# NEW ANTIBACTERIAL DRUGS

## Drug pipeline for Gram-positive bacteria

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НАУЧНО-ИССЛЕДОВАТЕЛЬСКИЙ ИНСТИТУТ
ПО ИЗЫСКАНИЮ НОВЫХ АНТИБИОТИКОВ
ИМЕНИ Г. Ф. ГАУЗЕ
РАМН

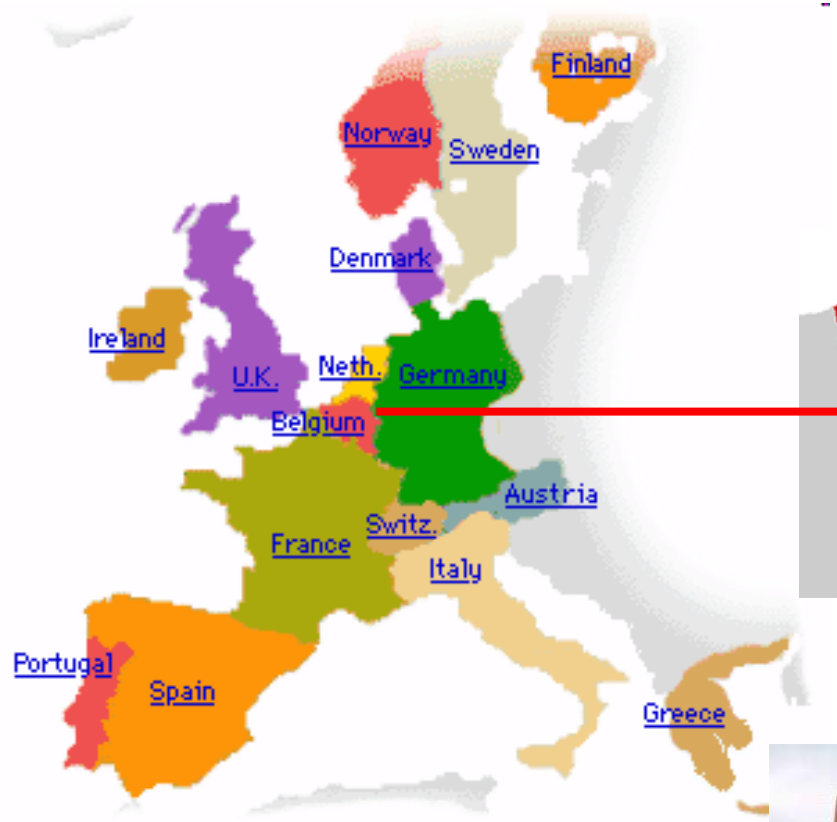
Based largely on presentations given at the 24th and 25th European Congress of Clinical Microbiology and Infectious Diseases and the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy

# Disclosures

Research grants for work on investigational compounds discussed in this presentation from

- Cempra Pharmaceuticals
- Cerexa
- GSK
- Melinta therapeutics
- The Medicine Company
- MerLion Pharmaceuticals
- Theravance
- Trius

# Belgium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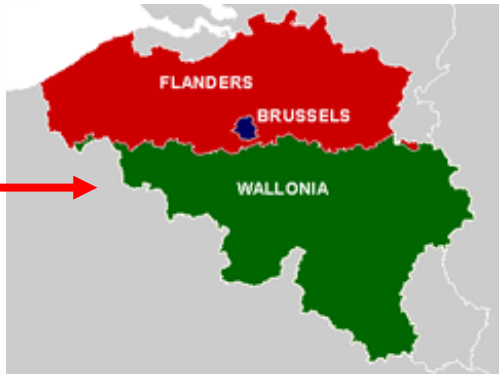
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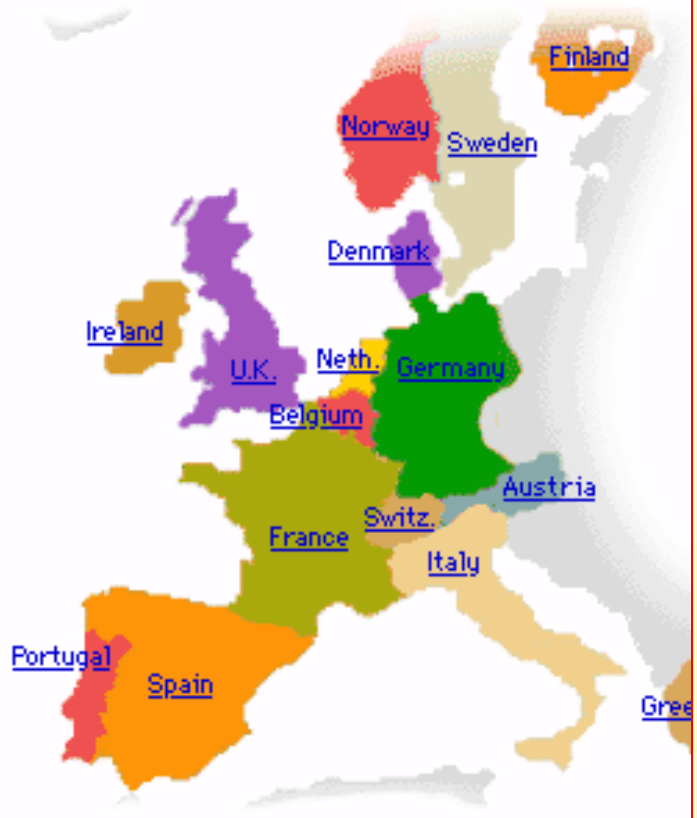
# Belgium



