Keystone isn't the only challenging pipeline: Antimicrobials for DTOs

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AMMI-CACMID 2015

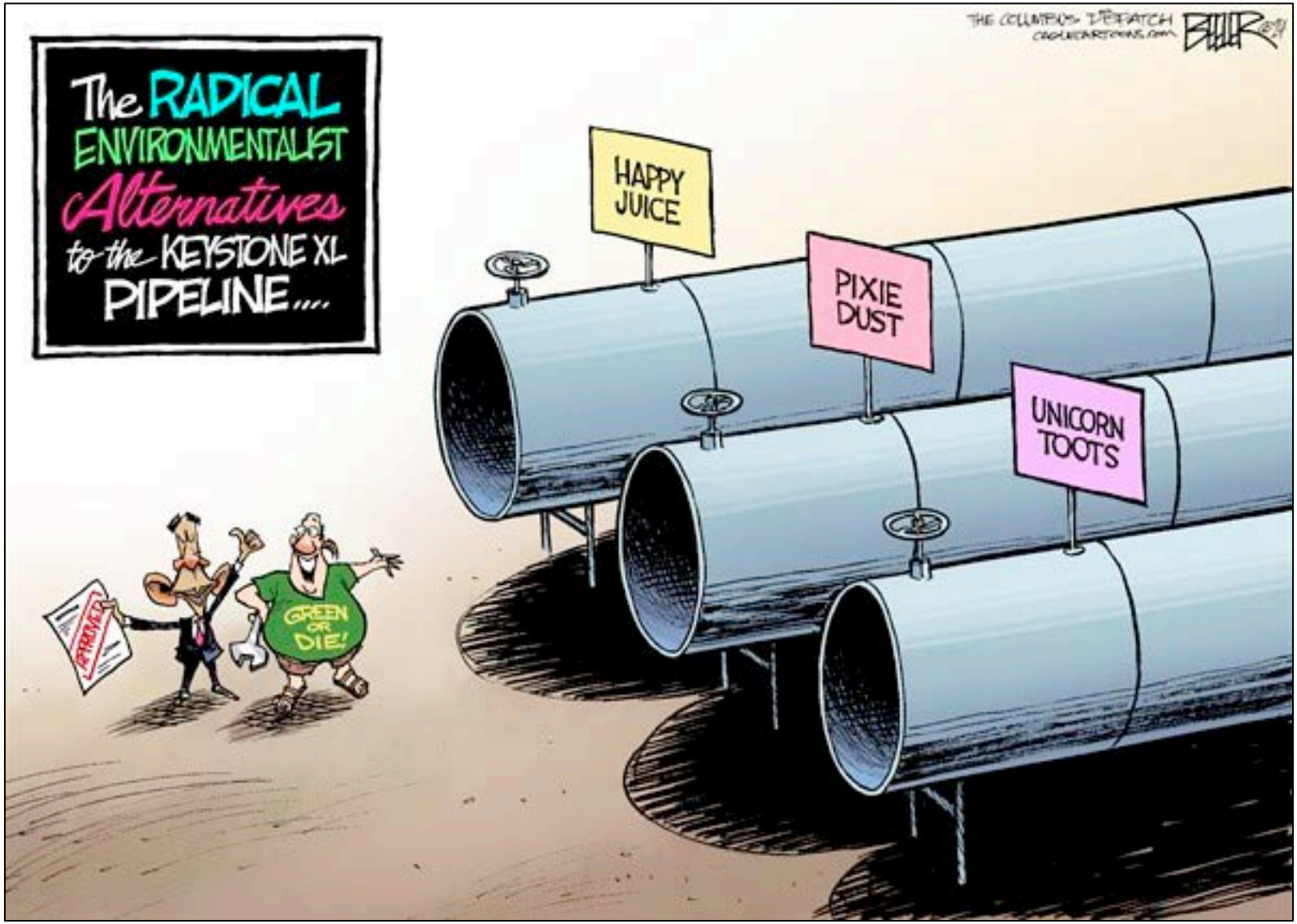
Objectives

At the end of this session, the participant will:

- Understand the challenges in developing new antimicrobials for DTOs
- Envisage the steps needed & barriers to implementing new antimicrobials for DTOs
- Be able to outline the chief therapeutic strategies for new antimicrobial agents for DTOs

Disclosures

- Public Health Ontario
- Ontario Ministry of Health & Long term Care
- Research
  - Merck
  - Astellas
  - Biocryst
- Advisory Board
  - Merck


The RADICAL ENVIRONMENTALIST Alternatives to the KEYSTONE XL PIPELINE....
HAPPY JUICE
PIXIE DUST
UNICORN TOOTS
GREEN OR DIE!

The Bad News

- Increasing resistance to available antimicrobials
  - Antibiotic Stewardship – Too little, too late?
- Stagnant antibiotic development
  - Investment lacking
  - Slow to recognize the need and inherent delays in finding and developing new antimicrobials
- The increasing importance of antimicrobials in modern medical practice
  - Increasing use of antimicrobials for those patients on immunosuppressants and managed in critical care

Infectious diseases

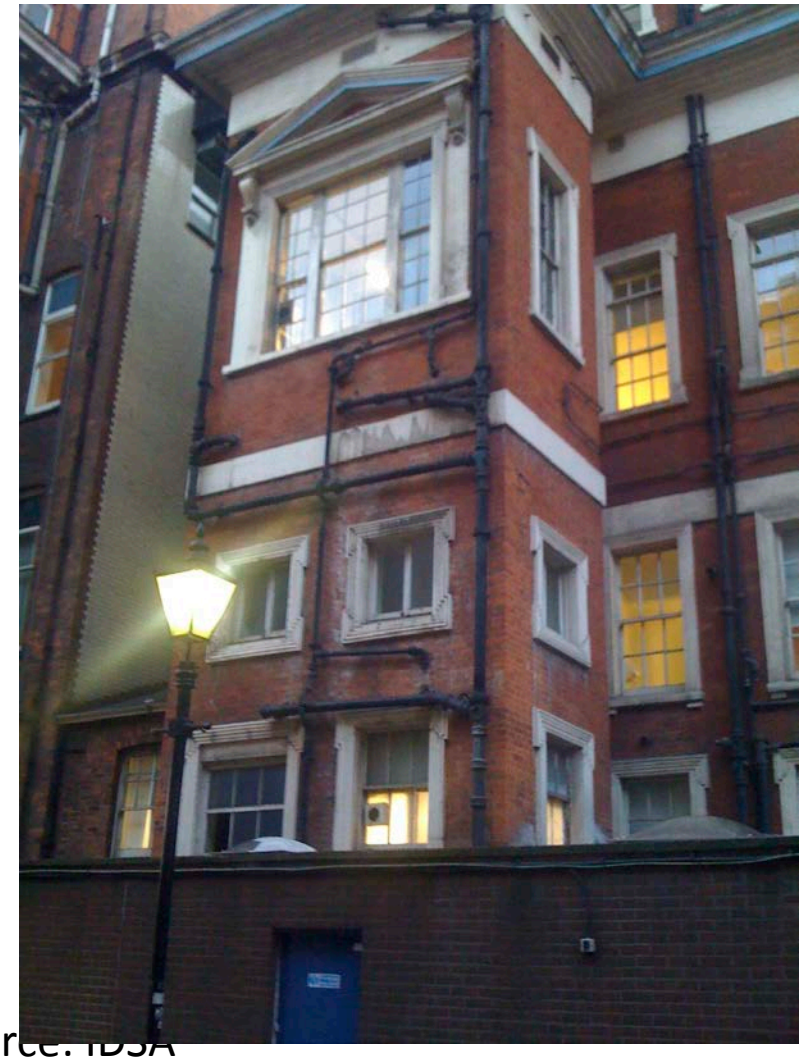
Outbreak of drug-resistant infection could kill 80,000 in UK, report warns

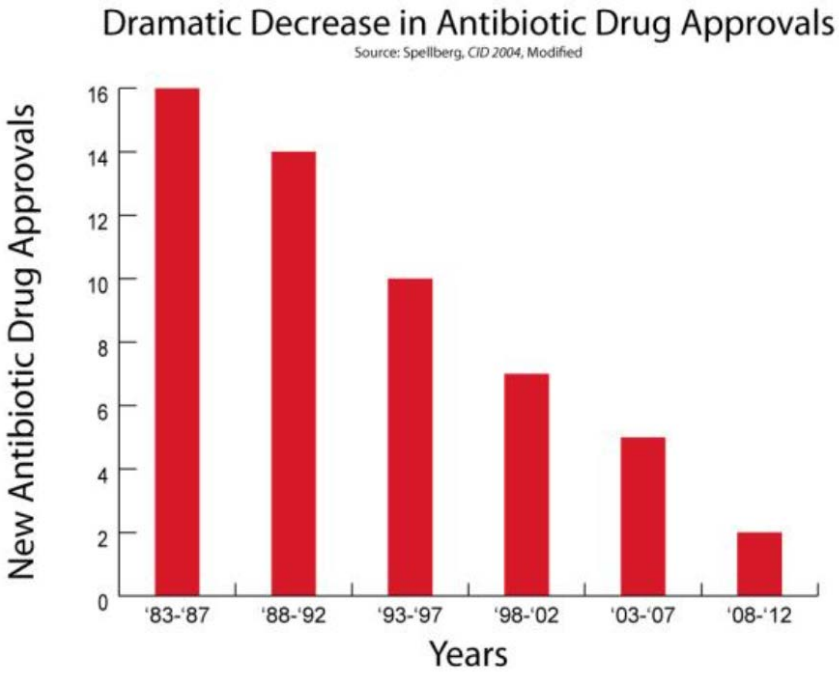
Forecast highlights danger of growth in antimicrobial resistance that could take surgery back to 19th-century mortality rates

Kevin Rawlinson

Monday 6 April 2015 01.02 BST

Antibiotic Development in the Face of Antimicrobial Resistance





Source: IDSA


SIR
ALEXANDER
FLEMING
1881-1955
DISCOVERED PENICILLIN
IN THE SECOND STOREY
ROOM ABOVE THIS
PLAQUE
PRAED
STREET W2
CITY OF WESTMINSTER

Global Antibiotic Consumption by Class 2000-2010

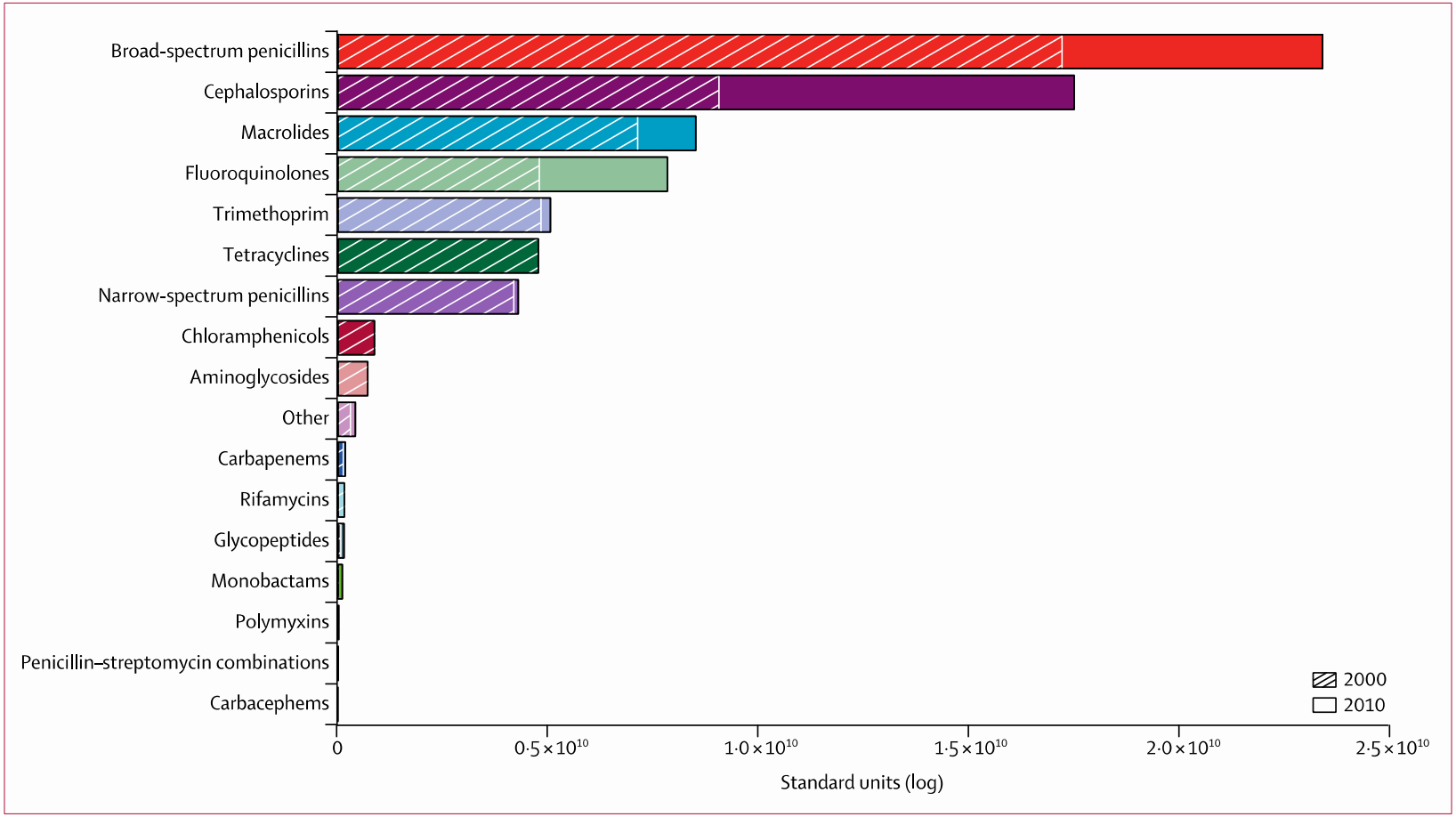


***Figure* 1: Global antibiotic consumption by class in 2000 and 2010**
Standard units are defined as a single dose unit (ie, pill, capsule, or ampoule).

Global Antibiotic Consumption 2000-2010

- Consumption of antibiotics increased by 36%
  - Brazil, Russia, India, China, and South Africa accounted for 76% of this increase
- There was increased consumption of carbapenems (45%) and polymixins (13%), two “last-resort” classes of antibiotic drugs.

Source: Van Boeckel et al Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data Lancet Infect Dis 2014; 14: 742–50

The Perspective of Big Pharma

- All pharmaceutical companies are under pressure by shareholders to maximize returns and sustain strong growth rates
  - Chronic care medications > acute care medications
  - Innovation > *Me-too's*
  - Specialized disease products > primary care products
- Pressures to maximize profitability do not necessarily align with appropriate use, promotion, or consumption of antibiotics
- Recognition of antibiotics as a finite strategic resource is rarely compatible with corporate commercial aspirations

Source: Alasdair MacGowan, University of Bristol

Net Present Value (NPV)

- NPV is the sum of the present values (PVs) of incoming and outgoing cash flows over a period of time
- A technique for evaluating the viability of an investment decision
  - Widely used in the pharmaceutical industry to determine both the viability of specific products and to compare investment strategies
- Enables economic costs and benefits of a development program to be estimated at current values
  - Describes the relationship between the projected costs of the project and the potential in terms of cash flow
- An NPV > 0 means that the project will usually benefit the company

Source: Alasdair MacGowan, University of Bristol

What impacts NPV for Pharma?

