抗生物質が効かない薬剤耐性菌は”脅威”　アジア12ヵ国が共同声明

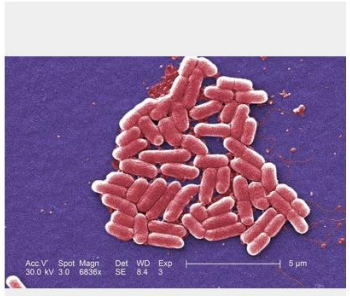
エコノミックニュース 5月8日(日)20時48分配信

薬剤耐性菌により薬が効かず、肺炎球菌などが報告され、既に世界で少なくとも70万人が死亡したとの試算が出ている。この薬剤耐性菌について、中国、韓国、フィリピン、オーストラリアなどのアジア太平洋地域の保健担当の官僚らと対策を話し合うとし、東京都内で会議が開かれた。

Search a new antibiotic kills pathogens without detectable resistance

あらゆる抗生物質が効かない「スーパー耐性菌」、米国で初の感染例

ロイター 5月27日(金)14時34分配信

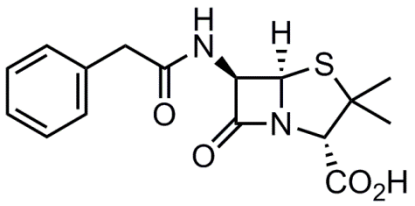


［２６日　ロイター］ - 米疾病管理予防センター（ＣＤＣＰ）は２６日、知られている抗生物質すべてに耐性を示す細菌への国内初の感染症例を報告し、この「スーパー耐性菌」が広がれば、深刻な危険をもたらしかねないと重大な懸念を示した。

D1　Yuri Takada

May 30, 2016

Battle of resistant bacteria

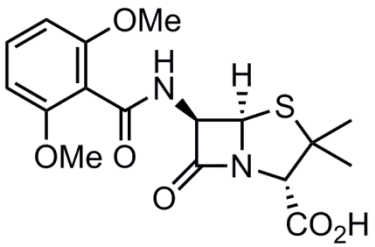


Penicillin

Emergence of resistant bacteria

modification

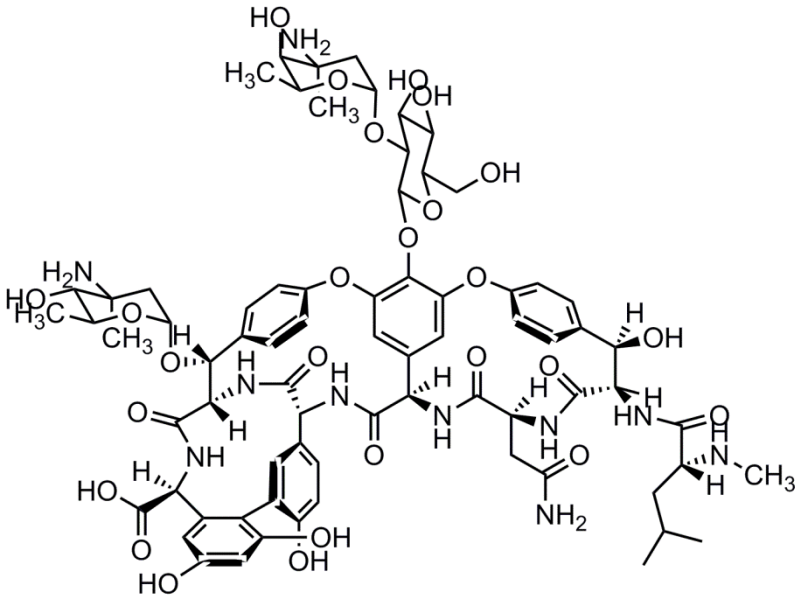
More potent antibiotic



methicillin

methicillin-resistant Staphylococcus aureus (MRSA)

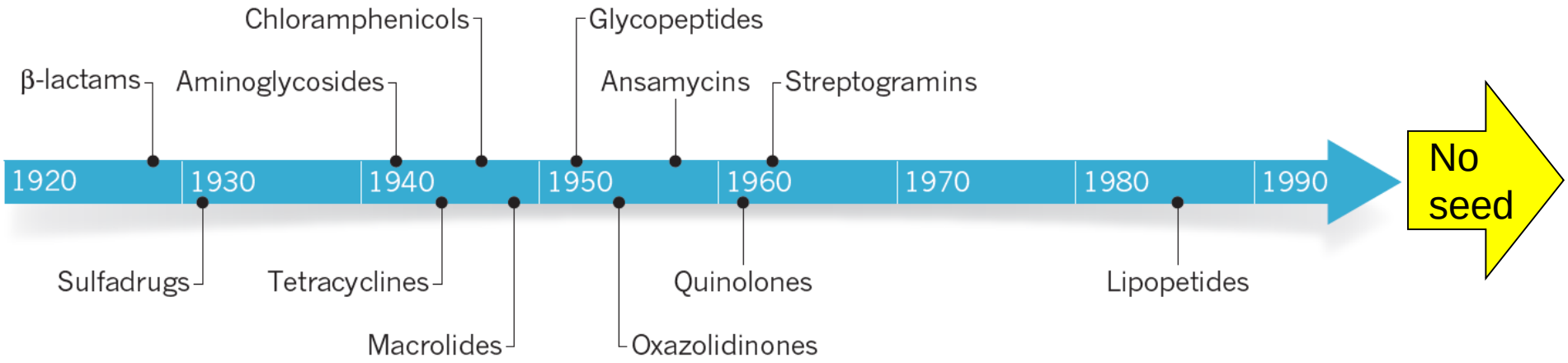
More potent antibiotic



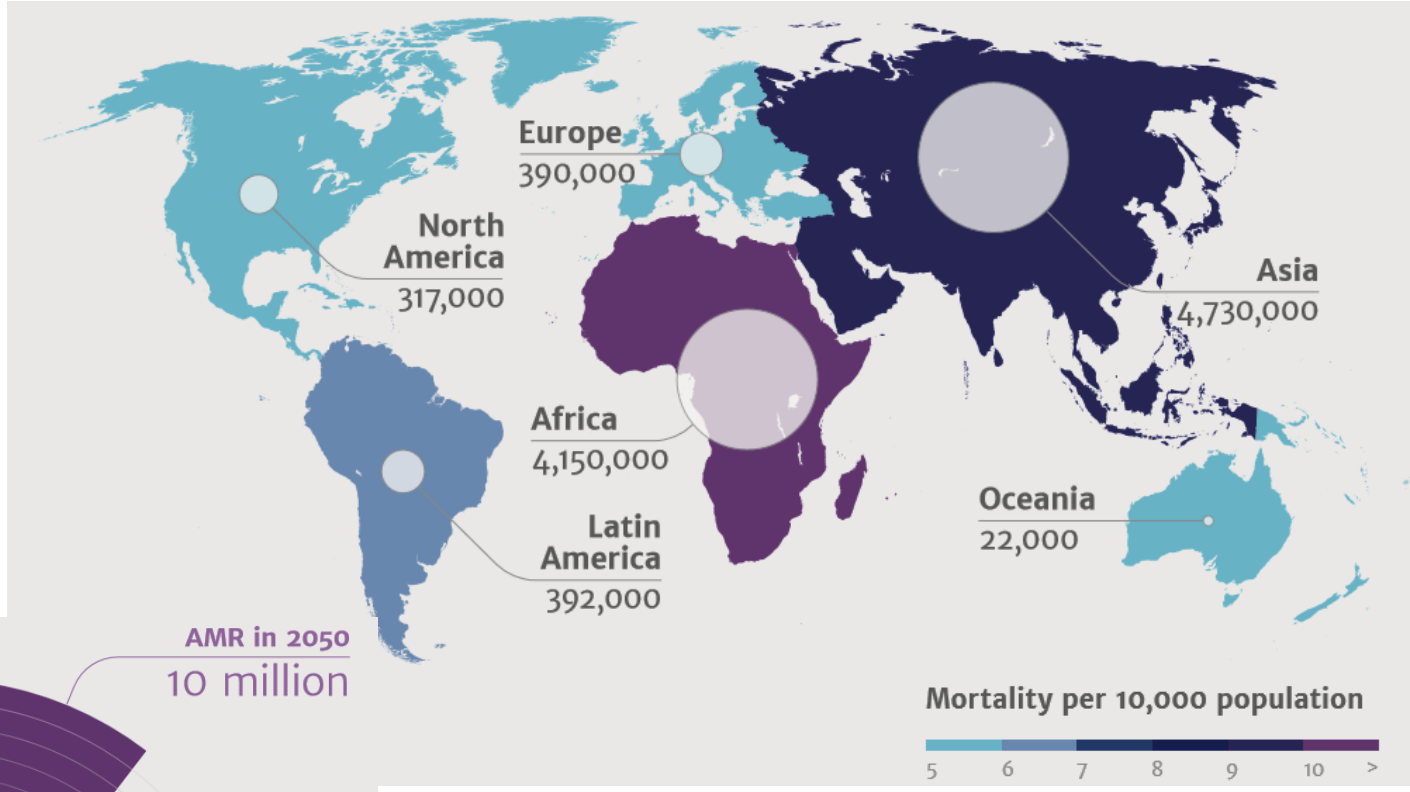
Vancomycin

vancomycin-resistant enterococci (VRE)

1. Lewis, K. *Nature* **2012**, 485 , 439.


Chloramphenicols
Glycopeptides
β-lactams
Aminoglycosides
Ansamycins
Streptogramins
1920
1930
1940
1950
1960
1970
1980
1990
No seed
Sulfadrugs
Tetracyclines
Quinolones
Lipopetides
Macrolides
Oxazolidinones

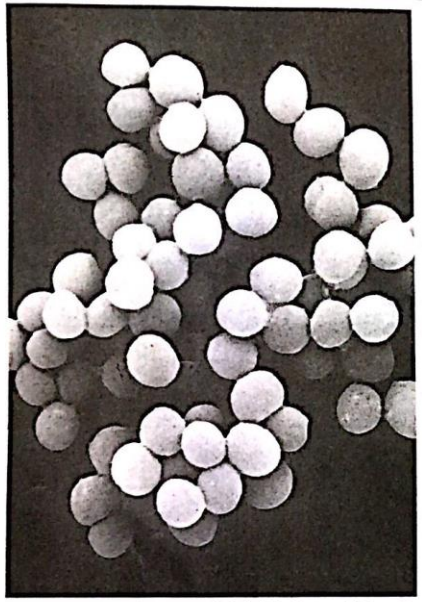
Death attributable to anti microbial resistance



1. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. O'Neill J, chair. December 2014

Death attributable to anti microbial resistance

第44411号　（第三種郵便物認可）　東奥日



メチシリン耐性黄色ブドウ球菌（ＭＲＳＡ）の電子顕微鏡写真（平松啓一順天堂大教授提供）

抗生物質などの薬が効かない薬剤耐性菌が世界で急速に拡大している。2050年には年間１千万人が耐性菌によって死亡するとの予測もある。抗生物質の使いすぎなどが背景にあるとされ、事態を重く見た世界保健機関（ＷＨＯ）は対策を強化。専門家は危機に対応する国際的な枠組みづくりを呼び掛けている。

薬効かない菌 世界拡大

2050年に死者１千万人予測も

2050年の耐性菌による死者数予測（年間）

※耐性菌に関する英調査チーム報告書による

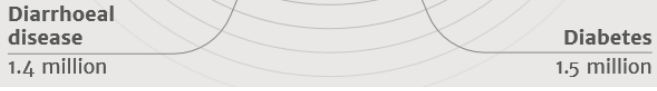
キャメロン英首相が立ち上げた耐性菌に関する調査チームは昨年12月に初の報告書を公表。効果的な措置を講じなければ、耐性菌による年間死者数は50年に現在の70万人（推定）の14倍以上に当たる1千万人になると予測した。地域別ではアジアが４７３万人で最も多く、アフリカ４１５万人、欧州39万人など。耐性菌拡大に伴う医療費負担増大も懸念されている。

報告書は「効果的な抗生物質がなくなれば、手術の際に感染症の危険が大きく高まる」と指摘。「世界各国、特に（中国やインドなど）新興国にとって保健、経済上の深刻な結果をもたらす恐れがある」と警告した。

ＷＨＯも昨年４月の報告書で耐性菌の拡大に警鐘を鳴らした。同５月の総会では各国に早急な対策を促す決議を採択。今年５月の総会では耐性菌対策に関する行動計画策定に向けた議論が行われる。

