Drug pipeline for Gram-negative bacteria

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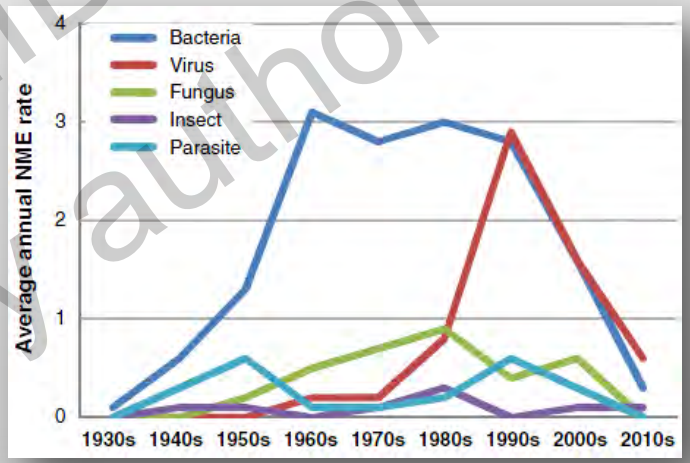
The antibiotic era

Small spectrum	Broad spectrum	Small spectrum	Small spectrum
Gram positive	Gram negative Gram positive	Gram positive	Gram negative targeted
1950-60s	1970-90s	2000s	2010s
Natural products	Medicinal chemistry, Semisynthetic products	Target based	Natural products? Alternative approaches?

Golden years of pills and profits

Fixing selected resistance problems



MS Kinch et al: Drug Discovery Today 2014, 19 (9)

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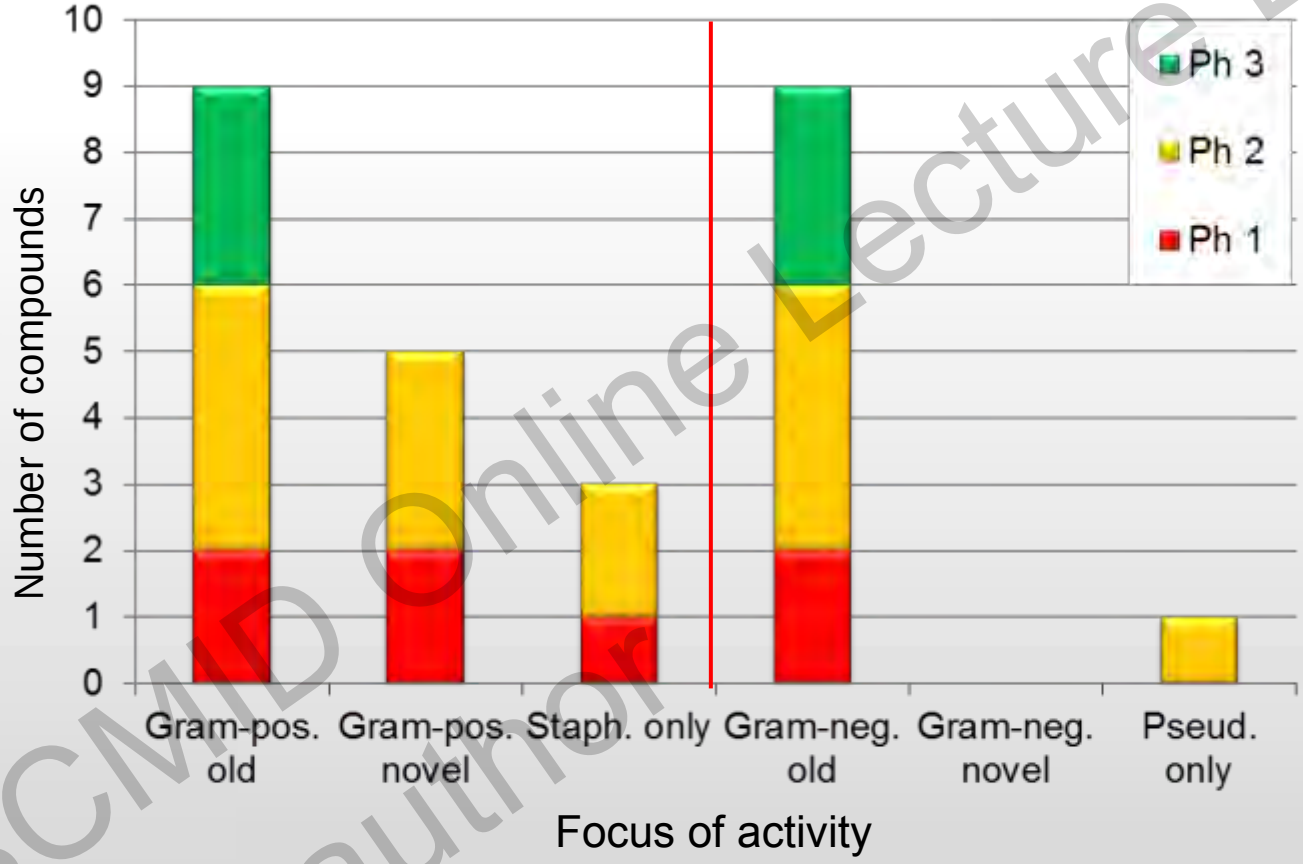
R&D Pipelines (4/2015)

