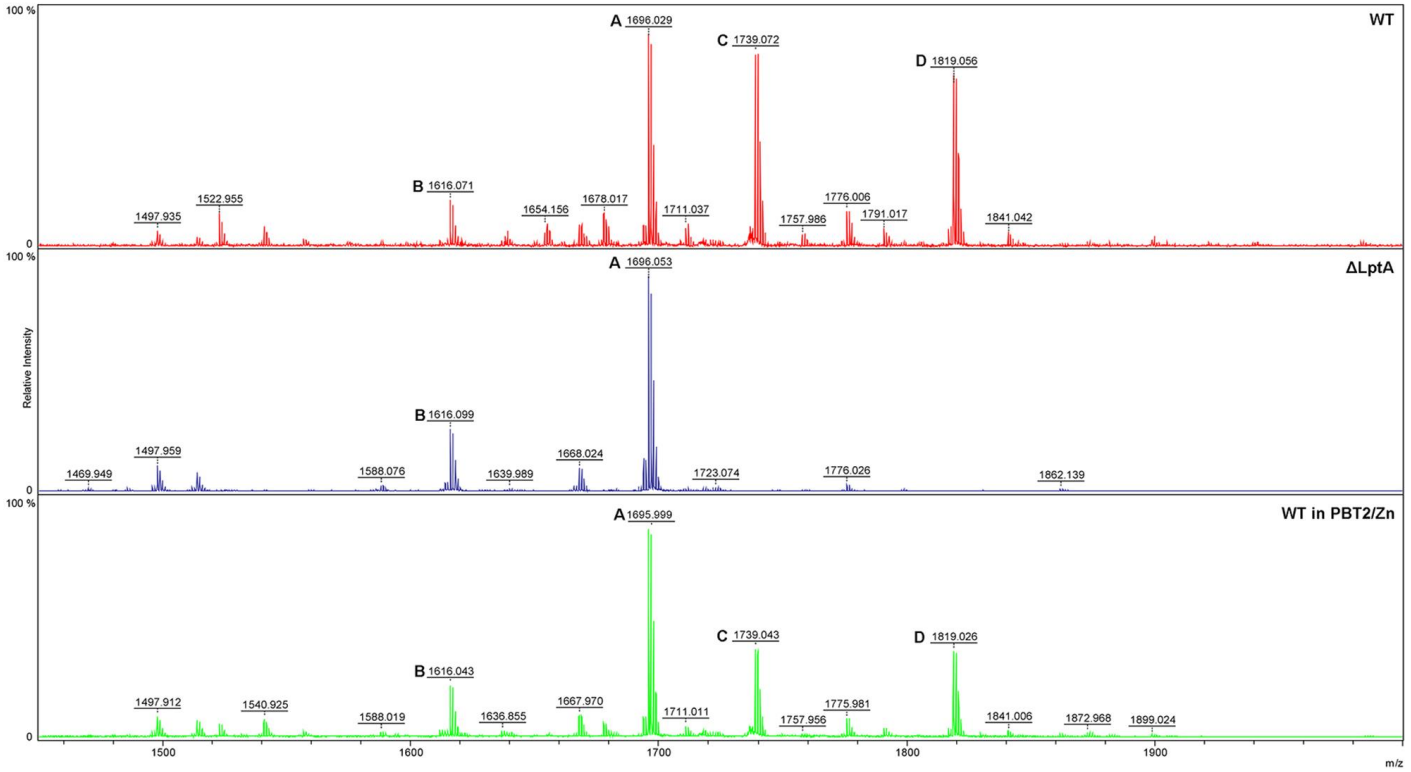
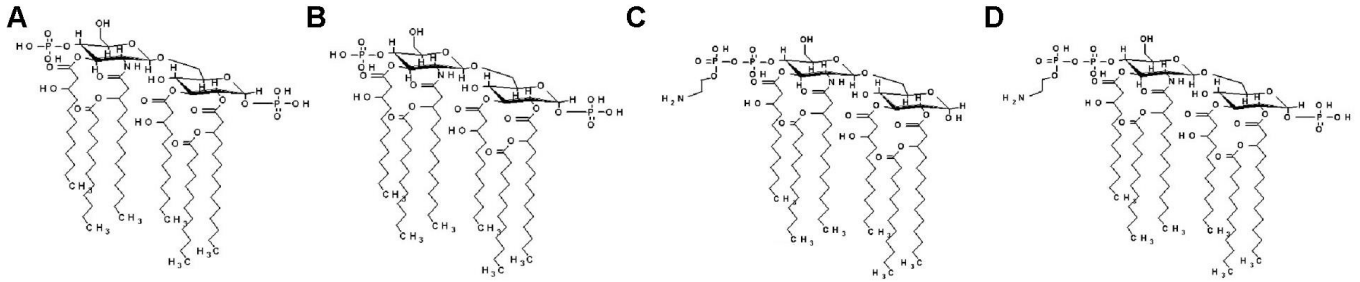
WT

Δ LptA

WT in PBT2/Zn





M =1715.90
Obs{M-H]¯=1696

M =1635.21
Obs{M-H]¯=1616

M =1838.34
Obs{M-H]¯ =1739

M =1838.34
Obs{M-H]¯=1819

PBT2 can synergise with antibiotics to reverse antimicrobial resistance.

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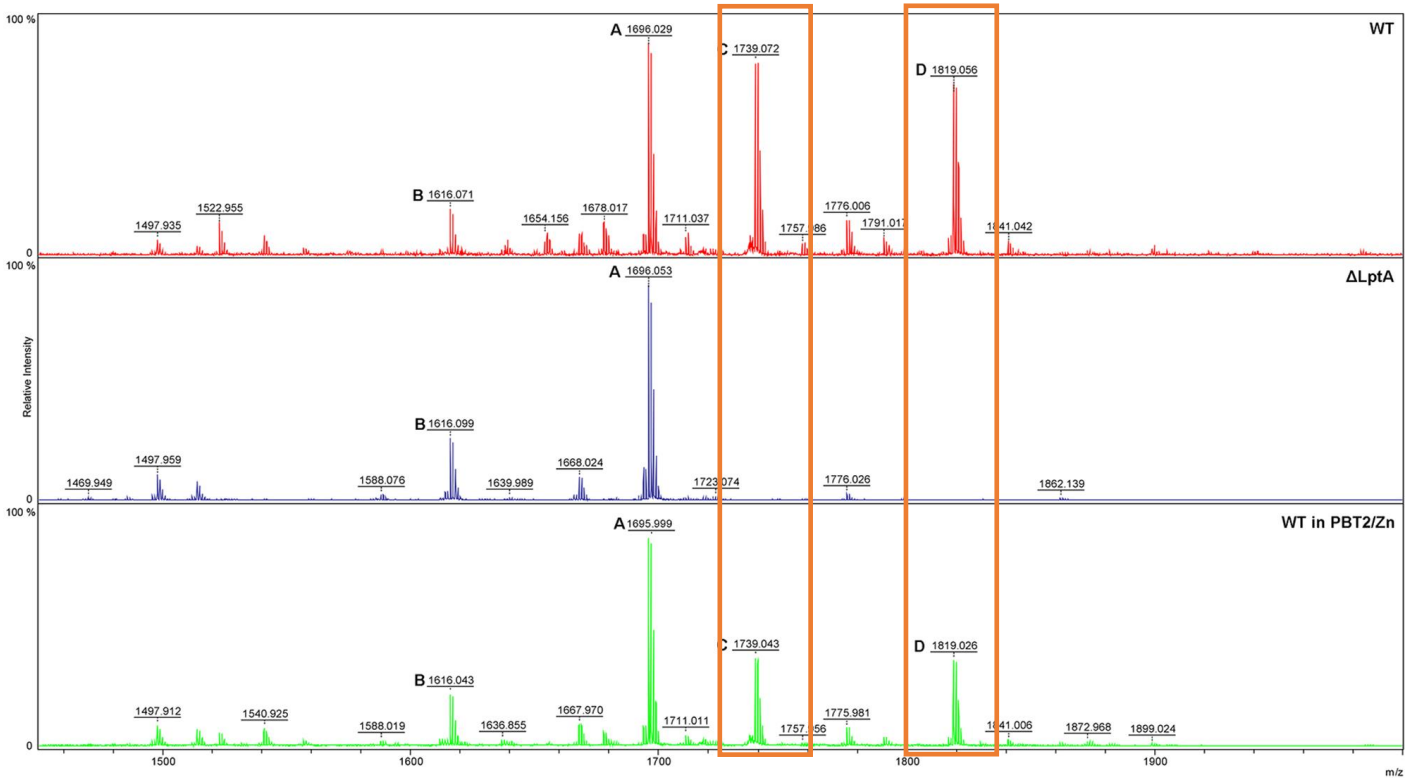

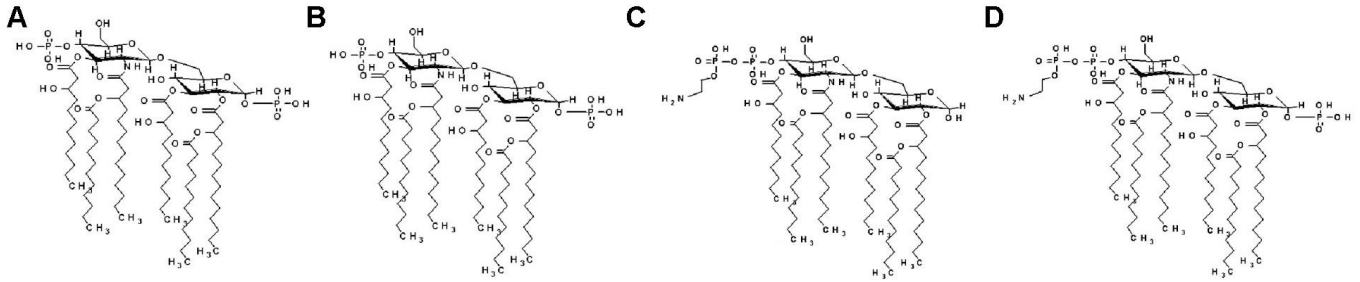

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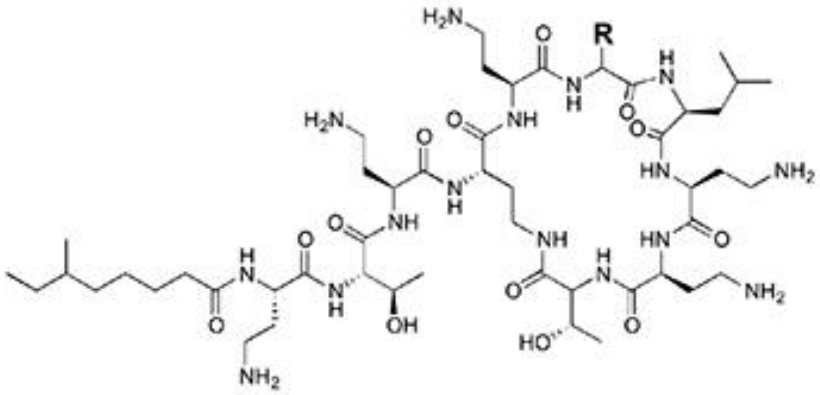


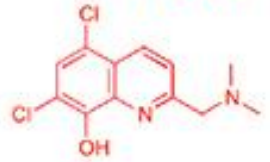
R =

Polymyxin B

R =

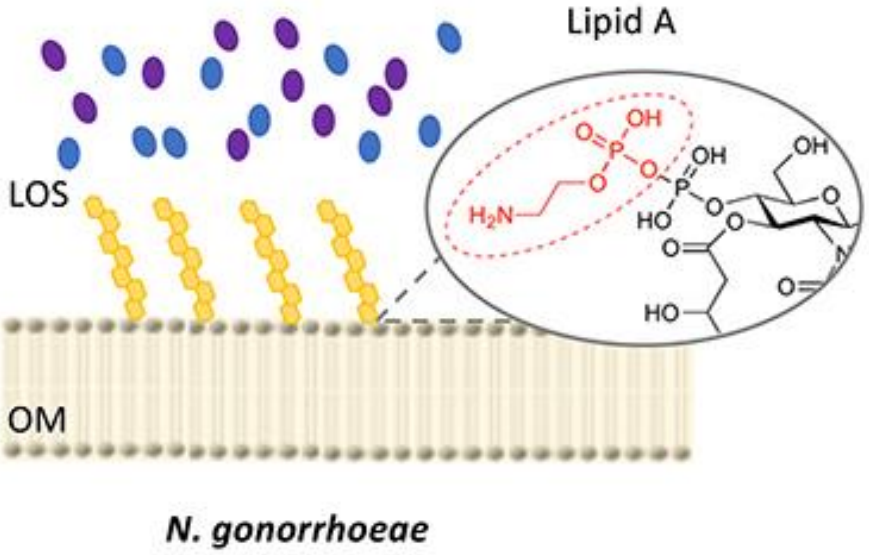
Colistin

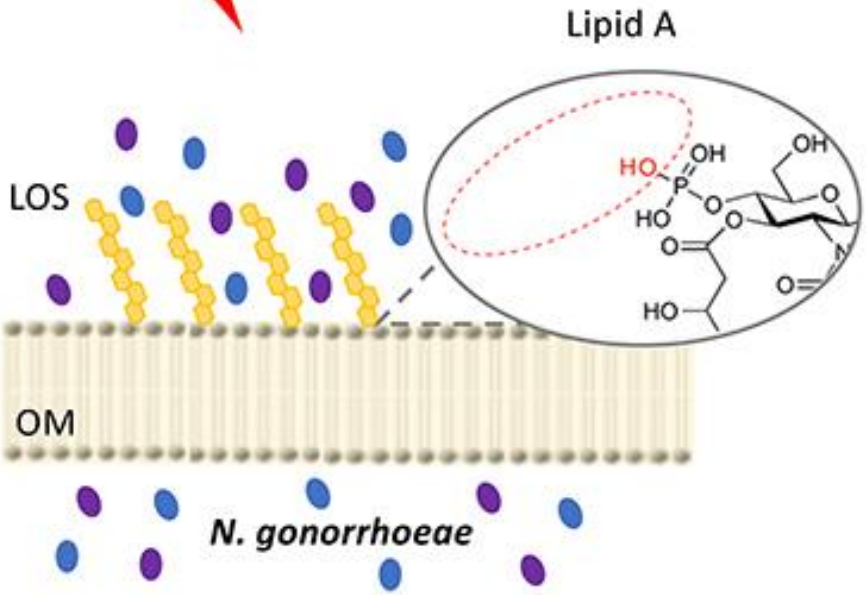
PBT2



+ Zn^{+2}

Synergy





PBT2 can synergise with antibiotics to reverse antimicrobial resistance.