- Restrictions on use
  - Reduce potential profit and thus NPV
- Increased regulatory hurdles
  - Increases risk/costs
  - May move acceptable projects in to more marginal projects
- Length of patent protection
  - Life-cycle extensions for successful antibiotics can be profitable

Source: Alasdair MacGowan, University of Bristol

Antibiotics and NPV

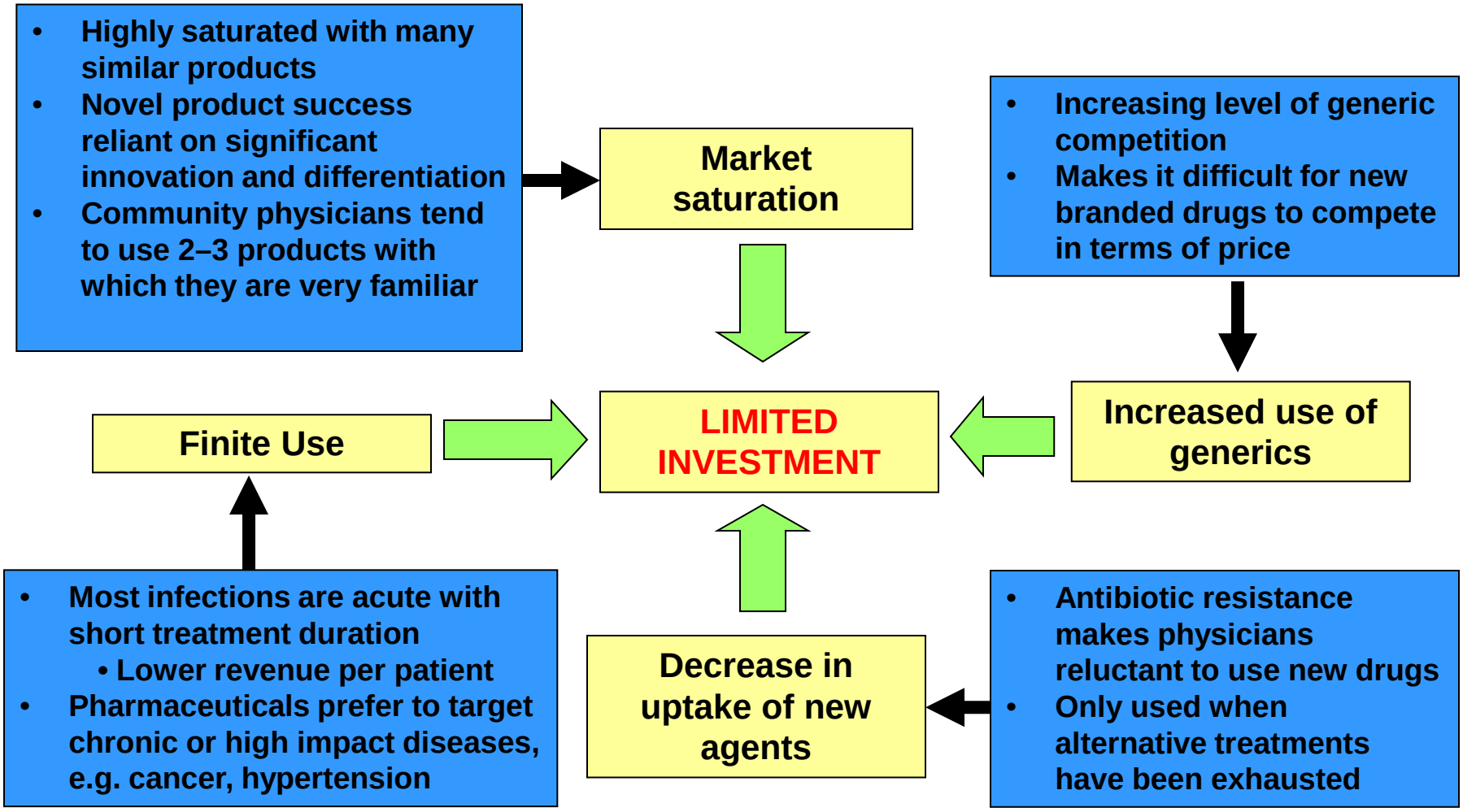
- Antibiotics perform poorly compared with drugs for chronic conditions

Drug Type	NPV
Antibiotic	100
Anti-cancer drug	300
Neurological drug	720
Musculoskeletal drug	1150

- Any drug with an NPV < 100 is unlikely to garner investment
- As a result, new antibiotic development is at the low-end of economic viability

Source: Alasdair MacGowan, University of Bristol

Antimicrobial Market Dynamics



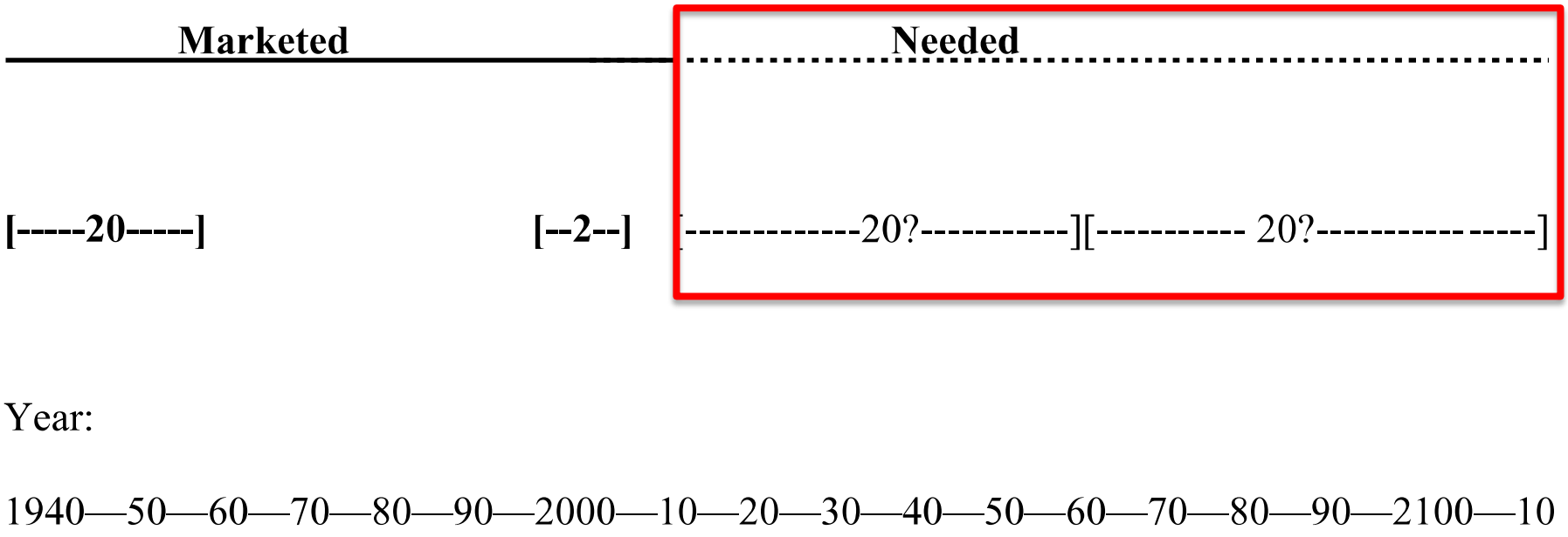
Source: Alasdair MacGowan, University of Bristol

The Causes of Stagnant Antimicrobial Growth

- The nature of antibiotic use
  - Antibiotics use is sufficient to generate resistance in bacteria but not enough for commercial viability
- Suboptimal approach to AMR
  - In an effort to curb inappropriate prescribing, a self-regulatory approach has had an adverse impact on the use of newer agents and future development
- Unbalanced development – "Market pressure"
- Uncertain future
  - The uncertainty of bacterial evolution means that resistance is not predictable
- Regulatory hurdles
  - Until recently, existing regulatory requirements have contributed to stifling progress on new antibiotic development

Source: Gould IM & Bal AM Virulence 2013;4:185–191

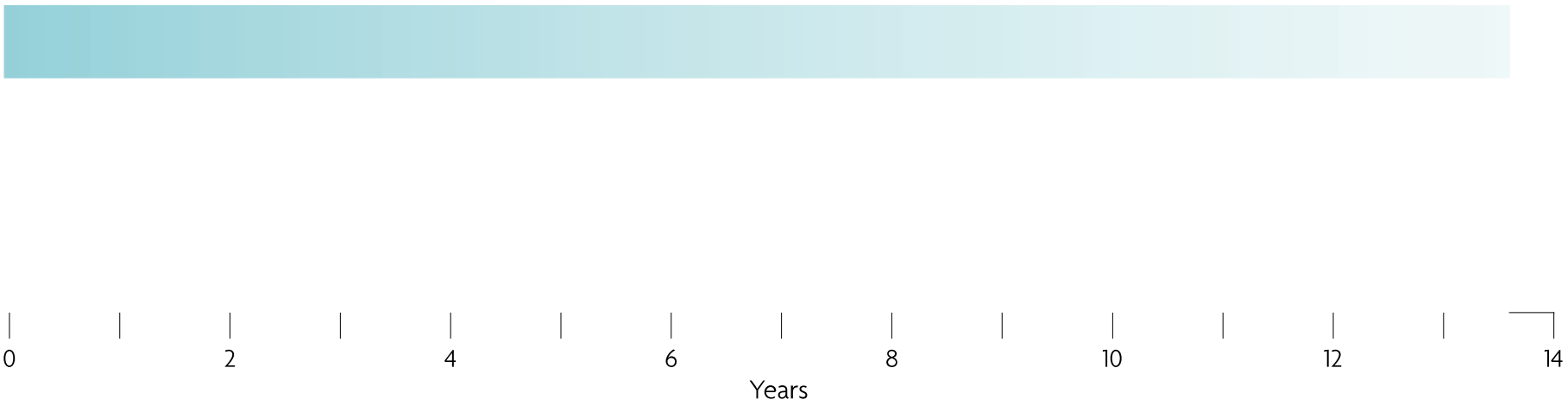
New Classes



The number of new classes of antibiotics which have reached the market, and need for novel classes of antibiotics during the next 100 years

Source: British Journal of Pharmacology 2011;163:184–194

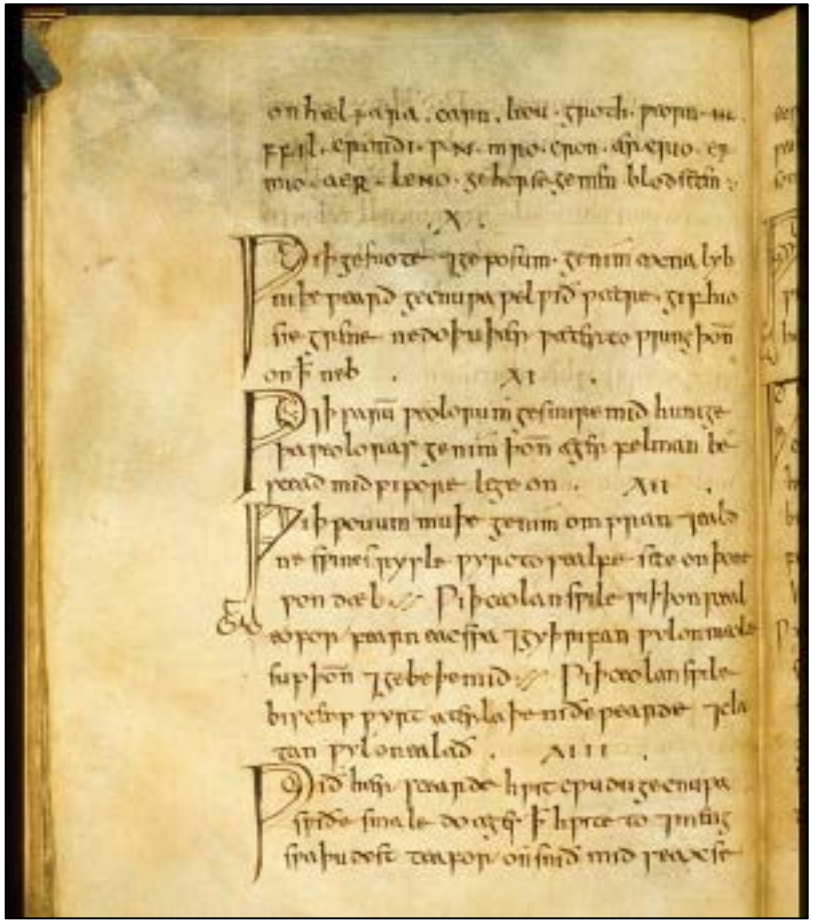
Antibiotic Development Timeline



Payne *et al. Nature Reviews Drug Discovery* **6**, 29–40 (January 2007) | doi:10.1038 / nrd2201


KEYSTONE XL
PIPELINE
WE'VE BEEN A BIT LAZY ABOUT ATTRACTING ANY INTEREST IN ANTIBOTICS

THE Answer to DTOs



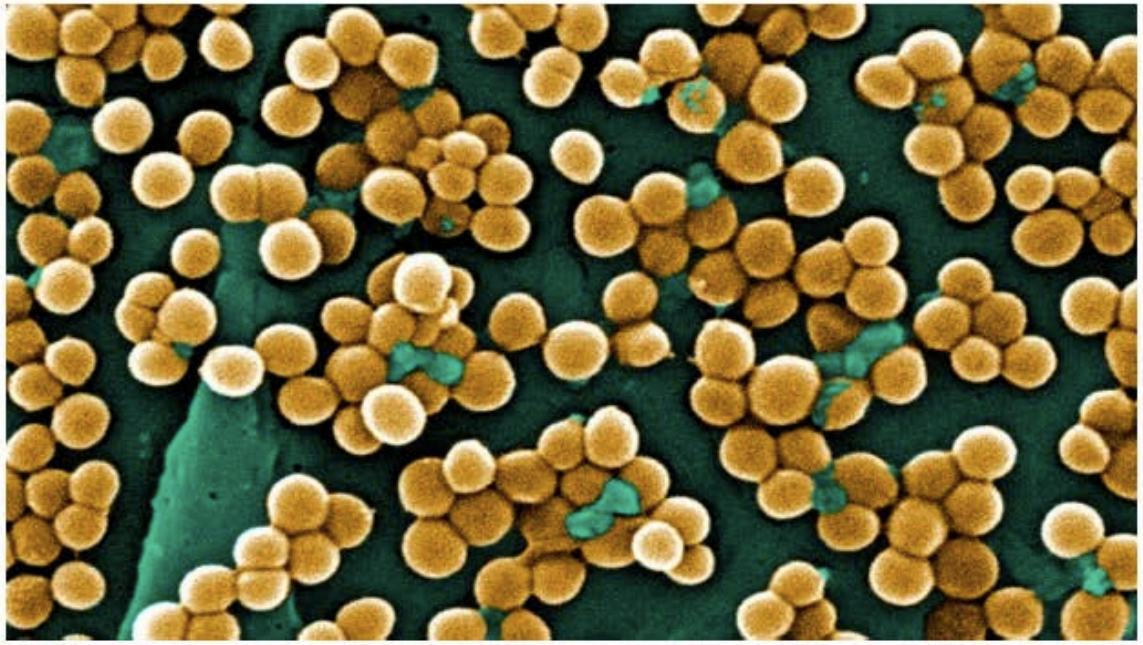
The recipe contains:

- Garlic
- Onion or leek
- Wine
- Oxgall, bile from a cow's stomach

Medieval potion kills antibiotic-resistant MRSA superbugs

Researchers 'blown away' by effects of 1,000-year-old recipe containing garlic, onion, wine, cow bile

CBC News Posted: Apr 03, 2015 1:31 PM ET | Last Updated: Apr 06, 2015 8:52 AM ET



MRSA is an antibiotic resistant so-called 'super-bug', which can cause deadly infections. The researchers found that none of the individual ingredients from the potion alone had any measurable effect on MRSA, but the combination was highly effective.

ARTICLE

doi:10.1038/nature14098

A new antibiotic kills pathogens without detectable resistance

Losee L. Ling[1]*, Tanja Schneider[2,3]*, Aaron J. Peoples[1], Amy L. Spoering[1], Ina Engels[2,3], Brian P. Conlon[4], Anna Mueller[2,3], Till F. Schäberle[3,5], Dallas E. Hughes[1], Slava Epstein[6], Michael Jones[7], Linos Lazarides[7], Victoria A. Steadman[7], Douglas R. Cohen[1], Cintia R. Felix[1], K. Ashley Fetterman[1], William P. Millett[1], Anthony G. Nitti[1], Ashley M. Zullo[1], Chao Chen[4] & Kim Lewis[4]

Antibiotic resistance is spreading faster than the introduction of new compounds into clinical practice, causing a public health crisis. Most antibiotics were produced by screening soil microorganisms, but this limited resource of cultivable bacteria was overmined by the 1960s. Synthetic approaches to produce antibiotics have been unable to replace this platform. Uncultured bacteria make up approximately 99% of all species in external environments, and are an untapped source of new antibiotics. We developed several methods to grow uncultured organisms by cultivation *in situ* or by using specific growth factors. Here we report a new antibiotic that we term teixobactin, discovered in a screen of uncultured bacteria. Teixobactin inhibits cell wall synthesis by binding to a highly conserved motif of lipid II (precursor of peptidoglycan) and lipid III (precursor of cell wall teichoic acid). We did not obtain any mutants of *Staphylococcus aureus* or *Mycobacterium tuberculosis* resistant to teixobactin. The properties of this compound suggest a path towards developing antibiotics that are likely to avoid development of resistance.

