What other new antibiotics will soon come to market?

U. Theuretzbacher – **C**enter **f**or **A**nti-**I**nfective **A**gents, Vienna, Austria

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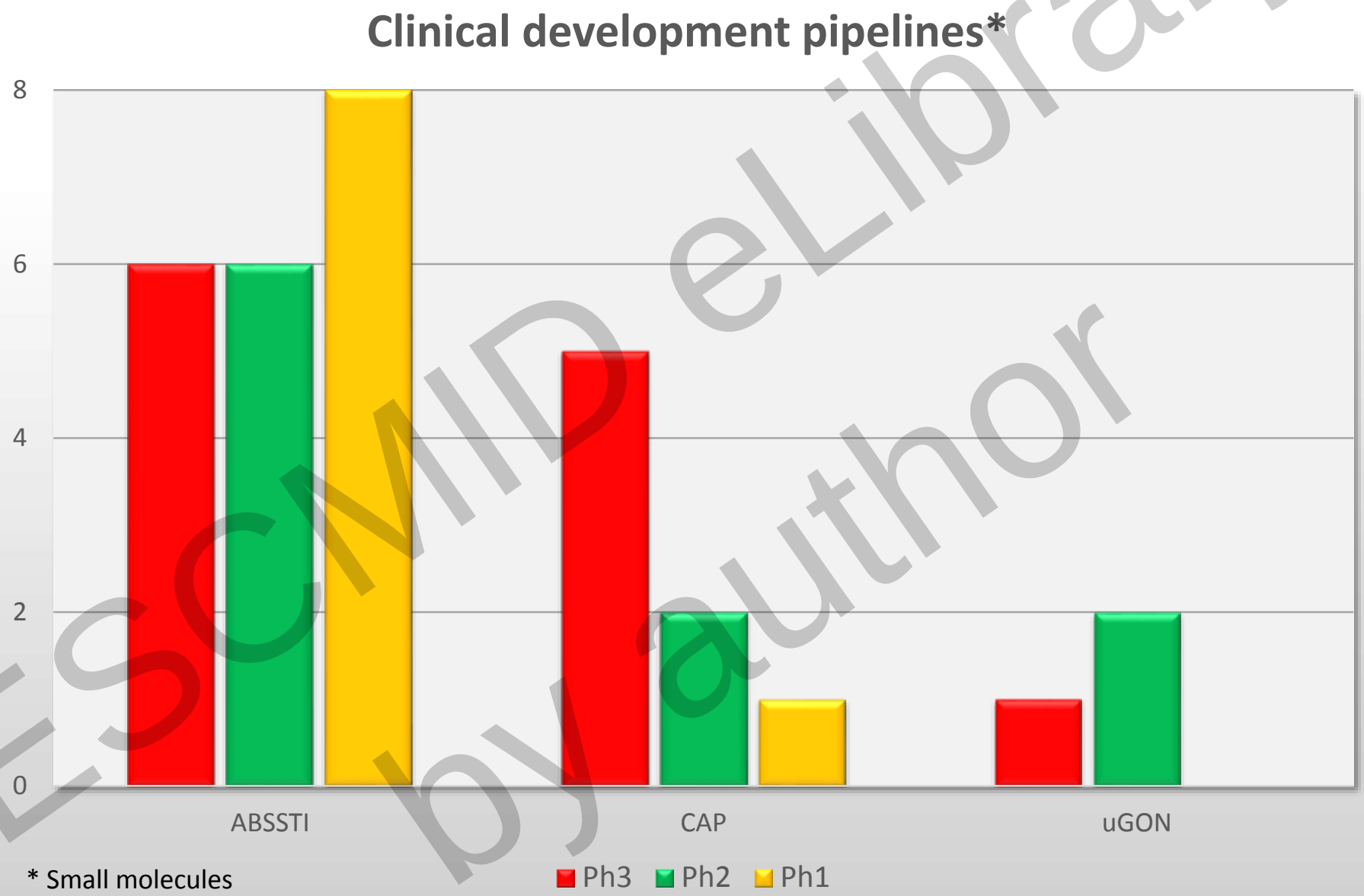
Systemic antibiotics in clinical development