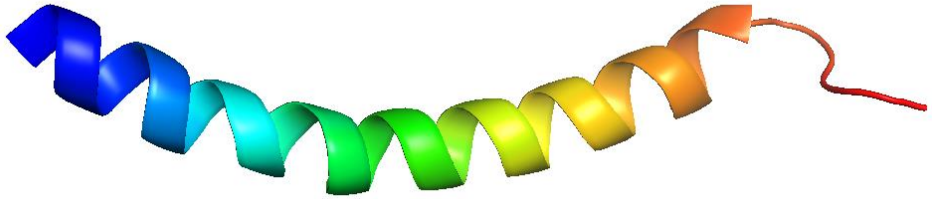
INSTITUTE FOR BIOMEDICINE AND GLYCOMICS

J Antimicrob Chemother 2021; **76**: 2850–2853
doi:10.1093/jac/dkab291 Advance Access publication 27 August 2021

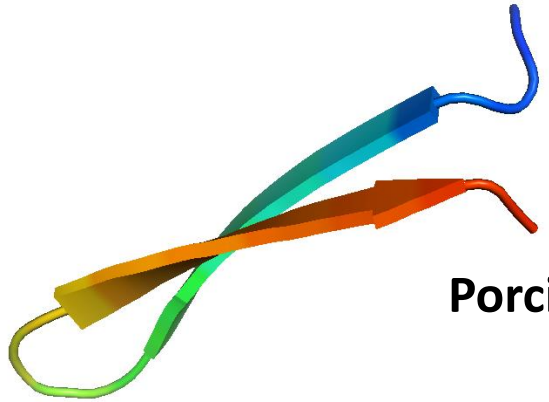
Journal of Antimicrobial Chemotherapy

A drug candidate for Alzheimer's and Huntington's disease, PBT2, can be repurposed to render *Neisseria gonorrhoeae* susceptible to natural cationic antimicrobial peptides

Freda E.-C. Jen[1], Ibrahim M. El-Deeb[1], Yaramah M. Zalucki[1], Jennifer L. Edwards[2], Mark J. Walker[3], Mark von Itzstein[1] and Michael P. Jennings[1]*



Human LL-37



Porcine PG-1

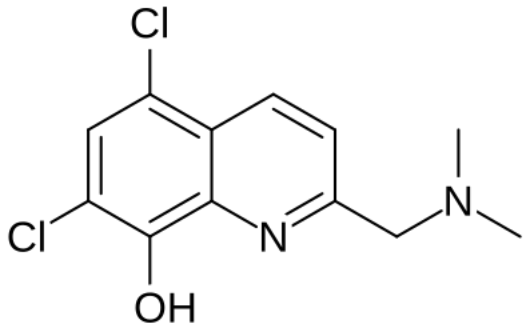
PBT2 can be a new treatment for *N. gonorrhoeae*

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

EXPERIMENTAL THERAPEUTICS
September 2022 Volume 66 Issue 9 e02318-21
https://doi.org/10.1128/aac.02318-21

Repurposing the Ionophore, PBT2, for Treatment of Multidrug-Resistant *Neisseria gonorrhoeae* Infections

Freda E.-C. Jen[a], Jennifer L. Edwards[b], Ibrahim M. El-Deeb[a], Mark J. Walker[c], Mark von Itzstein[a], Michael P. Jennings[a]



PBT2

Phase II clinical trials: Clinically, the plasma AUC of PBT2 (1.66 µg·h/mL after 250 mg/day for 72 hours) is about 5-fold higher than its MIC (**0.313 µg/mL**) against MDR *N. gonorrhoeae*.

PBT2 can be a new treatment for *N. gonorrhoeae*

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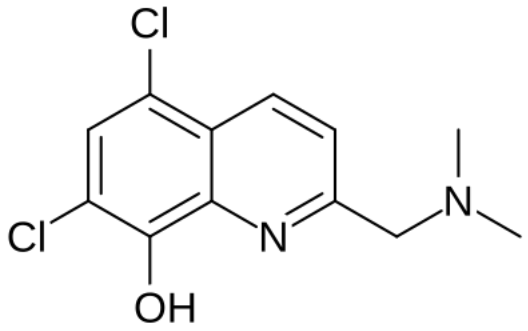

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Phase II clinical trials: Clinically, the plasma AUC of PBT2 (1.66 µg·h/mL after 250 mg/day for 72 hours) is about 5-fold higher than its MIC **(0.313 µg/mL)** against MDR *N. gonorrhoeae*.

The PBT2 MICs of ATCC strain 49226, the laboratory strain MS11, and 13 MDR clinical strains are **0.156–0.3125 µg/mL** [broth]; **0.3125-0.625 µg/mL** [agar].

PBT2 can be a new treatment for *N. gonorrhoeae*

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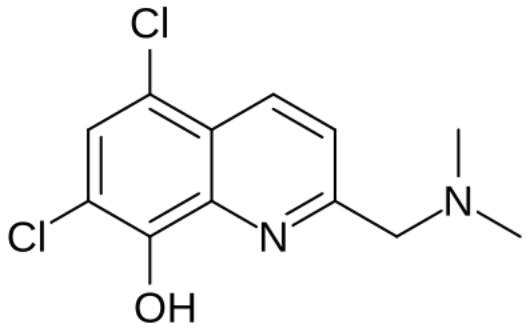


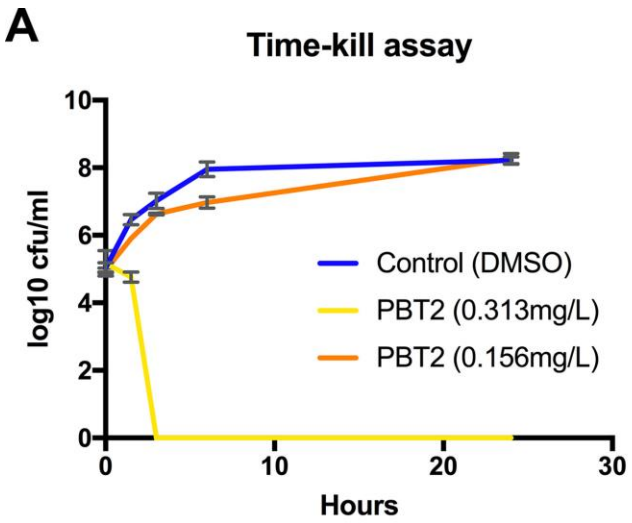
PBT2

***N. gonorrhoeae* is exclusively sensitive to PBT2.**

PBT2 can be a new treatment for *N. gonorrhoeae*

INSTITUTE FOR BIOMEDICINE AND GLYCOMICS

PBT2 killed MDR Ng within 3 h.



PBT2 can be a new treatment for *N. gonorrhoeae*

INSTITUTE FOR BIOMEDICINE AND GLYCOMICS

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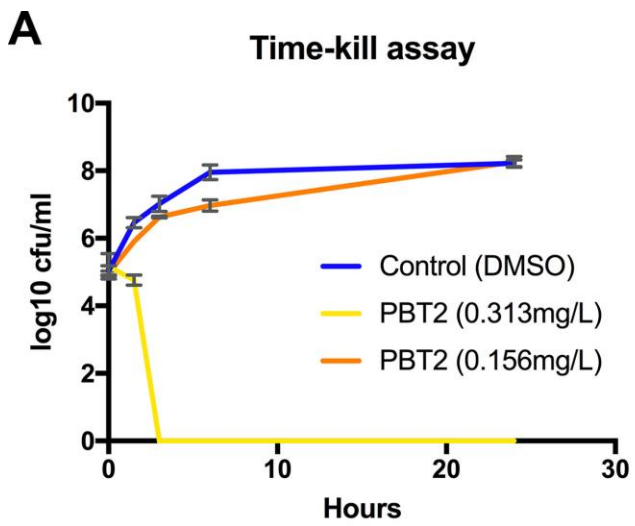

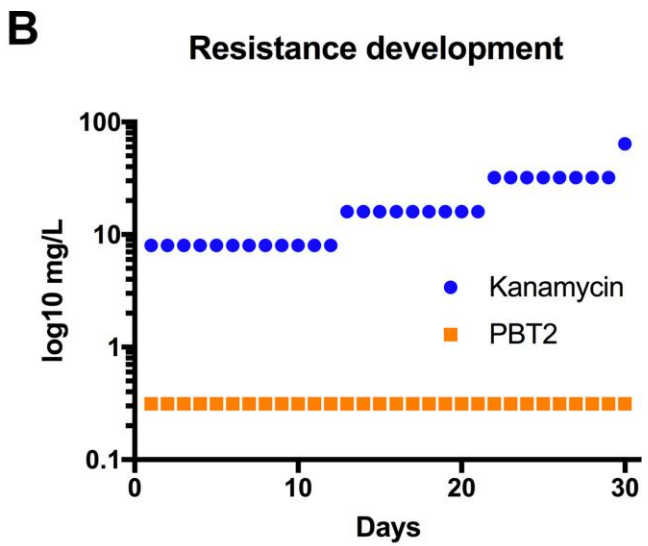

No antibiotic resistance was observed after 30 consecutive daily cycles.

PBT2 can be a new treatment for *N. gonorrhoeae*

INSTITUTE FOR BIOMEDICINE AND GLYCOMICS

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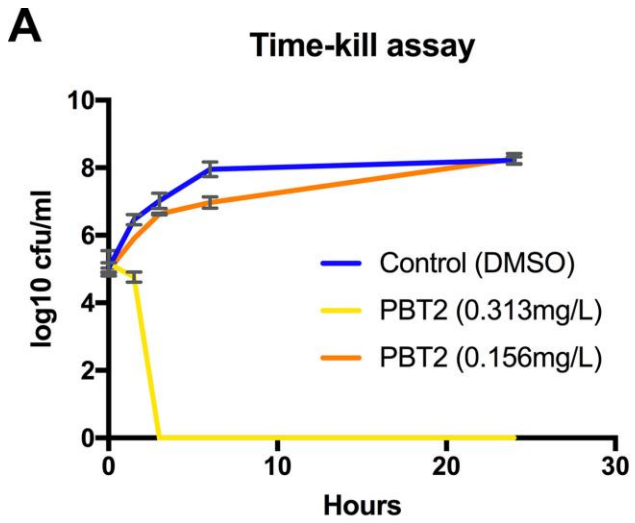

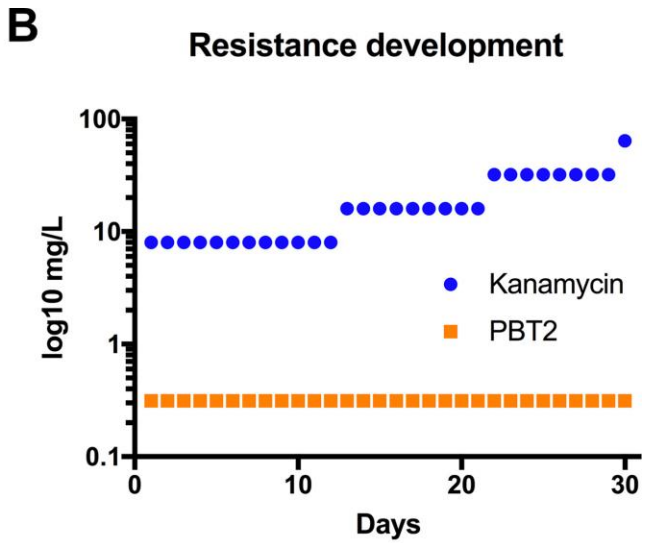

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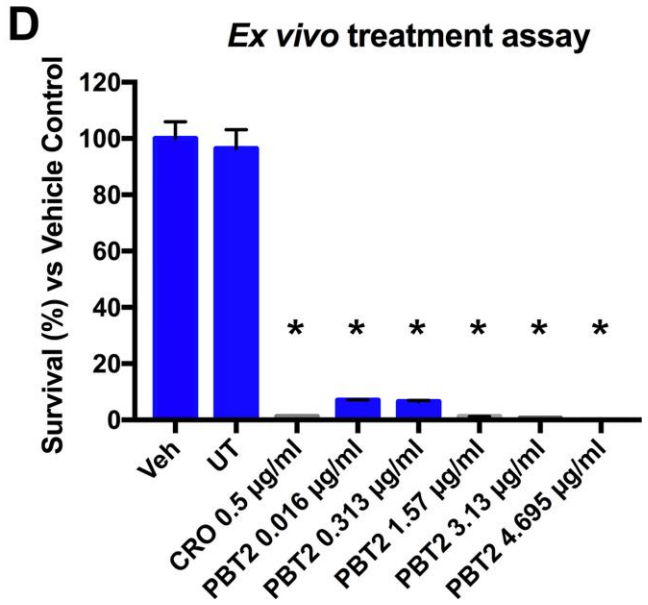
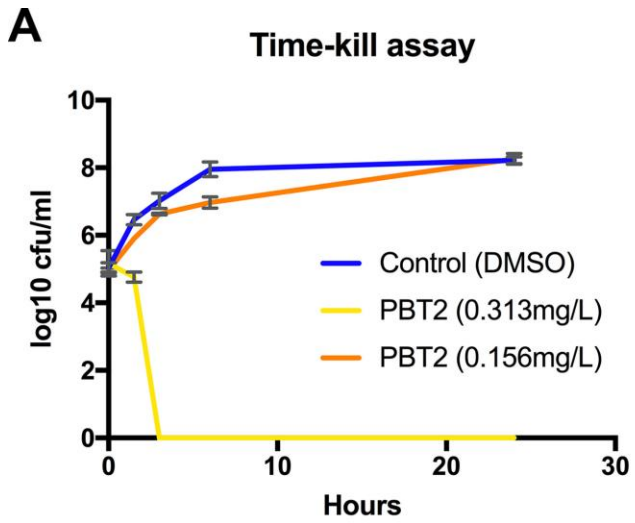