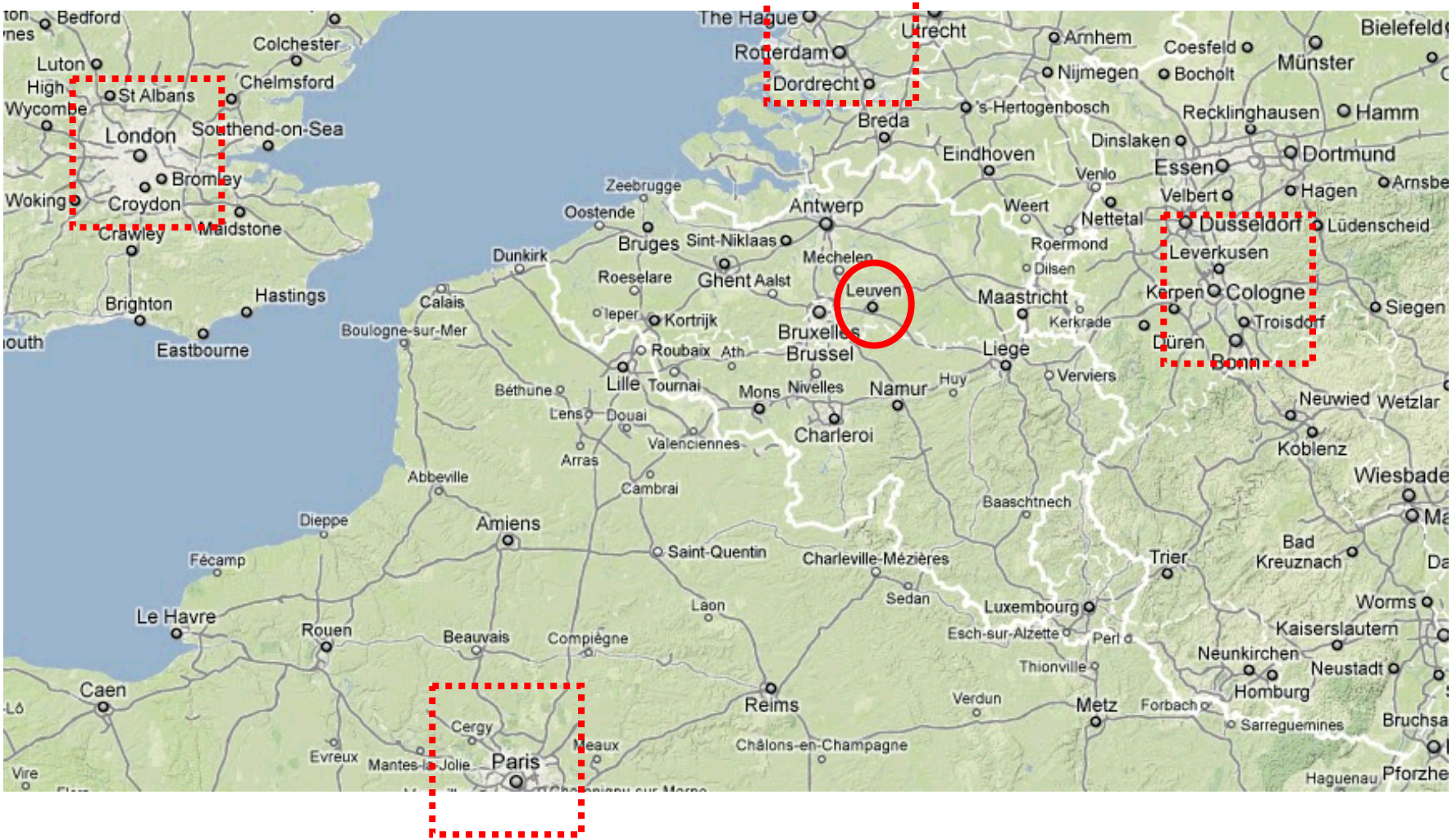

**10 millions inhabitants …**

**10 Nobel prizes (10/850)**

- **Peace**
  - Institute of International Law, Ghent (1904)
  - Auguste Beernaert (1909)
  - Henri Lafontaine (1913)
  - Father Dominique Pire (1958)
- **Literature**
  - Maurice Maeterlinck, Ghent (1911)
- **Medicine**
  - Jules Bordet, Brussels (1919)
  - Corneille Heymans, Ghent (1938)
  - Christian de Duve, Louvain (1974)
  - Albert Claude, Brussels (1974)
- **Chemistry**
  - Ilya Prigogyne, Brussels (1977)
- **Physics**
  - François Englert, Brussels (2013)

# The *Catholic University of Louvain* in brief (1 of 4)

- originally founded in **1425** in the city of **Louvain** (in French and English; known as **Leuven** in Flemish)

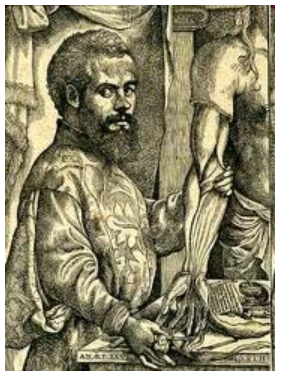


# The *Catholic University of Louvain* in brief (2 of 4)

- It was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)


**The University in the 1500's**

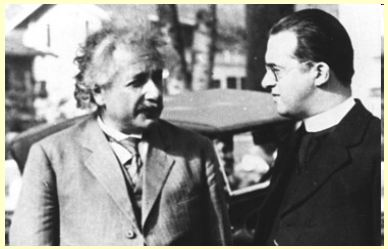
**Erasmus**



**Vesalius**

# The *Catholic University of Louvain* in brief (3 of 4)

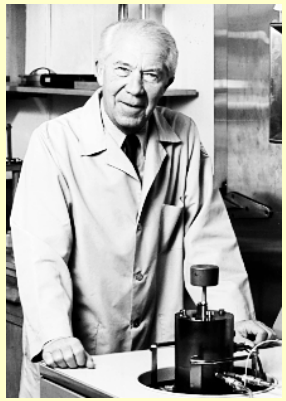
- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…



Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("*big bang*")
(here in conversation with A. Einstein)

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…)

(here in front of a centrifuge)



- in 1968, the University was divided into
  - a French-speaking ***Université catholique de Louvain***
  - a Flemish-speaking ***Katholieke Universiteit Leuven…***

# The *Catholic University of Louvain* in brief (4 of 4)

- The Flemish-speaking ***Katholieke Universiteit Leuven*** has remained in Louvain (Leuven) and is named in English "**Catholic Universiteit Leuven**".
- The French-speaking ***Université catholique de Louvain*** has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwé)