* Small molecules

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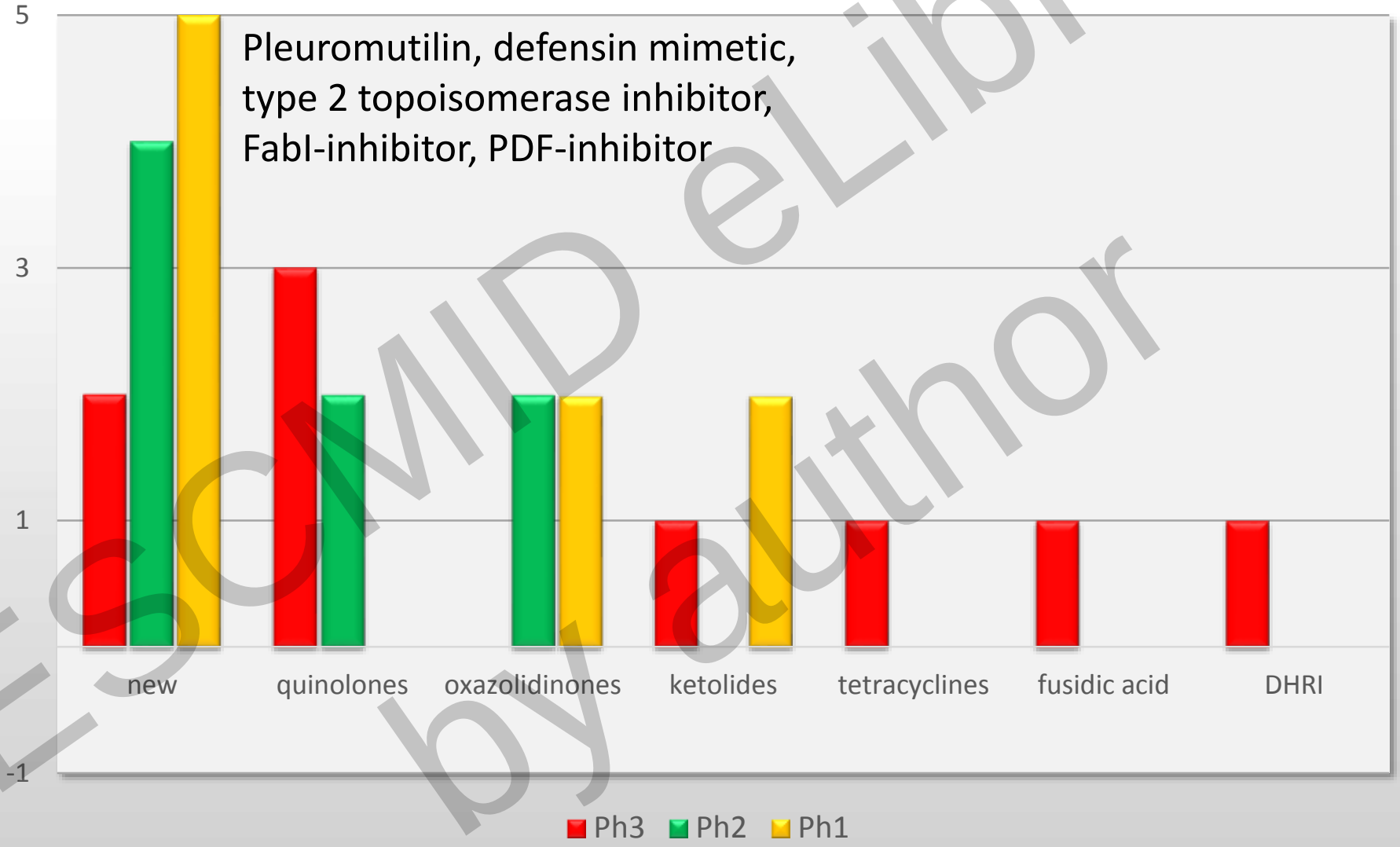
Systemic antibiotics in clinical development

Clinical development pipelines for ABSSTI, CAP, uGON



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Systemic antibiotics in clinical development

- CAP

Phase 3	Phase 2
Lefamulin	Avarofloxacin
Omadacycline	(Radezolid)
Solithromycin	
Nemonoxacin	
Zabofloxacin	
Lascufloxacin (Japan)	

- Uncomplicated gonococcal infection

Phase 3	Phase 2
Solithromycin (Ketolide)	Zoliflodacin (Topoisomerase II Inh.)
	Gepotidacin (Topoisomerase II Inh.)