Source: Ling et al Nature 2015 doi:10.1038/nature14098

The Good News

- IDSA's 10 X '20
- FDA-GAIN Act (2012)
  - QIDP – qualified infectious disease product
    - Fast track
    - Priority review
    - Longer period of exclusivity (>5 years)
- European Innovative Medicines Initiative
  - Increase academic-industrial collaboration

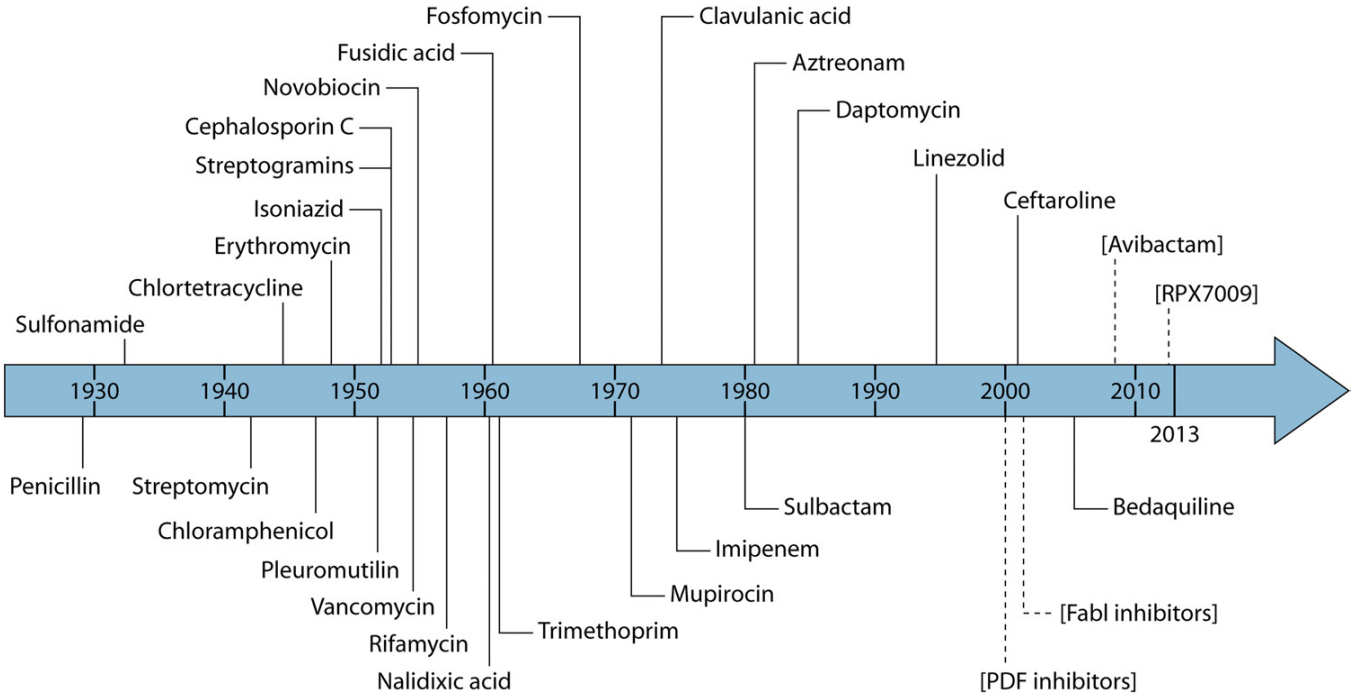


FIG 9 Timeline of the first reports of antibacterial agents or inhibitors with novel structures or activities. Brackets and dashed lines indicate unapproved investigational agents or classes.

Source: Pucci & Bush Clin Micro Rev 2013;26:792–821

Antimicrobials in Clinical Phase of Development

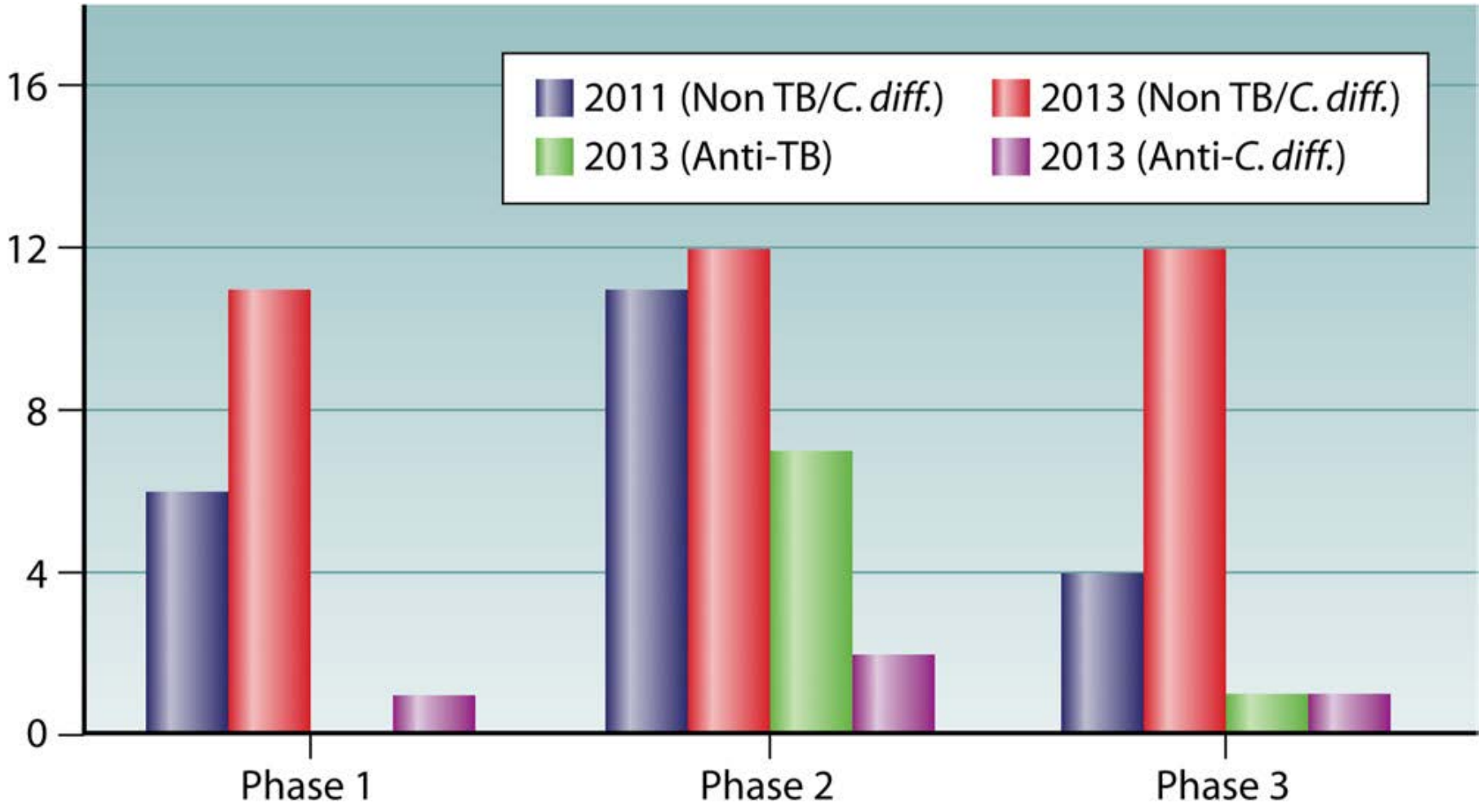
Source: Pew Trust January 2015

Drug name	Development phase[2]	Company	Drug class	Cited for potential activity against Gram-negative pathogens?[3]	Known QIDP[4] designation?
Debio 1450	Phase 1	Debiopharm Group	FabI inhibitor (Debio 1452 pro-drug)		Yes
Aztreonam+Avibactam[7] (ATM-AVI)	Phase 1[10]	AstraZeneca/Actavis (formerly Forest Laboratories)	Monobactam + novel beta-lactamase inhibitor	Yes	
BAL30072	Phase 1	Basilea Pharmaceutica	Monosulfactam	Yes	
CRS3123	Phase 1	Crestone	Methionyl tRNA synthetase (MetRS) inhibitor		
LCB01-0371	Phase 1[10]	LegoChem Biosciences (South Korea)	Oxazolidanone		
MRX-I	Phase 1	MicuRx Pharmaceuticals	Oxazolidinone		
TD-1607	Phase 1	Theravance Biopharma	Glycopeptide-cephalosporin heterodimer		Yes
WCK 2349	Phase 1	Wockhardt	Fluoroquinolone (WCK 771 pro-drug)		Yes
WCK 771	Phase 1	Wockhardt	Fluoroquinolone		Yes
AZD0914	Phase 2	AstraZeneca	DNA gyrase inhibitor	Yes	Yes
S-649266	Phase 2	Shionogi	Cephalosporin	Yes	
POL7080 (RG 7929)	Phase 2[10]	Polyphor (Roche licensee)	Macrocycle (protein epitope mimetic) LptD inhibitor	Yes (*Pseudomonas*)	Yes
Debio 1452	Phase 2	Debiopharm Group	FabI inhibitor		Yes
Avarofloxacin	Phase 2	Actavis (formerly Furiex Pharmaceuticals)	Fluoroquinolone	Yes	Yes
Brilacidin	Phase 2	Cellceutix	Defensin-mimetic		Yes
Ceftaroline+Avibactam	Phase 2	AstraZeneca/Actavis (formerly Forest Laboratories)	Cephalosporin + novel beta-lactamase inhibitor	Yes	

Drug name	Development phase[2]	Company	Drug class	Cited for potential activity against Gram-negative pathogens?[3]	Known QIDP[4] designation?
CG-400549	Phase 2	CrystalGenomics	FabI inhibitor		
Finafloxacin	Phase 2[13]	MerLion Pharmaceuticals	Fluoroquinolone	Yes	Yes
GSK2140944	Phase 2	GlaxoSmithKline	Type 2 topoisomerase inhibitor	Yes	
Lefamulin (BC-3781)	Phase 2	Nabriva Therapeutics	Pleuromutilin	Yes	Yes
Imipenem/ cilastatin+relebactam (MK-7655)	Phase 2	Merck	Carbapenem + novel beta-lactamase inhibitor	Yes	Yes
Nemonoxacin[8]	Phase 2	TaiGen Biotechnology	Quinolone	Yes	Yes
Omadacycline	Phase 2	Paratek Pharmaceuticals	Tetracycline	Yes	Yes
Radezolid	Phase 2	Melinta Therapeutics	Oxazolidinone	Yes	Yes
Ramoplanin	Phase 2	Nanotherapeutics	Lipoglycopeptide		
Zabofloxacin	Phase 2	Dong Wha Pharmaceutical	Fluoroquinolone	Yes	
SMT 19969	Phase 2	Summit			Yes
Cadazolid	Phase 3	Actelion Pharmaceuticals	Quinolonyl-oxazolidinone		Yes
Taksta (Fusidic acid)[9]	Phase 3	Cempra Inc.	Fusidane		

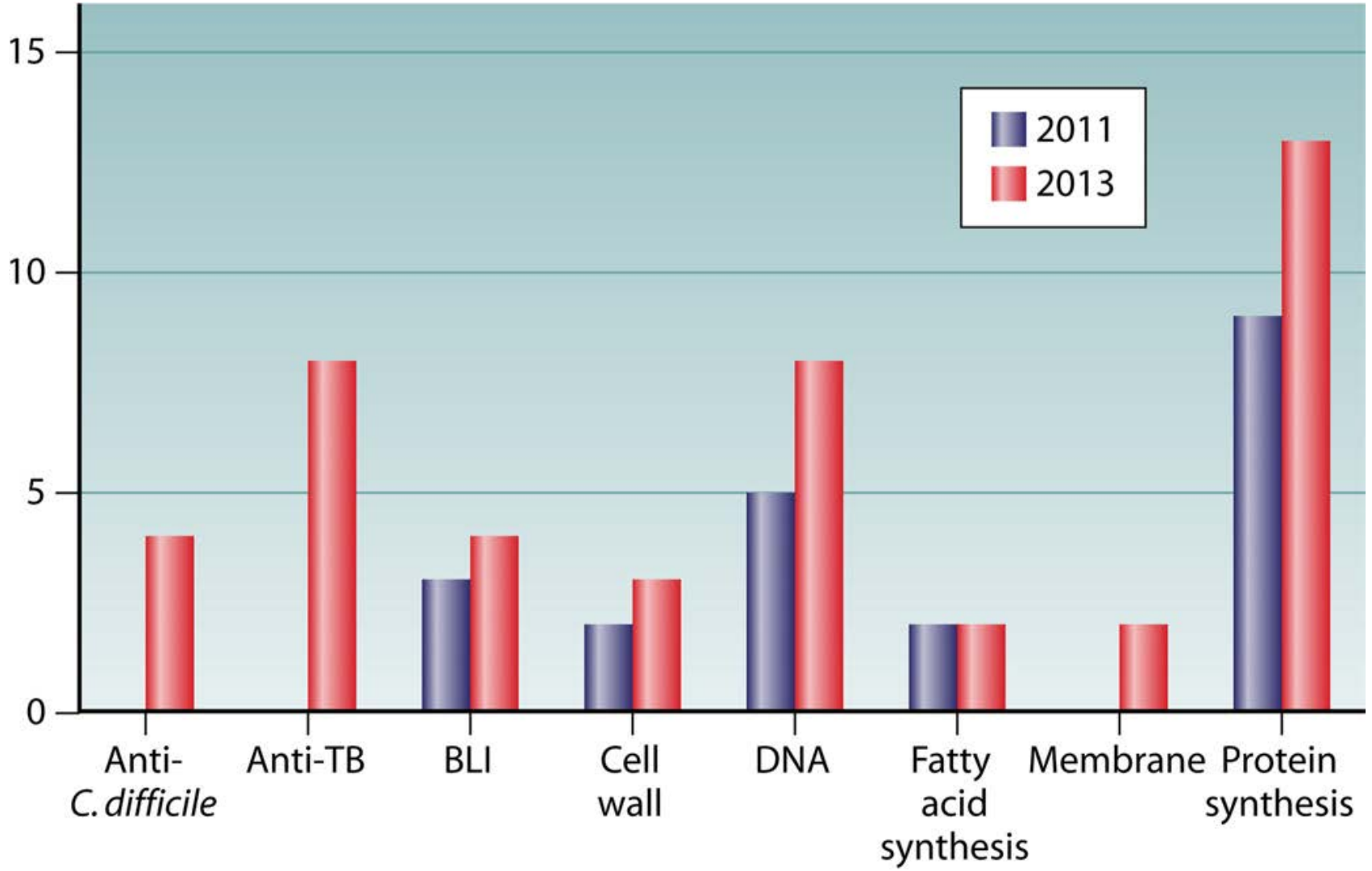
Drug name	Development phase[2]	Company	Drug class	Cited for potential activity against gram-negative pathogens?[3]	Known QIDP[4] designation?
Carbavance (RPX709+meropenem)	Phase 3	Rempex Pharmaceuticals (wholly owned subsidiary of The Medicines Co.)	Meropenem + novel boronic beta-lactamase inhibitor	Yes	Yes
Delafloxacin	Phase 3	Melinta Therapeutics	Fluoroquinolone	Yes	Yes
Eravacycline	Phase 3	Tetraphase Pharmaceuticals	Tetracycline	Yes	Yes
Plazomicin	Phase 3	Achaogen	Aminoglycoside	Yes	Yes[11]
Solithromycin	Phase 3	Cempra Inc.	Macrolide (fluroketolide)	Yes	Yes
Surotomycin	Phase 3	Cubist Pharmaceuticals	Lipopeptide		Yes