**Université catholique de Louvain**
**http://www.uclouvain.be**


**Katholieke Universiteit Leuven**
**http://www.kuleuven.be**

- Together, the two Universities have about **55,000 students**

# What do we do ?

- Teaching of Pharmacology and Pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective Pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- novel antibiotics
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacine…)
  - kétolides (solithromycin…)
  - oxazolidinones (tedizolid …)

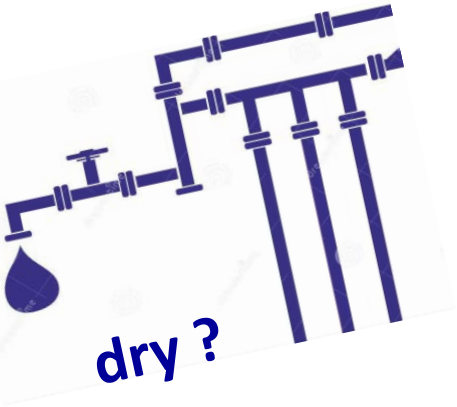
www.facm.ucl.ac.be

- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

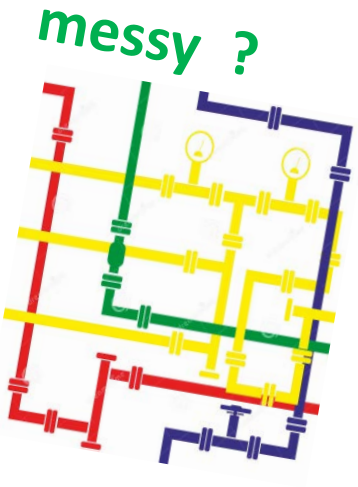
ISAP

www.isap.org

# New antibiotics: what is your own view of the pipeline ?





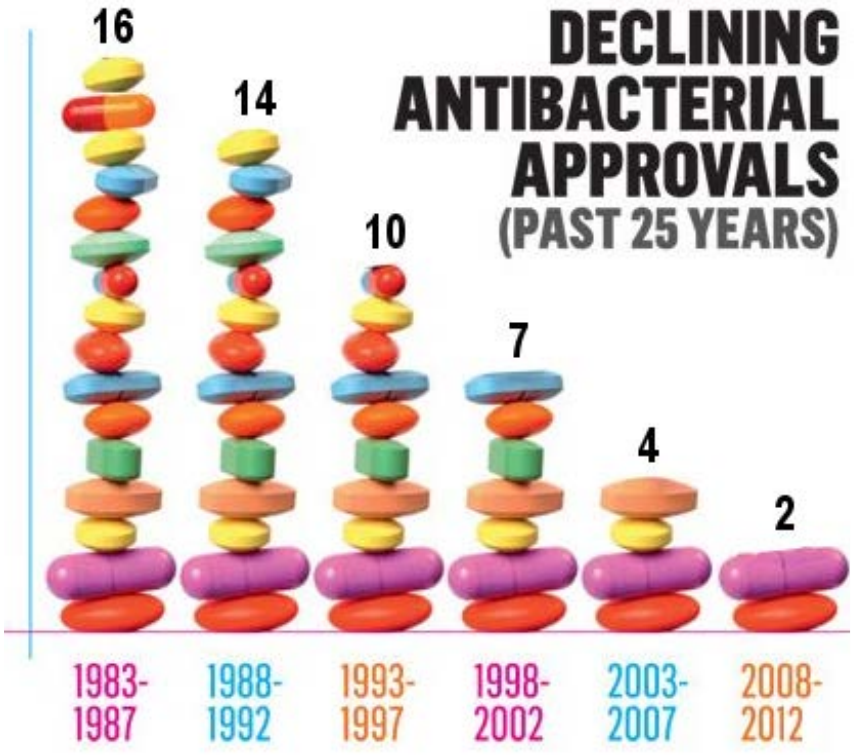






# New antibiotics: where are we ?

## Approvals by FDA/EMA – systemic antibiotics

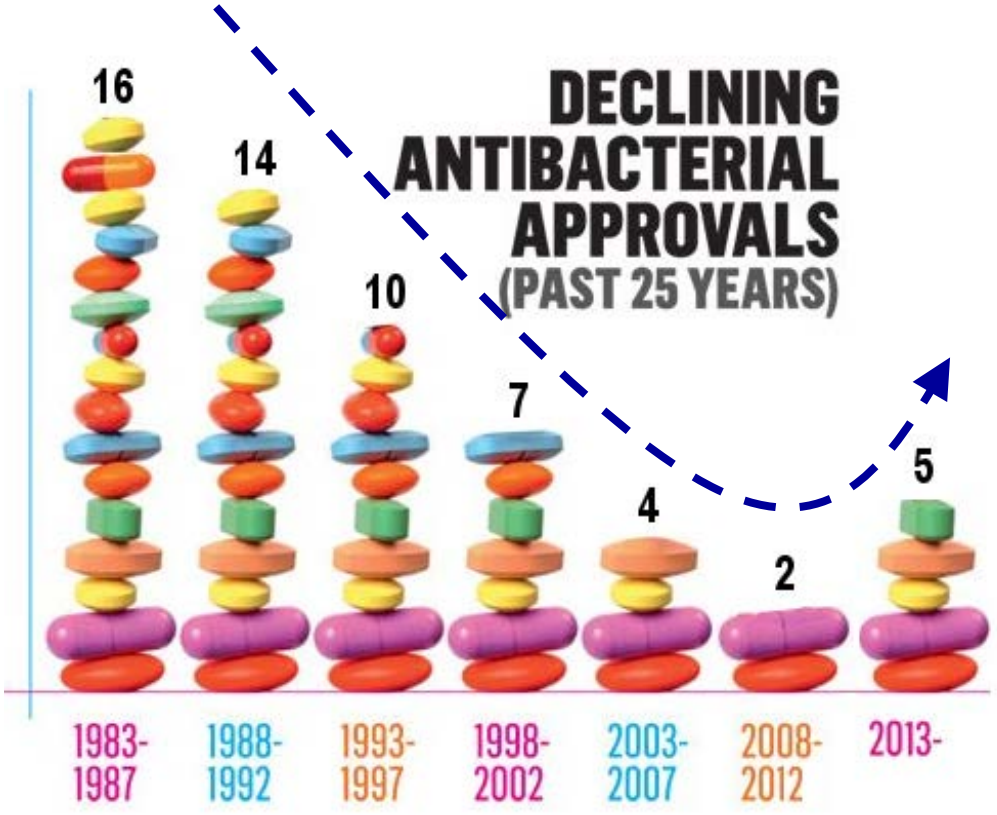



→ telavancin

→ ceftaroline

# New antibiotics: where are we ?

## Approvals by FDA/EMA – systemic antibiotics





Shall we succeed ?