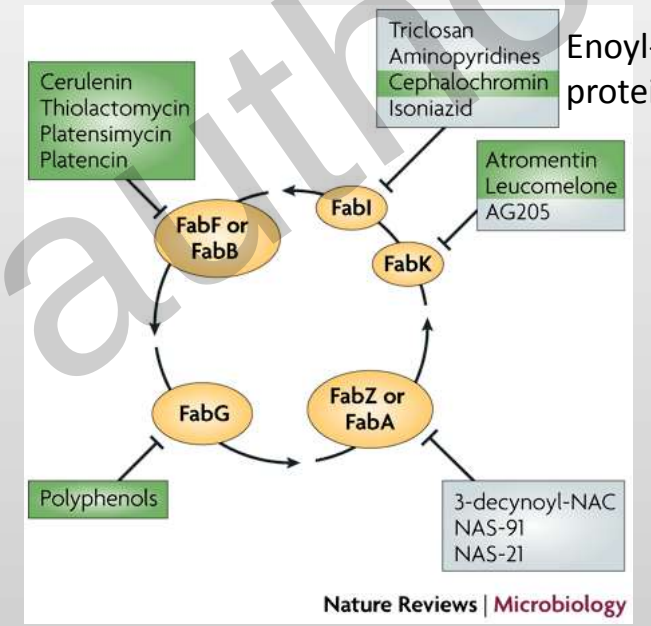
Systemic antibiotics in clinical development

New antibiotic classes for ABSSTI, CAP, uGON

- **Pleuromutilins**
  - Natural products, discovered 1950,
  - 2007 retapamulin
  - Lefamulin (Ph 3), iv and oral, CAP, ABSSTI
  - CAP-spectrum