Source: Pew Trust January 2015



Source: Pucci & Bush Clin Micro Rev 2013;26:792–821

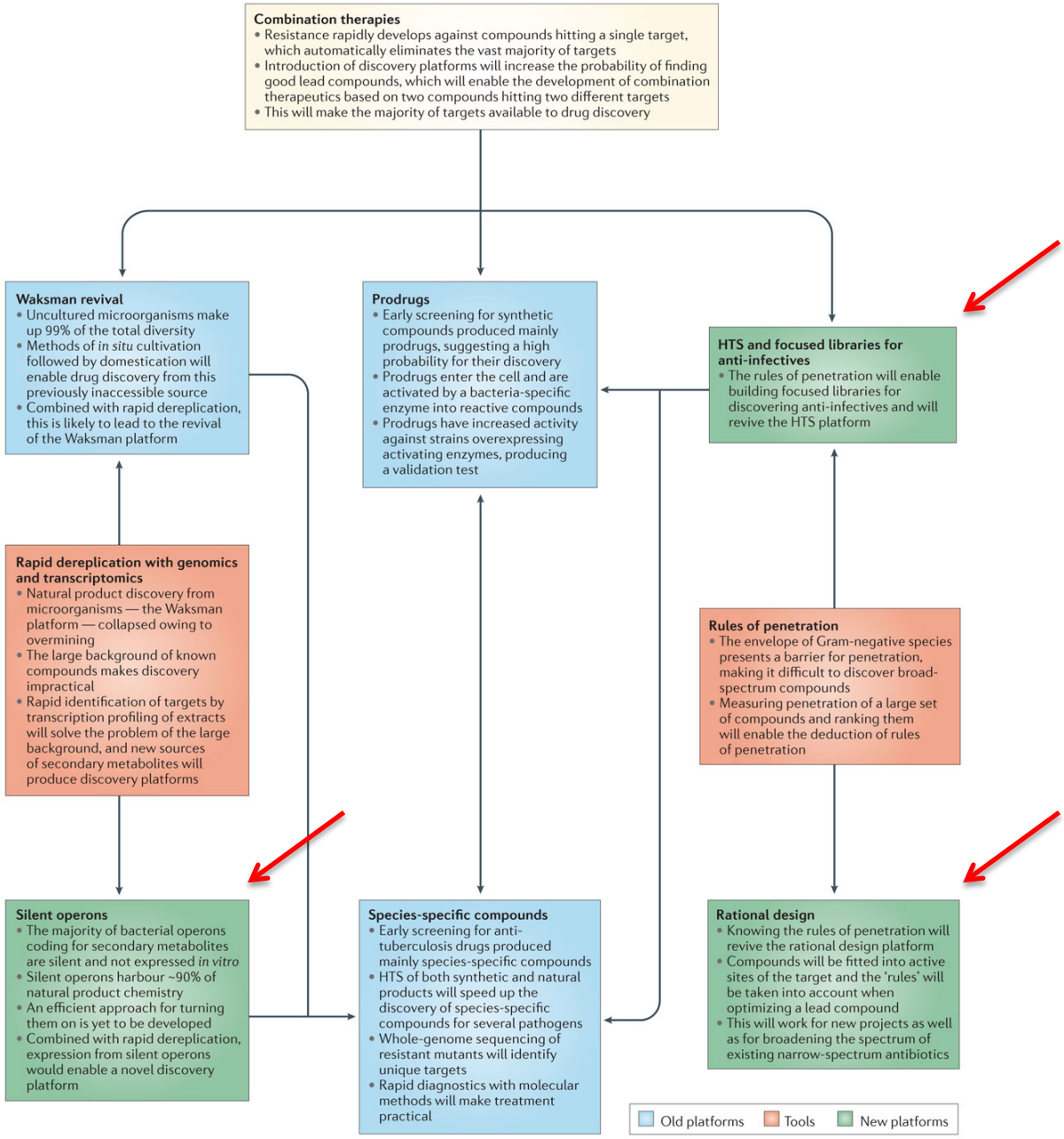
New Antimicrobials by MoA



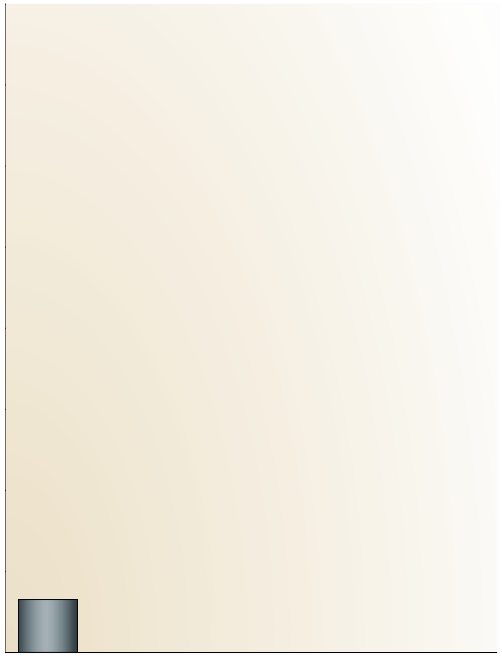
Source: Pucci & Bush Clin Micro Rev 2013;26:792–821

More Good News?

- New drug discovery methods are proving fruitful
- At least 4 novel classes based on previously unexploited mechanisms of action have reached the clinical phase of development



Source: Lewis K Nature Reviews Drug Discovery 2013;12:371–387

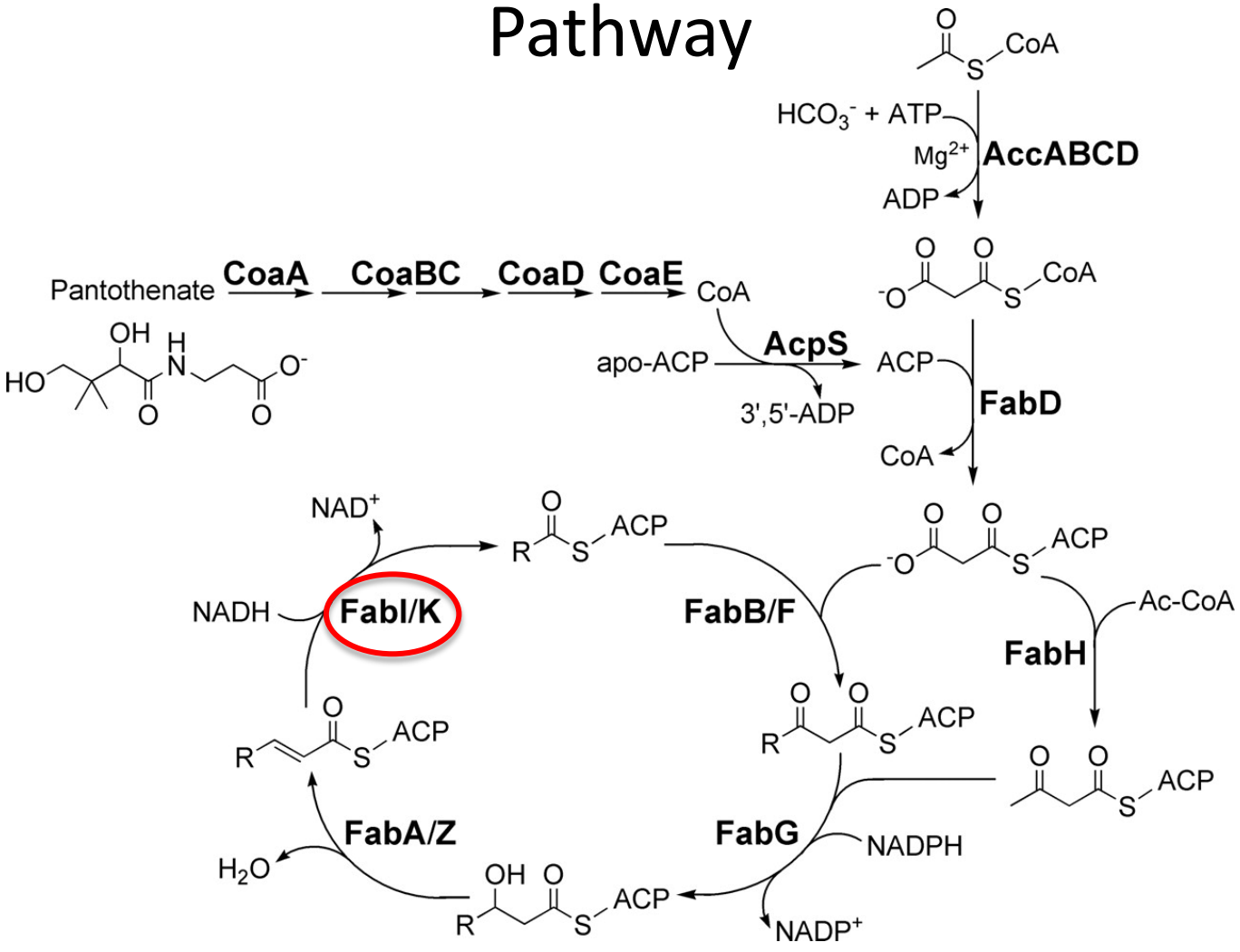


Payne *et al. Nature Reviews Drug Discovery* **6**, 29–40 (January 2007) | doi:10.1038 / nrd2201

Novel Mechanisms & Agents

1. Fatty acid synthesis inhibitors
   - FabI – Enoyl-acyl carrier protein (ACP) reductase
2. Membrane-acting agents (Defensins)
   - Antimicrobial peptides (AMPs) and mimetics
3. PDF Inhibitors
   - Peptide deformylase – an essential bacterial metalloenzyme in peptide synthesis
   - An essential role in protein maturation and is a highly conserved target
4. Pleuromutilins
   - Selective binding of prokaryotic ribosomes leading to protein synthesis inhibition

The Bacterial Type II Fatty Acid Biosynthetic Pathway



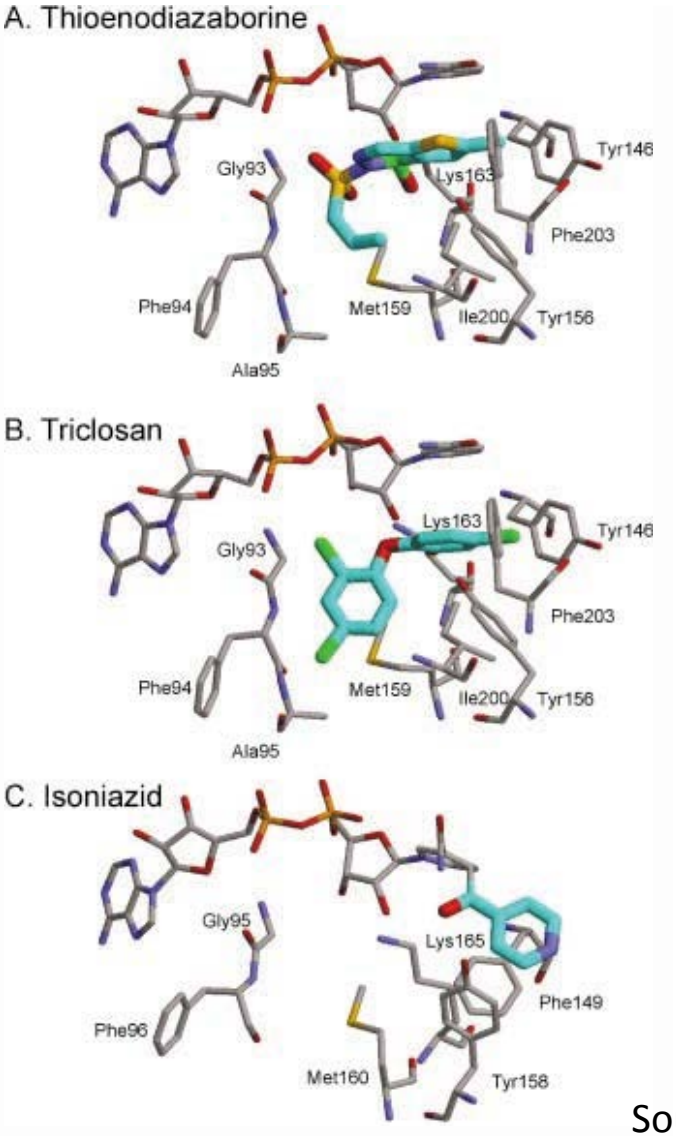
Yong-Mei Zhang et al. J. Biol. Chem. 2006;281:17541-17544

Table 1 Expression of enoyl-ACP reductase isoforms in different organisms

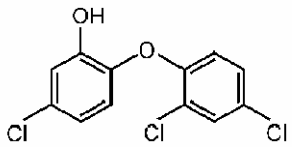
Organism	Enoyl-ACP reductase isoform(s) expressed		
	FabI	FabK	FabL
Escherichia coli	Yes	No	No
Streptococcus pneumoniae	No	Yes	No
Bacillus subtilus	Yes	No	Yes
Pseudomonas aeruginosa	Yes	Predicted[b]	No
Staphylococcus aureus	Yes	No	No
Mycobacterium tuberculosis	Yes[a]	Predicted[c]	No
Plasmodium falciparum	Yes	No	No

Source: Heath et al Appl Microbiol Biotechnol 2002;58:695–703

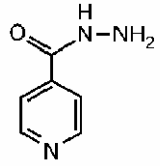
Fatty Acid Synthesis Inhibitors



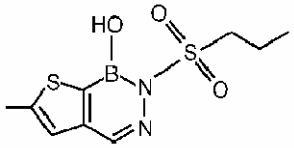
B. Inhibitors of fatty acid synthesis



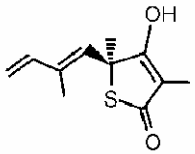
Triclosan



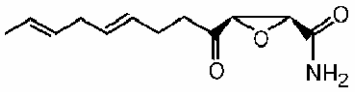
Isoniazid



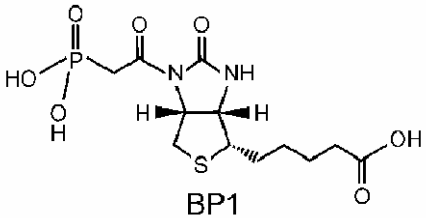
Thioenodiazaborine



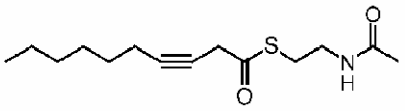
Thiolactomycin



Cerulenin



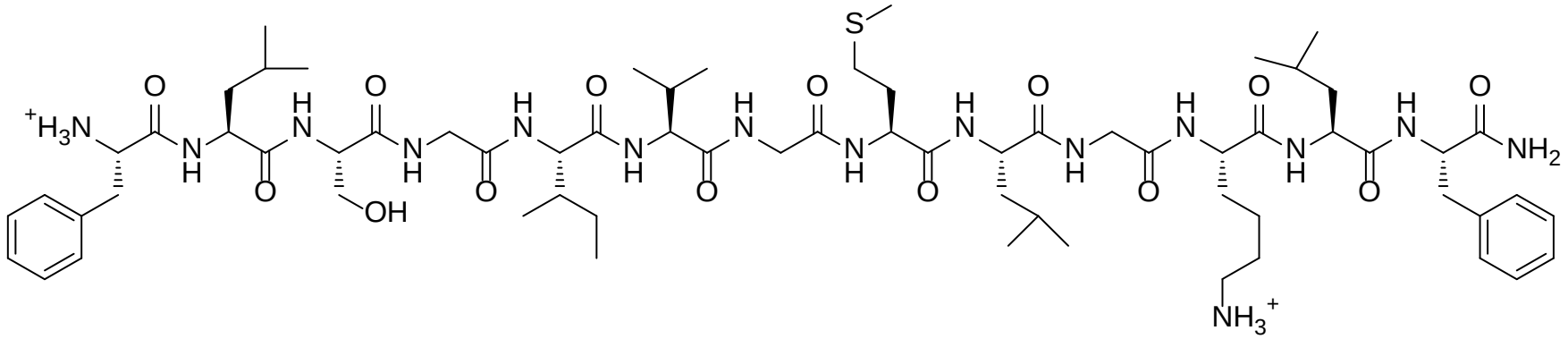
BP1

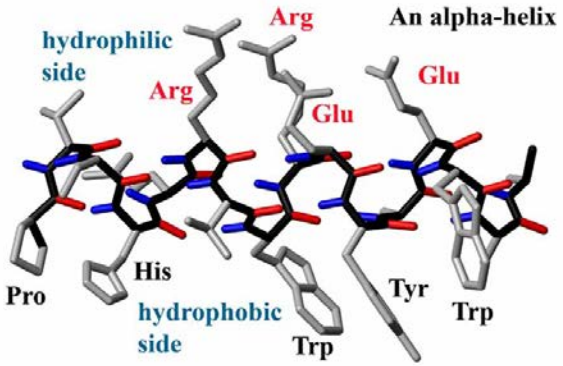


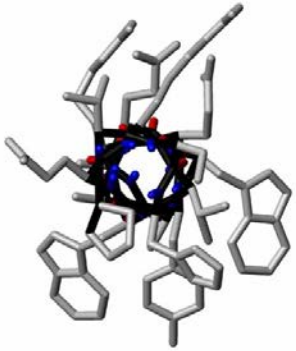
cis-3-decynoyl-NAC

Source: Heath et al Appl Microbiol Biotechnol 2002;58:695–703

Antimicrobial Peptides (Defensins)