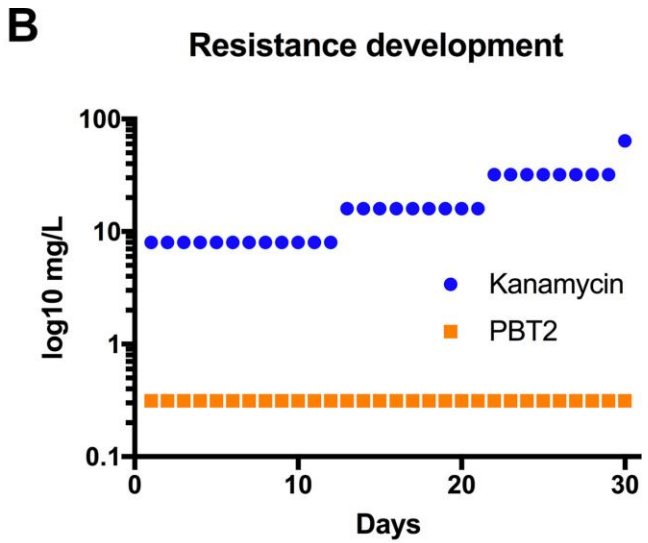
≥0.157 mg/L PBT2 left <8% viable gonococci in Pex lysates.

PBT2 can be a new treatment for *N. gonorrhoeae*

INSTITUTE FOR BIOMEDICINE AND GLYCOMICS

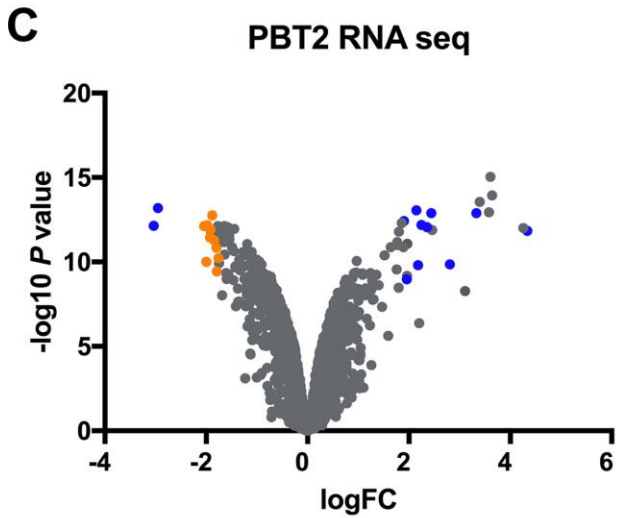
PBT2 killed MDR Ng within 3 h.

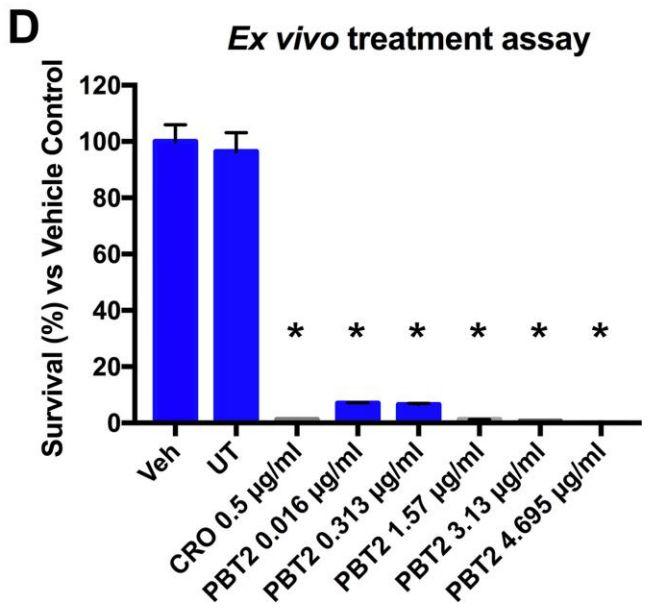




No antibiotic resistance was observed after 30 consecutive daily cycles.

PBT2 disrupts metal homeostasis and upregulates *mpeR* (iron-repressed), increasing *Ng* sensitivity to Triton X-100.





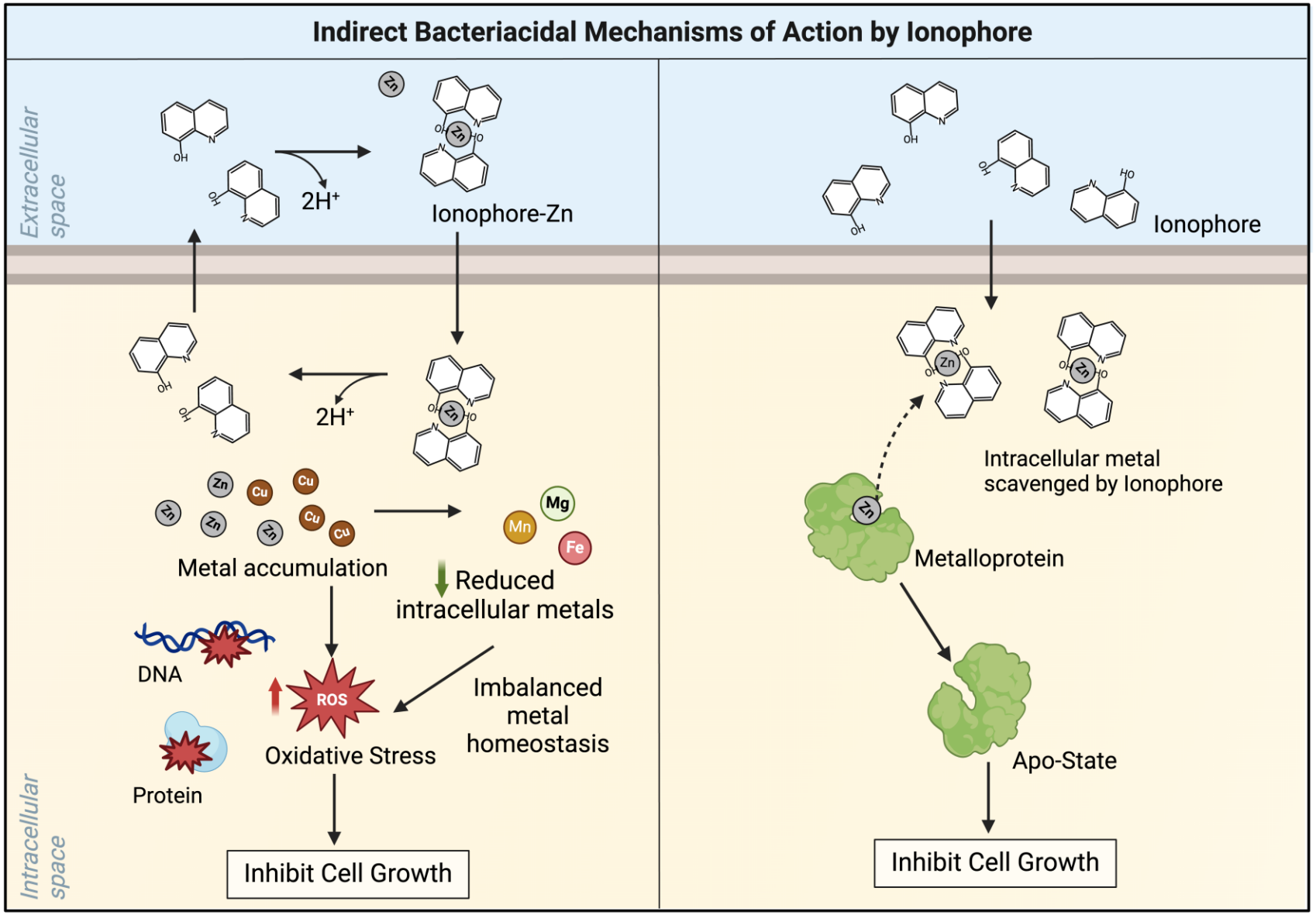
≥0.157 mg/L PBT2 left <8% viable gonococci in Pex lysates.

Neisseria meningitidis strains are sensitive to PBT2

The MIC of *N. meningitidis* strains tested against PBT2

***N. meningitidis* strains (serogroup)**	**PBT2 (µg/mL) Broth**	**PBT2 (µg/mL) Agar**
Z2491 (A)	0.1563	0.039
MC58 (B)	0.1563	0.039
8013 (C)	0.1563	0.078
PMC1 (X)	0.1563	0.039
PMC2 (Z/29E)	0.1563	0.039
PMC10 (Y)	0.625	0.156
PMC19 (W)	0.1563	0.078

Mode of action of PBT2



PBT2 has modes of action to inhibit cell growth:

- disrupting metal homeostasis
- inducing metal toxicity and oxidative stress
- interacting with metalloproteins or metalloenzymes and affecting their structural integrity and function.

Mode of action of PBT2

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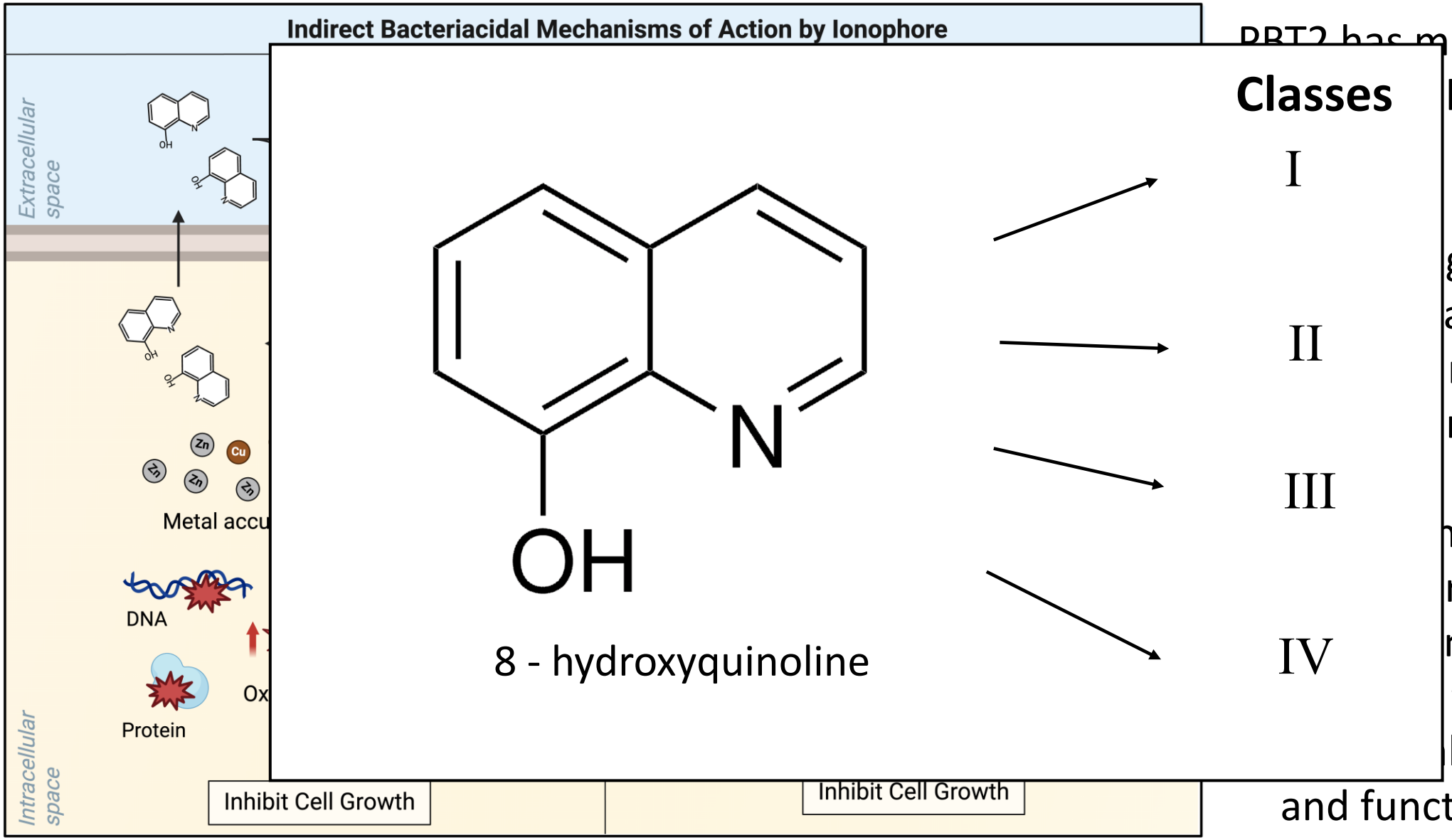

PBT2 has mechanisms of
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Mode of action of PBT2