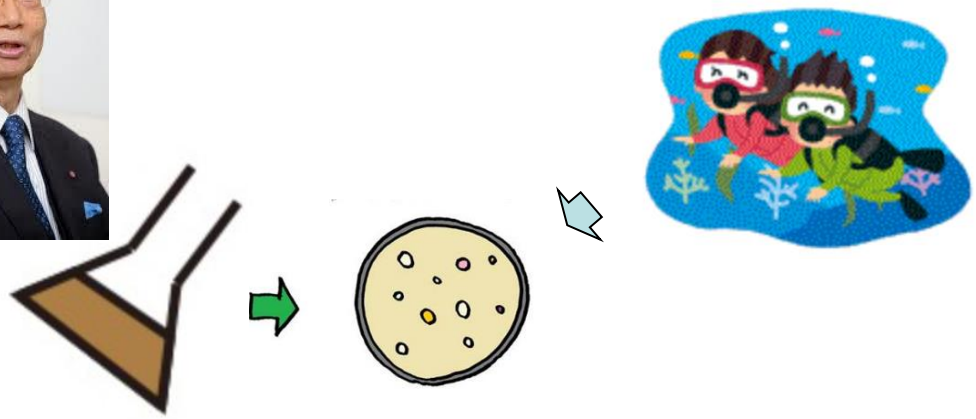
米国や英国、スウェーデンなどの専門家グループは２月、ＷＨＯ機関誌に論説を発表、耐性菌対策のための法的拘束力のある国際的枠組みづくりを訴えた。

耐性菌をめぐっては医療現場でメチシリン耐性黄色ブドウ球菌（ＭＲＳＡ）や、ほとんどの治療薬が効かない多剤耐性緑膿菌（りょくのうきん）などが特に問題になっている。ＷＨＯは抗生物質の処方を最小限に抑えるよう医療従事者に勧告。一般患者には医師が処方した時のみ抗生物質を使うよう呼び掛けている。（ジュネーブ共同）



1. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. O’Neill J, chair. December 2014

Search a new antibiotic

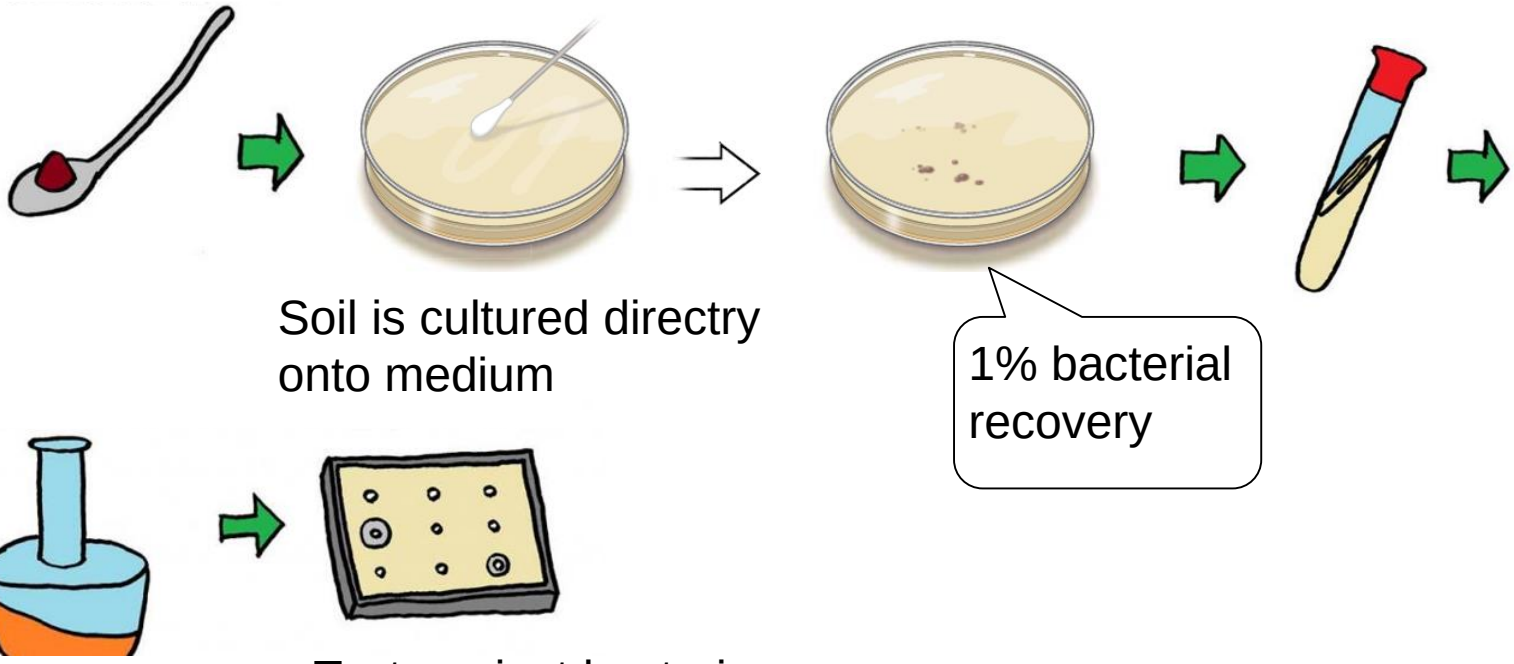


- Isolation (soil, seawater, sponge)
- Synthetic modification

“Expansion of antibiotic seeds”

Methods of culturing microorganisms from soil

Traditional Antibiotic Search

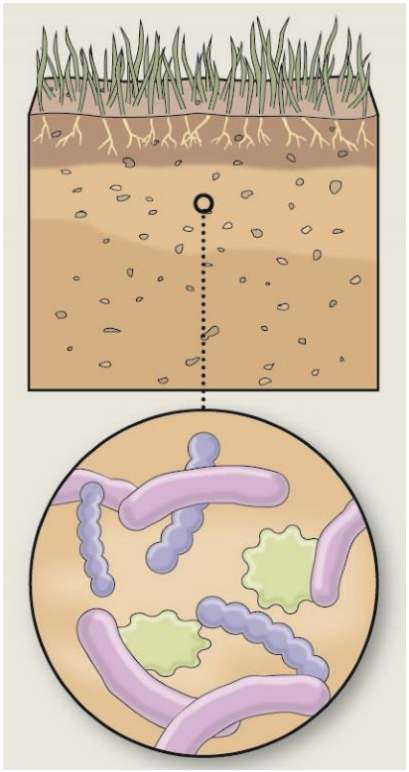


"Expansion of antibiotic seeds from soil"

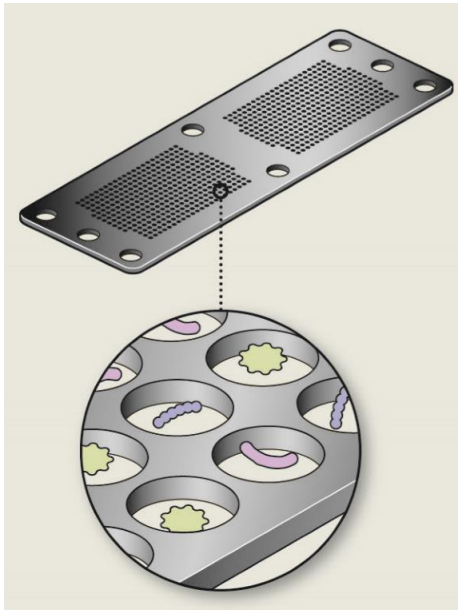
1. Lewis, K. *Nature* **2012**, 485 , 439.

New method “iChip”

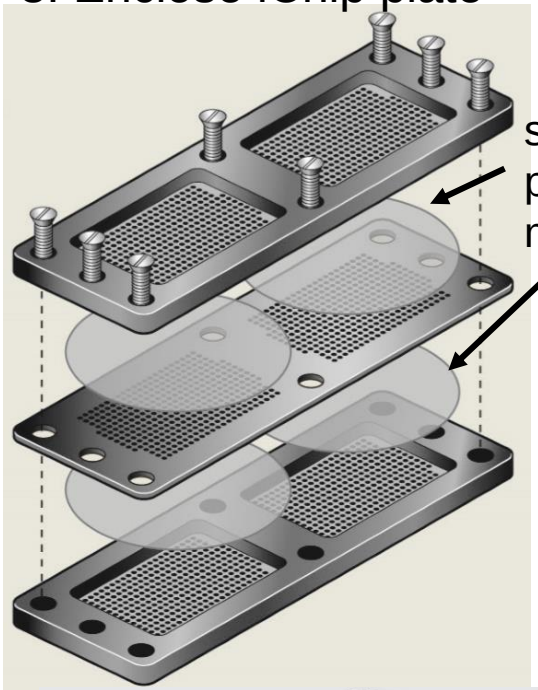
1. Collect sample



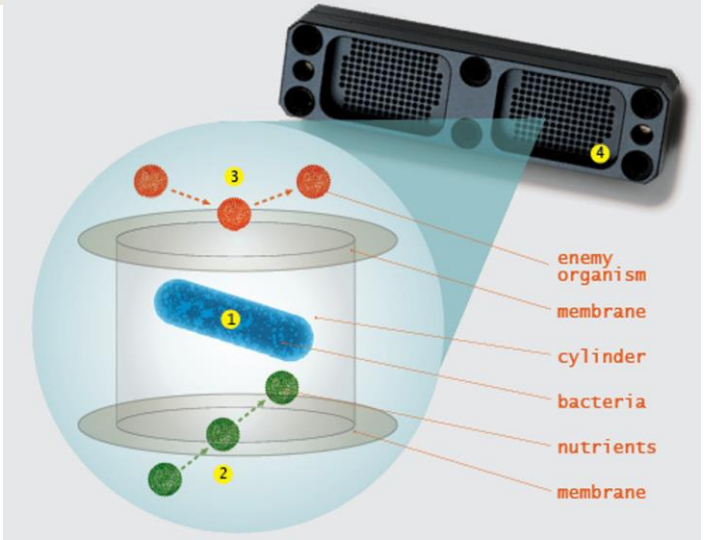
2. Place iChip plate
one bacterium per well



3. Enclose iChip plate



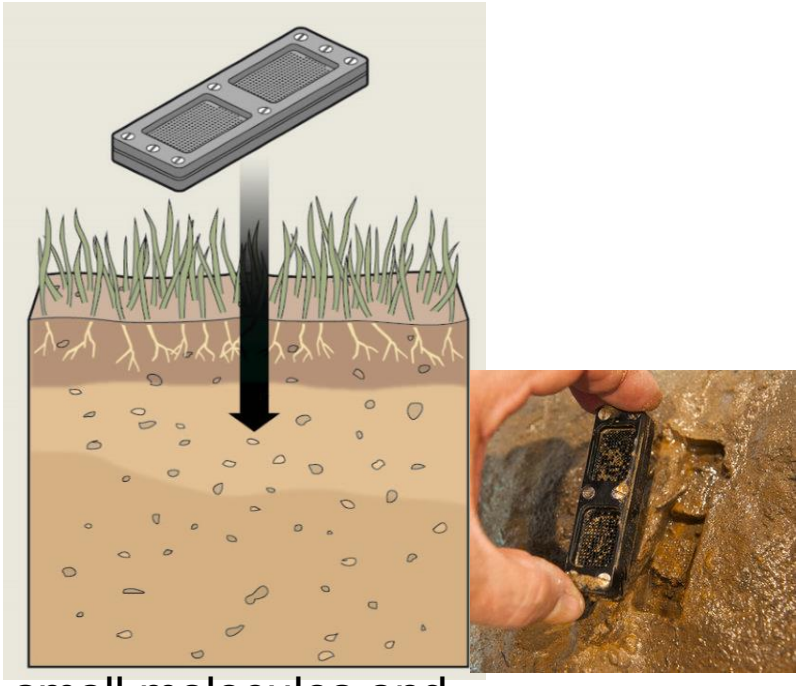
breathable membrane that
allows for bacterial communication



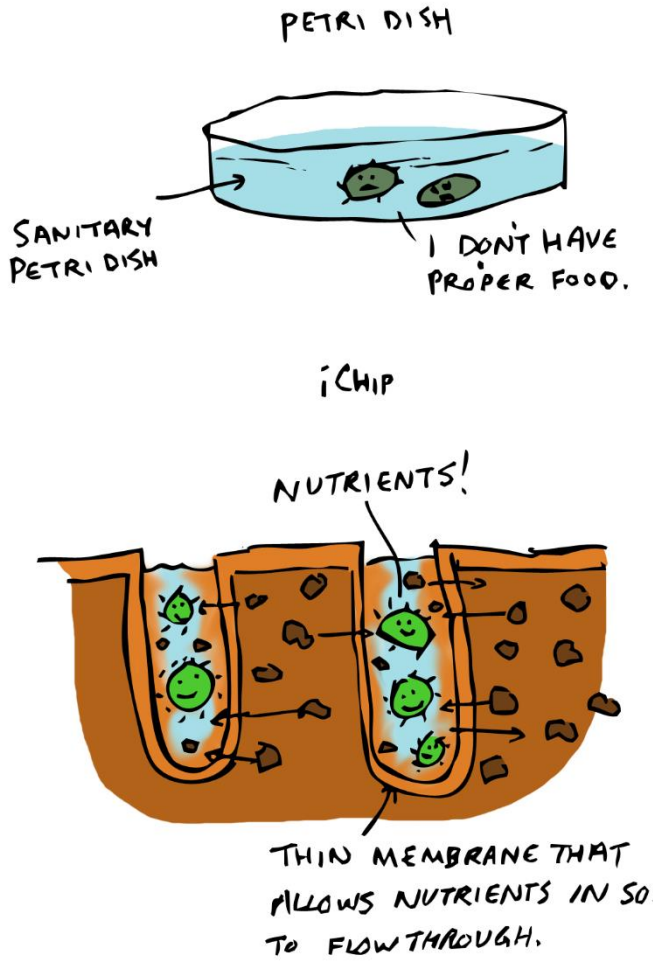
1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.
2. Nichols, D. et al. *Appl. Environ. Microbiol.* **2010**, *76*, 2445.