Small molecules in clinical development Phase 1-3



Old: Analog of used antibacterial class
Novel: New antibacterial class

U. Theuretzbacher: IJAA, 2012, 39:295– 299 (updated)

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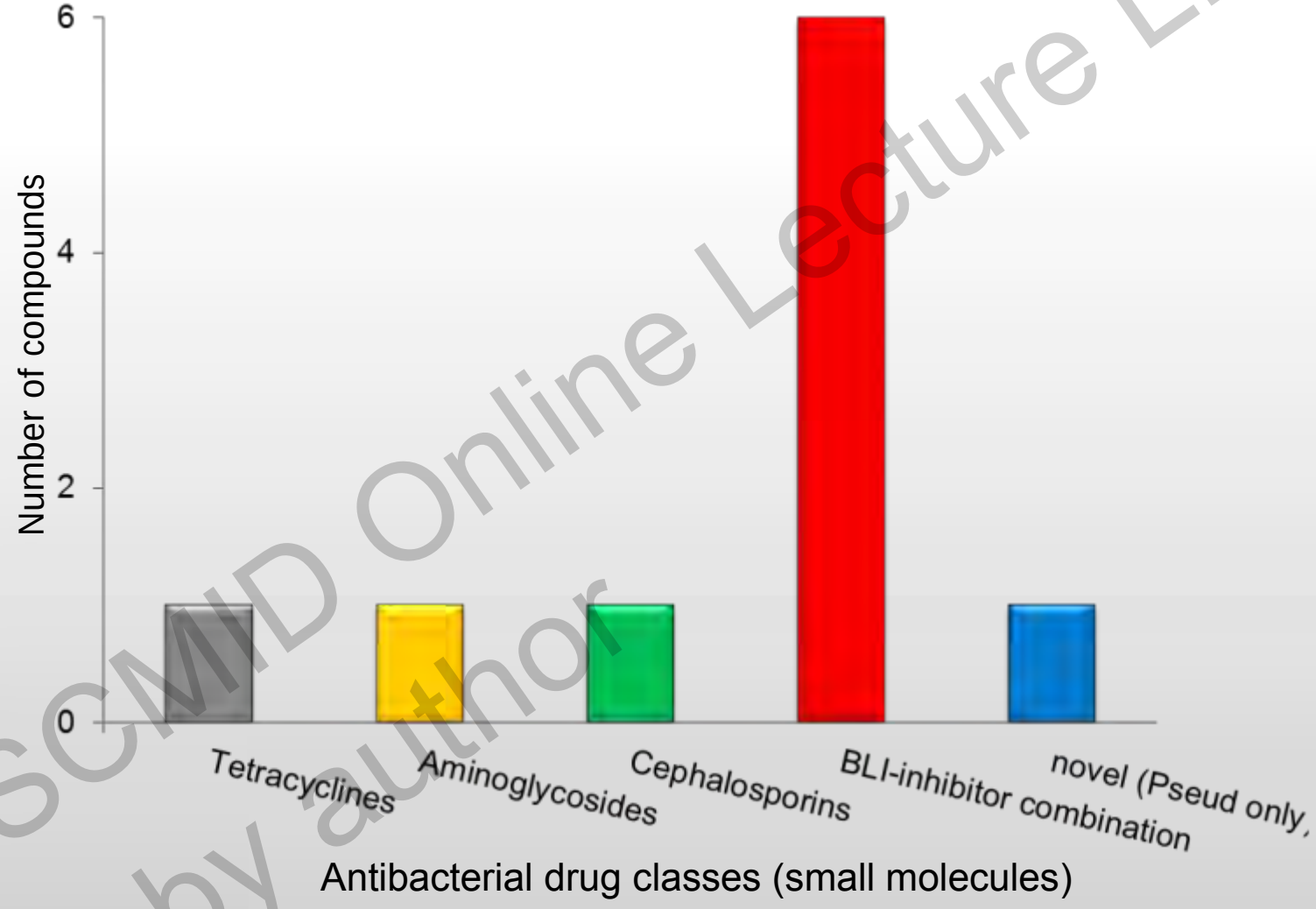
Gram-negative R&D Pipelines 4/2015