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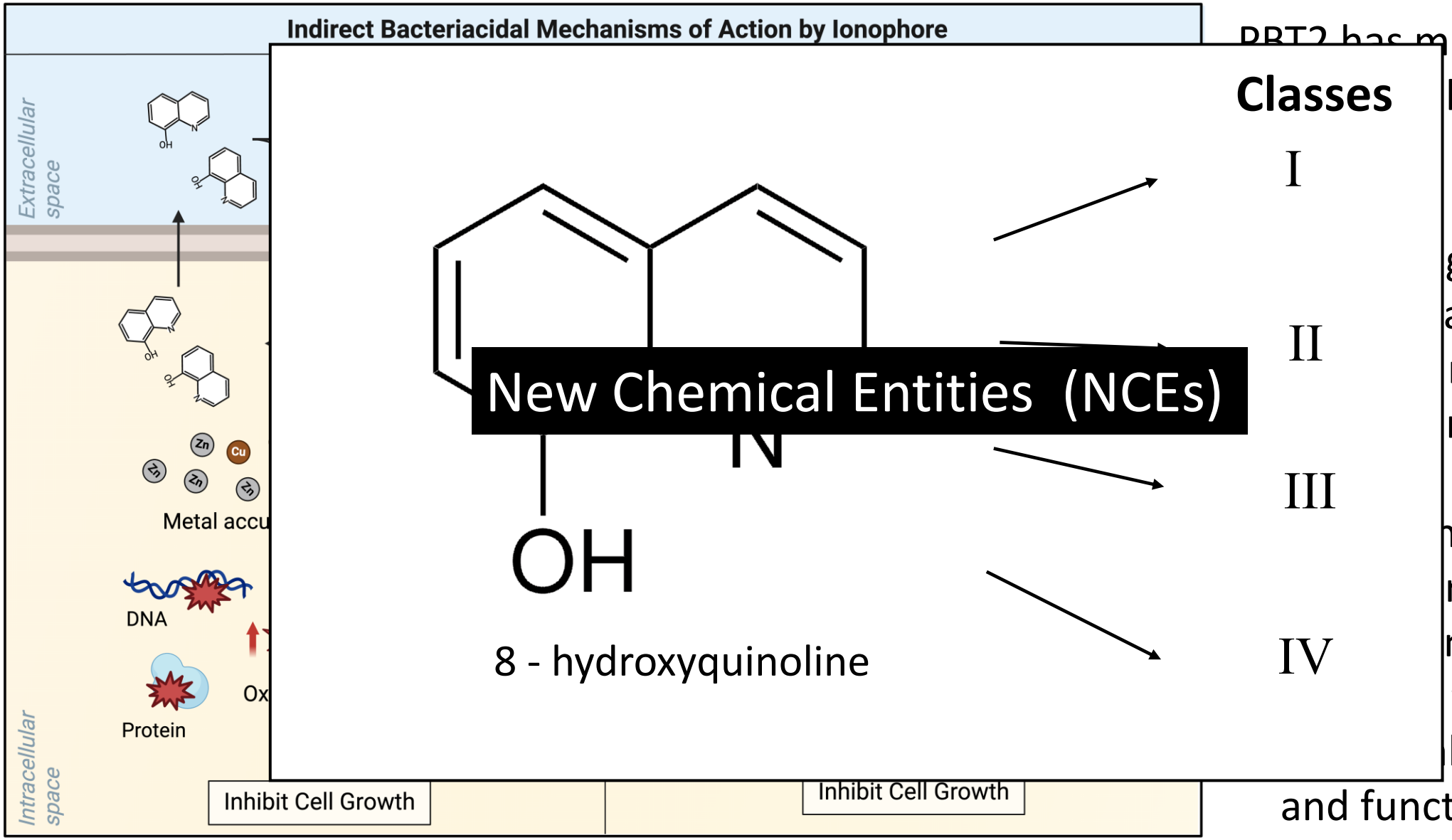

PBT2 has mechanisms of
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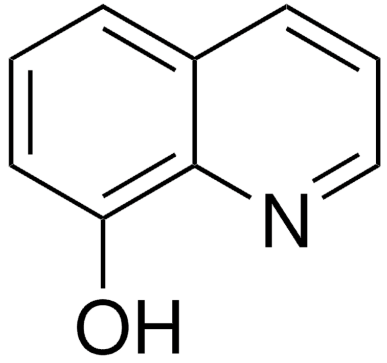
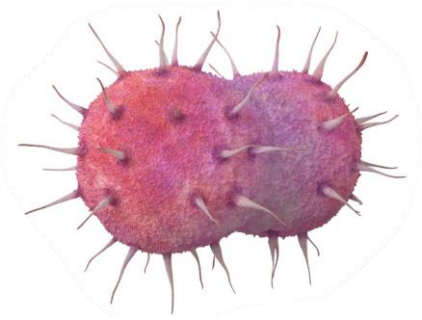
New Chemical Entities (NCEs)



8 - hydroxyquinoline

- More potent than PBT2
- Less toxic than PBT2
- Bactericidal activity
- No resistance observed after 30 days of treatment
- Proteomic analysis indicates NCEs modulate key pathways with high efficacy
- Supports the future development of novel antibiotics to treat MDR *N. gonorrhoeae*



Summary

- Multidrug-resistant *Neisseria gonorrhoeae* is a serious antimicrobial resistance threat and an escalating public health concern.
- PBT2, a repurposed drug originally developed for neurodegenerative diseases, has shown promise as a novel treatment for *N. gonorrhoeae* and other pathogens, including *N. meningitidis*.
- Building on our understanding of PBT2's structure and mode of action, we have developed a new class of novel chemical entities (NCEs) with enhanced antimicrobial activity—potentially superior to PBT2.

Acknowledgments

Institute for Biomedicine and Glycomics

Michael Jennings
Mark von Itzstein
Ibrahim El-Deeb
Arun Everest-Dass
Andrea Maggioni
Huitiing Chen

The Ohio State University & Nationwide Children's Hospital

Jennifer Edwards

University of Queensland

SCMB MS facility - Amanda Nouwens

Funding

National Health and Medical Research Council, Australia,
Development Grant, Ideas Grant

Anthony Coates

Anthony Coates is the Founder and Chief Scientific Officer of Helperby Therapeutics Group Ltd, a biopharmaceutical company dedicated to developing the next generation of lifesaving antibiotics. The company has several therapies in clinical trials targeting unmet needs in areas of significant market value, including candidates for urinary tract and skin infections.

Anthony is also Professor of Medical Microbiology at St. George's University of London. He leads several research teams, is the author of over 180 publications and has edited 13 books. He is a named inventor on 200 patent applications of which 127 have been granted and was a member of GARDP's Scientific Advisory Committee until 2025.

The development of zidovudine as a repurposed antimicrobial

Anthony Coates

Founder, Director, CSO, Helperby Therapeutics Group Ltd

Professor Medical Microbiology, City St Georges', University of London

Key messages

Bacterial resistance → Antibiotics ↓ → sepsis deaths ↑

Pharma industry is not generating enough new antibiotics

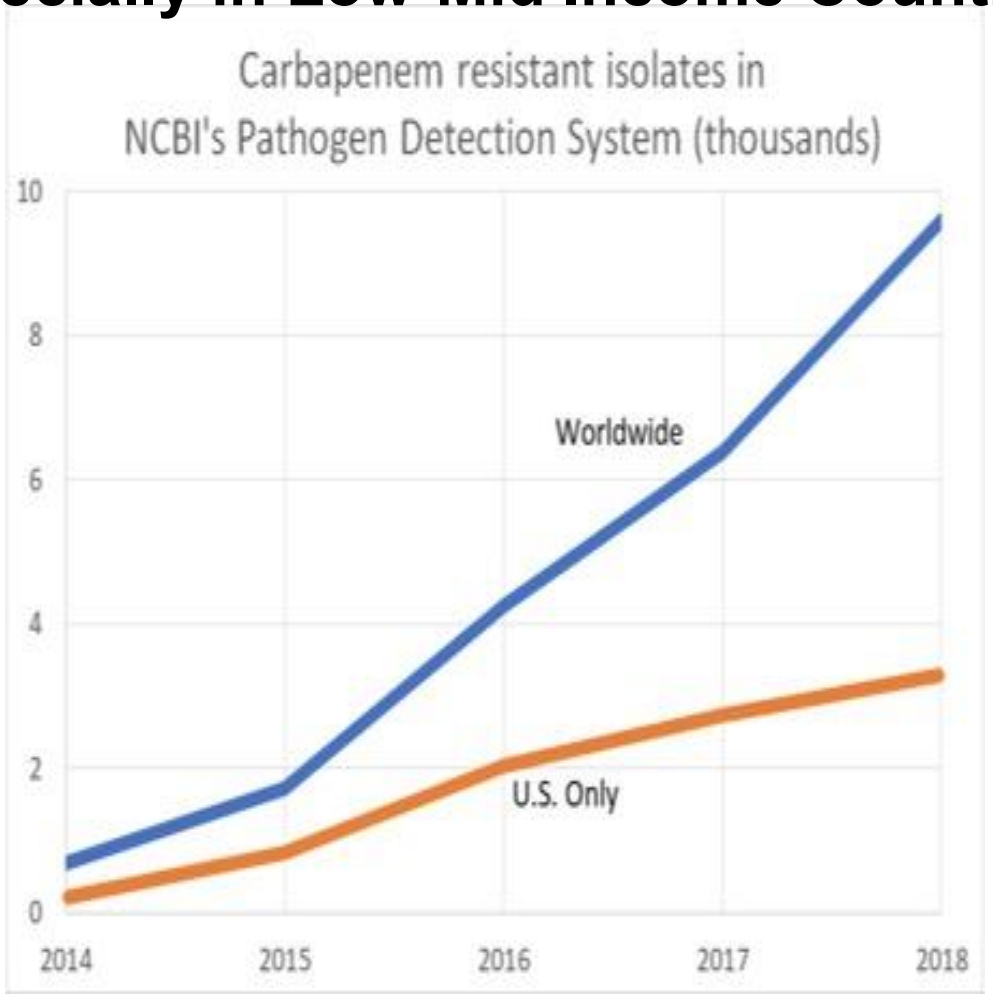
Repurposing antiviral zidovudine as a LOW COST antimicrobial in combination with colistin/meropenem

↓

Synergistic kill of highly resistant bacteria

Carl’s story

Unexpected high growth in resistance, especially in Low-Mid Income Countries



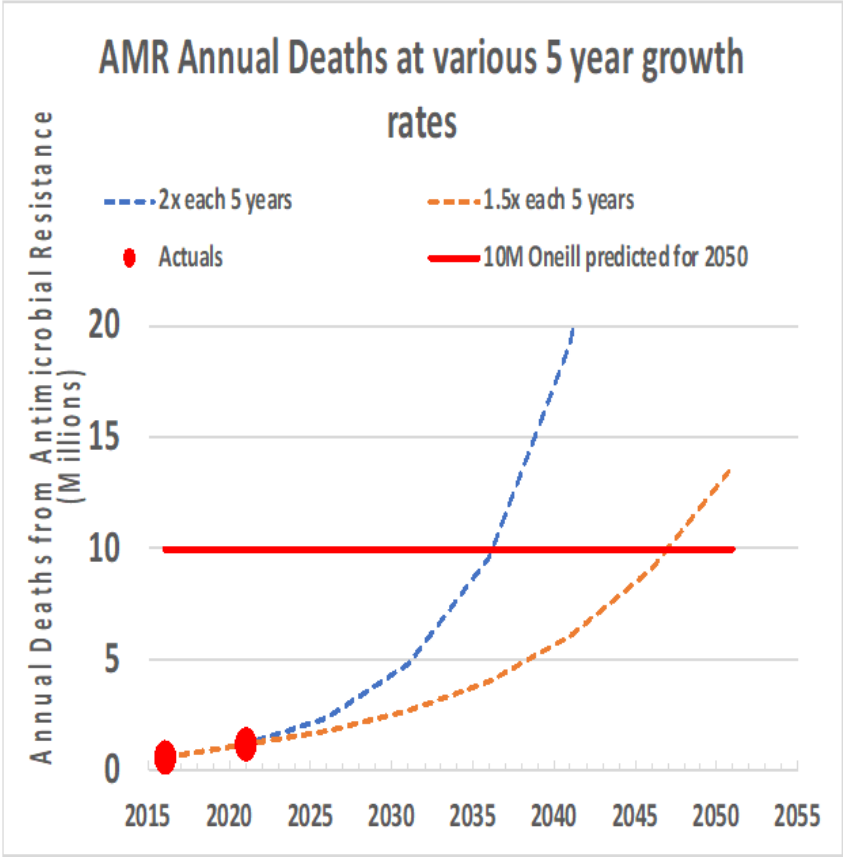
10x actual growth in 4 years

> 3.6X actual growth in 4 years

US National Centre for Biotechnology Information including National Database of Antibiotic Resistant Organisms
https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/

Unexpected high growth in global sepsis deaths from antibiotic resistant bacteria – doubled over 5 years

Projected deaths



www.thelancet.com Published online January 20, 2022 https://doi.org/10.1016/S0140-6736(21)02724-0

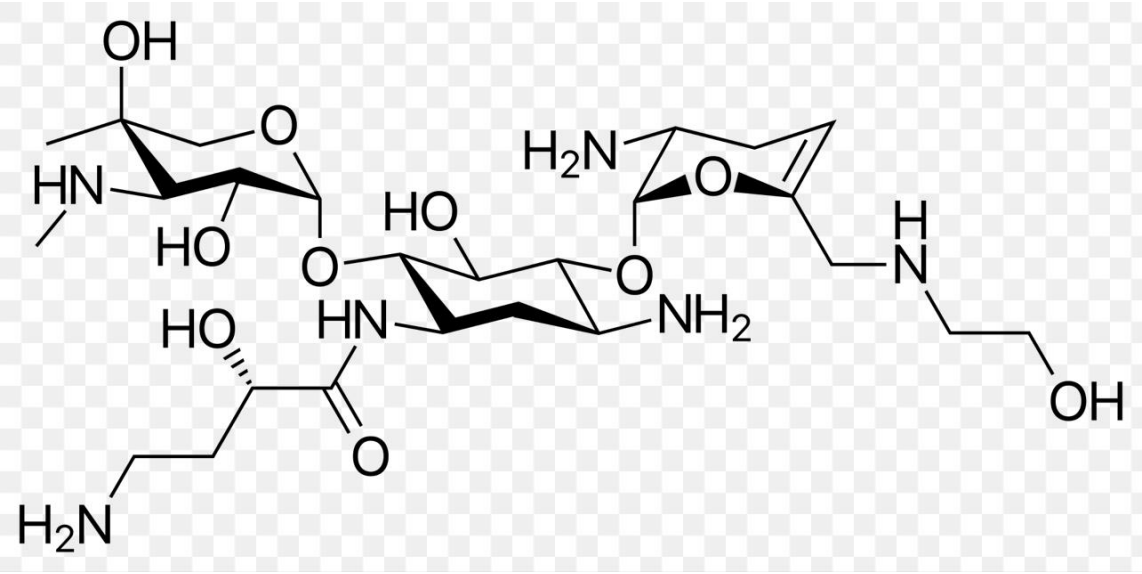
https://amr-review.org

Now we need new antibiotic treatments

Story of Achaogen

Traditional NEW CHEMICAL ENTITY

Plazomicin (derivative of sisomicin)



Reorg solutions. Case summary: Superbug Biopharmaceutical company Achaogen 4/15/2019. Reorg.com. Accessed 8/8/2024

What can we learn from the Achaogen bankruptcy?