New method “iChip”

4. Place iChip device back into the environment sample



small molecules and metabolities can promote bacterial growth

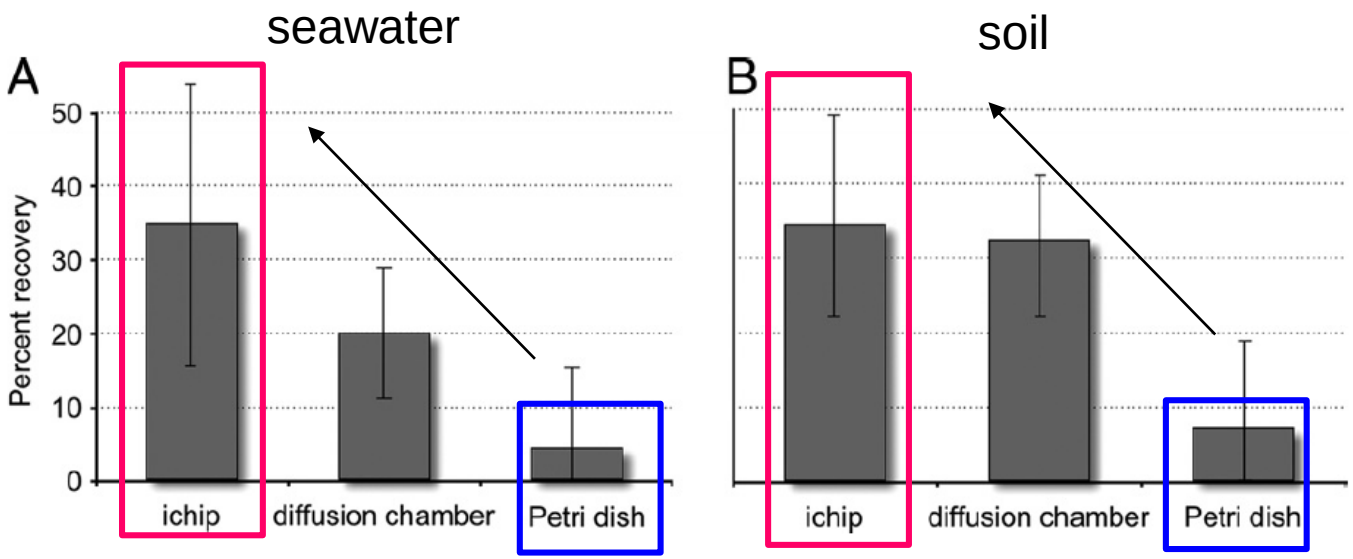


Diffusion of nutrients and growth factors through the chambers

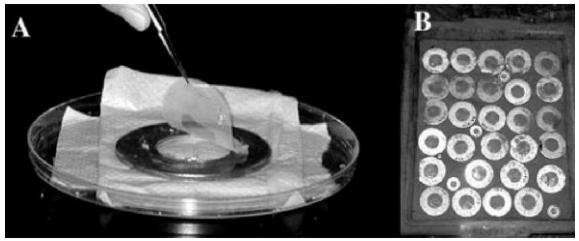
→ growth of uncultured bacteria in their natural environment

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.
2. Nichols, D. et al. *Appl. Environ. Microbiol.* **2010**, *76*, 2445.

High microbial recovery of “iChip”



The growth recovery by “iChip” method

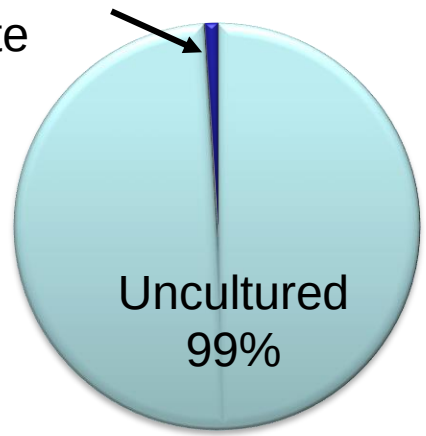


diffusion chamber

approach 50% of cells from soil that will grow on a nutrient Petri dish

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.
2. Nichols, D. et al. *Appl. Environ. Microbiol.* **2010**, *76*, 2445.

Isolation of “Teixobactin”

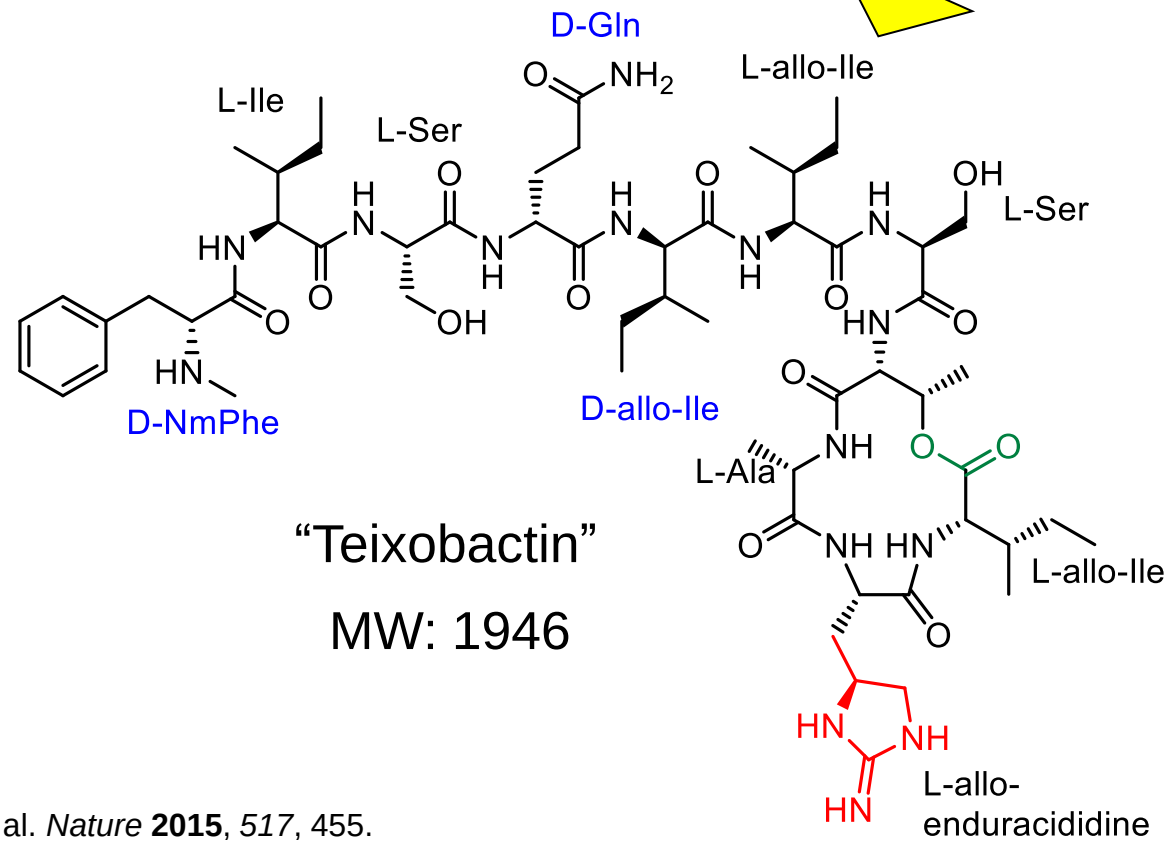


“iChip”

screening

10000 kinds of bacterial strains

New 25 compounds



“Teixobactin”

MW: 1946

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Activity against pathogenic microorganisms

Table 1

Organism and genotype	Teixobactin MIC ($\mu g\ ml^{-1}$)
S. aureus (MSSA)	0.25
S. aureus + 10% serum	0.25
S. aureus (MRSA)	0.25
Enterococcus faecalis (VRE)	0.5
Enterococcus faecium (VRE)	0.5
Streptococcus pneumoniae (penicillin^R)	≤0.03
Streptococcus pyogenes	0.06
Streptococcus agalactiae	0.12
Viridans group streptococci	0.12
B. anthracis	≤0.06
Clostridium difficile	0.005
Propionibacterium acnes	0.08
M. tuberculosis H37Rv	0.125
Haemophilus influenzae	4
Moraxella catarrhalis	2
Escherichia coli	25
Escherichia coli (*asmB1*)	2.5
Pseudomonas aeruginosa	>32
Klebsiella pneumoniae	>32

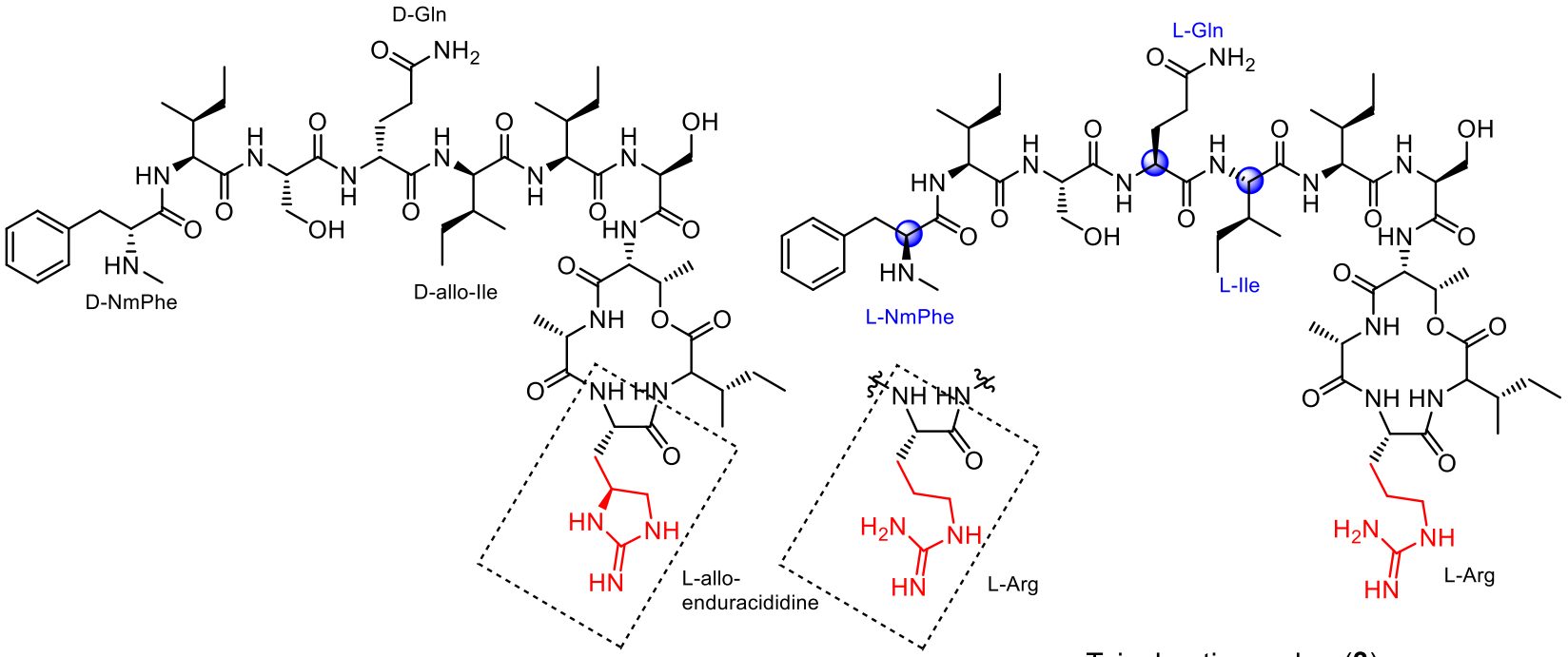
The MIC was determined by broth microdilution. MSSA, methicillin-sensitive *S. aureus*; VRE, vancomycin-resistant enterococci.