Gram-negative drugs in clinical development Phase 1-3



U. Theuretzbacher: IJAA, 2012, 39:295– 299 (updated)

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Non-ß-lactams in clinical development

- Aminoglycoside
- Tetracycline
- Peptidomimetic
- Monoclonal antibody
- Vaccine
- Adjunctive therapies

Aminoglycoside: Plazomicin

- Derived from sisomicin
- Phase 3 (partly publicly funded)
  - Pathogen-specific trial
    - Bacteremia and NAP/VAP caused by CRE
    - Plazomicin + meropenem or tigecycline vs colistin + meropenem or tigecycline
    - All-cause mortality at 28 days +disease-related complications at day 28
    - Superiority vs colistin
    - Individualized patient dosing, PK/PD, TDM
  - cUTI (single trial + Phase 2 data)
- NDA end of 2017

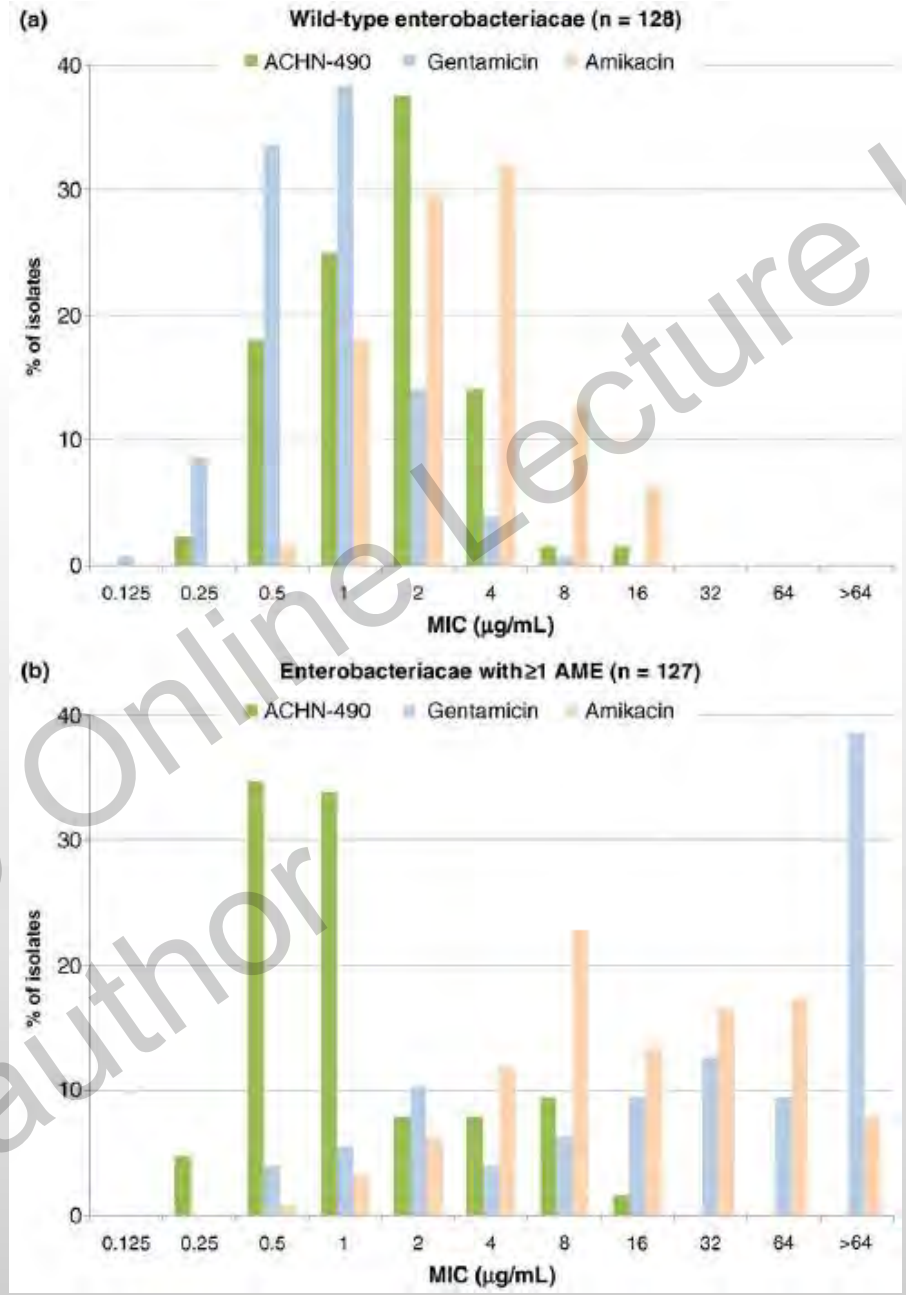
Aminoglycoside: Plazomicin

E. coli

Phenotype	MIC (µg/ml)			
	SIS	AMK	GEN	PLAZO
ATCC 25922	0.5	2	1	1
ANT(2″)-I	64	4	>64	1
AAC(6′)-I	32	32	4	0.25
AAC(3)-II	>64	4	>64	2
APH(3′)-Ib	0.25	0.5	0.25	0.25
AAC(3)-IVa	32	4	32	1
armA methylase	>64	>64	>64	>64

J Aggen et al: AAC 2010; 54:4636-42

Aminoglycoside: Plazomicin



E. Armstrong et al: Current Opinion in Microbiology 2010, 13:565–573