New Chemical Entity antibiotics are NOT COMMERCIALLY VIABLE

(NB GARDP's important role in addressing this)

↓ **Development costs too high**

Most big pharma given up. **Almost all small pharma fail in the market**

↓

Develop a lower cost way of making new effective antibiotic treatments.

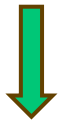
↓ **Nearer generic sales price**

Repurpose old drugs in SYNERGISTIC combinations

What do we need?

A commercially viable antibiotic company
(Helperby Therapeutics Ltd)

Low cost platform technology

Repurposed combinations of
low cost synergistic drugs 10-50x 

Synergy

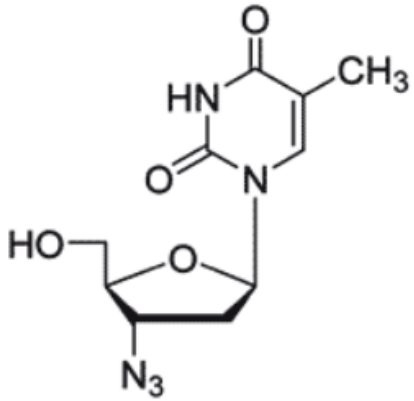
Antibiotics work together to produce an effect more potent than if each antibiotic were applied singly.

ADDITIVE 1+1=2 **SYNERGY 1+1=100**

Kohanski, Michael A.; Dwyer, Daniel J.; Collins, James J. (2010). "How antibiotics kill bacteria: from targets to networks". Nature Reviews Microbiology. 8 (6): 423–435. doi:10.1038/nrmicro2333. PMC 2896384. PMID 20440275.

Azidothymidine (AZT)

- Also called Zidovudine
- To prevent and treat HIV/AIDS
- Active against Gram-negative bacteria



*Elwell LP et al (1987) AAC, 31,274-280

Why develop zidovudine as a repurposed antimicrobial?

Low cost

Low toxicity in humans

Synergy with colistin and other drugs

Combination

Can kill highy resistant bacteria

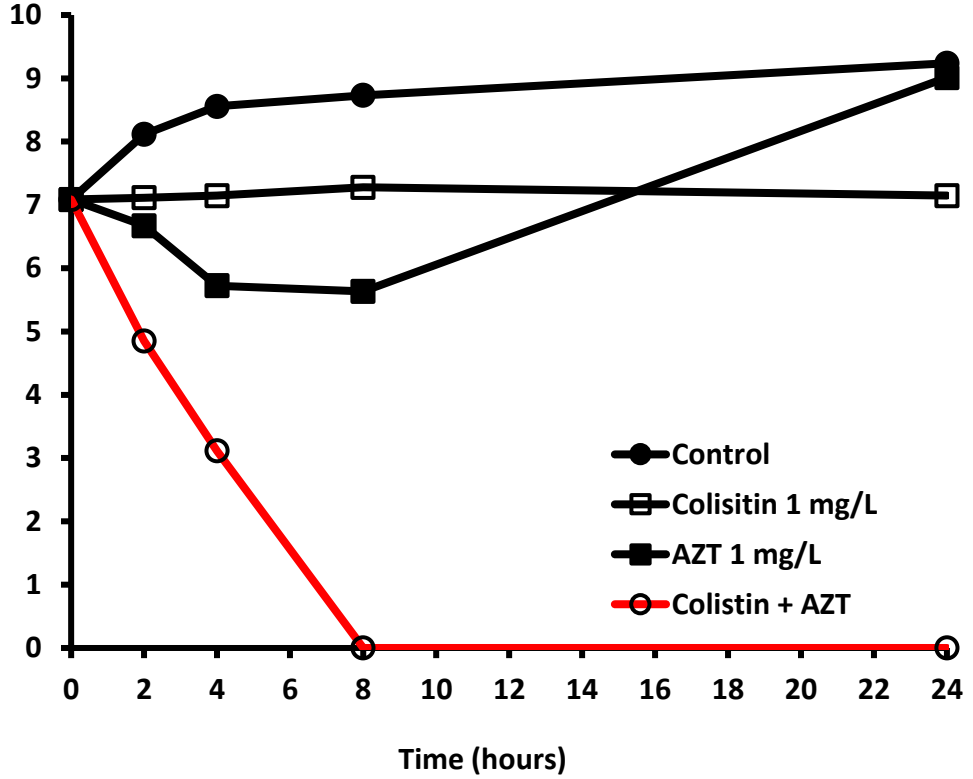
Colistin can be used at a lower concentration

reduced cost and lower side effects.

St George's University of London

HELPERBY THERAPEUTICS

AZT in combination with colistin produces synergistic bactericidal activity against NDM-1 *K. pneumoniae*



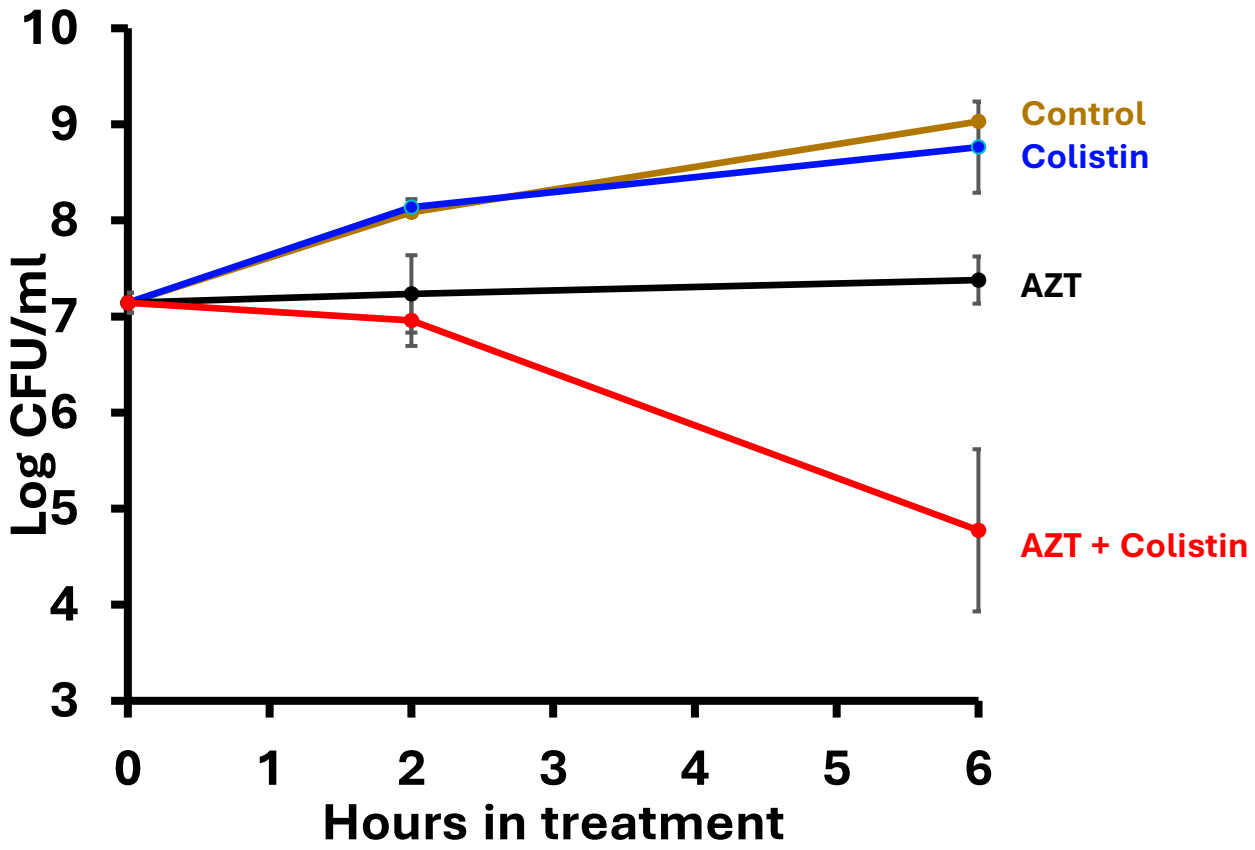
Azidothymidine and colistin are synergistically or additively active against100 colistin+carbapenem resistant *Klebsiella pneumoniae* isolates

SYNERGY/ADDITIVE

Synergy ΣFIC<0.5	AdditiveΣFIC 0.5-≤1
79	21

Matthew E. Falagas et al 2019. Synergistic activity of colistin with azidothymidine against colistin resistant Klebsiella pneumoniae clinical isolates collected from inpatients in Greek hospitals. IJAA, 53(9),855-858

AZT synergising with colistin killed NDM-1 *K. pneumoniae* in mice



Phase 1 Clinical Trial
27 volunteers

Azidothymidine(new class antibacterial)

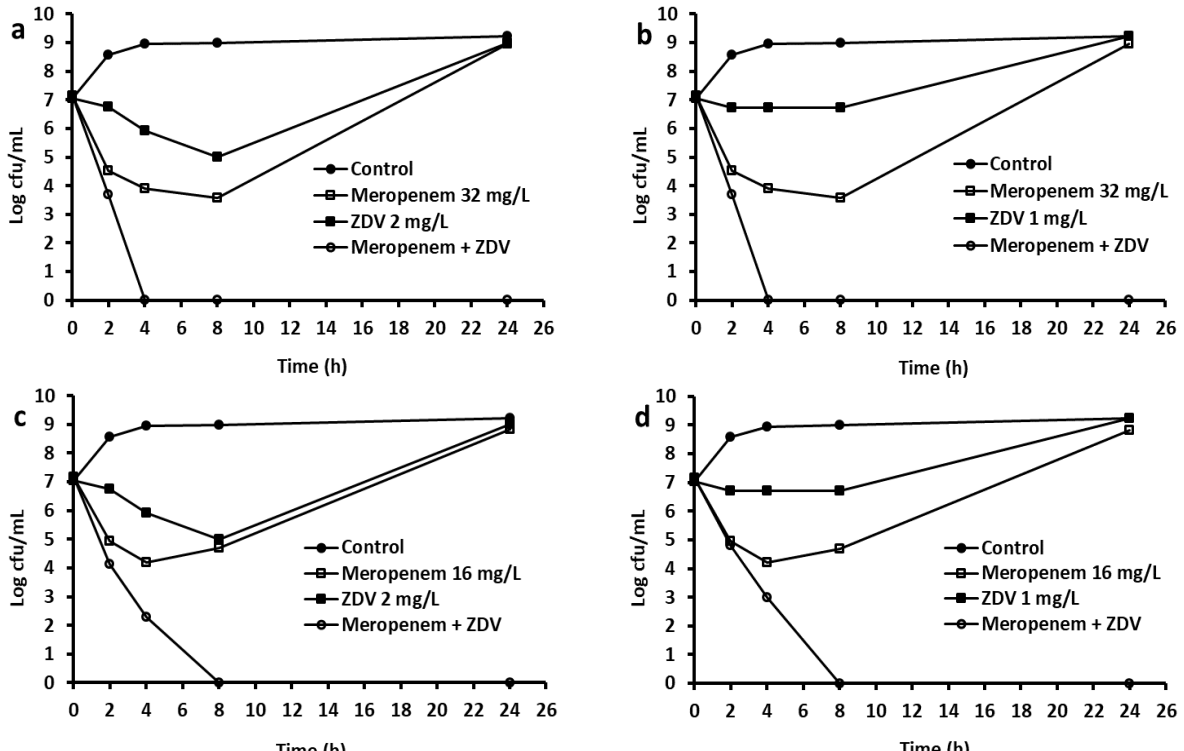
+

Colistin (CMS) (last resort)

Helperby Therapeutics

AZT synergises with meropenem against NDM-1 producing Enterobacteriaceae

(Hu Y, Coates 2021 J Antimicrob Chemotherapy, 76(9), 2302-2305)



Progress so far
Helperby Therapeutics Group Ltd

130 granted patents world-wide.

£140 million market cap.