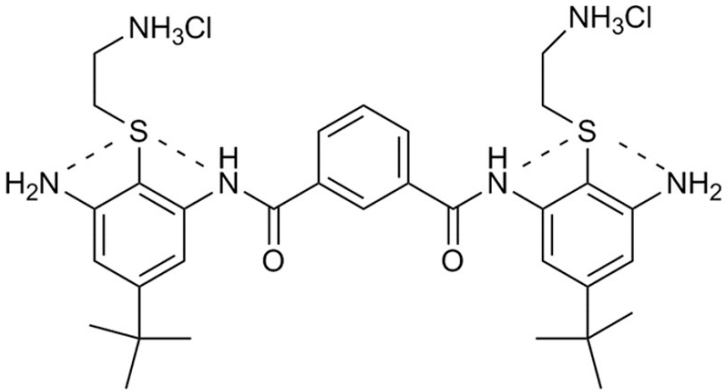




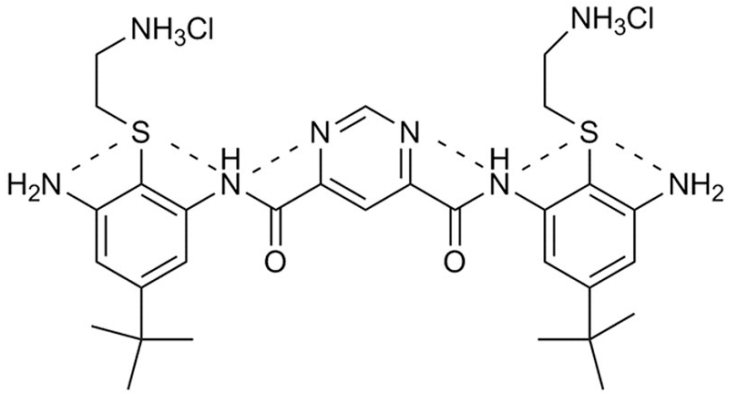


- Positively charged peptide molecules (charge typically between +2 to +9).
- They range in size from 12 to 100 amino acids in length.
- Extremely potent (nM) against a broad spectrum of bacteria, viruses and fungi

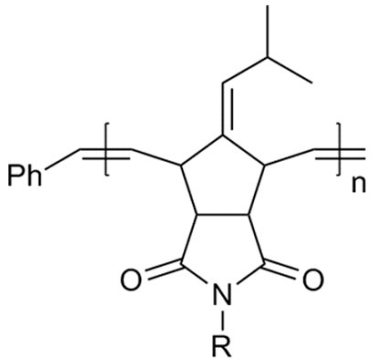
Initial design of AMP mimetics and more advanced analogues



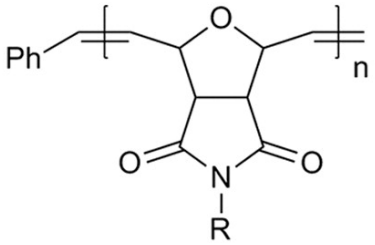
AMP Mimetic A



AMP Mimetic B



AMP Mimetic C

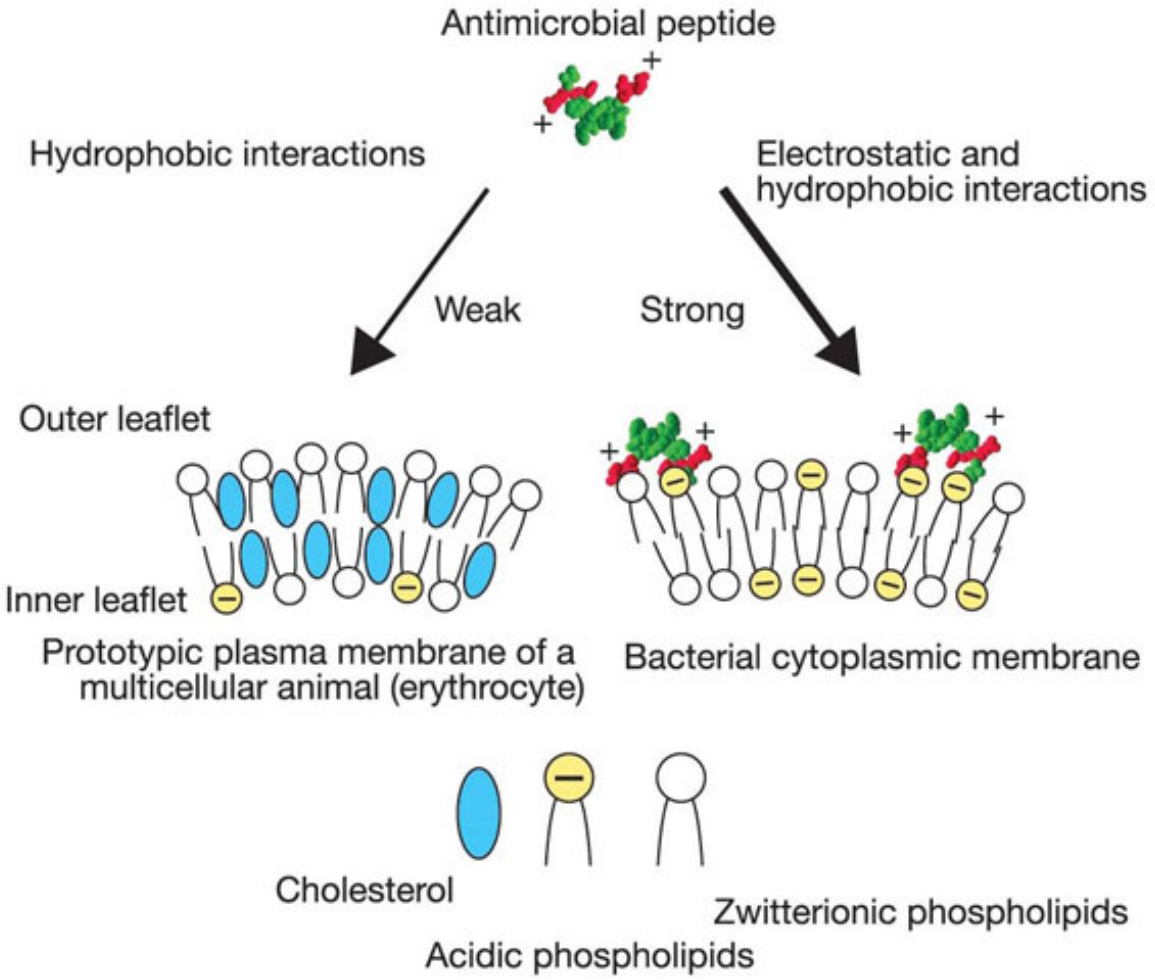


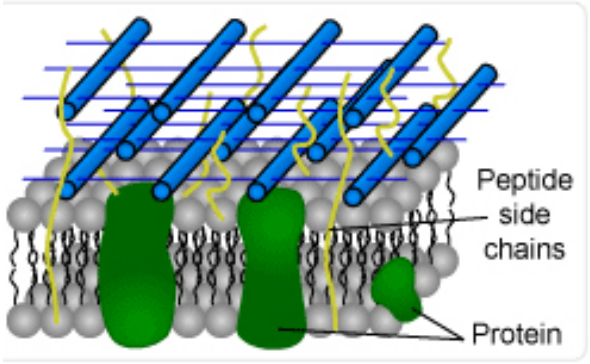
AMP Mimetics D, E

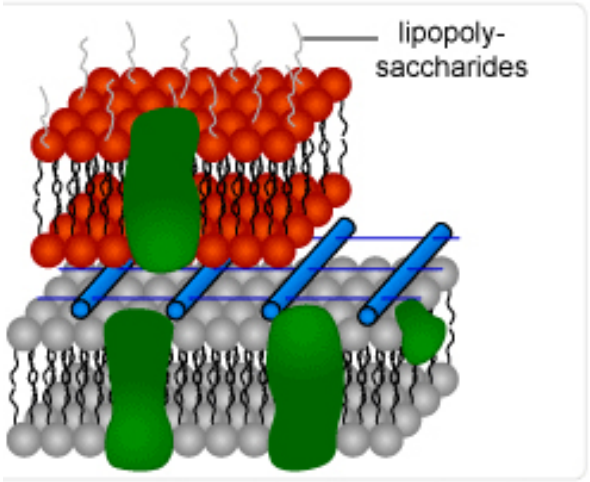
C1	R = $CH_2CH_2NH_3^+$	**D1**	R = $CH_2CH_2NH_3^+$
C2	R = $CH(CH_2NH_3)_2^{2+}$	**D2**	R = $CH(CH_2NH_3)_2^{2+}$
C3	R = $C(CH_2NH_3)_3^{3+}$	**D3**	R = $C(CH_2NH_3)_3^{3+}$
		E	R = $(CH_2)CN_3H_5^+$