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Aminoglycoside: Plazomicin

Carbapenem-resistant enterobacteriaceae

Enzymes produced (no. isolates)	MIC (mg/L)											
	≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
ACHN-490												
KPC (12)	1	5	6									
SME-1				1								
IMP (13)	1	9	3									
NDM-1 (17)		1								1	5	10
VIM (5)		3	1	1								
OXA-48 (19)	1	17			1							
ESBL + impermeability (10)	1	8	1									
AmpC + impermeability (5)		3	2									

D. Livermore et al: JAC 2011;66 :48-53

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Tetracyclines: Eravacycline

- Fully synthetic tetracycline
- Phase 3
  - cIAI (vs ertapenem), cUTI (vs levofloxacin) iv-oral
  - NDA 4Q/2015, MAA 2Q/2016
- Partly publicly funded
- Gram-positive, Enterobacteriaceae, Acinetobacter
- S. aureus: not effected by NorA or MepA efflux pumps

Tetracyclines: Eravacycline

E. coli expressing recombinant major tetracycline resistance genes

Antibiotic	MIC (µg/ml) for E. coli strain expressing:					
	lacZ	tet(M)	tet(K)	tet(A)	tet(B)	tet(X)
Eravacycline	0.063	0.063	0.031	0.25	0.063	4
Tigecycline	0.063	0.13	0.063	1	0.063	2
Minocycline	0.5	64	1	8	16	4
Doxycycline	2	64	4	32	32	16
Tetracycline	2	128	128	>128	>128	128