Contract signed for $75 million from USA.

Low cost story

Conclusion

New chemical entity antibiotics are not commercially viable –costs too high

Low cost Zidovudine plus colistin kills highly resistant bacteria at a low dose of colistin

Acknowledgments

City St George's

Yanmin Hu

Anthony Coates

Helperby Therapeutics Group plc

James Phipson

Mike Dey

Jurgen Dobmeyer

Kurt Naber

Dennis Molnar

Grants

EU,

MRC

BBSRC

British Business Bank

Helperby Therapeutics Group plc

François Franceschi

François Franceschi is Associate Director of the Serious Bacterial Infections at GARDP. He has over 30 years of experience in the area of antimicrobials, previously serving as Program Officer for Therapeutics Development (antibacterial and antifungal) at the NIAID in Bethesda, Maryland, USA.

He has also held various Director positions in antibiotic R&D at Rib-X Pharmaceuticals (now Melinta Therapeutics) and was Principal Investigator at the Max Planck Institute for Molecular Genetics in Berlin, Germany, where his research was devoted to the structure and function of ribosomes, especially in complex with antibiotics. His group was a pivotal part of an international consortium led by Ada Yonath, who won the Nobel Prize in Chemistry in 2009. François received his PhD in Chemistry at the Frei Universität Berlin, Germany.

A One-Health approach to AMR: GARDP's exploration of a veterinary antibiotic for its therapeutic potential in humans. The case for apramycin

François Franceschi, PhD

Associate Director, Serious Bacterial Infections Program

GARDP

Global Antibiotic Research & Development Partnership

GARD P
Global Antibiotic Research & Development Partnership

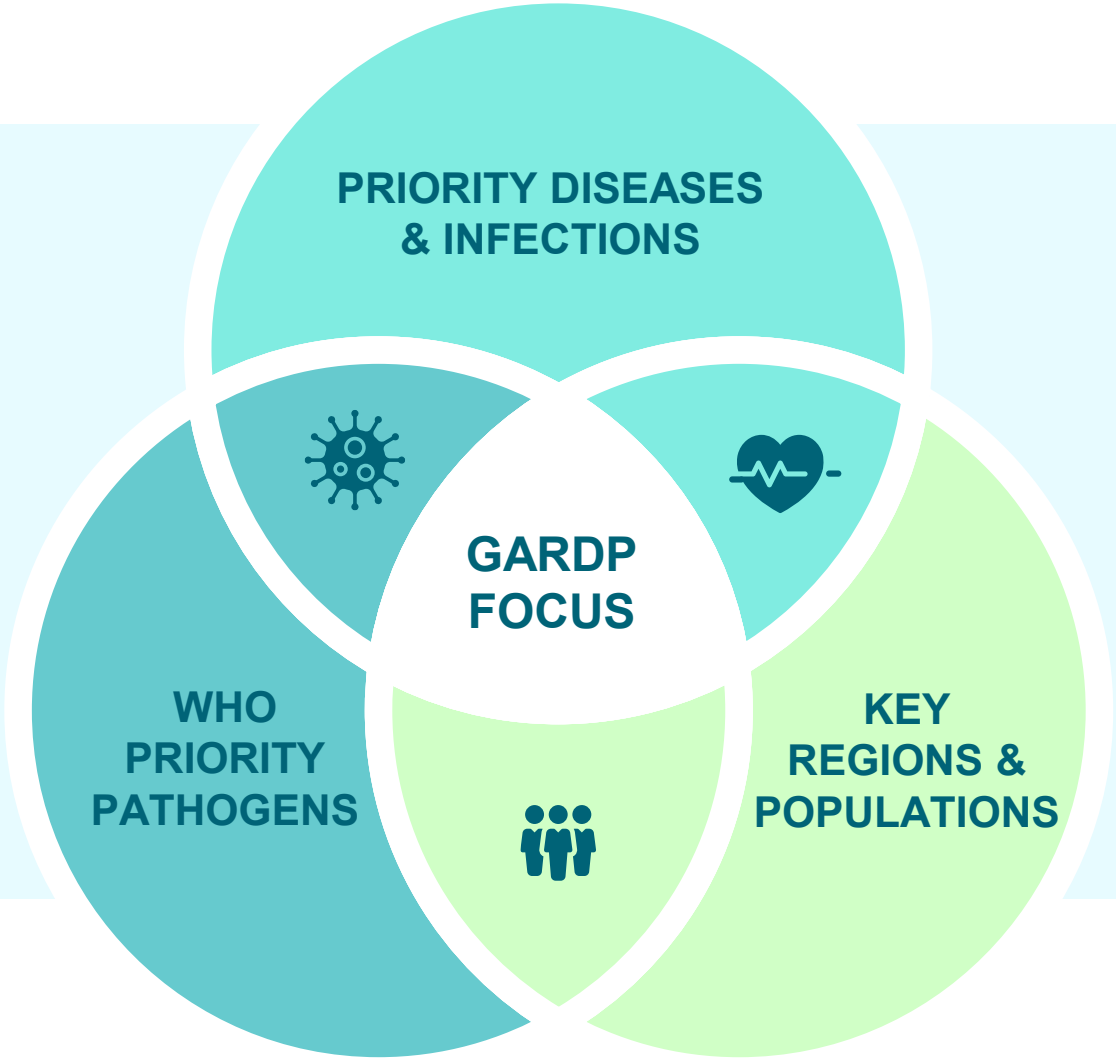
Our Vision

All infections are treatable
for everyone, everywhere

Our Mission

We accelerate the **development and access of treatments** for drug-resistant bacterial infections

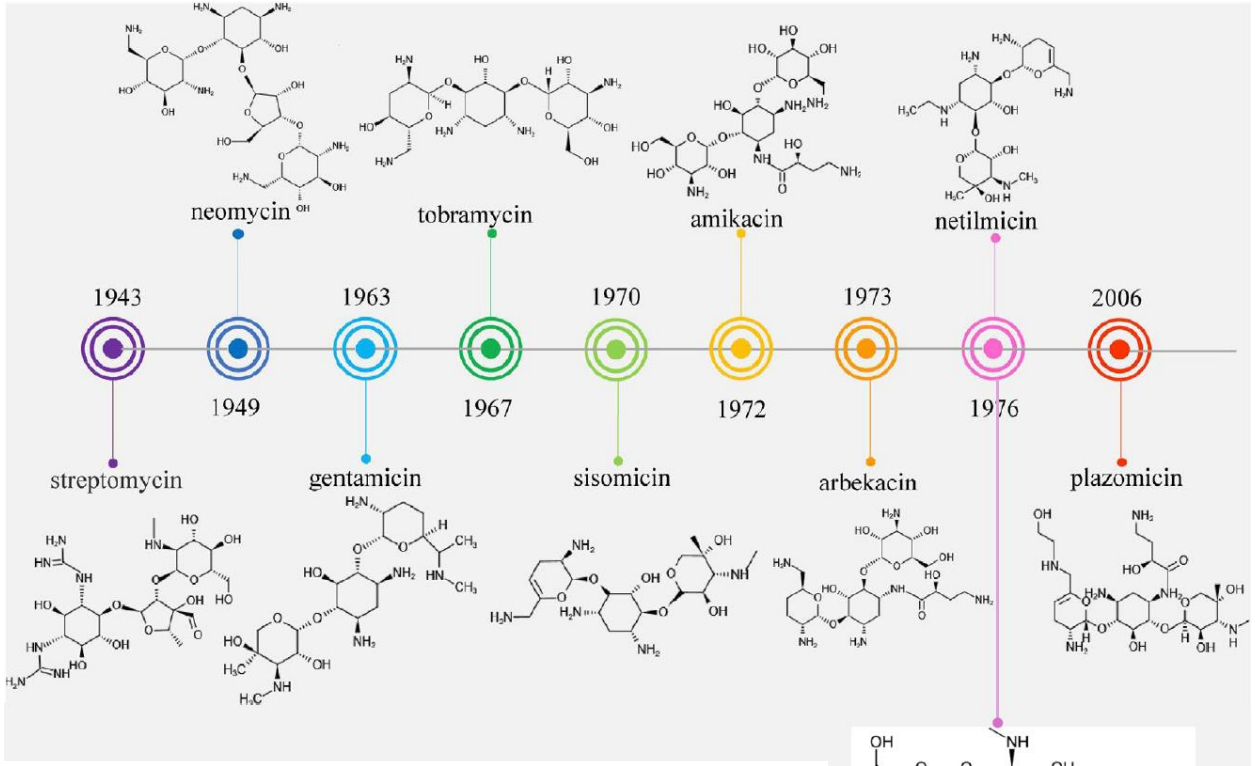
GARDP’s strategic approach

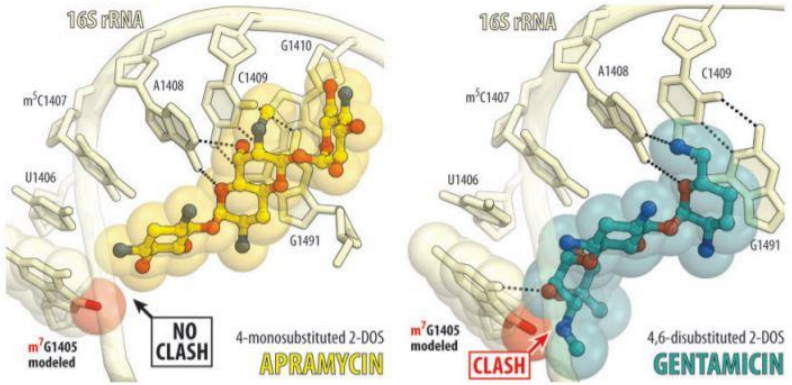


Apramycin: a veterinary aminoglycoside antibiotic

- **Aminoglycosides** (AGs) have been a cornerstone of antibacterial chemotherapy since streptomycin was first isolated from *Streptomyces griseus* and introduced into clinical use in 1944
- **Aminoglycosides** are potent, bactericidal, broad-spectrum antibiotics that act through inhibition of protein synthesis
- Several other members of the class were introduced in the clinic following streptomycin, including neomycin (1949), kanamycin (1957), gentamicin (1963), netilmicin (1967, derived from sisomicin), tobramycin (1967), amikacin (1972, derived from kanamycin), arbekacin (1976, derived from kanamycin), and plazomicin (2006, derived from sisomicin)
- Although some of them are still widely used, a shift away from systemic use of **aminoglycosides** began in the 1980s with the availability of the third-generation cephalosporins, carbapenems, and fluoroquinolones, which were perceived to be less toxic (**ototoxicity and nephrotoxicity**) and/or provide broader coverage than the **aminoglycosides**. This shift led to apramycin being approved **ONLY** for veterinary use