- dalbavancin
- oritavancin
- tedizolid
- ceftazidime/avibactam
- ceftolozane/tazobactam

- telavancin
- ceftaroline

# Anti Gram-positive recently approved drugs

| company | drug | class | indications | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Theravance | Telavancin | lipoglyco-peptide | cSSSI / HABP/VABP | ✓ | ✓ | VanB only |
| Durata Ther. | Dalbavancin | lipoglyco-peptide | ABSSSI | ✓ | ✓ | VanB only |
| The MedCo | Oritavancin | lipoglyco-peptide | ABSSSI | ✓ | ✓ | ✓ |
| MSD | Tedizolid | oxazolidinone | ABSSSI | ✓ | ✓ | ✓ |
| Forrest Astra-Zeneca | Ceftaroline | β-lactam | ABSSSI / CABP | ✓ | ✓ | ✓ |
| Basilea | Ceftobiprole* | β-lactam | CAP / HAP | ✓ | ✓ | ✓ |

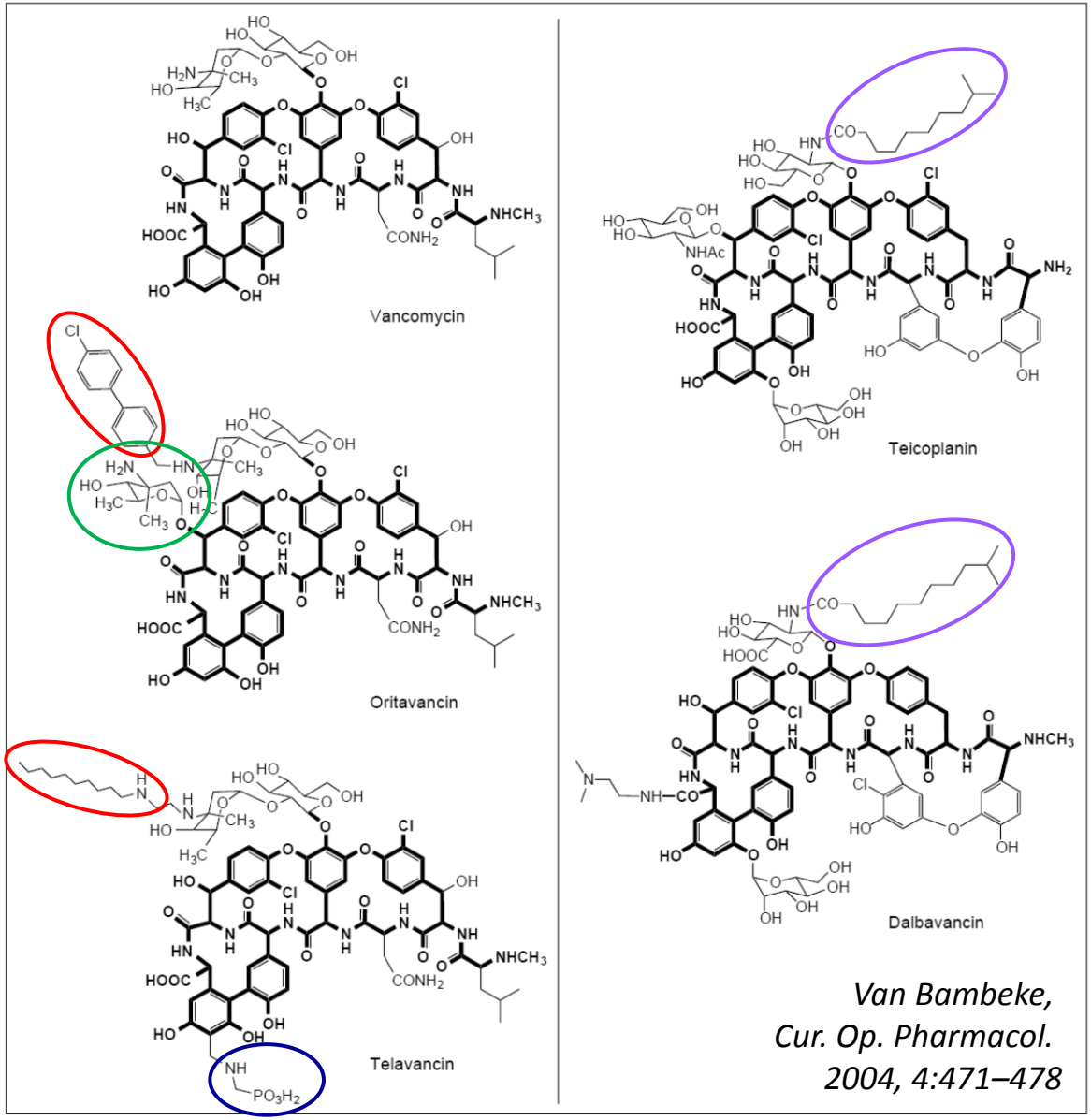
* licensed in 13 countries: AT, BE, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK; reimbursement and pricing authorization ongoing in most of them