Findlay et al Antimicrob. Agents Chemother. 2010;54:4049-4058

Antimicrobial Peptides: Selectivity for bacteria



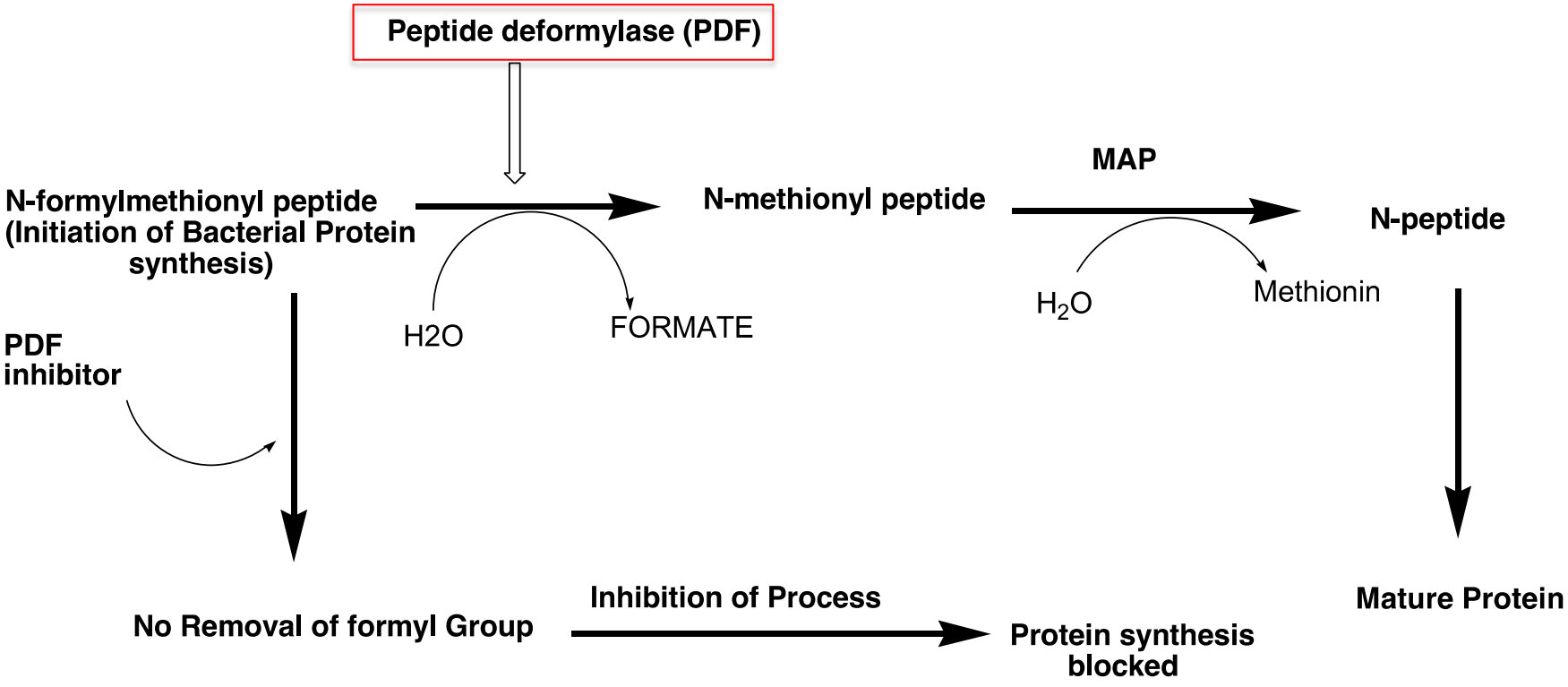




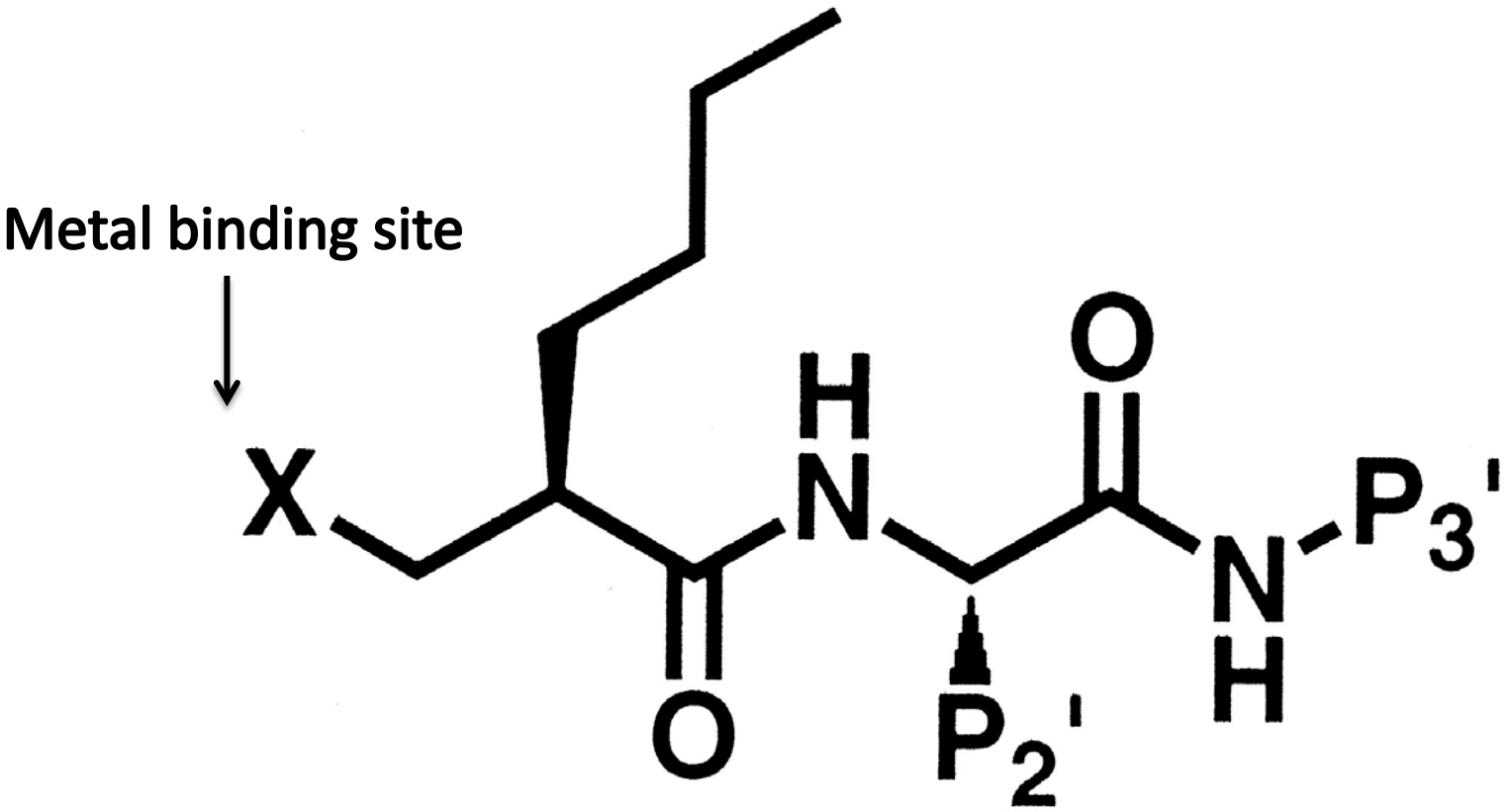
Dept. Biol. Penn State ©2002

Role of PDF and its Inhibitors in Bacterial Protein Synthesis

Sanjay Kumar Verma *et al.* / *Pharmacophore* 2011, Vol. 2 (2), 114-123



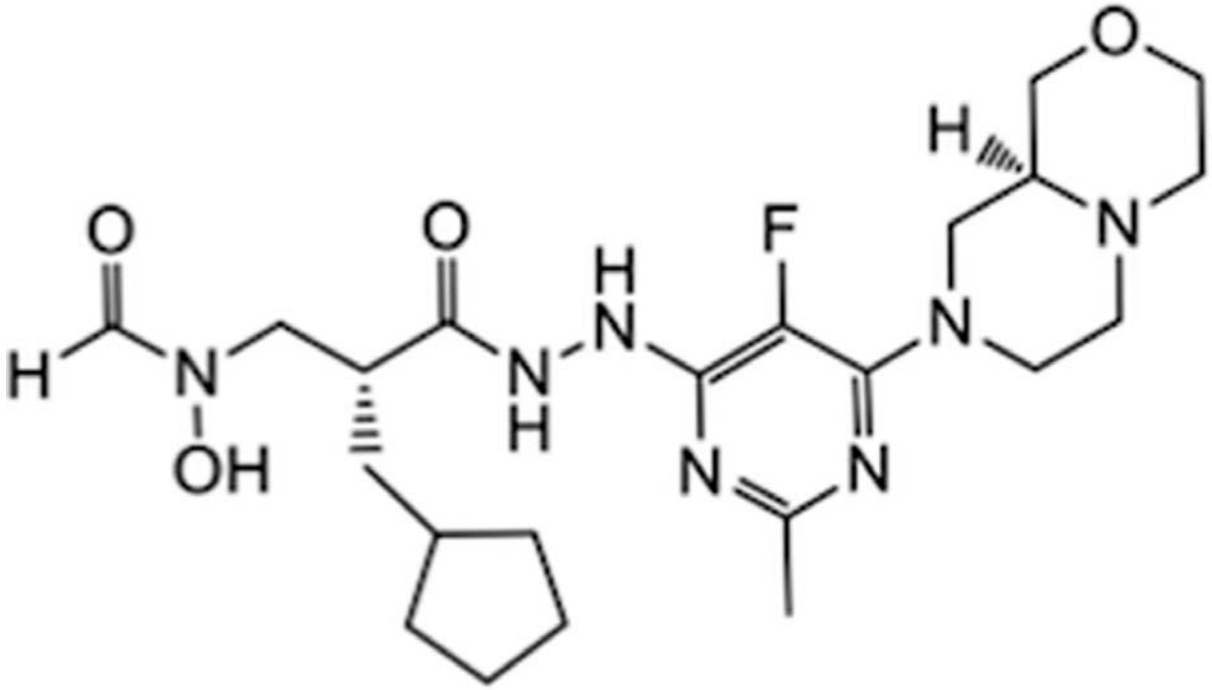
Generic PDF inhibitor structure



D. Chen et al. Antimicrob. Agents Chemother. 2004;48:250-261

Antimicrobial Agents and Chemotherapy

GSK1322322



Karen O'Dwyer et al. Antimicrob. Agents Chemother. 2013;57:2333-2342

Antimicrobial Agents and Chemotherapy

Antimicrobial Activity of GSK 1322322

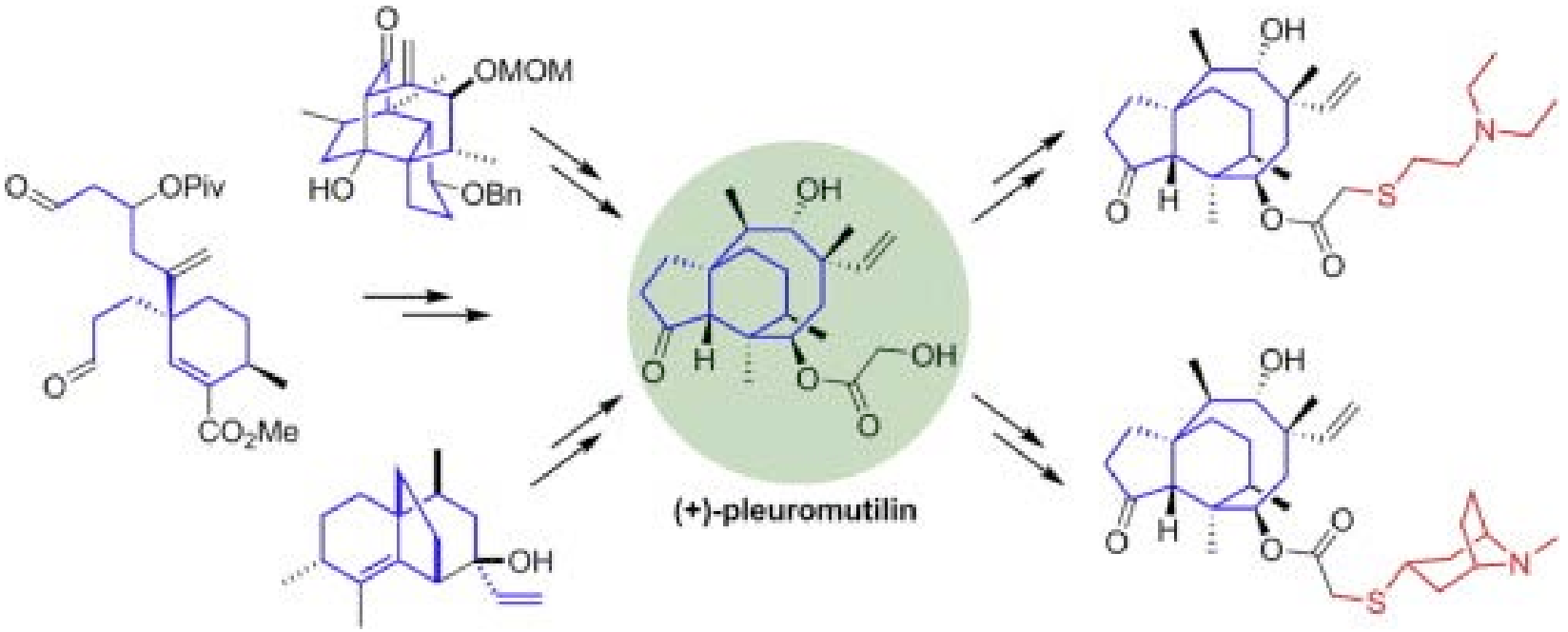
TABLE 1 Summary of antimicrobial activities of GSK1322322 at individual MICs

Organism or phenotype (no. of isolates)	Cumulative % of strains inhibited by GSK1322322 at MIC (μg/ml) of:										
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
All *H. influenzae* (2,370)	0.1	0.4	0.8	2.2	16.1	48.1	*78.2*	**93.0**	98.6	99.9	100
β-Lactamase-positive *H. influenzae* (517)	0.2	0.6	0.8	1.5	15.7	44.7	*74.9*	88.8	**97.7**	99.8	100
M. catarrhalis (115)		1.7	5.2	7.0	23.5	**93.9**	100				
S. pneumoniae (947)	0.8	2.2	4.8	13.3	48.7	*88.0*	**98.7**	100			
Penicillin resistant (165)		0.6	4.2	17.6	*71.5*	**97.0**	100				
Levofloxacin resistant (45)		2.2	6.7	13.3	*51.1*	**93.3**	100				
Macrolide resistant (329)	0.3	1.8	5.5	15.8	*59.9*	**91.2**	99.4	100			
S. aureus (940)			0.2	1.1	10.3	31.7	*82.1*	**97.6**	99.9	100	
MRSA (414)			0.2	0.7	6.8	29.5	*82.9*	**96.9**	100		
Levofloxacin resistant (308)			0.3	1.0	10.1	35.1	*80.5*	**95.8**	100		
Macrolide resistant (482)			0.2	0.6	8.1	30.1	*81.5*	**96.7**	100		
RTI (238)				1.7	13.0	34.5	*78.2*	**95.4**	99.6	100	
SSSI (702)			0.3	0.9	9.4	30.8	*83.5*	**98.3**	100		
S. pyogenes (617)	0.2	3.6	14.7	48.8	**95.1**	99.8		100			
Macrolide resistant (62)		22.6	35.5	*74.2*	**100**						
RTI (218)		5.1	17.4	*61.0*	**95.0**	99.6		100			
SSSI (399)	0.3	2.8	13.3	42.1	**95.2**	100					

[a] MIC_{50}s are in italics.
[b] MIC_{90}s are in bold.

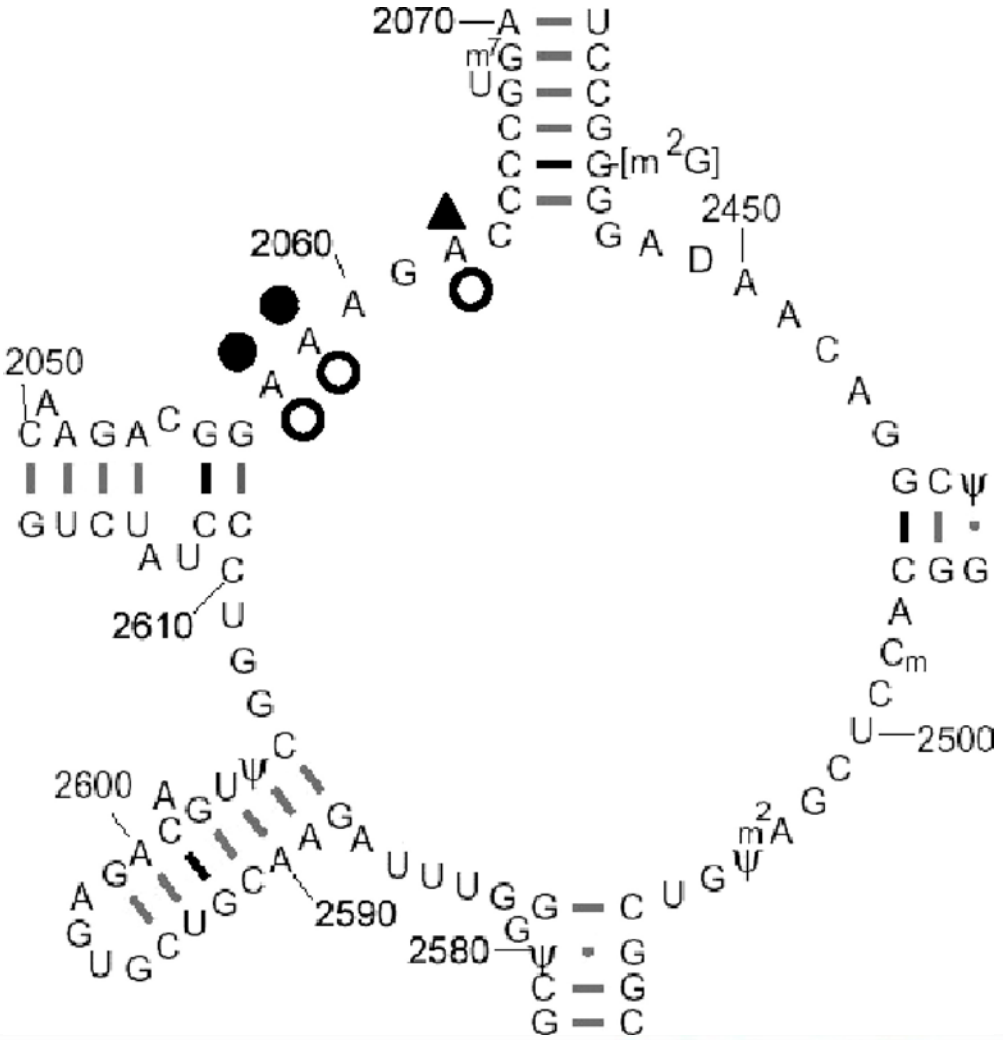
Source: O'Dwyer et al AAC 2013;57:2333–2342

Pleuromutilins



Cultures of the Basidomycete *Pleurotus mutilis* produced a substance with antibacterial activity which was called pleuromutilin

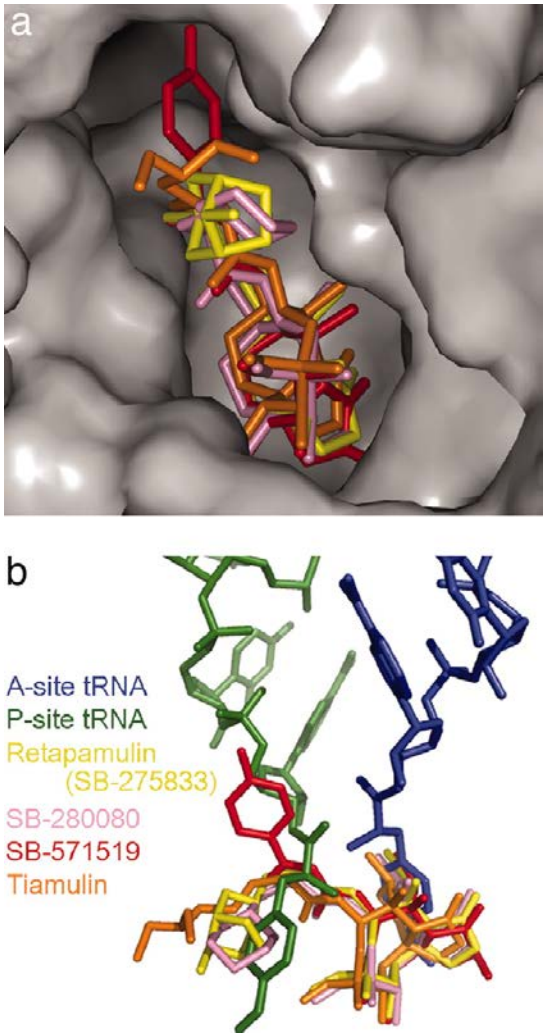
Chemical footprint of retapamulin and telithromycin on E. coli 23S rRNA



Kang Yan et al. Antimicrob. Agents Chemother. 2006;50:3875-3881

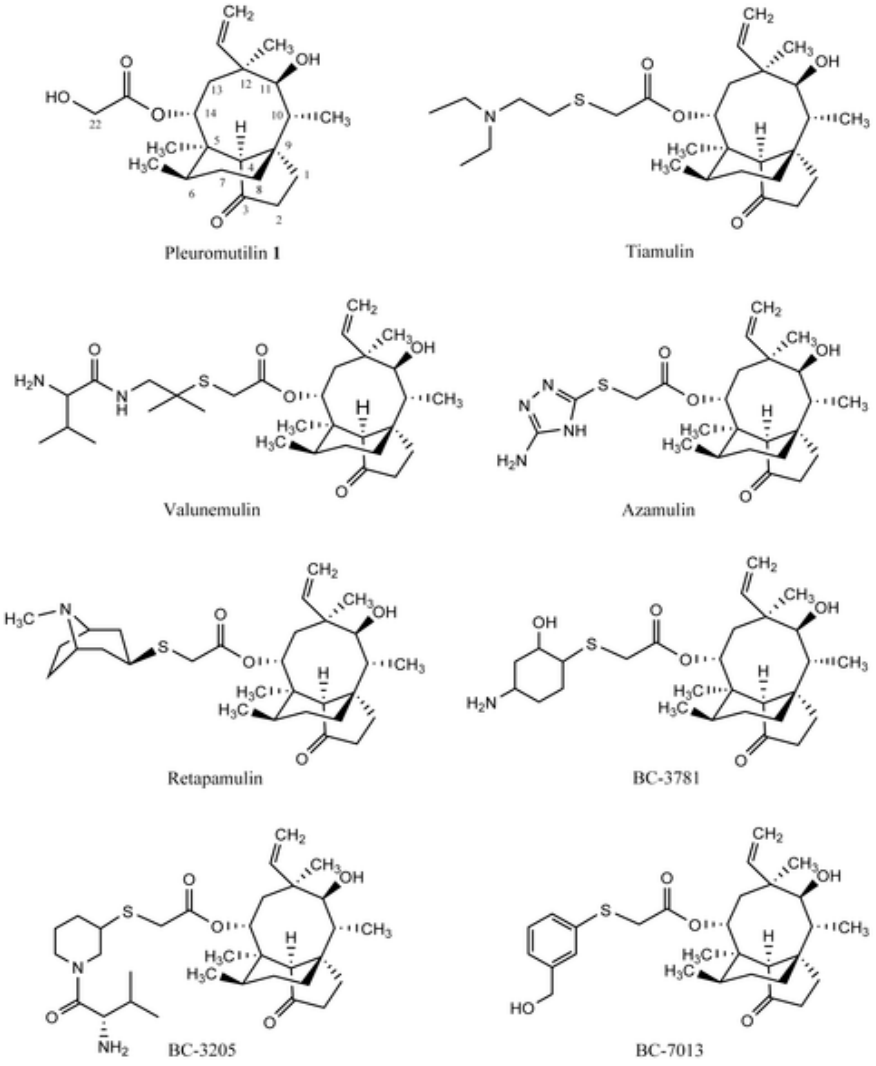
Antimicrobial Agents and Chemotherapy

Pleuromutilin Derivatives superimposed in the RNA binding pocket



Chen Davidovich et al. PNAS 2007;104:4291-4296

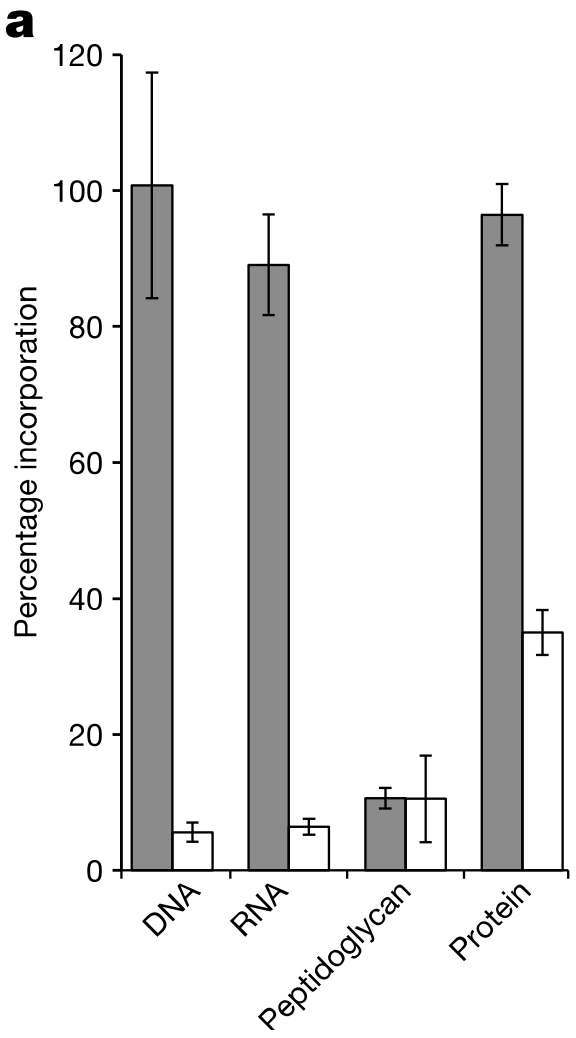
Figure 1. Structural formulas of pleuromutilin (1) and derivatives.