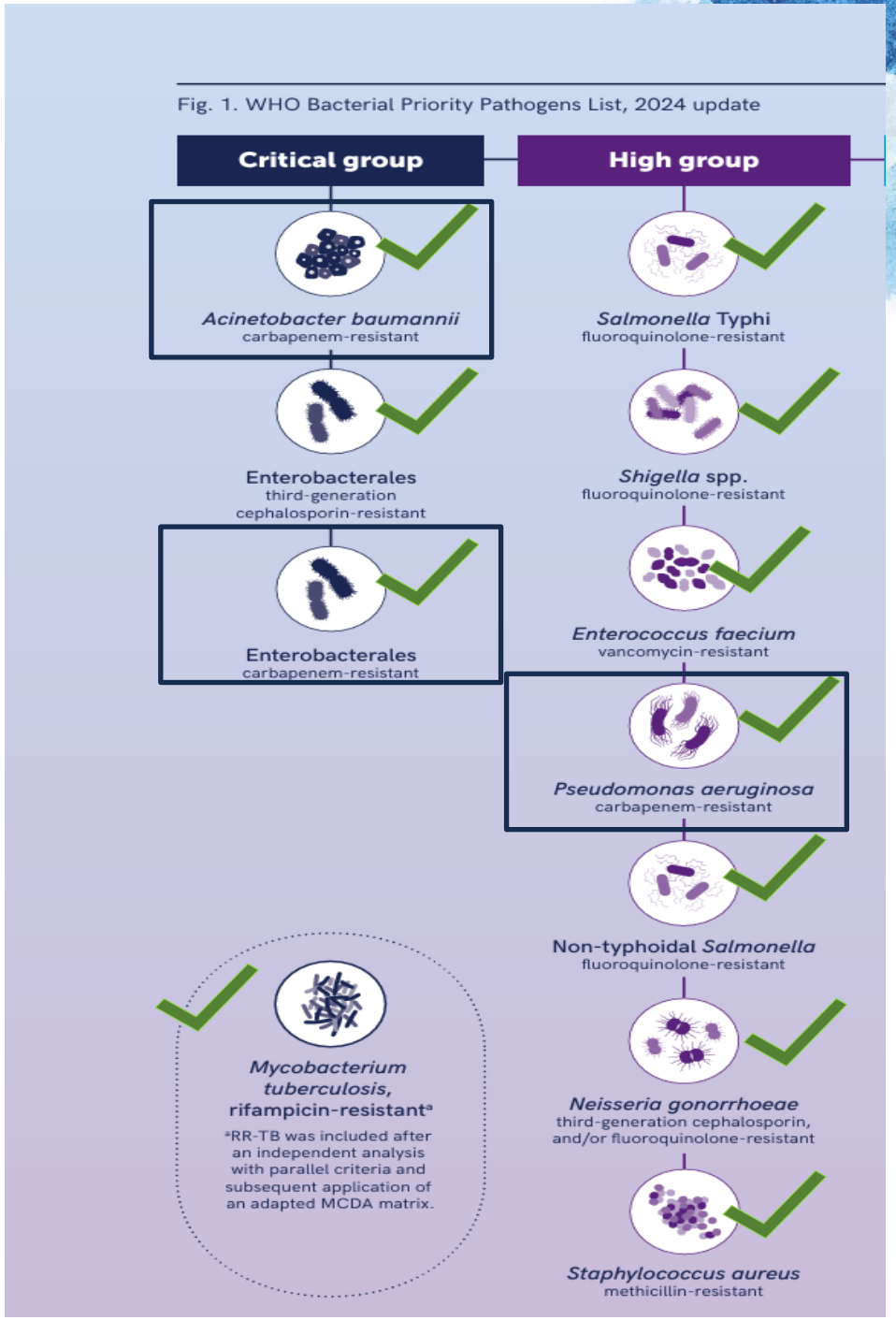
Apramycin Differentiation



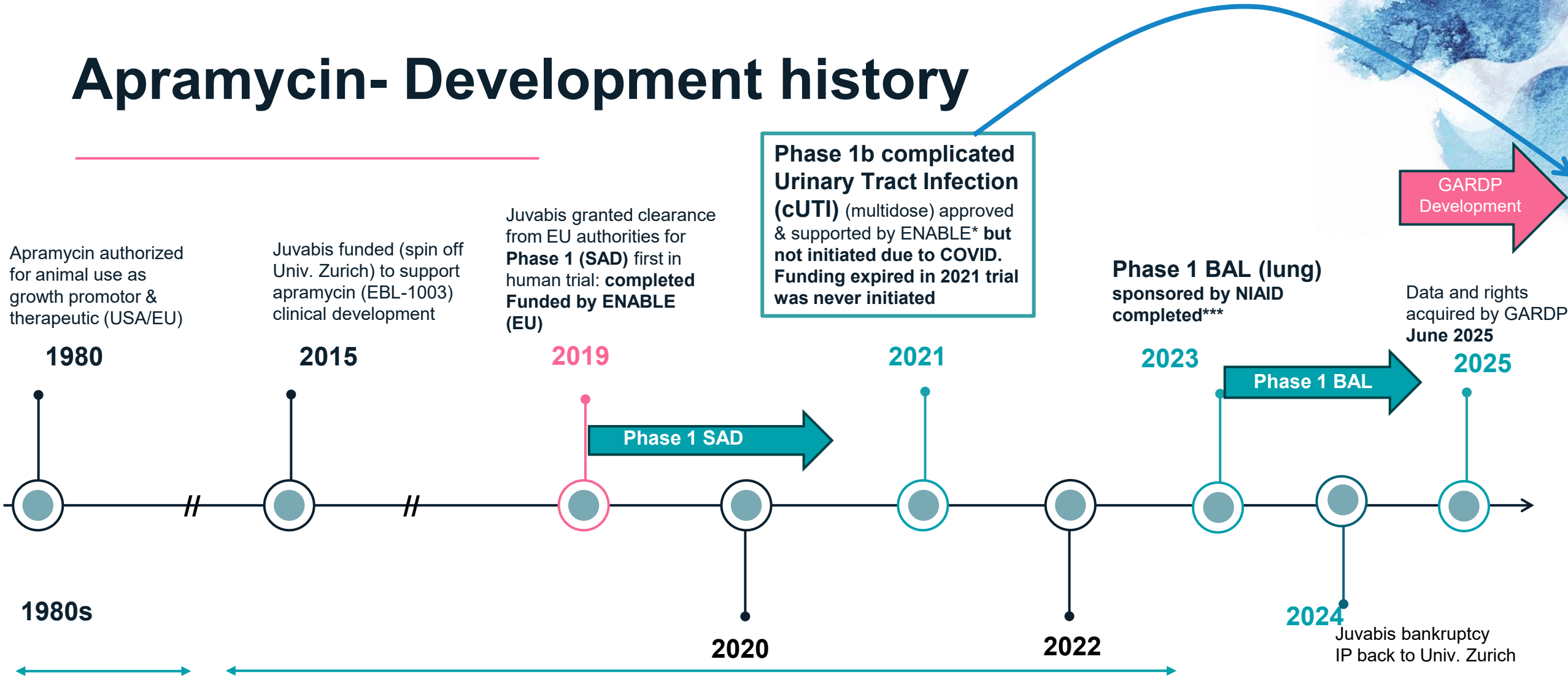


- Approved only for veterinary use
- **Mono-substituted**, **bicyclic deoxystreptamine** as opposed to other AGs (di-substituted and monocyclic)
- Broad spectrum of activity. **Resilient to almost all AGs resistance mechanisms** typically **found in MDR and XDR Gram-negative bacteria** (incl.16S RNA methylases (**common in carbapenem-resistant and metallo-β-lactamase producing strains**)
- The only clinically relevant resistance mechanism is via AAC(3)-IV that confers resistance through N-acetylation (low ↓ prevalence in clinical isolates)
- **Preclinical & Animal** data suggest **lower** nephrotoxicity and ototoxicity than other AGs

Apramycin antibacterial spectrum (WHO-PPL 2024). Based on in vitro data and animal models (for some of the pathogens)

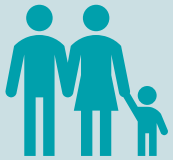


Apramycin- Development history



**: European Gram-Negative Antibacterial Engine (ENABLE)- IMI's initiative*
***: Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)*
**** Last cohort (24 h time point) not recruited due to Juvabis liquidation*

Aminoglycosides (AGs) in human and veterinary medicine



WHO

WHO List of Medically Important Antimicrobials: a risk management tool for mitigating antimicrobial resistance due to non-human use- Report 2024

AGs are listed as **Critically important antimicrobials** (CIA) for human health. **plazomicin** is the only AG restricted for human use

WOAH*

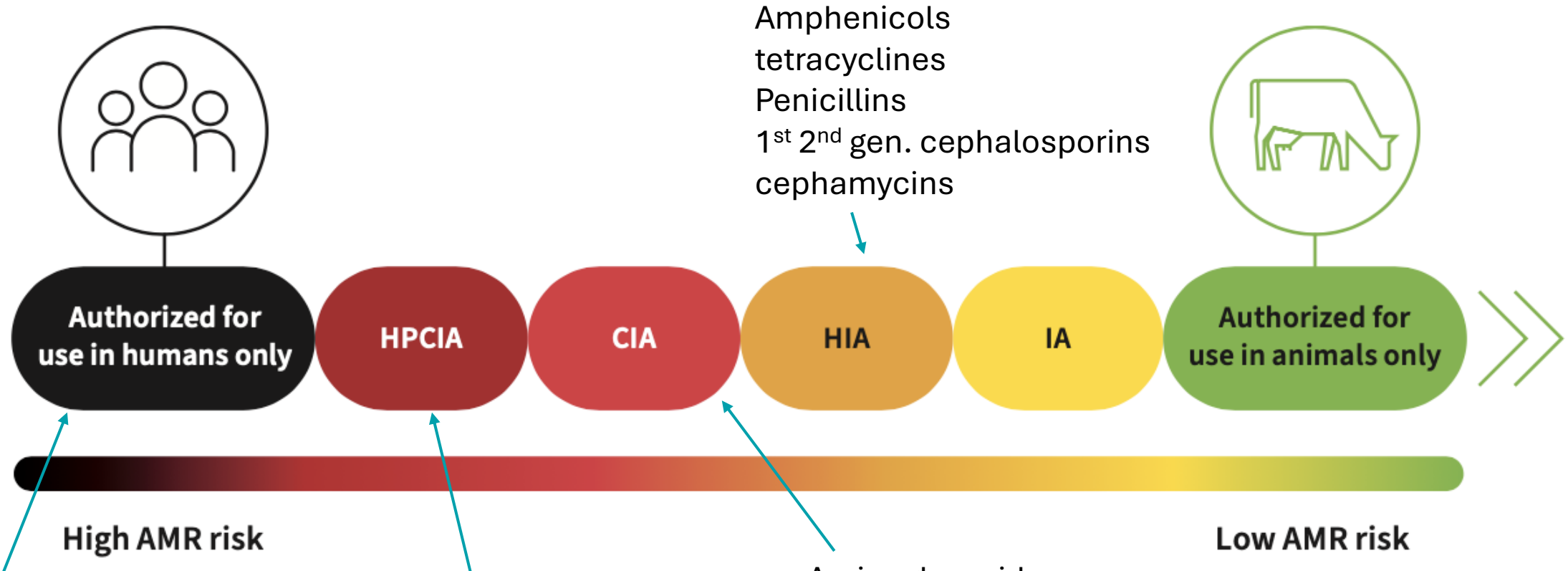
Annual Report on Antimicrobial Agents Intended for Use in Animals- May 2024

AGs are listed as **Veterinary Critically Important Antimicrobial Agents (**VCIA) with few economic alternatives

GARDP and WOAH met in October 2024 and agreed that it was worthwhile for GARDP to explore the potential for apramycin use in human medicine

***WOAH: World Organization for Animal Health**

Prioritization of antimicrobial classes in the WHO Medically Important Antimicrobial List



HPCIA: highest priority critically important antimicrobial
CIA: Critically important antibiotic

HIA: Highly important antimicrobial
IA: Important antimicrobial

Apramycin resistance in human isolates? After 40 years of veterinary use: little reason for concern!

- A study of 591,140 genomes of pathogen Gram-neg bacteria deposited in the NCBI National Database of Antibiotic-Resistant Organisms, showed that aac(3)-IV (the only apramycin-resistant gene of clinical relevance) was detected only in 0.7% of isolates, despite 45 years of veterinary use.
- Several publications document low levels of resistance to apramycin among MDR/XDR human clinical isolates:
  - 84 CR/hypervirulent Klebsiella strains from China (2020) were **ALL sensitive** to apramycin while being resistant to amikacin and carbapenems. doi.org/10.3389/fmicb.2020.00425
  - From 470 MDR GNB isolates (2022) from health care facilities in Cambodia, Laos, Singapore, Thailand, and Vietnam, **98.3% were susceptible to apramycin**. All carbapenem-resistant isolates were sensitive to apramycin. The sample included 65 colistin-resistant isolates from which only four (6.2%) were resistant to apramycin. doi.org/10.5167/uzh-220040
  - Apramycin in vitro activity was tested against multidrug-resistant, extensively drug-resistant, and pandrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Only 2% of A. baumannii and P. aeruginosa had an MIC greater than an epidemiological cutoff value of 64 µg/ml. doi.org/10.1016/j.diagmicrobio.2017.03.006
- There had been speculation that the low levels of resistance to apramycin seen in human isolates could be due to a high fitness cost for apramycin resistance. A recent Nature publication seems to suggest that acquiring apramycin resistance indeed has a fitness cost. “Exploring the principles behind antibiotics with limited resistance. Nature Comms 2025 /doi.org/10.1038/s41467-025-56934-3

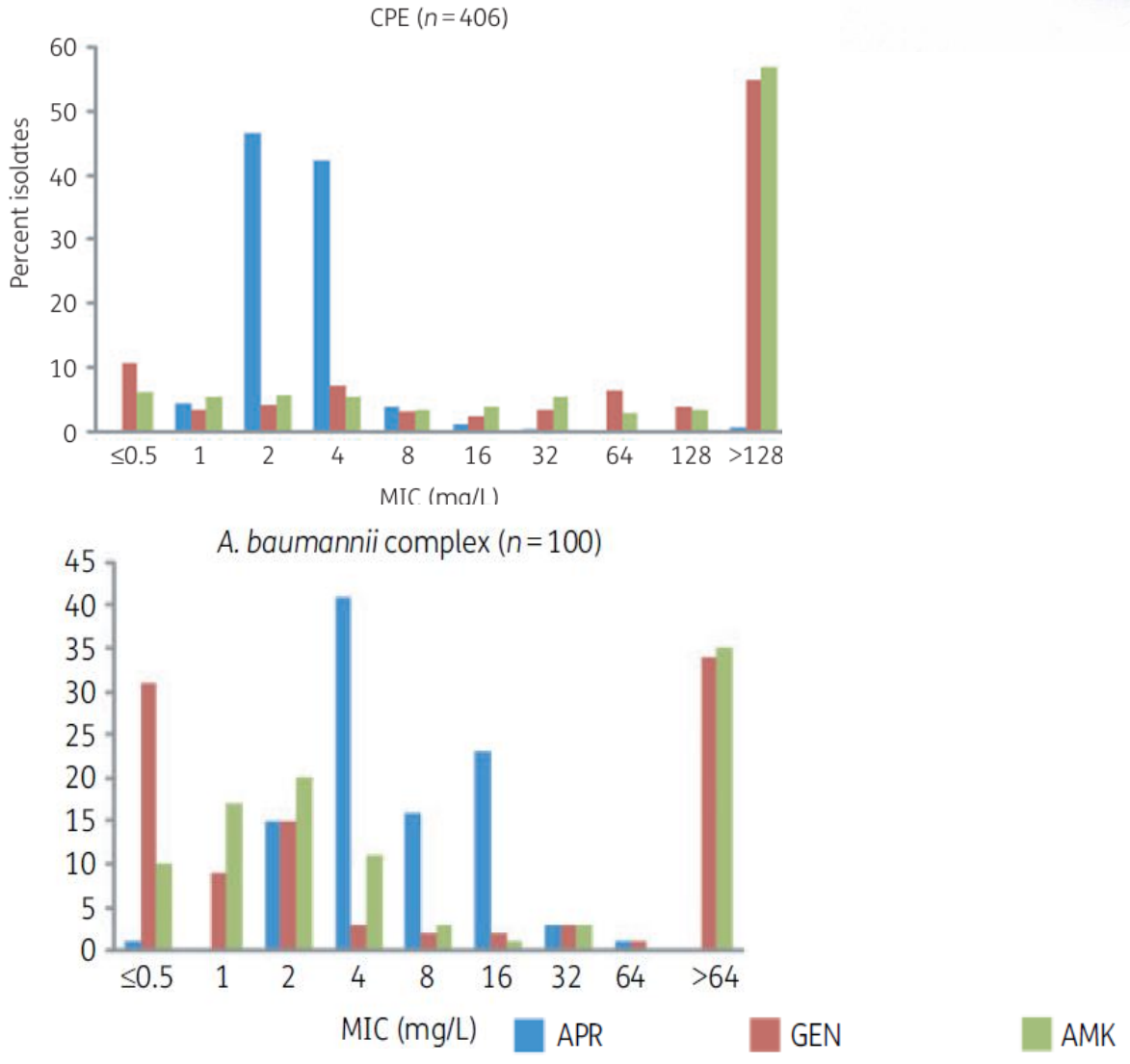
Apramycin- In vitro differentiation…

- ✓ 2019 Study shows clear differentiation between apramycin and amikacin/gentamicin