- ineffective against Gram-negative bacteria
- good activity against a strain of *E. coli asmB1* with a defective outer membrane permeability barrier

Teixobactin had excellent activity against Gram-positive pathogens including drug-resistant strains

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Structure activity relationship



Teixobactin (TEIX, **1**) Teixobactin analog (**2**) Teixobactin analog (**3**)

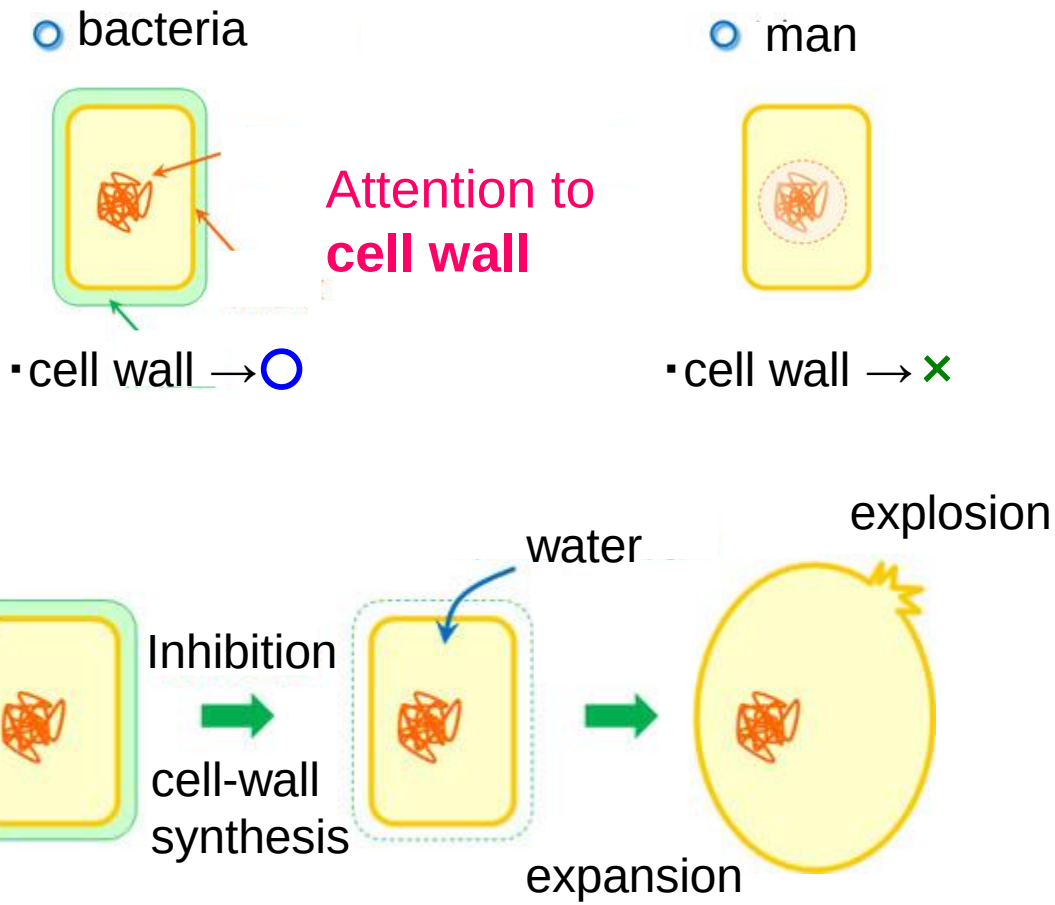
Table MIC (μg ml^{-1}) for Teixobactin (**1**), **2**, and **3**

entry	Organism	Teixobactin (**1**)[a]	**2**	**3**	meropenem
1	*S. aureus* ATCC (25923)	0.25	2	128	2.6
2	*E. coli* ATCC (25922)	25	64	GAW[b]	0.16

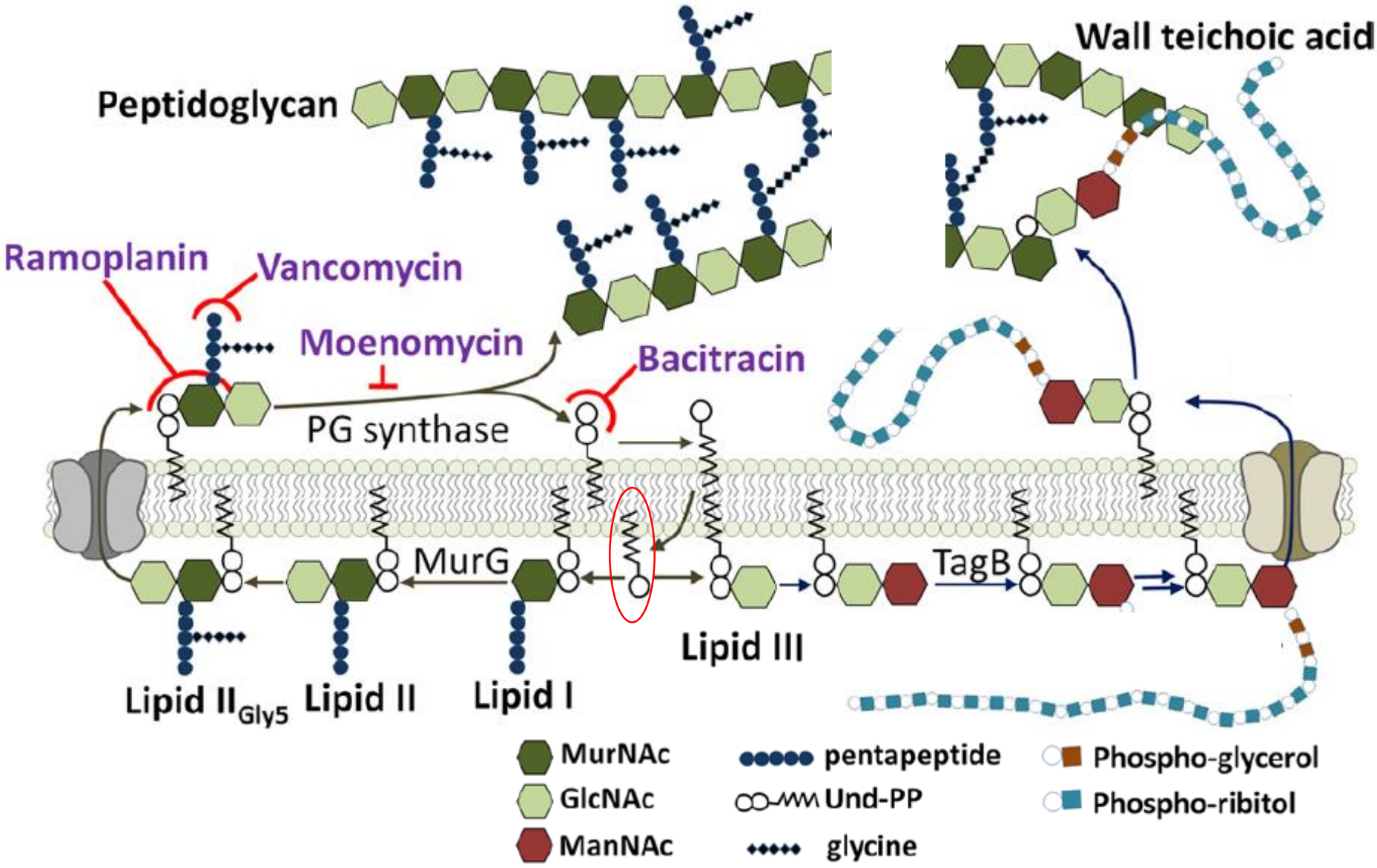
[a] different strain of *S. aureus.* [b] Growth in all wells.

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.
2. Jad, Y. E.; Acosta, G. A.; Naicker, T.; Ramtahal, M.; El-Fahman, A.; Govender, T.; Kruger, H. G.; de la Torre, B. G.; Albericio, F. *Org. Lett*. **2015**, *17*, 6182.
3. Parmar, A.; Iyer, A.; Vincent, C. S.; Lysebetten, D. V.; Prior, S. H.; Madder, A.; Taylor, E. J.; Singh, I. *Chem. Commun*. **2016**, *52*, 6060.