# Lipoglycopeptides

dimerization

- prolonged half-life
- membrane anchoring

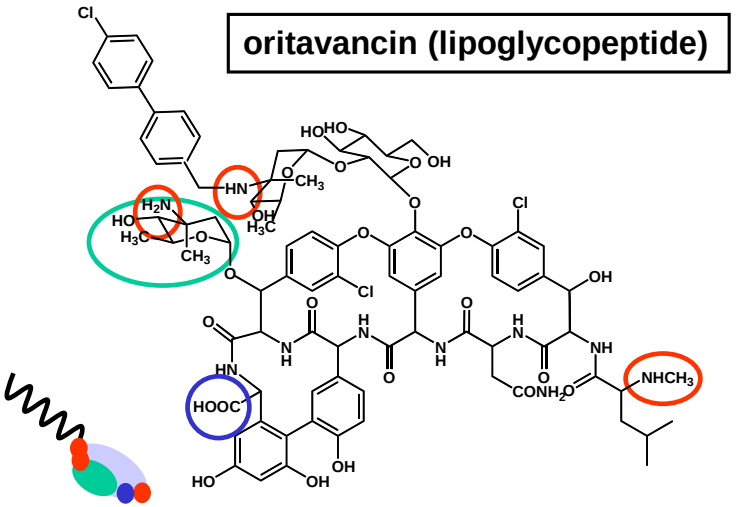
decreased half-life

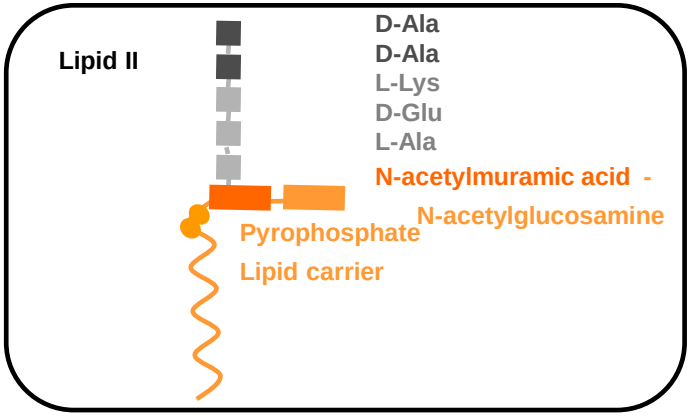



prolonged half-life

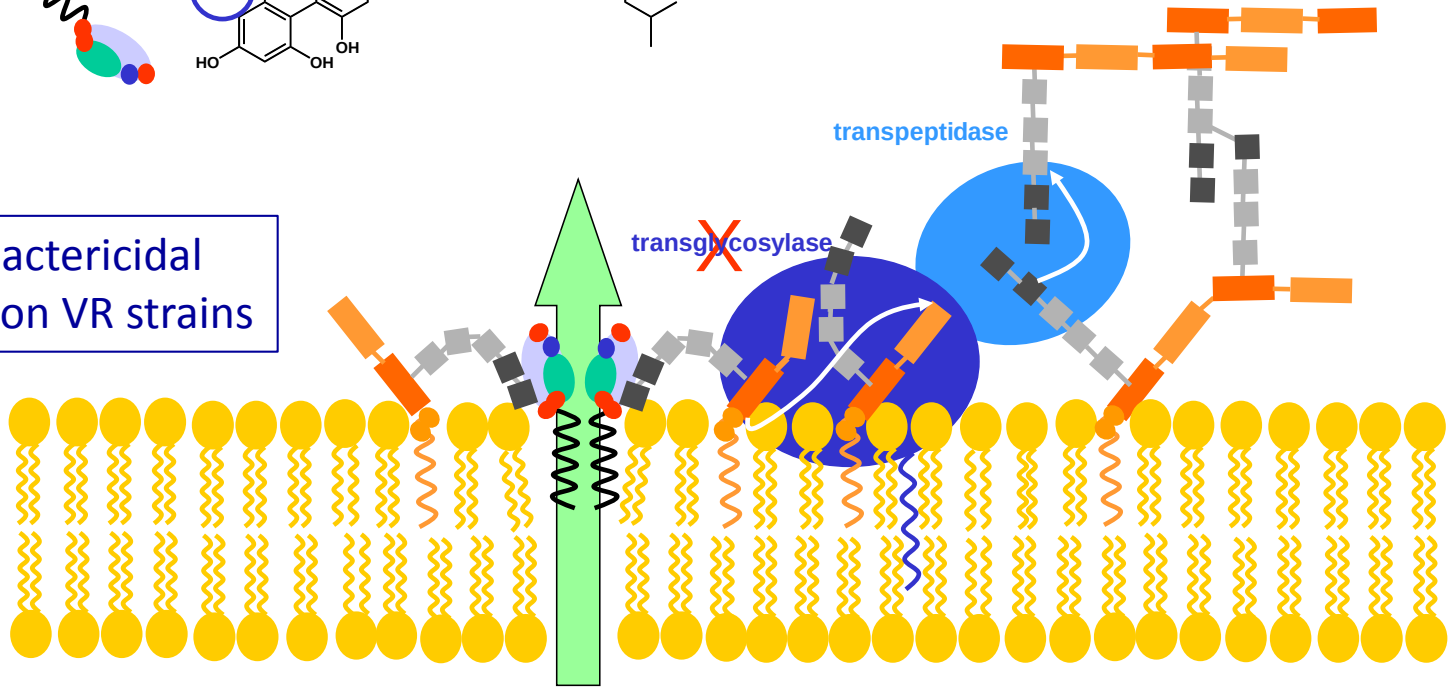
*Van Bambeke, Cur. Op. Pharmacol. 2004, 4:471–478*