TH Grossman et al: AAC 2012; 56(5): 2559–2564

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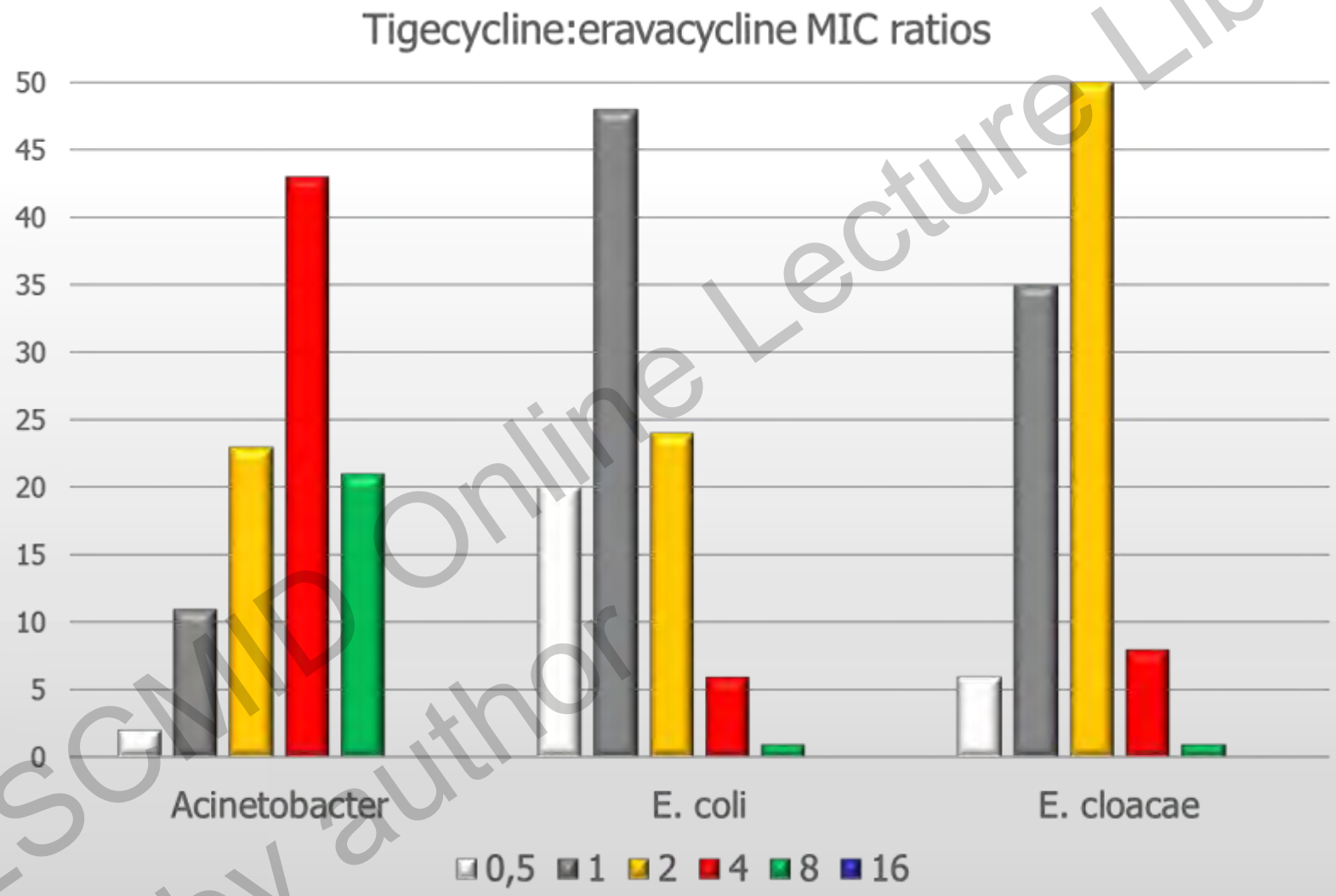
Tetracyclines: Eravacycline