One of targets of antibiotics: Cell wall

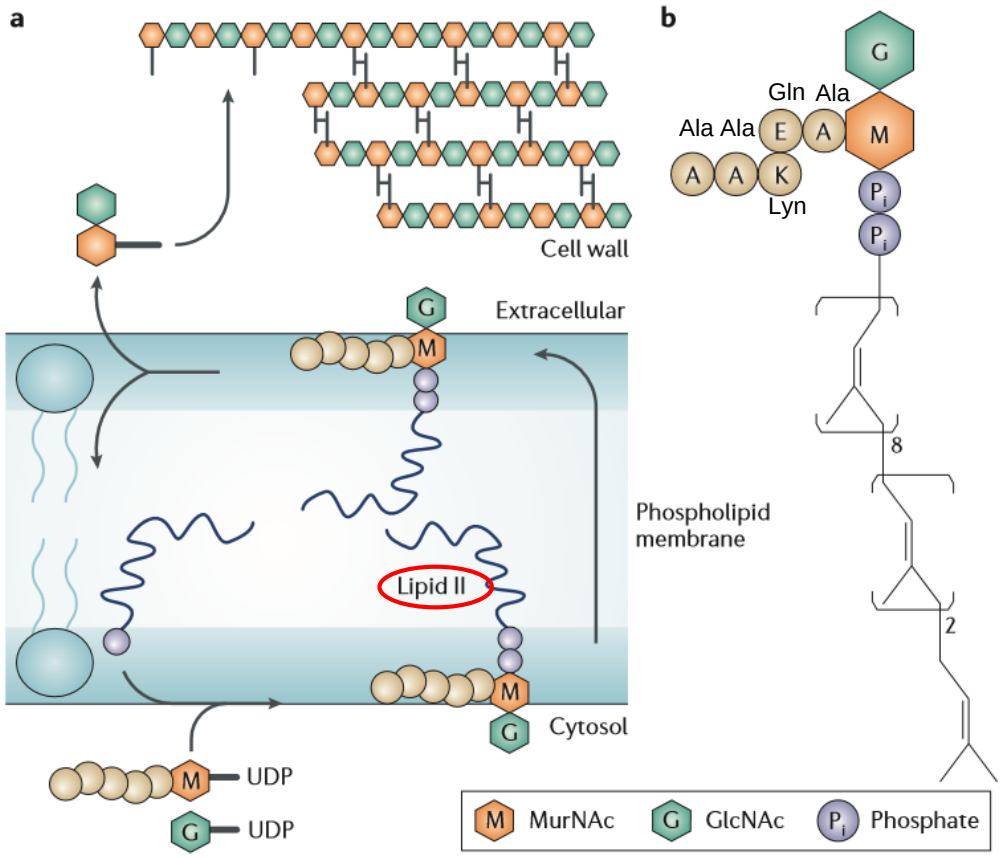


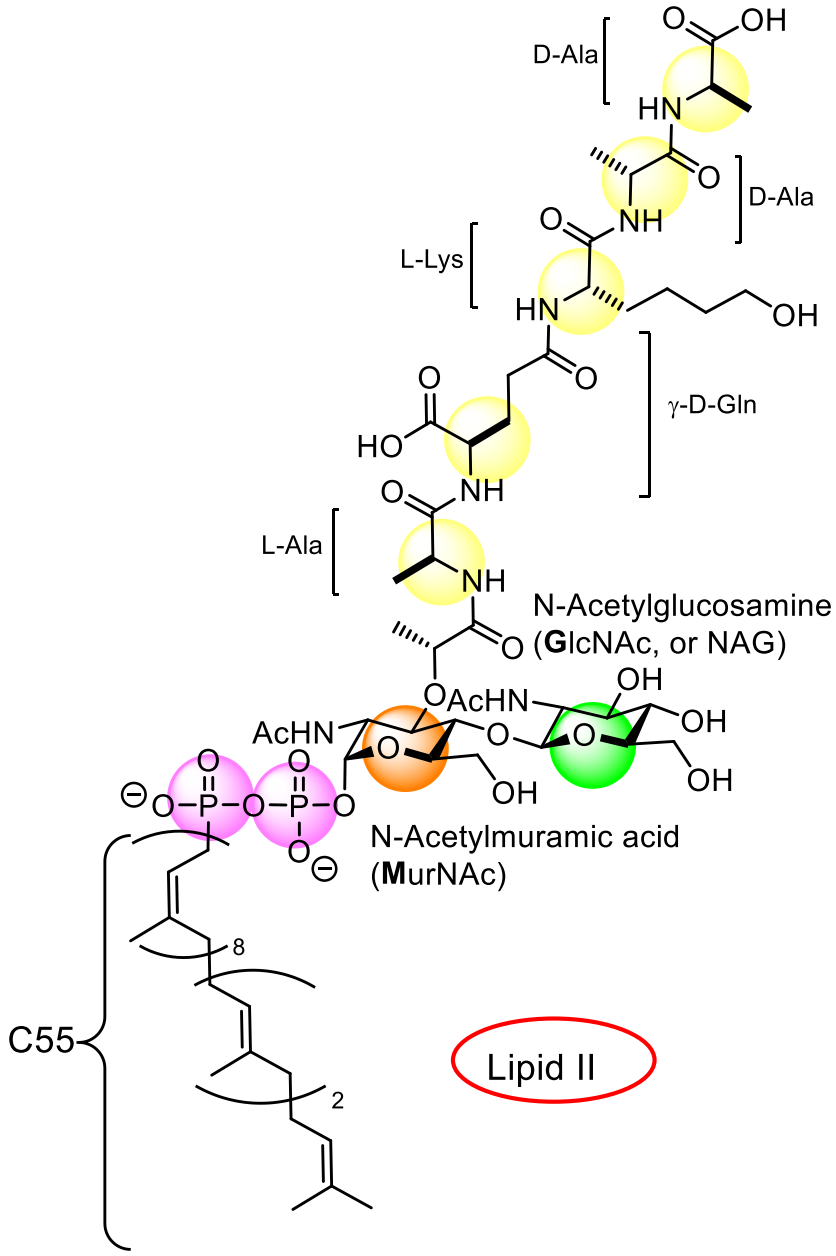
cell-wall synthesis cycle



1. Breukink, E.; Ben, K. D. *Nature Reviews Drug Discovery* **2006**, *5*, 321.

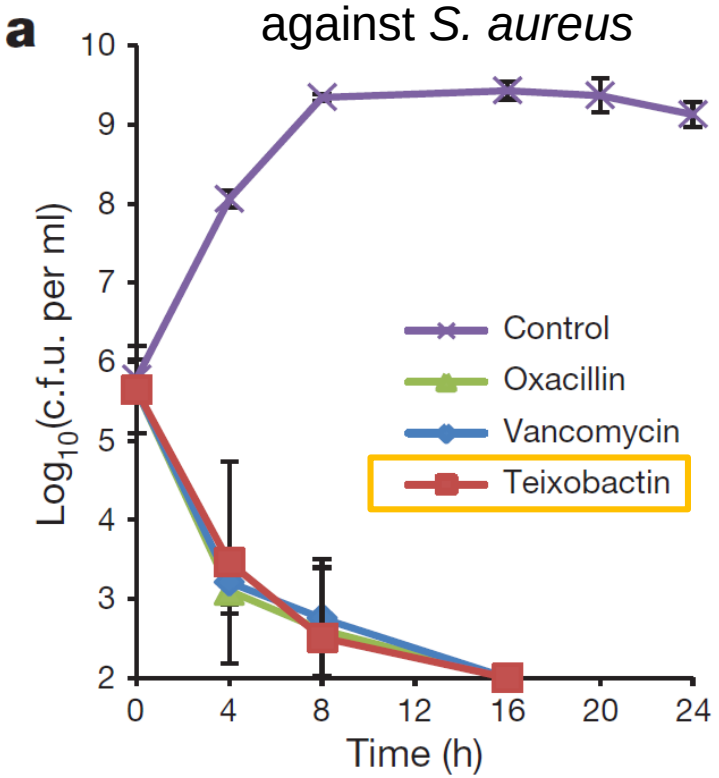
cell-wall synthesis cycle and structure of Lipid II



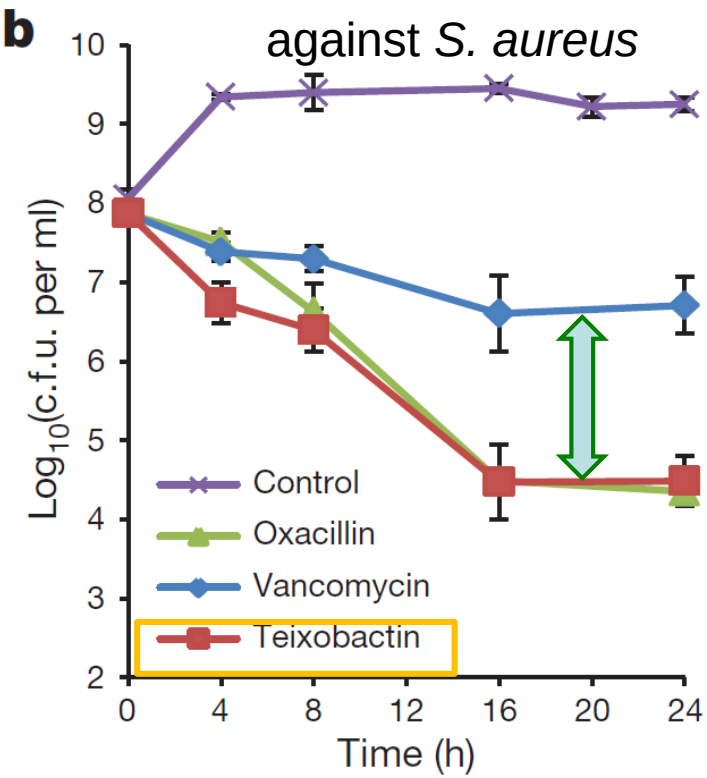


1. Breukink, E.; Ben, K. D. *Nature Reviews Drug Discovery* **2006**, *5*, 321.

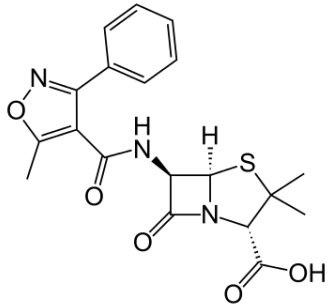
Bacterial activity against *S. aureus*



early exponential phase (2h)

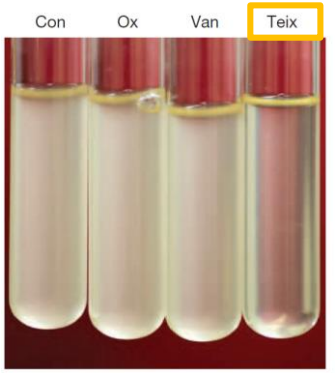


late exponential phase (5h)



Oxacillin

β lactam:
like penicillin

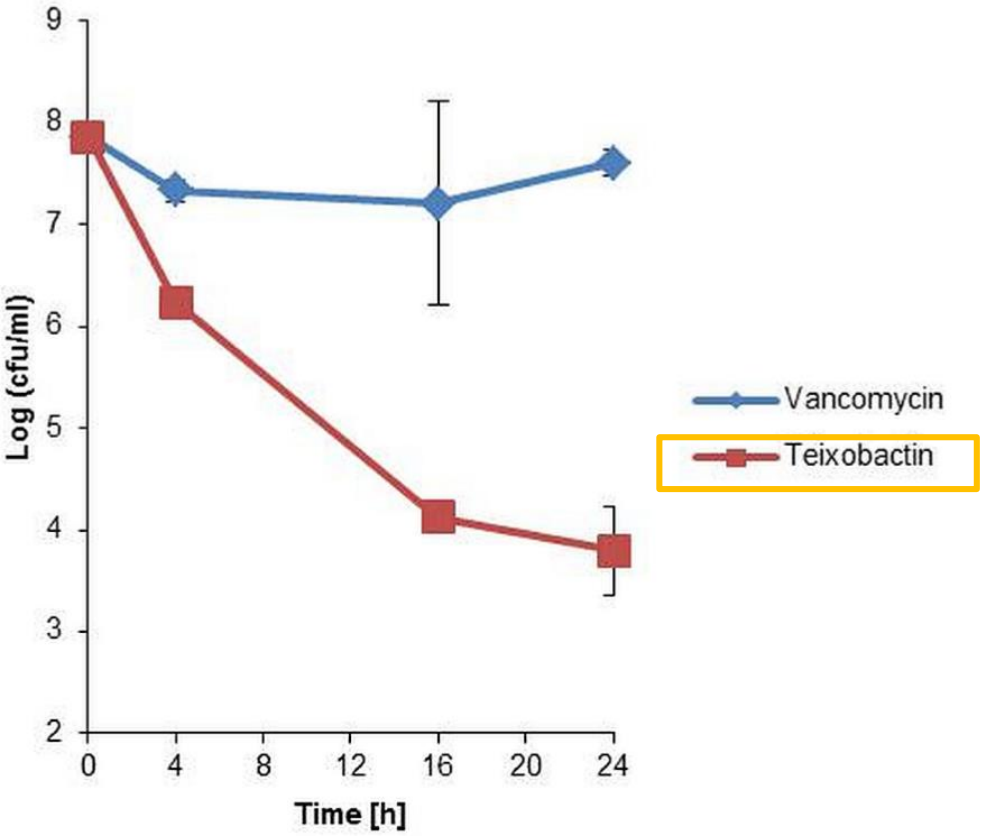


Teixobctin show excellent bacterial activity against *S. aureus*

superior to vancomysin in killing late exponential phase populations

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Bacterial activity against vancomycin-resistant strains

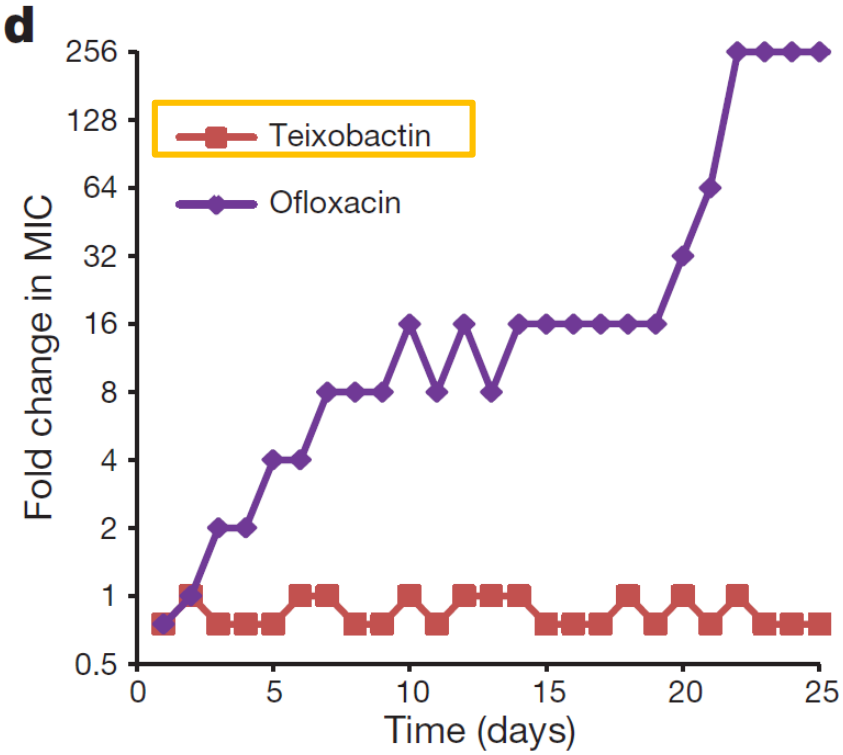


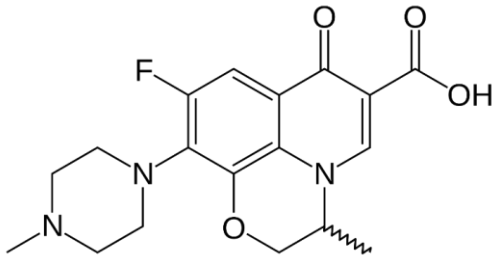
Teixobctin show excellent bacterial activity against vancomycin-intermediate resistance *S. aureus* (VISA)