# Lipoglycopeptides: dual mode of action




- highly bactericidal
- activity on VR strains




*Van Bambeke et al, TIPS 2008, 29:124-134*

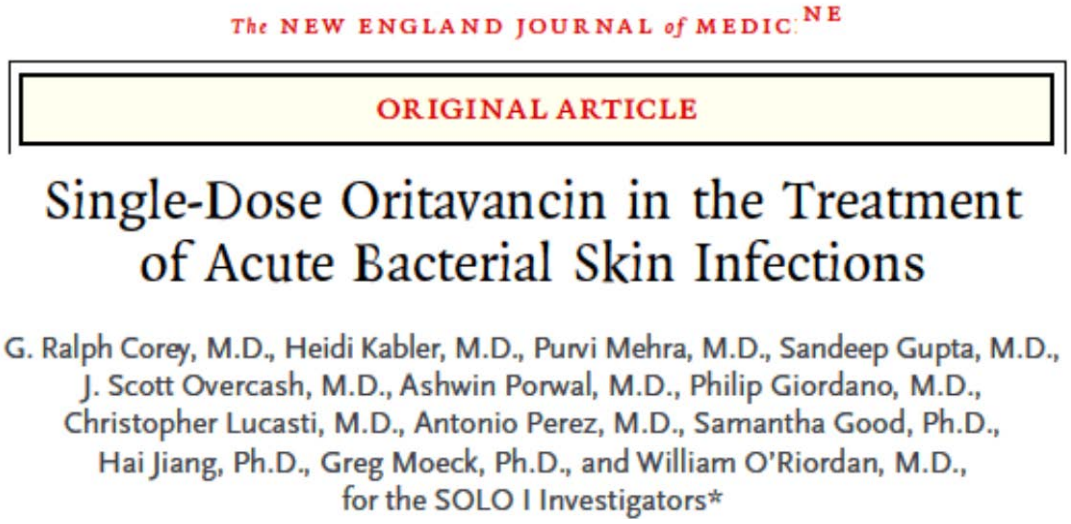
# Lipoglycopeptides: pharmacokinetics

| parameter | VAN | ORI | TLV | TEC | DAL |
|---|---|---|---|---|---|
| Dosage | 15 mg/kg | 1200 mg | 10 mg/kg | 6 mg/kg | 1000 mg |
| Cmax (mg/L) | 20-50 | 138 | 93 | 43 | 287 |
| AUC (mg.h/L) | 260 | 1110 (24h)<br>2800 (tot) | 668 | 600 | 3185 (24h)<br>23443 (tot) |
| (%) prot. binding | 55 | 85 | 95 | 88-94 | 99 |
| T ½ (h) | 1 (β)<br>3-9 (γ) | 14 (β)<br>245 (γ) | 8 | 10 (β)<br>168 (γ) | 346 (γ) |

single dose treatment

once-a-week dose treatment (2 doses)

# Oritavancin: a unusual development …



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

N Engl J Med 2014;370:2180-90.

Participants underwent randomization in a 1:1 ratio to receive either

- a single intravenous dose of 1200 mg of oritavancin followed by intravenously administered placebo, or
- an intravenous dose of vancomycin (1 g, or 15 mg per kilogram of body weight) every 12 hours for 7 to 10 days

# Oritavancin: a unusual development …

| Subgroup | Oritavancin | Vancomycin | Percentage-Point Difference (95% CI) |
|---|---|---|---|
| | *no. of events/total no. (%)* | | |
| Modified intention-to-treat population | | | |
| Primary efficacy outcome at ECE | 391/475 (82.3) | 378/479 (78.9) | 3.4 (−1.6 to 8.4) |
| Investigator-assessed clinical cure at PTE | 378/475 (79.6) | 383/479 (80.0) | −0.4 (−5.5 to 4.7) |
| Lesion size reduction ≥20% at ECE | 413/475 (86.9) | 397/479 (82.9) | 4.1 (−0.5 to 8.6) |
| CE population | | | |
| Primary efficacy outcome at ECE | 344/394 (87.3) | 342/397 (86.1) | 1.2 (−3.6 to 5.9) |
| Investigator-assessed clinical cure at PTE | 357/394 (90.6) | 352/397 (88.7) | 1.9 (−2.3 to 6.2) |
| Lesion size reduction ≥20% at ECE | 362/394 (91.9) | 370/397 (93.2) | −1.3 (−5.0 to 2.3) |
| Patients infected with MRSA in intention-to-treat population with microbiologic evaluation | | | |
| Primary efficacy outcome at ECE | 84/104 (80.8) | 80/100 (80.0) | 0.8 (−10.1 to 11.7) |
| Investigator-assessed clinical cure at PTE | 86/104 (82.7) | 83/100 (83.0) | −0.3 (−10.7 to 10.0) |
| Lesion size reduction ≥20% at ECE | 94/104 (90.4) | 84/100 (84.0) | 6.4 (−2.8 to 15.5) |
| Patients infected with MSSA in intention-to-treat population with microbiologic evaluation | | | |
| Primary efficacy outcome at ECE | 96/116 (82.8) | 92/110 (83.6) | −0.9 (−10.6 to 8.9) |
| Investigator-assessed clinical cure at PTE | 89/116 (76.7) | 88/110 (80.0) | −3.3 (−14.0 to 7.4) |
| Lesion size reduction ≥20% at ECE | 98/116 (84.5) | 94/110 (85.5) | −1.0 (−10.3 to 8.3) |

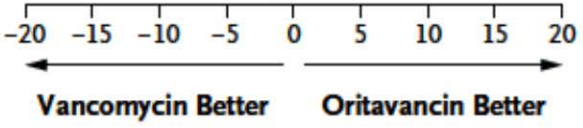



**Figure 2. Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup.**

CE denotes clinical evaluation, ECE early clinical evaluation, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-susceptible *S. aureus*, and PTE post-therapy evaluation.

N Engl J Med 2014;370:2180-90.

# Oritavancin: a unusual development …

**Table 2. Primary Efficacy Outcome at Early Clinical Evaluation According to Pathogen Detected at Baseline (Intention-to-Treat Population Who Could Be Evaluated Microbiologically).***

| Pathogen | Oritavancin (N=244) | Vancomycin (N=242) | Difference (95% CI)† |
|---|---|---|---|
| | *no./total no. (%)* | | *percentage points* |
| Detection of at least one pathogen | 201/244 (82.4) | 196/242 (81.0) | 1.4 (–5.5 to 8.3) |
| *Staphylococcus aureus* | 180/220 (81.8) | 172/210 (81.9) | –0.1 (–7.4 to 7.2) |
| MRSA | 84/104 (80.8) | 80/100 (80.0) | 0.8 (–10.1 to 11.7) |
| MSSA | 96/116 (82.8) | 92/110 (83.6) | –0.9 (–10.6 to 8.9) |
| Streptococcus species | 25/31 (80.6) | 31/38 (81.6) | –0.9 (–19.5 to 17.6) |
| *S. anginosus* group‡ | 12/13 (92.3) | 14/16 (87.5) | |
| *S. agalactiae* | 6/7 (85.7) | 8/8 (100.0) | |
| *S. pyogenes* | 5/8 (62.5) | 5/10 (50.0) | |
| *S. dysgalactiae* | 2/3 (66.7) | 3/3 (100.0) | |
| *Enterococcus faecalis* | 6/7 (85.7) | 4/5 (80.0) | |

* The pathogens listed are gram-positive pathogens known to cause acute bacterial skin and skin-structure infections, whether isolated from an infection site-culture or a blood culture. The pathogens listed include only those detected in both treatment groups. Patients with multiple pathogens were counted once in the rows for each pathogen. MSSA denotes methicillin-susceptible *S. aureus*.