- **FabI inhibitors**
  - Since 1950s
  - New: Staphylococcus-specific

Fatty acid synthase II pathway

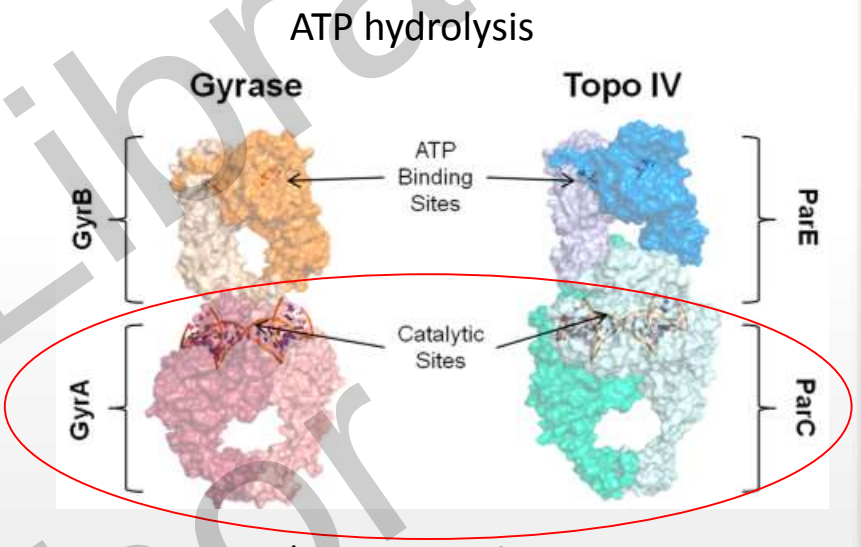


YM Zhang, CO Rock: Nature Rev Microbiol 2008, 6, 222-233

Systemic antibiotics in clinical development

Type II topoisomerase inhibitors

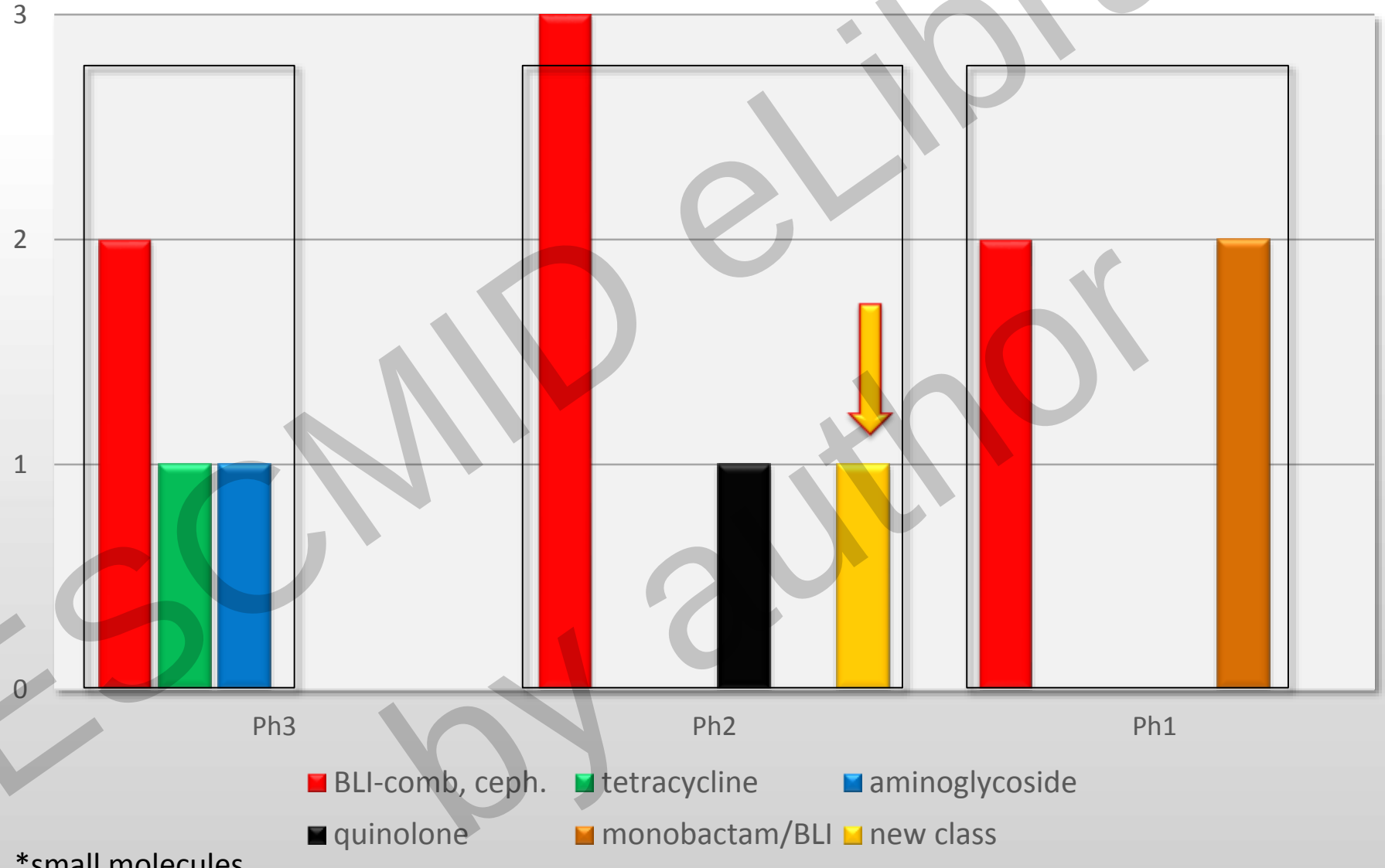
- Catalytic site inhibitors
  - Fluorquinolones
  - Novel Bacterial Topoisomerase Inhibitors
    - Non-fluoroquinolone molecules
    - Bind near the catalytic center of GyrA/ParC (mechanistically distinct from fluoroquinolones)
    - Gram-pos. and Gram-neg. cocci (permeation/efflux issues)
    - Gepotidacin, Zoliflodacin
- ATP-site inhibitors
  - Novobiocin