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

No resistance acquisition

serial passaging in the presence of sub-MIC levels of antimicrobials





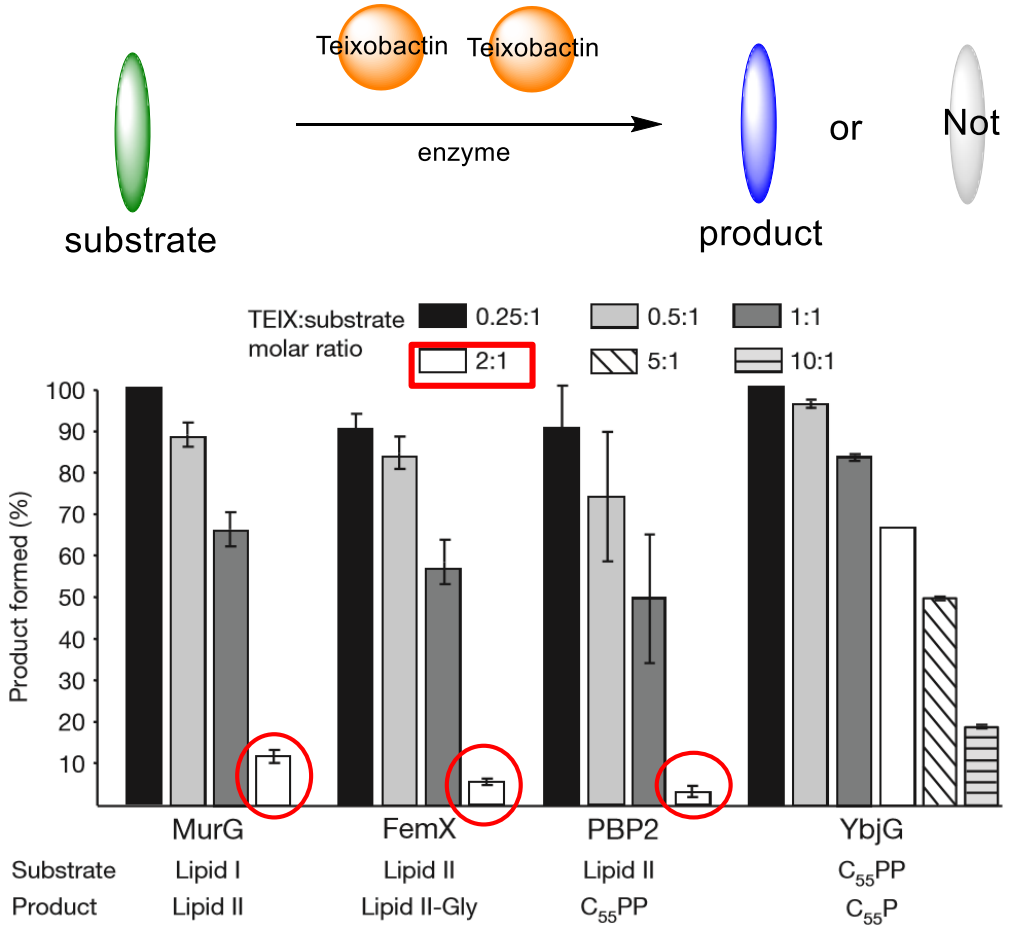
Ofloxacin

Inhibition of DNA synthesis

- Not mutants of *S. aureus* or *M. tuberculosis* resistant even when plating on media with a low dose
- Serial passage of *S. aureus* in the presence of sub-MIC levels of teixobactin over a period of 27 days failed to produce resistant mutants

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

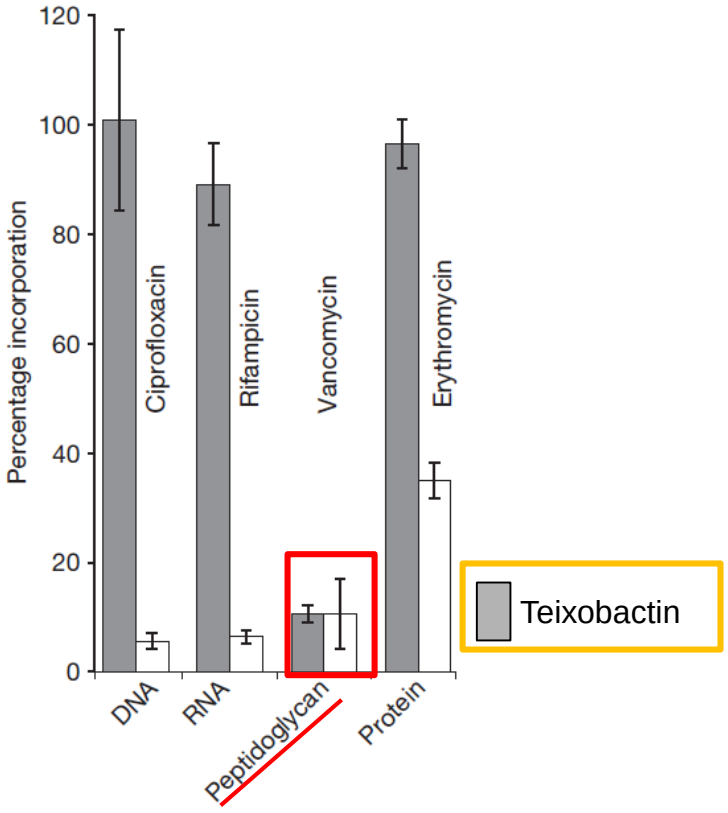
Teixobactin binds to cell wall precursors



An almost complete inhibition at a twofold molar excess of teixobactin with respect to the lipid substrate Lipid I, Lipid II

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Teixobactin inhibit to synthesis cell wall

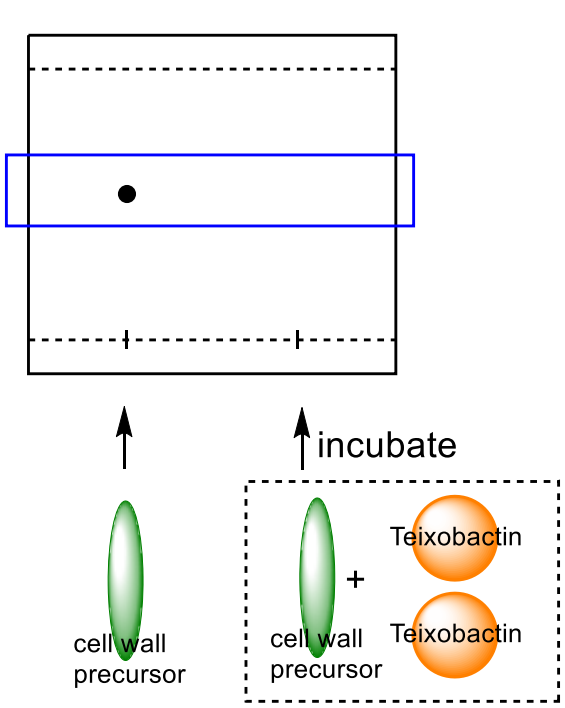


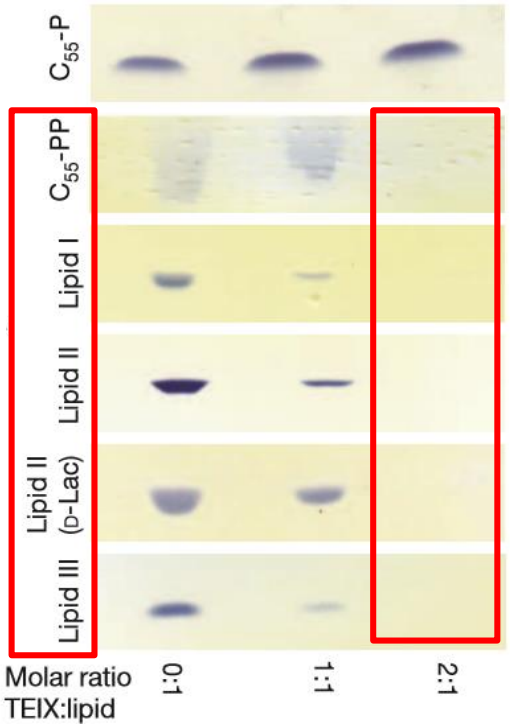
Teixobactin strongly inhibited synthesis of peptidoglycan, but had virtually no effect on label incorporation into DNA, RNA and protein

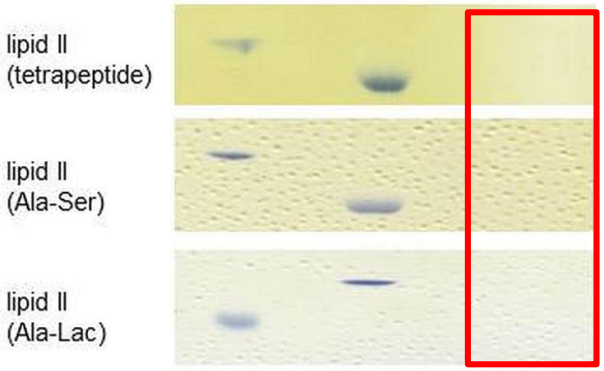
Teixobactin is a new peptidoglycan synthesis inhibitor?

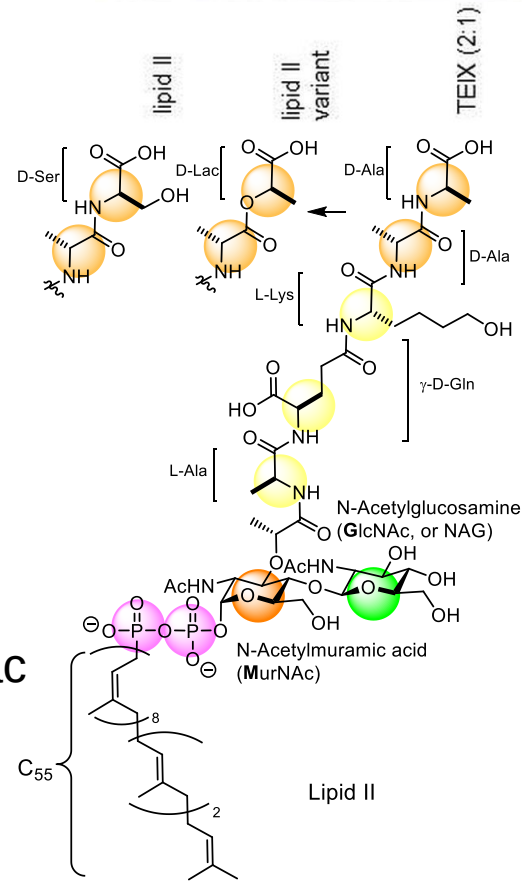
1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Teixobactin binds to cell wall precursors