Shang R, Wang S, Xu X, Yi Y, et al. (2013) Chemical Synthesis and Biological Activities of Novel Pleuromutilin Derivatives with Substituted Amino Moiety. PLoS ONE 8(12): e82595. doi:10.1371/journal.pone.0082595
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0082595

Teixobactin

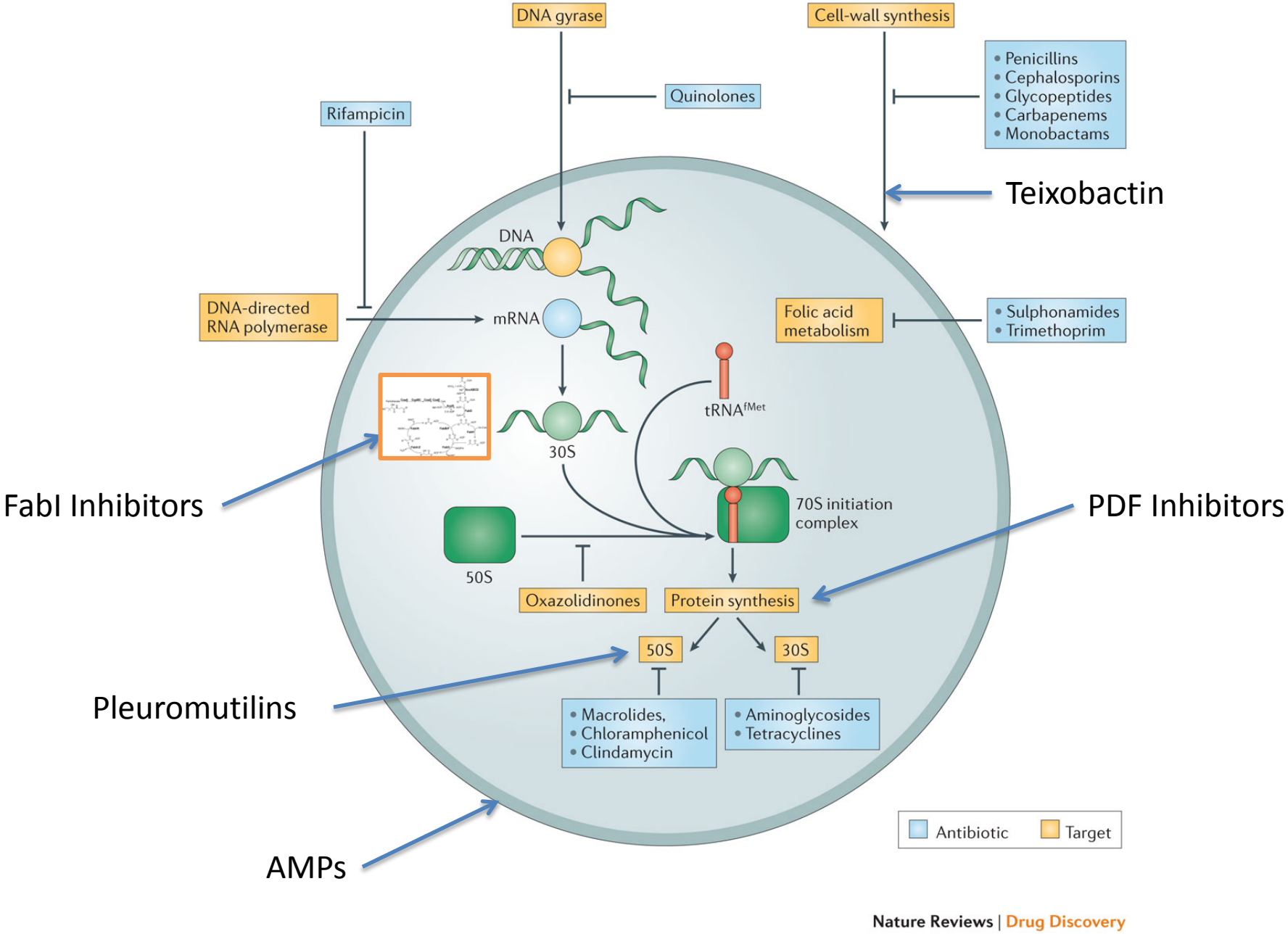
- A depsipeptide which contains enduracididine, methylphenylalanine, and four D-amino acids
- Inhibits synthesis of peptidoglycan, but no effect on label incorporation into DNA, RNA and protein



Source: Ling et al Nature 2015 doi:10.1038/nature14098

Teixobactin

Source: Ling et al Nature 2015 doi:10.1038/nature14098



Source: Lewis K Nature Reviews Drug Discovery 2013;12:371–387

Difficult to Treat Organisms

- MRSA
- Antibiotic-resistant GNBs
- MDR-TB
- *C. difficile*

Scientists discover a new superbug.


CENTERS FOR DISEASE CONTROL
THE DRUG-RESISTANT STAPH INFECTION KNOWN AS MRSA...
...IS SPREADING LIKE WILDFIRE...
KILLING THOUSANDS UPON THOUSANDS!...
We urge the public not to panic.
MARGULIES
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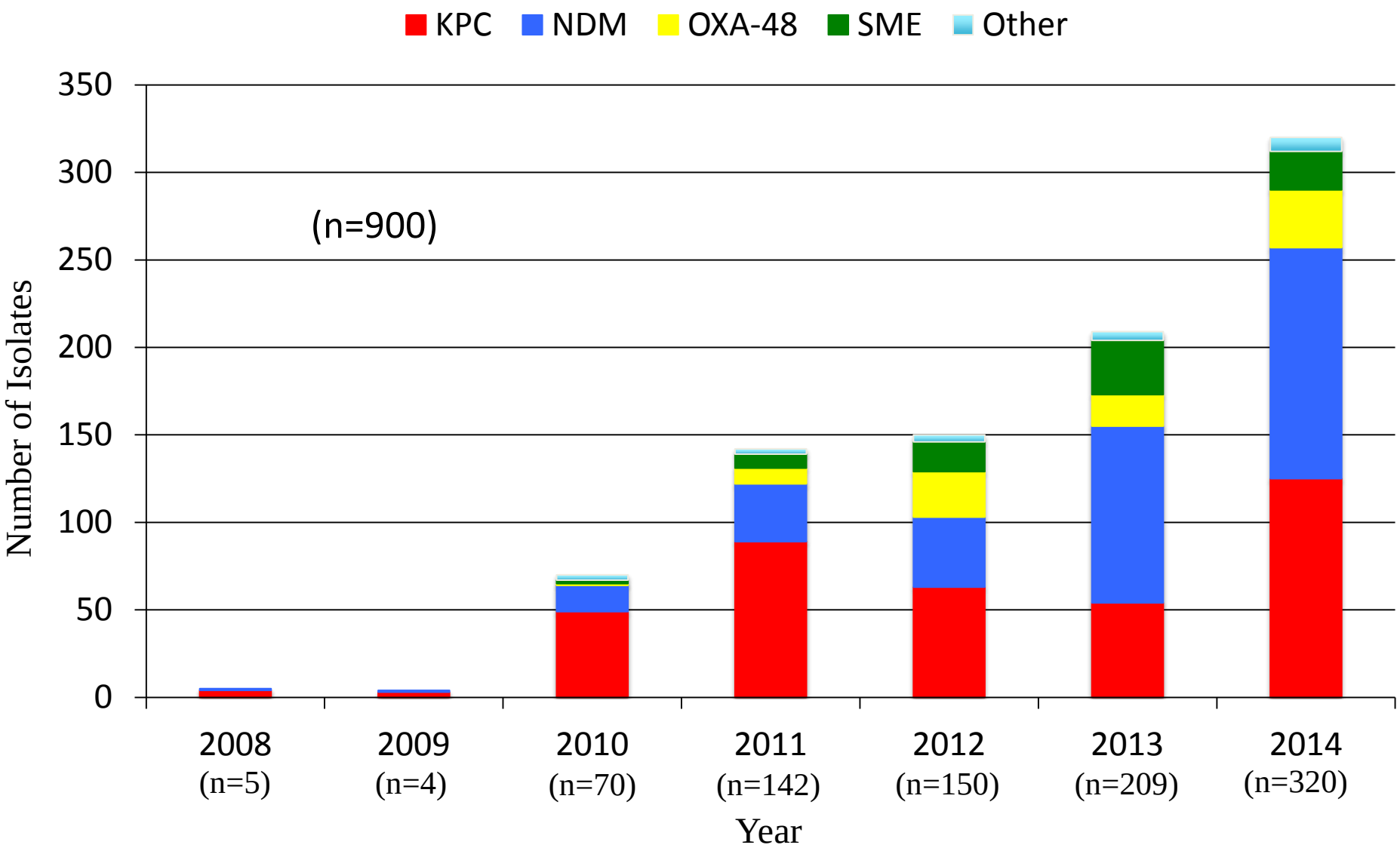
MRSA: New Agents

		MIC_{90} µg/mL	Clinical Phase	Availability?
FQs	Nemonoxacin	1	3 (CAP, DFI)	2018
	Delafloxacin	0.5	3 (cSSSI, CAP, HAP, cIAI)	2020
	Avarofloxacin	0.5	2 (ABSSSI, CAP)	>2020
Tetracyclines				
	Eravacycline	0.25	3 (cIAI, HAP, cUTI)	2020
Oxazolidinones				
	Tedizolid	0.5	3 (cSSSI)	2015
	Radezolid	0.5	2 (CAP, uSSSI)	2018
BLI combinations				
	Ceftaroline-avibactam	1	2 (cUTI)	2015/2018

MRSA: Novel-acting Agents

	MIC_{90} µg/mL	Clinical Phase	Availability?
Pleuromutilins			
Lefamulin	0.25	2 (ABSSSI)	>2020
Antimicrobial peptide mimetics			
Brilacidin	1	2 (ABSSSI)	2020
PDF inhibitors			
GSK1322322	4	? 2 (ABSSSI)	>2020
FabI inhibitors			
AFN-1252	<0.12	2 (SA SSSI)	>2020

CPE in Canada: CPHLN Data



Courtesy of M Mulvey CPHLN and CNISP 2015

Novel Agents for Antibiotic-resistant GNBs

	MDR PsA	AB	MBL	KPC	ESBL	Clinical Phase
FQs						
DS-8587		✔				1
Aminoglycosides						
Plazomicin			?	✔	✔	3
Tetracyclines						
Eravacycline		?	?	✔	✔	3
Pleuromutilin						
AN3365	✔				✔	Pre-clinical
AMPs						
Brilacidin	?		?	?	✔	2
POL7080	✔					1
ACHN-975	✔				✔	1

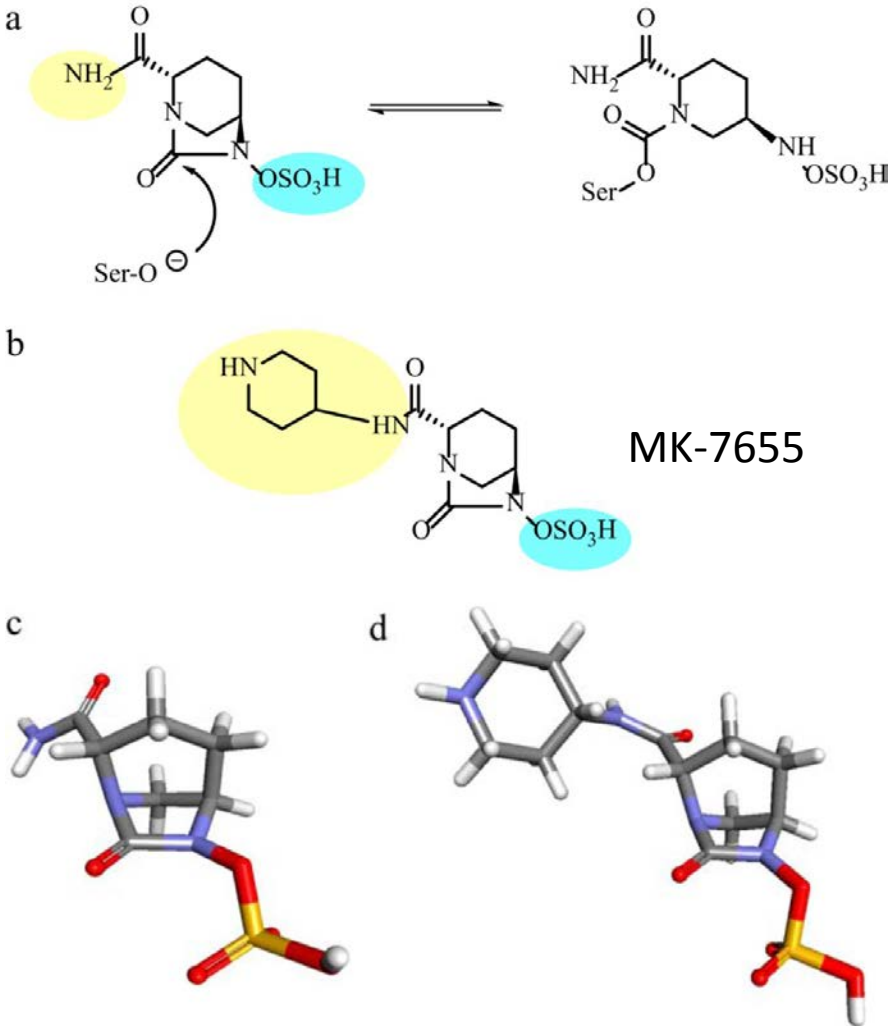
Overly Simplified Beta Lactamase Classification

Bush Group	Ambler Class	Inhibited by CA or TAZ	Type/Kind	Examples
1	C	No	AmpC and others	Cephalosporinases
2	A	Yes	Serine β lactamases	Pencillinases/ESBLs/KPC Carbapenemases
2	D	Variable	Oxa β lactamases	Oxacillinases, Carbapenemases
3	B	No	Metallo β lactamases	Carbapenemases

Avibactam

- Compared with currently available BLI
  - Has lower 50% inhibitory concentrations
  - Decreased reactivation rates of β-lactamases
  - Inhibition is believed to be reversible and the active inhibitor is regenerated
  - Active against Class A and C β-lactamases including:
    - TEM-1
    - KPC-2
    - *E. cloacae* P99
    - AmpC from *Pseudomonas aeruginosa*