JA Sutcliffe et al: 2013; 57(11): 5548–5558

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Peptidomimetic

- POL 7080
- Protein epitope mimetic of AMP protegrin I, synthetic cyclo-peptide targeting outer-membrane biogenesis of LPS
- Pseudomonas specific
- Phase 1 completed

Monoclonal antibody

- Panobacumab
  - Human IgM mAb against the O-polysaccharide of P. aeruginosa serotype O11
  - Phase 2
- Aerucin
  - Human mAb binds the polysaccharide alginate on the cell surface of P. aeruginosa
  - Phase 1
- MEDI3902
  - Serotype-independent human mAbs, binds three distinct epitopes of P. aeruginosa Psl (exopolysaccharide, host cell attachment and formation and maintenance of biofilms)
  - Phase 1
- KB001
  - anti-PcrV humaneered, PEGylated monoclonal antibody fragment against P. aeruginosa
  - Failed in Phase 2 in CF

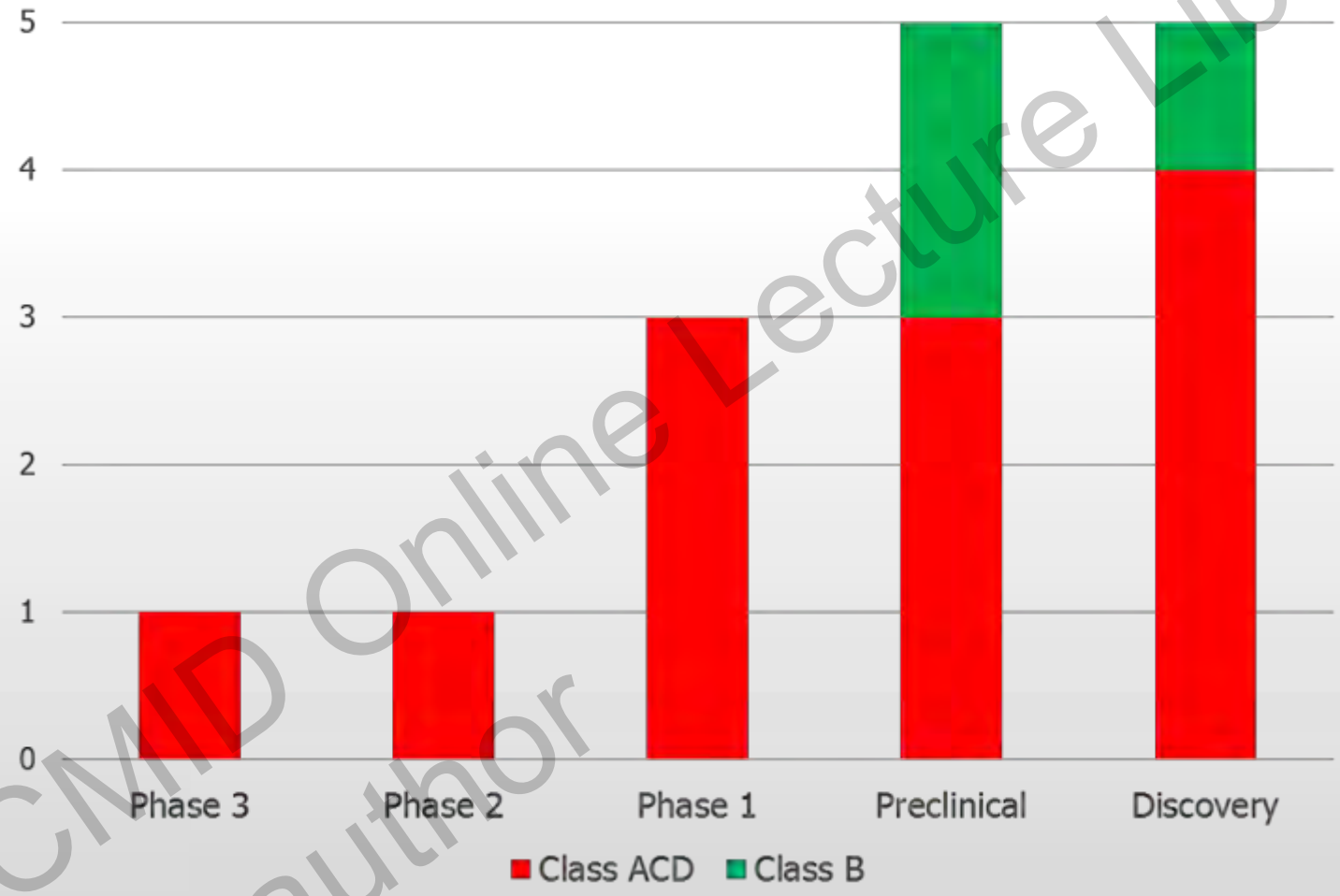
Vaccines

- P. aeruginosa antigens
  - LPS, outer membrane proteins, extracellular proteins, flagella, pili, exotoxins
  - killed whole cells and live attenuated P. aeruginosa
- IC43