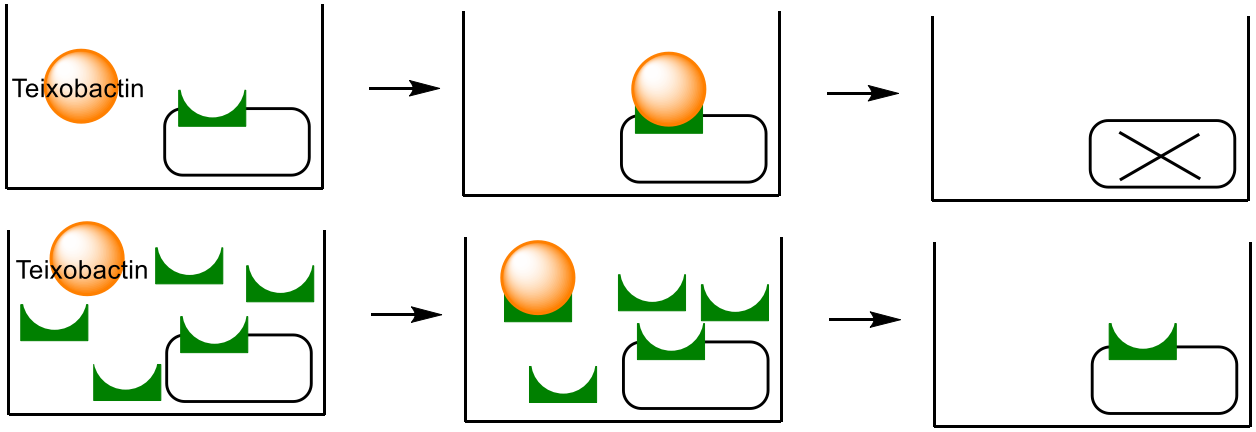




- Teixobactin leads to the formation of a 2:1 stoichiometric complex
- Teixobactin was active against vancomycin-resistant *enterococci* that have modified lipid II (lipid II-D-Ala-D-Lac or lipid II-DAla-D-Ser instead of lipid II-D-Ala-D-Ala)

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Antagonization of the antimicrobial activity by cell wall precursors



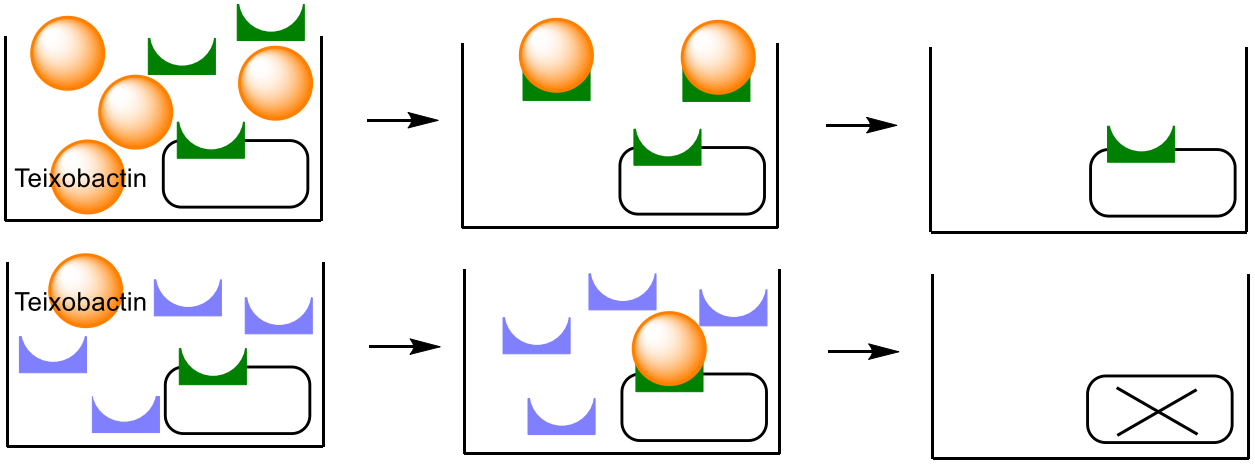
antagonist	C_{55}-P	C_{55}-PP	C_{15}-PP	lipid I	lipid II	lipid III	UDP-MurNAc-pentapeptide	UDP-GlcNAc
teixobactin	-	+	+	+	+	+	-	-
vancomycin	-	-	nd	+	+	-	nd	nd

(+) antibiotic activity antagonized, (-) antibiotic activity unaffected, (nd) not determined

- The addition of peptidoglycan precursor prevented teixobactin from inhibiting growth of *S. aureus*
- Teixobactin specifically interacts with the peptidoglycan precursor, rather than interfering with the activity of one of the enzymes

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Antagonization of the antimicrobial activity of teixobactin by cell wall precursors



lipid intermediate	molar ratio of precursor to teixobactin						
	0 x	0.5 x	1 x	2.5 x	5 x	7.5 x	10 x
lipid II	-	+	+	+	+	+	+
C_{55}-PP	-	-	-	-	+	+	+

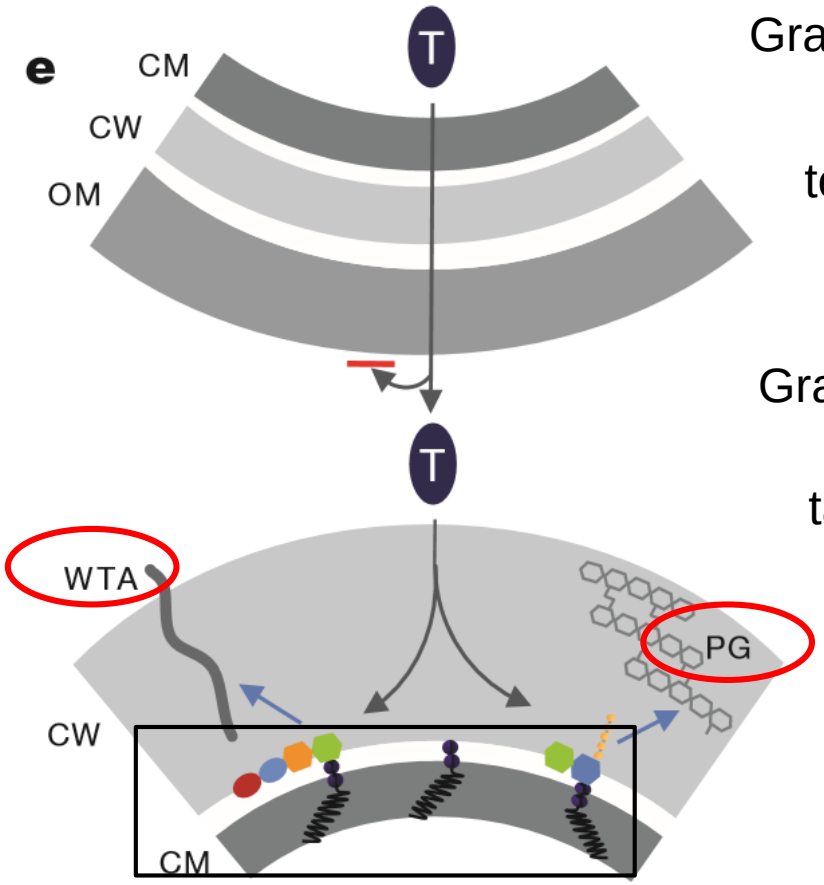
(+) antibiotic activity antagonized, (-) antibiotic activity unaffected,

The addition of purified lipid II prevented teixobactin from inhibiting growth of *S. aureus*

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

A model of teixobactin targeting and resistance

Gram-negative bacterium



Gram-positive bacterium

Gram-negative bacterium (have outer membrane)

⇩

teixobactin

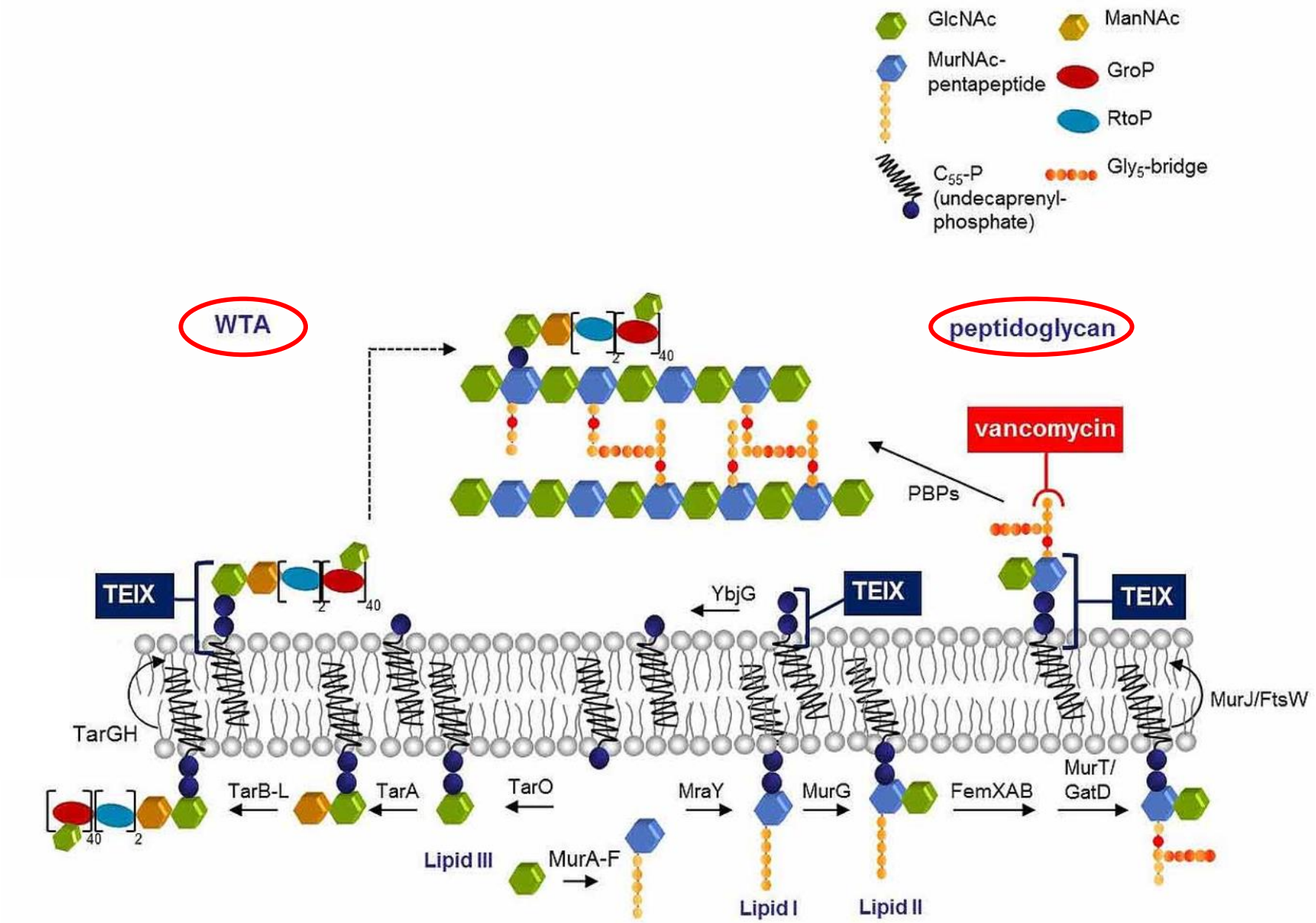
Gram-positive organisms (lack of outer membrane)

targets ⇨
- precursors of peptidoglycan (PG)
- wall teichoic acid (WTA)

CM; cytoplasmic membrane
CW; cell wall
OM; outer membrane
T; teixobactin.