Avibactam and MK-7655



Source: Drawz et al Antimicrob. Agents Chemother. 2014;58:1835-1846

Activity of Avibactam Combinations

TABLE 1 MICs of β-lactam and β-lactam-avibactam combinations against select pathogens[a]

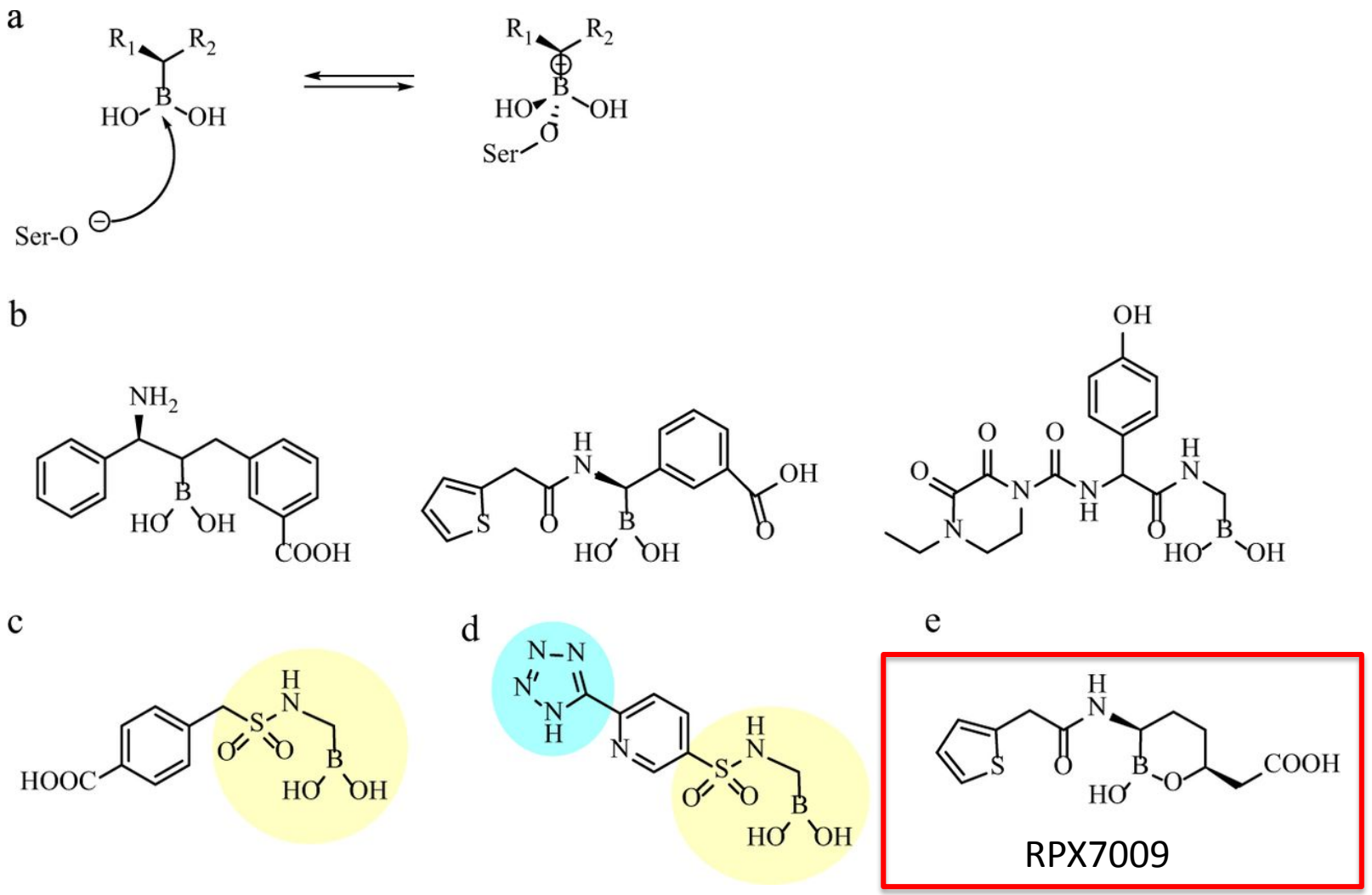
Pathogen	MIC (μg/ml)[b]					
	CAZ	CAZ-AVI	CPT	CPT-AVI	ATM	ATM-AVI
K. pneumoniae with OXA-48	256/512	0.25/0.5				
K. pneumoniae with CTX-M-15	8/64	0.06/0.25				
K. pneumoniae with KPC-2	≥512/≥512	0.25/1			≥512/≥512	≤0.06/≤0.06
E. coli with ESBL	16/64	0.12/0.25				
E. coli with AmpC	16/64	0.12/0.5				
E. coli with OXA-48	4	<0.008				
E. coli with IMP-1	256	64				
Enterobacteriaceae with multiple β-lactamases, including KPC-2			>64/>64	0.5/2		
Enterobacteriaceae with multiple β-lactamases, including AmpC			256/>256	0.5/2		
Enterobacteriaceae with VIM	64–512	64–512			0.25–256	0.12–0.5
P. aeruginosa	8/64	4/8	>64/>64	16/>32	16/32	8/32
P. aeruginosa with ESBL PER-1	128/128	4/16				
A. baumannii			>64/>64	32/>32		
A. baumannii with PER-1, OXA-51, and OXA-58	128/≥512	32/256				
S. aureus			1/2	1/2		

[a] Data were adapted from references 15, 16, 19, 20, 21, and 24. Avibactam was added at 4 μg/ml. Abbreviations: CAZ, ceftazidime; AVI, avibactam; CPT, ceftaroline; ATM, aztreonam.

[b] Numbers separated by a forward slash indicate MIC_{50}/MIC_{90} values. Empty cells indicate that values were not reported.

Source: Drawz et al Antimicrob. Agents Chemother. 2014;58:1835-1846

Boronic Acid Containing β-lactamases



Source: Drawz et al Antimicrob. Agents Chemother. 2014;58:1835-1846

Novel β lactams for Antibiotic-resistant GNBs

	MDR PsA	Acinet	MBL	KPC	ESBL	Clinical Phase
Beta lactams						
BAL30072	✔	✔	✔			1
BLI combinations						
Biapenem/RPX7009	✔	✔		✔	✔	1
Ceftolozane-tazobactam	?				✔	3
Imipenem/MK-7655	?			✔	✔	2
Avibactam-combinations						
Ceftazidime-avibactam	?			✔	✔	3
Ceftaroline-avibactam				✔	✔	2
Aztreonam-avibactam			✔			


EMERGENCY ROOM
MAYBE WE'RE NOT TAKING THIS WHOLE C.DIFFICILE THING SERIOUSLY ENOUGH...
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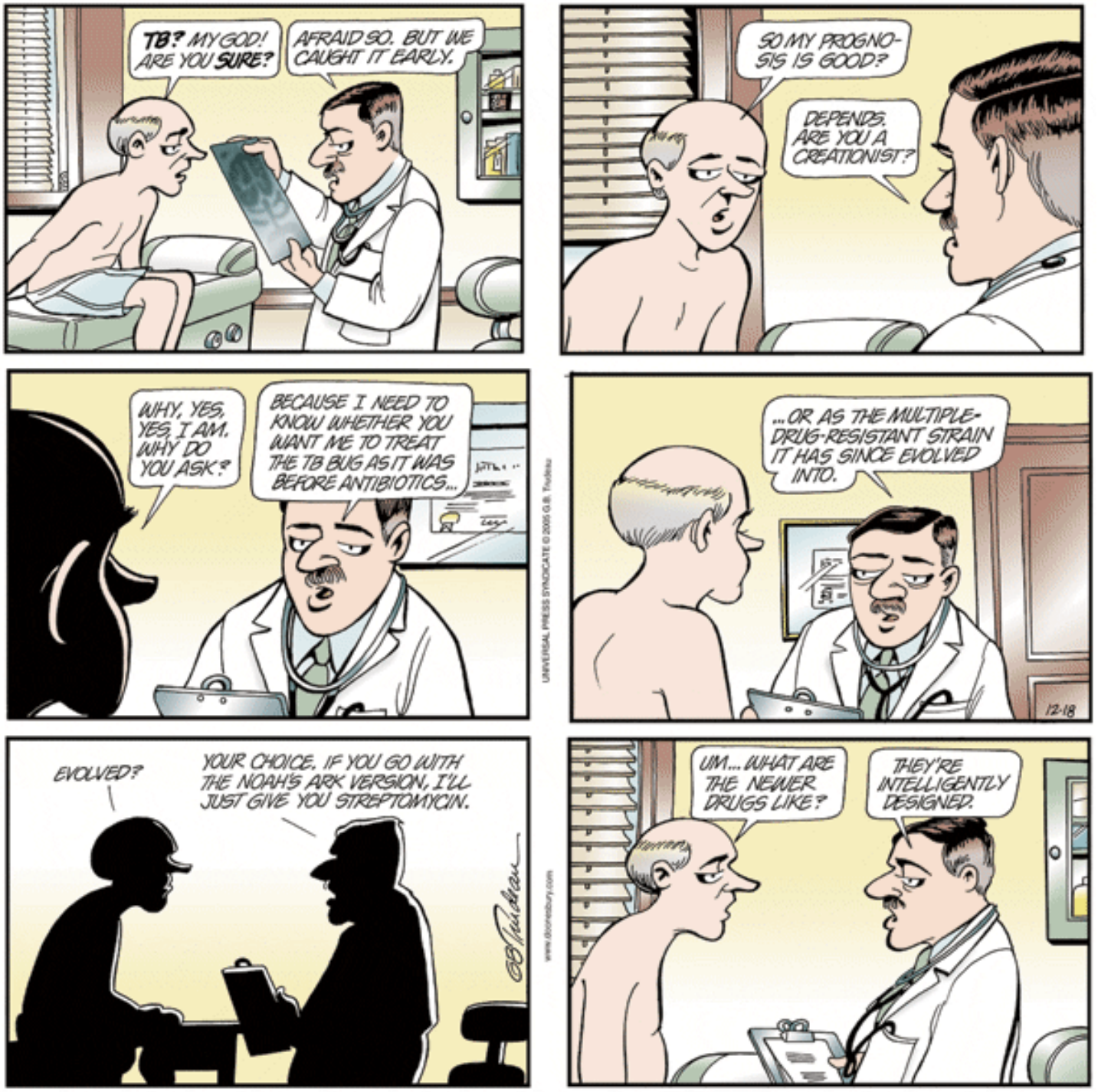
CDI: New Agents

	MIC_{90} µg/mL	Clinical Phase	Availability?
Oxazolidinone/quinolone chimera			
Cadazolid	0.5	2	2018
Inhibitor of bacterial translocation (via elongation factor Tu)			
LFF571	< 0.25	2	2020
Type B Lantibiotic (inhibit peptidoglycan synthesis)			
NVB302	1	1	> 2020
Lipopeptide			
CB-315	0.5	3	2016

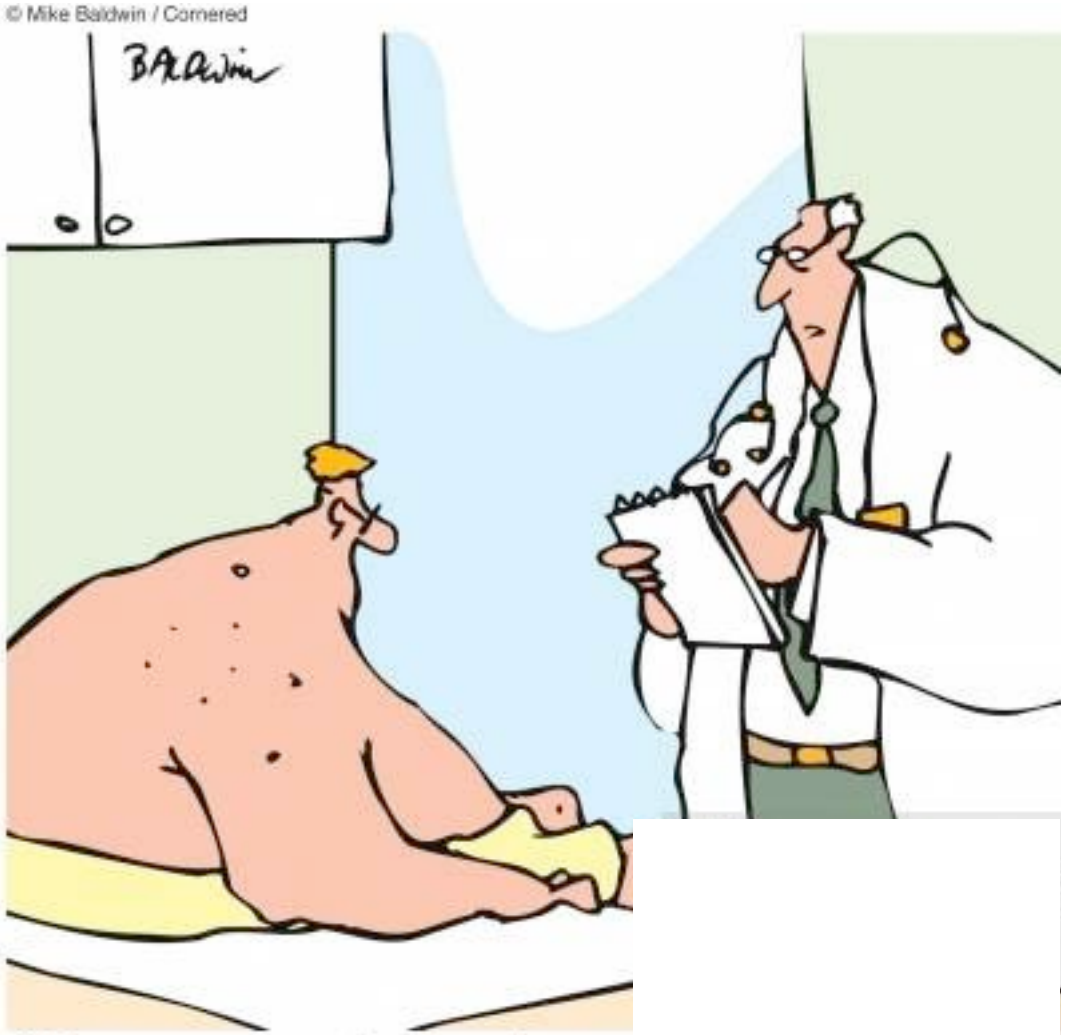

TB? MY GOD! ARE YOU SURE?
AFRAID SO. BUT WE CAUGHT IT EARLY.
SO MY PROGNOSIS IS GOOD?
DEPENDS. ARE YOU A CREATIONIST?
WHY, YES, YES, I AM. WHY DO YOU ASK?
BECAUSE I NEED TO KNOW WHETHER YOU WANT ME TO TREAT THE TB BUG AS IT WAS BEFORE ANTIBIOTICS...
...OR AS THE MULTIPLE-DRUG-RESISTANT STRAIN IT HAS SINCE EVOLVED INTO.
12-18
EVOLVED?
YOUR CHOICE. IF YOU GO WITH THE NOAH'S ARK VERSION, I'LL JUST GIVE YOU STREPTOMYCIN.
UM... WHAT ARE THE NEWER DRUGS LIKE?
THEY'RE INTELLIGENTLY DESIGNED.
UNIVERSAL PRESS SYNDICATE © 2005 G.B. Trudeau
www.doonesbury.com

MDR-TB: New Agents

Mechanism of action	Agent	MIC_{90} µg/mL	Clinical Phase	Availability?
Mycolic acid synthesis inhibitor	Delamanid	0.024	3	2018
Protein-lipid inhibitor	PA-824	< 1	2	2020
Disrupts cell wall assembly	SQ109	< 1	2	2020
Mycobacterial cell wall target	SQ609	≤ 4	Pre-clinical	>2025
Oxazolidinones	Sutezolid	0.125	2a	2020
	Posizolid	1	2	2020
ATP synthase inhibitor	Bedaquiline	≤ 0.063	3	2016

Summary

- The development pipeline for new antimicrobials is emerging out of period of stagnation
- Agents from older antibiotic classes predominate in current development for DTOs
- New agents with novel mechanisms of action are entering clinical development and appear promising
- Development of new antimicrobials are part of a multi-pronged approach to dealing with DTOs



"It's a prescription for one of those new super-antibiotics. You won't just get better, you'll get even."