† Differences and 95% confidence intervals are shown only for speciated pathogens identified from 10 or more patients in each treatment group.

‡ This group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.

N Engl J Med 2014;370:2180-90.

# Oritavancin: a unusual development …

**Table 3. Patients with Adverse Events (Safety Population).***

| Adverse Event | Oritavancin (N=473) | Vancomycin (N=481) |
|---|---|---|
| | *no. of patients (%)* | |
| At least 1 adverse event that developed during treatment | 284 (60.0) | 307 (63.8) |
| Related to study drug | 108 (22.8) | 151 (31.4) |
| Leading to discontinuation of study drug | 18 (3.8) | 28 (5.8) |
| Serious adverse event† | 35 (7.4) | 35 (7.3) |
| Related to study drug | 3 (0.6) | 3 (0.6) |
| Leading to discontinuation of study drug | 11 (2.3) | 13 (2.7) |
| Death | 1 (0.2) | 2 (0.4) |

N Engl J Med 2014;370:2180-90.

# Oritavancin: a

**Table 3. Patients with Adverse Event**

| Adverse Event |
|---|
| At least 1 adverse event that develop during treatment |
| Related to study drug |
| Leading to discontinuation of stu |
| Serious adverse event† |
| Related to study drug |
| Leading to discontinuation of stu |
| Death |

| Most frequently reported adverse events‡ | oritavancin | vancomycin |
|---|---|---|
| Nausea | 52 (11.0) | 43 (8.9) |
| Headache | 34 (7.2) | 38 (7.9) |
| Pruritus | 16 (3.4) | 44 (9.1) |
| Infusion-site reaction | 19 (4.0) | 34 (7.1) |
| Infusion-site extravasation | 18 (3.8) | 23 (4.8) |
| Vomiting | 23 (4.9) | 18 (3.7) |
| Constipation | 19 (4.0) | 21 (4.4) |
| Diarrhea | 23 (4.9) | 17 (3.5) |
| Cellulitis | 20 (4.2) | 17 (3.5) |
| Pyrexia | 15 (3.2) | 20 (4.2) |
| Dizziness | 15 (3.2) | 15 (3.1) |
| Insomnia | 14 (3.0) | 13 (2.7) |
| Chills | 10 (2.1) | 12 (2.5) |
| Urticaria | 7 (1.5) | 15 (3.1) |
| Pruritus, generalized | 11 (2.3) | 9 (1.9) |
| Subcutaneous abscess | 9 (1.9) | 11 (2.3) |
| Abscess on limb | 13 (2.7) | 5 (1.0) |
| Infusion-site phlebitis | 8 (1.7) | 10 (2.1) |
| Alanine aminotransferase elevation | 11 (2.3) | 5 (1.0) |
| Fatigue | 10 (2.1) | 6 (1.2) |

* A study investigator determined whether there was a causal relationship between an adverse event and the study drug.

N Engl J Med 2014;370:2180-90.

# Tedizolid

Available online at www.sciencedirect.com
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Bioorganic & Medicinal Chemistry 12 (2004) 5909–5915
Bioorganic & Medicinal Chemistry

## Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring

Yeong Woo Jo,[a,b] Weon Bin Im,[b] Jae Keol Rhee,[b] Mi Ja Shim,[c] Won Bae Kim[b] and Eung Chil Choi[a,*]

[a]College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Korea
[b]Dong-A Pharmaceutical Co., Ltd, Research Laboratories, Yongin, Kyunggi 449-905, Korea
[c]Department of Life Science, The University of Seoul, Seoul 130-743, Korea

Received 29 July 2004; revised 18 August 2004; accepted 18 August 2004
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European Journal of Medicinal Chemistry 46 (2011) 1027–1039

Contents lists available at ScienceDirect

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journal homepage: http://www.elsevier.com/locate/ejmech

1178×506

Original article

## Discovery of torezolid as a novel 5-hydroxymethyl-oxazolidinone antibacterial agent

Weon Bin Im[a,b], Sun Ho Choi[b], Ju-Young Park[a], Sung Hak Choi[b], John Finn[c], Sung-Hwa Yoon[a,*]

[a]Department of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea
[b]Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
[c]Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

# Dong-A pharmaceuticals and tedizolid: step #1

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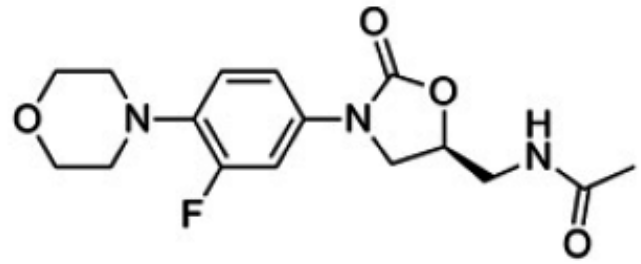
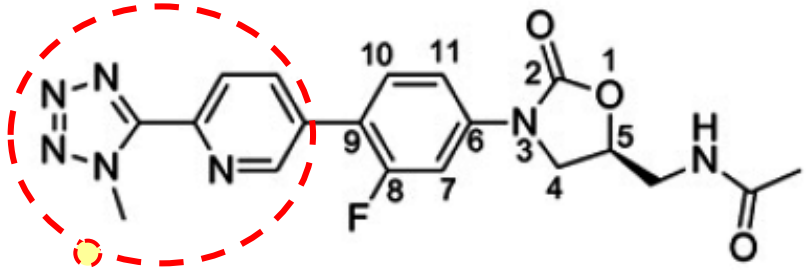


**Linezolid**



**DA-7867**

| | MIC |
|---|---|
| MSSA | 0.78 ug/ml |
| MRSA | 0.78 ug/ml |
| VRE | 0.125 ug/ml |
| PRSP | 0.39 ug/ml |