Cleavage/religation of the DNA strand

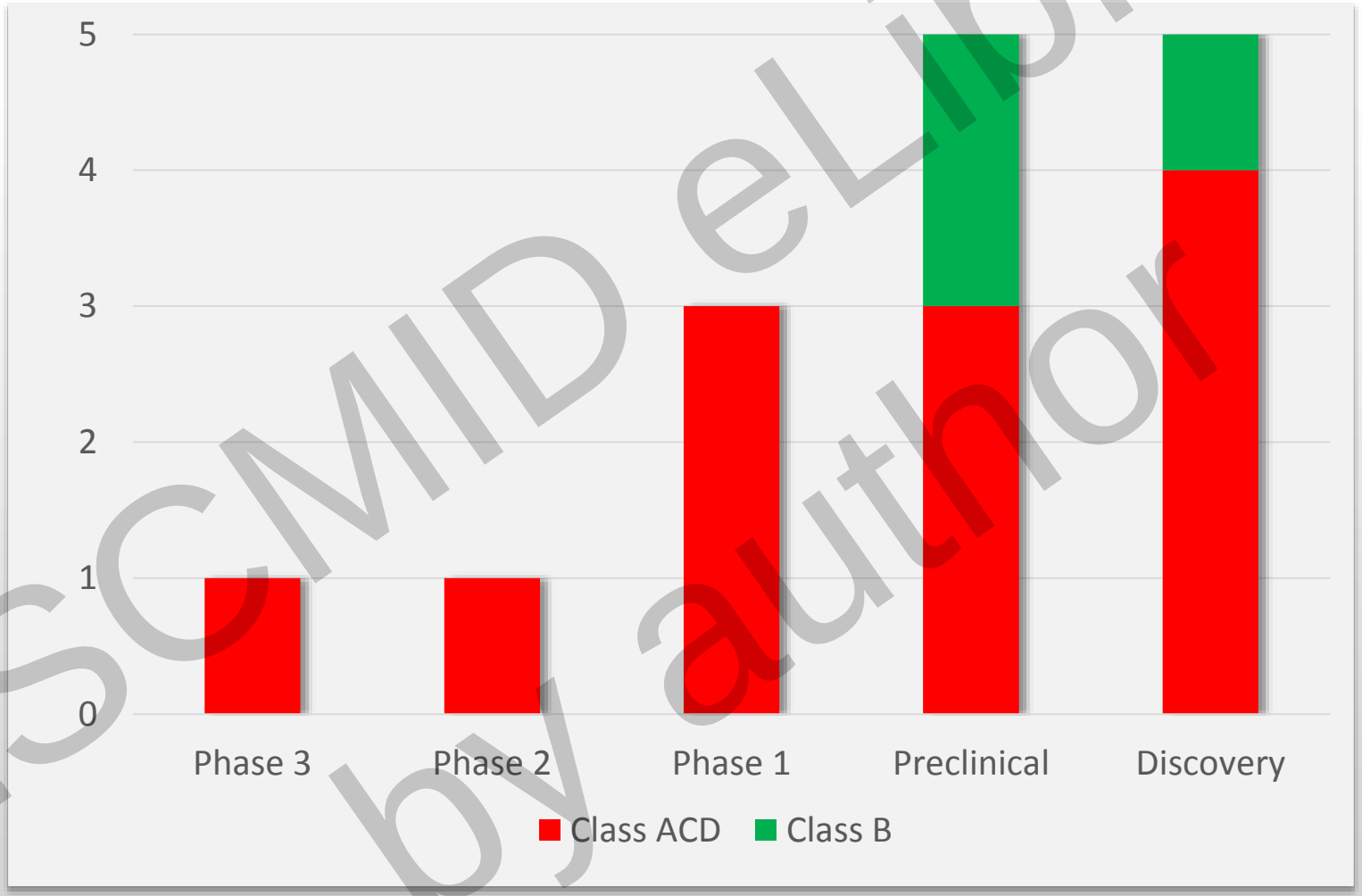
Systemic antibiotics in clinical development