Table 1. MIC_{90} of apramycin in comparison with gentamicin and amikacin against clinical isolates of Enterobacteriaceae and *A. baumannii* isolated between 2014 and 2017

Species	No.	MIC_{90} (mg/L)		
		APR	GEN	AMK
Enterobacteriaceae (all)	1132	8	>64	>64
Escherichia coli	250	8	>64	>64
Klebsiella pneumoniae	372	4	>64	>64
Enterobacter spp.	179	4	>64	>64
Morganella morganii	37	8	>64	4
Citrobacter freundii	131	8	>64	>64
Providencia spp.	80	8	>64	>64
Proteus mirabilis	32	8	>64	>64
Serratia marcescens	51	8	>64	>64
CPE only (all)	406	4	>128	>128
Escherichia coli	74	8	>128	>128
Klebsiella pneumoniae	236	4	>128	>128
Enterobacter spp.	48	8	>128	>128
Citrobacter freundii	48	4	>128	>128
A. baumannii	100	16	>64	>64
CPA only	17	16	>256	>256
Geographic origin				
Europe	799	8	>64	>64
Asia	240	8	>256	>256
Africa	107	8	>256	>256
South America	86	4	>256	>256

APR, apramycin; AMK, amikacin; GEN, gentamicin; CPE, carbapenemase-producing Enterobacteriaceae; CPA, carbapenemase-producing *A. baumannii*.



J Antimicrob Chemother 2019; 74: 944–952 doi:10.1093/jac/dky546

Apramycin in the literature

European Journal of Clinical Microbiology & Infectious Diseases (2023) 42:843–852
https://doi.org/10.1007/s10096-023-04616-7

ORIGINAL ARTICLE

In vitro activities of omadacycline, eravacycline, cefiderocol, apramycin, and comparator antibiotics against *Acinetobacter baumannii* causing bloodstream infections in Greece, 2020–2021: a multicenter study

Irene Galani[1] · Vassiliki Papoutsaki[2] · Ilias Karaiskos[3] · Nikolaos Moustakas[1] · Lamprini Galani[3] · Sofia Maraki[4] · Viktoria Eirini Mavromanolaki[4] · Olga Legga[5] · Kimon Fountoulis[6] · Evangelia D. Platsouka[7] · Panagiota Giannopoulou[8] · Helen Papadogeorgaki[2] · Maria Damala[9] · Efrosini Chinou[10] · Aggeliki Pasxali[11] · Ioannis Deliolanis[12] · Helen Vagiakou[13] · Efthymia Petinaki[14] · Anastasia Chli[15] · Eleni Vagdatli[16] · Polyzo Kazila[17] · Vassiliki Papaioannou[18] · Konstantina Kontopoulou[19] · Atalia Noemi Ferke[20] · Eleni Moraitou[21] · Anastasia Antoniadou[1] · Helen Giamarellou[3]

Received: 3 January 2023 / Accepted: 26 April 2023 / Published online: 3 May 2023

International Journal of Antimicrobial Agents
Volume 60, Issue 4, October 2022, 106659

Short Communication

Apramycin susceptibility of multidrug-resistant Gram-negative blood culture isolates in five countries in Southeast Asia

Marina Gysin [a], Pei Yun Hon [b], Pisey Tan [c], Amphonesavanh Sengduangphachanh [d], Manivone Simmalavong [d], Pattaraporn Hinfonthong [e], Napaporn Kaewphanderm [e], Thai Duy Pham [f], Thanh Ha Nguyen [f], Klara Haldimann [a], Katja Becker [a], H. Rogier van Doorn [g h], Jill Hopkins [c h], Andrew J.H. Simpson [d h], Elizabeth A. Ashley [d h], Thomas Kesteman [g h], Hoang Huy Tran [f], Shawn Vasoo [b 1], Clare L. Ling [e h 1], Tamalee Roberts [d h 1]...Sven N. Hobbie [a 1]

PNAS

Dissociation of antibacterial activity and aminoglycoside ototoxicity in the 4-monosubstituted 2-deoxystreptamine apramycin

Tanja Matt[a,1], Chyan Leong Ng[b,1,2], Kathrin Lang[b,1], Su-Hua Sha[c,1,3], Rashid Akbergenov[a,1], Dmitri Shcherbakov[a,1], Martin Meyer[a], Stefan Duscha[a], Jing Xie[c,4], Srinivas R. Dubbaka[d], Déborah Perez-Fernandez[d], Andrea Vasella[d], V. Ramakrishnan[b], Jochen Schacht[c], and Erik C. Böttger[a,5]

Lower ototoxicity and absence of hidden hearing loss point to gentamicin C1a and apramycin as promising antibiotics for clinical use

Masaaki Ishikawa[1,11], Nadia García-Mateo[2], Alen Čusak[3], Iris López-Hernández[2], Marta Fernández-Martínez[4,5], Marcus Müller[6], Lukas Rüttiger[1], Wibke Singer[1], Hubert Löwenheim[6], Gregor Kosec[3], Štefan Fujs[3], Luis Martínez-Martínez[7,8,9], Thomas Schimmang[2], Hrvoje Petković[3,10], Marlies Knipper[1] & M. Beatriz Durán-Alonso[2]

Clinical Pharmacology & Therapeutics

Article | Open Access

Model-Informed Drug Development for Antimicrobials: Translational PK and PK/PD Modeling to Predict an Efficacious Human Dose for Apramycin

Tomás Sou, Jon Hansen, Edgars Liepinsh, Maria Backlund, Onur Ercan, Solveiga Grinberga, Sha Cao, Paraskevi Giachou, Anna Petersson, Magdalena Tomczak, Malgorzata Urbas, Dorota Zabicka, Carina Vingsbo Lundberg, Diarmaid Hughes, Sven N. Hobbie, Lena E. Friberg ... See fewer authors

Neonatal sepsis due to NDM-1 and VIM-2 co-producing Pseudomonas aeruginosa in Morocco.

Daaboul D, Osman M, Kassem II, Yassine I, Girlich D, Proust A, Mounir C, Zerouali K, Raymond J, Naas T, Oueslati S.

J Antimicrob Chemother. 2024 Jul 1;79(7):1614-1618. doi: 10.1093/jac/dkae153.

PMID: 38804143

RESULTS: P. aeruginosa O82J1 co-expressed two metallo-beta-lactamases, blaNDM-1 and blaVIM-2, and was susceptible to colistin and **apramycin** only. It belonged to ST773 that is frequently reported worldwide as a high-risk P. aeruginosa clone. ...CONCLUSIONS: The isolation of ...

Journal of Global Antimicrobial Resistance
Volume 33, June 2023, Pages 21-25

In vitro activity of apramycin against 16S-RMTase-producing Gram-negative isolates

François Caméléna [a b 1], Mathilde Liberge [a b 1], Inès Rezzoug [a], Manel Merimèche [a b], Thierry Naas [c d e], Béatrice Berçot [a b]

GARDP Planned Activities: Short & Medium-term

Generate PK/PD information in Hollow Fibre and Animal Models alone & combinations	Investigate Probability of Target Attainment (PTA)/dose for coverage of critical priority pathogens/syndromes
Generate IMP material from veterinary supplies	Initially, utilize the same veterinary apramycin providers as Juvabis to generate 1.5 to 2 kg of GMP material for phase 1b clinical trial
Conduct a phase 1b trial (multiday dosing @30mg/kg) in cUTI patients (N= ~40)	Primary endpoints safety and PK • Nephrotoxicity • Audiometry (ototoxicity) • PK
Establish a supply chain for apramycin	Locate GMP facilities with the capability to produce apramycin API/DP (India, EU, USA) for human use Improve fermentation process
Contact regulatory authorities to discuss apramycin regulatory path	Define regulatory path Start development of Paediatric Investigational/Study Plan (PIP/PSP) once Phase 1b is underway

Summary: Why Apramycin?

- Known class/known liabilities with potential to cover all WHO-critical priority pathogens.
- Based on the known synergies between aminoglycoside and beta-lactam antibiotics, apramycin has the potential to become a solid backbone for combination therapies (incl. for neonatal sepsis).
- Apramycin appears less ototoxic and nephrotoxic than currently used AGs, potentially due to differences in uptake and accumulation in renal cells and lower potential to damage cochlear hair cells when compared to clinically used AGs.
- Combines “premium coverage” with excellent COGs (few USD/dose)
- Would allow GARDP to explore a new path for development of a low-cost, high-public impact antibiotic deployable in LMICs

Ministry of Foreign Affairs

Federal Ministry
of Research, Technology
and Space

Ministry of Health, Welfare and Sport

With funding from the

Federal Ministry
for Economic Cooperation
and Development

through KFW

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Confederaziun svizra

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REPUBLIQUE
ET CANTON
DE GENEVE

POST TENEBRAS LUX

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GAMRIF

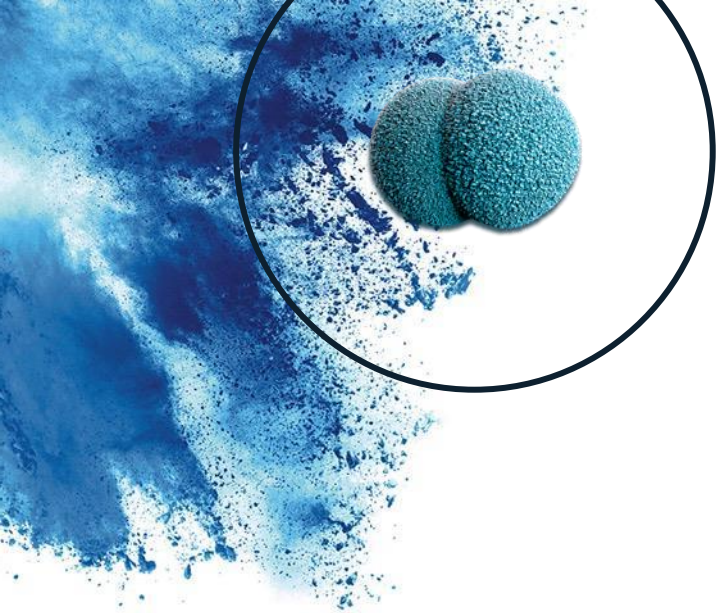
Research Investment for Global Health Technologies
RiGHT
국제보건기술연구기금

Gouvernement Princier
PRINCIPAUTÉ DE MONACO

GSK

wellcome

saMRC
advancinglife

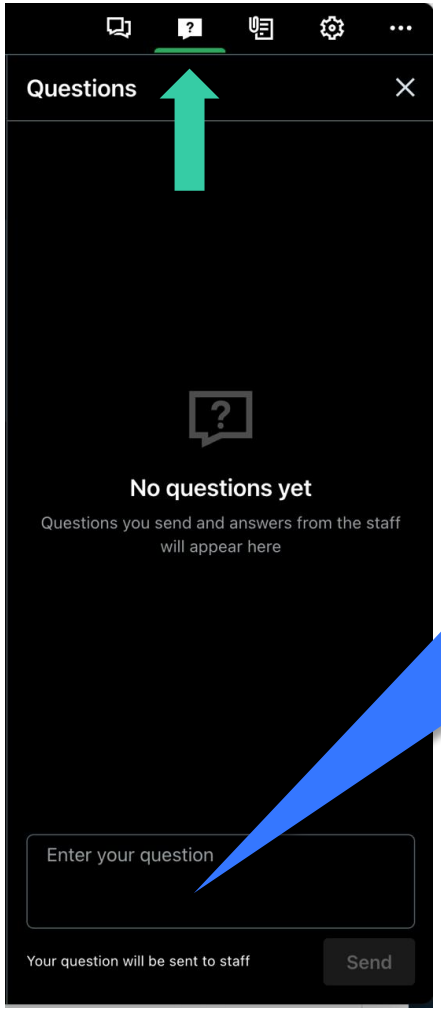


Thank you

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.



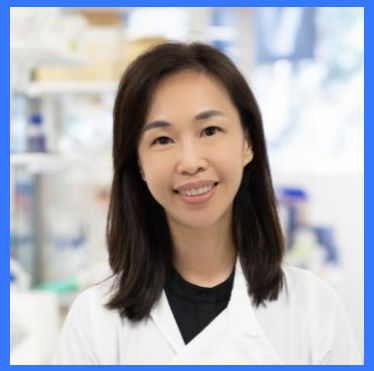
Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

Today's speakers

REVIVE by GARDP

Repurposing drugs to address the crisis of antimicrobial resistance

Moderator:
Jennifer Smart
GARDP,
Switzerland



Freda Jen
Griffiths University,
Australia

Anthony Coates
Helperby
Therapeutics, UK

François Franceschi
GARDP,
Switzerland

Upcoming webinars

REVIVE by GARDP

Overcoming challenges of tuberculosis drug discovery and development

- With Jeremy Rock, Dirk Schnappinger & Laura Cleghorn
- 9 September 2025, 15:30-17:00 CEST

Thank you for joining us