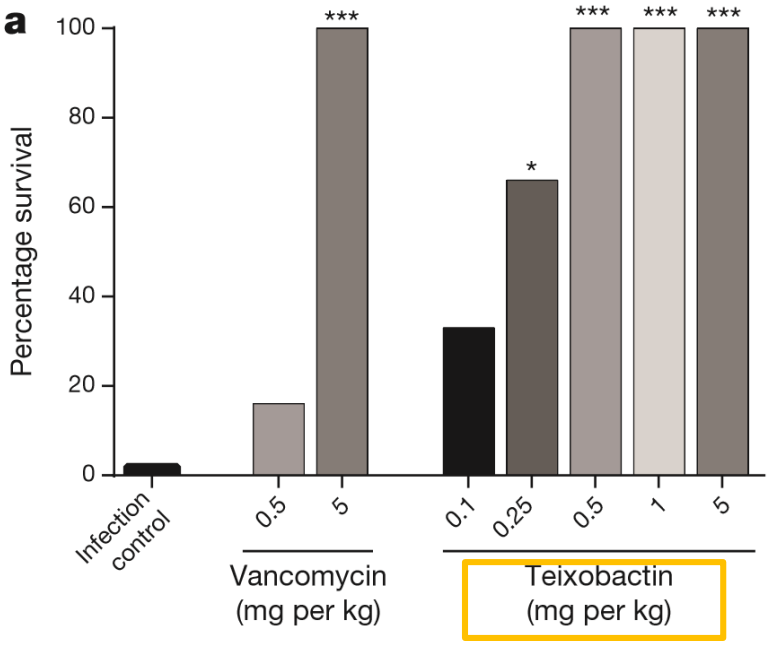
1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Model for the mechanism of action of teixobactin



1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

In vivo efficacy in mouse models of infection

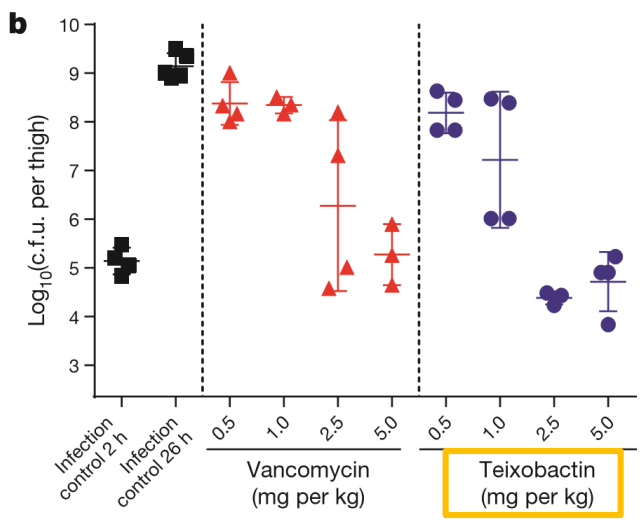


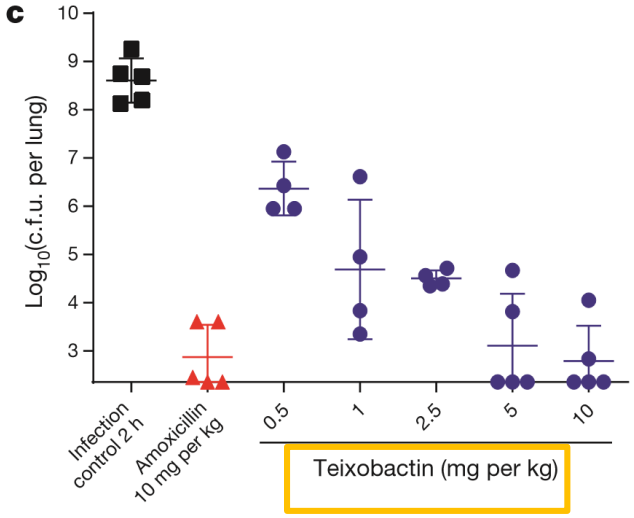
- Single dose treatment with teixobactin and vancomycin in septicemia protection model using MRSA
- Survival is depicted 48 h after infection

PD_{50} (protective dose atwhichhalf oftheanimals survive)
Teixobactin: 0.2mg per kg
Vancomycin: 2.75mg per kg

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

In vivo efficacy in mouse models of infection





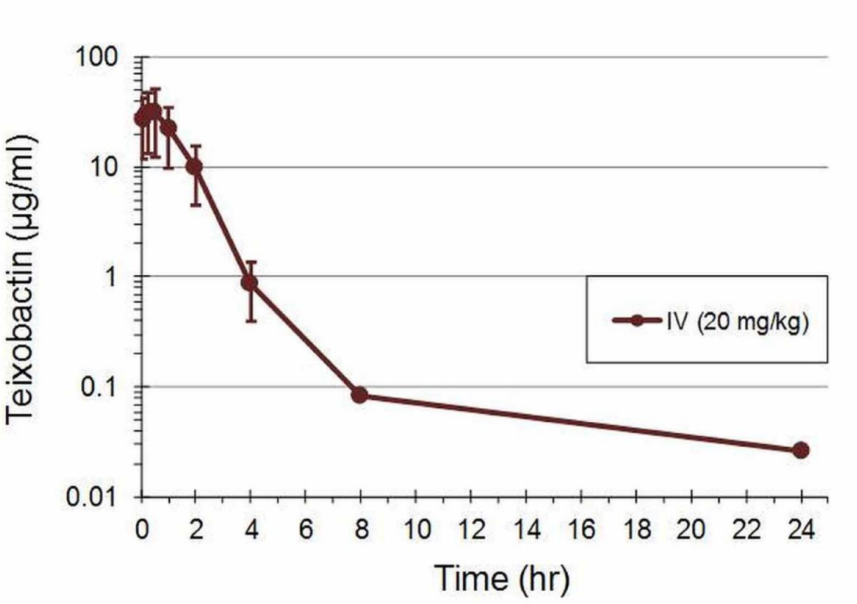
- Single dose treatment with teixobactin and vancomycin in neutropenic mouse thigh infection model using MRSA ATCC33591
- Colony forming units (c.f.u.) are determined after 26h

- Two dose treatment with teixobactin (i.v., 24h and 36h post-infection) and single dose treatment with amoxicillin (subcutaneous, 24h post-infection) in immunocompetent lung infection model using *S. pneumoniae* ATCC6301 for mice
- c.f.u. are determined at 48h post infection

Teixobactin showed good efficacy to MRSA

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Pharmacokinetic analysis of teixobactin

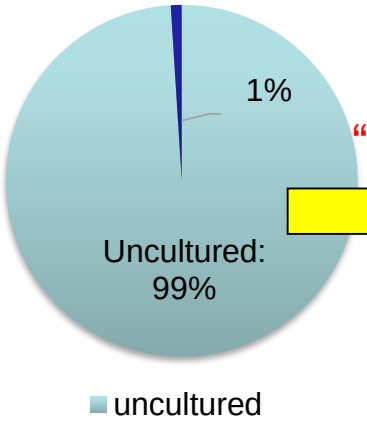


- after i.v. injection of 20mg per kg dose teixobactin in mice

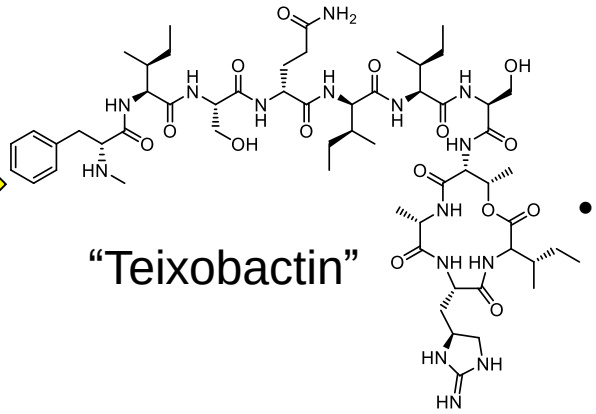
The teixobactin level is kept above the MIC for 4 h

1. Ling, L. L.; Schneider, T.; Lewis, K. et al. *Nature* **2015**, *517*, 455.

Summary



“iChip”



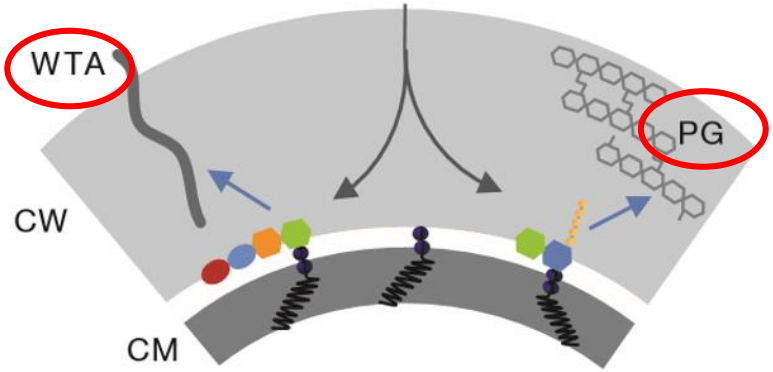
“Teixobactin”

- Inhibits cell wall synthesis by binding Lipid II and Lipid III

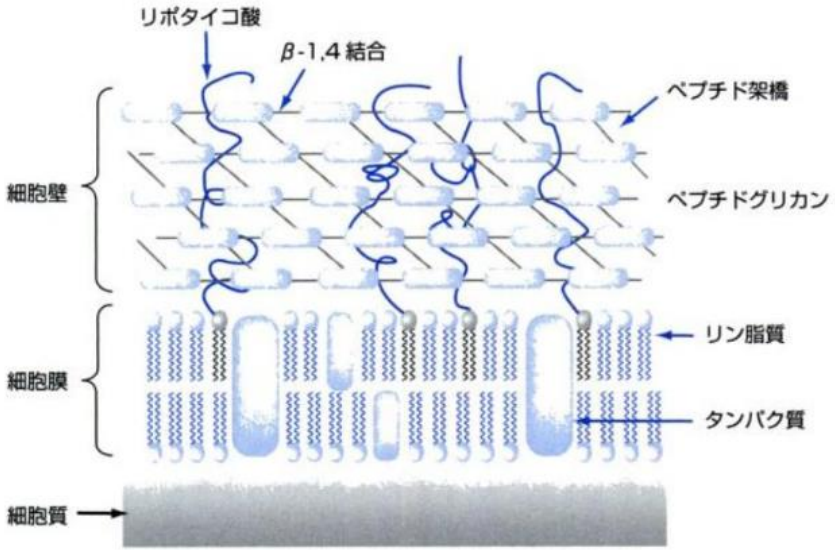
  “multiple sites of action”

- No resistant bacteria against *Staphylococcus aureus* or *Mycobacterium tuberculosis*

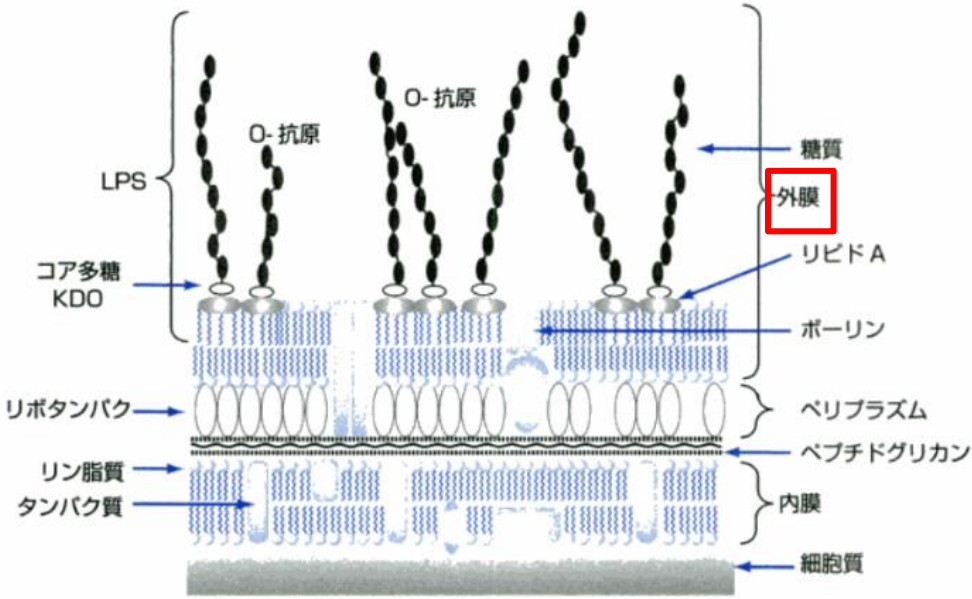
“Teixobactin”



New antibiotics that are likely to avoid development of resistance



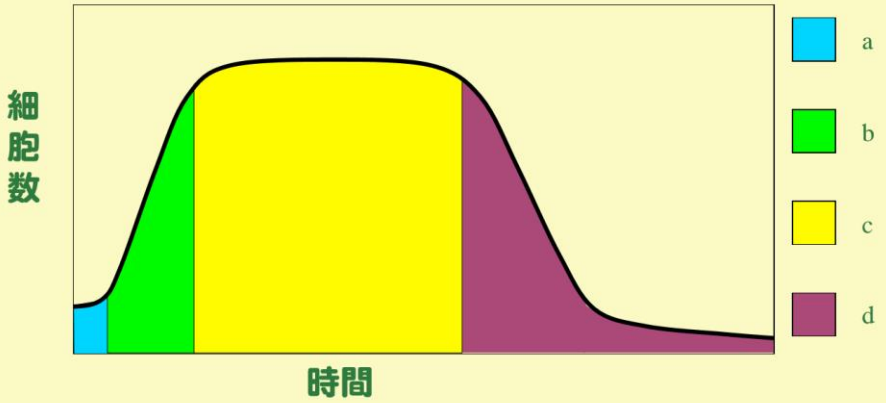
Gram positive



Gram negative

細胞の個体数の典型的な増殖曲線

微生物の増殖（増殖曲線）



a Lag phase　遅延期（誘導期）
b Log phase (exponential phase)　対数期（対数増殖期）
c Stationary phase　定常期
d Mortality phase　死滅期