Clinical development pipelines for Gram-negatives*



*small molecules

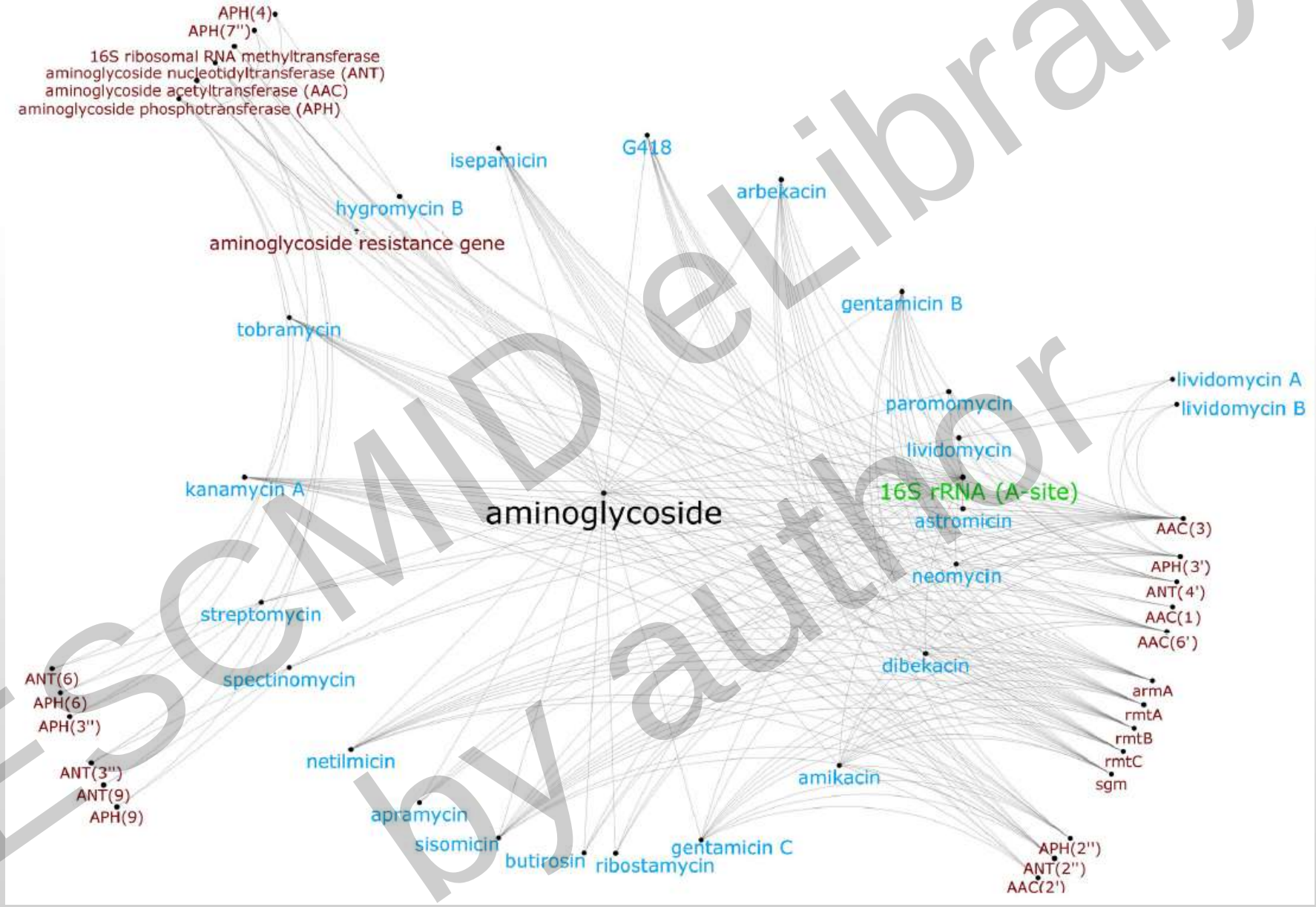
ß-Lactamase Inhibitors



New aminoglycoside: Plazomicin

- Clinical development
  - cUTI: Plazomicin vs meropenem
  - Pathogen focused: CRE (HAP/VAP, BSI, plazomicin in combination vs colistin in combination
- Safety
  - ?