  - Hybrid molecule of two of the outer membrane proteins of P. aeruginosa (OprF and OprI)
  - Phase 2: seroconversion at day 14 as determined by OprF/I-specific IgG antibody titer
  - Phase 2/3: ventilated ICU patients, vaccinated at hospital admission and at particular risk of life threatening Pseudomonas infections

Adjunctive and other treatments

- Phages
  - Lytic bacteriophages
  - Bioengineered phages
  - Enzymes derived from phages (eg endolysin)
- Microbiome
- Antivirulence
- Persisters
- Potentiators
- Resistance mechanism targeting

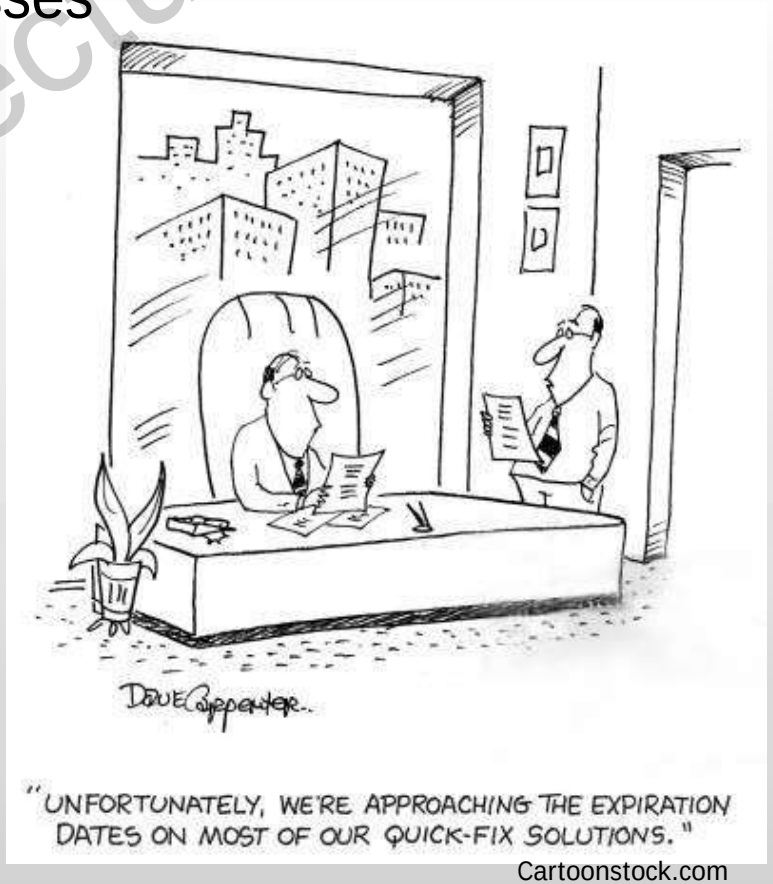
ß-Lactamase Inhibitors



Summary

- Gram-negative R&D pipelines

- Mainly fixing problems of old classes
- Antibiotics are a common good
- New approaches are needed



Cartoonstock.com

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IMI - DRIVE-AB

Developing new economic models to incentivise antibiotic R&D +
researching and advocating their appropriate use

DRIVE AB RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

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