Aminoglycosides – Cross-resistance



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New 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

New aminoglycoside: Plazomicin

Activity of plazomicin and selected antimicrobial agents against carbapenemase-producing Enterobacteriaceae

Micro-organism/antimicrobial agent	MIC (mg/L)		
	MIC_{50}	MIC_{90}	Range
All isolates ($n = 164$)			
Plazomicin	0.25	1	0.12–4
Amikacin	4	16	0.5–64
Gentamicin	4	256	0.5 to >256
Tobramycin	8	64	2–128
Fosfomycin	16	256	1 to >256
Tigecycline	1	4	0.25–16
Colistin	1	128	0.25 to >128

Rodríguez-Avial I, et al. Int J Antimicrob Agents 2015, 46 (6): 616–621

TABLE 1 Activity of plazomicin and selected antimicrobial agents against *A. baumannii* isolates

Isolate type and antimicrobial agent	MIC (μg/ml)		
	MIC_{50}	MIC_{90}	Range
Carbapenem resistant ($n = 69$ isolates)			
Plazomicin	16	16	0.5–64
Amikacin	32	256	0.5–512
Imipenem	256	512	32–>512
Meropenem	128	256	4–512
Gentamicin	>512	>512	1–>512
Tobramycin	128	256	0.25–512
Fosfomycin	128	512	8–512
Tigecycline	2	2	0.25–2
Colistin	1	2	1–2

C García-Salguero et al: AAC 2015, 59 (10):5959-5966

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Vaccines

- VLA43 (Valneva/GSK) - *Pseudomonas aeruginosa*
  - Hybrid molecule of two of the outer membrane proteins of *P. aeruginosa* (OprF and OprI)
  - Phase II/III: 800 ventilated ICU patients, vaccinated at hospital admission and at high risk of *Pseudomonas* infections
- Valneva *C. difficile* vaccine
  - Neutralizes the effects of *C. difficile* toxins A and B
  - Phase II: induced strong immune responses to toxins A and B

Human mAB - Bezlotoxumab

- Human mAb against *C. difficile* toxin B, single infusion co-administered with standard-of-care antibiotics
- Reduction in *C. difficile* recurrence through week 12 as adjunctive to antibiotic for the treatment of *C. difficile*
- Recurrence rate: Antibiotic + bezlotoxumab 15-17%, antibiotic 25-27%
- Clinical relevance
  - High-risk groups

Human mAb

- MEDI4893
  - Alpha-toxin of ***Staphylococcus aureus***
  - IMI Combacte-Net: Phase 2, 3, prevention of VAP
- MEDI3902
  - ***Pseudomonas aeruginosa***
  - Bispecific IgG targeting Psl (surface exopolysaccharide) and PcrV (toxin injection)
  - IMI Combacte-Magnet: Phase 2, 3, prevention of VAP, Paediatric PK/Safety study
- Diagnostic collaboration with Cepheid

Future

- Targeted therapies, diagnostics
  - Staph only
  - Pseduomonas only, (Acinetobacter only)
- Pipelines are inadequate to meet medical need in the future
  - New economic models linked to sustainable use
    - Policies to restrict unnecessary use
    - Depend on fast and reliable microbiological diagnostics
    - Strong stewardship policies to safeguard old antibiotics
- Regulatory requirements less stringent
  - Not enough data about clinical effecacy and safety in target patient populations
  - Non-inferior to old antibiotics, descriptive designs
- Prevention
  - Defining risk groups

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