Replacing the morpholinyl by a **pyridinyl** and adding a **methyl-tetrazolyl** moiety

- **increases activity**
- **prolong half-life**

rial potency of lead compound (DA-7867).

a novel 5-hydroxymethyl-oxazolidinone

agent

Weon Bin Im [a,b], Sun Ho Choi [b], Ju-Young Park [a], Sung Hak Choi [b], John Finn [c], Sung-Hwa Yoon [a,*]

[a] Department of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea
[b] Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
[c] Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

# Tedizolid has more interactions with the ribosome…

W.B. Im et al. / European Journal of Medicinal Chemistry 46 (2011) 1027–1039

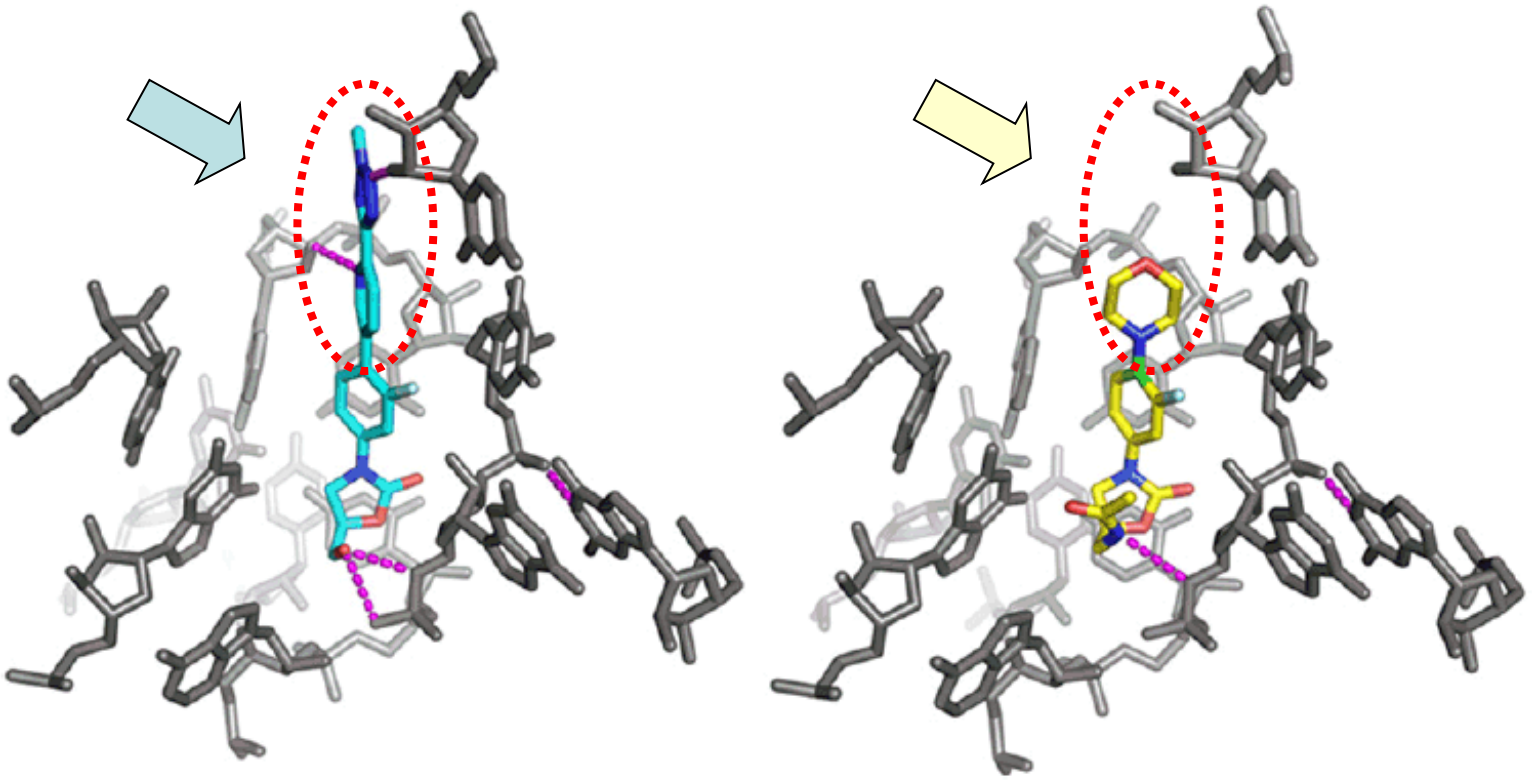
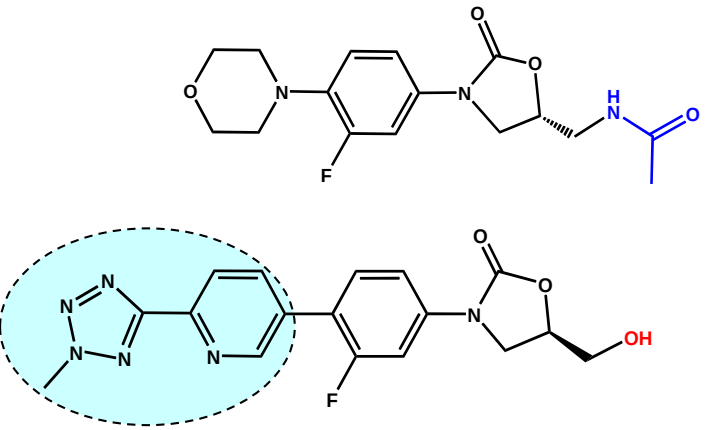


**Fig. 2.** Models of **11** (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

# Tedizolid is systematically 3-4-x more active than linezolid against LSD$^S$ strains



**potential role of the tetrazolyl moiety**

**Table 1.** Susceptibility of the strains of *S. aureus*, *L. monocytogenes* and *L. pneumophila* used in this study to linezolid and torezolid

| Species, phenotype and strain no. | | MIC (mg/L)[a] linezolid | torezolid |
|---|---|---|---|
| *Staphylococcus aureus* | | | |
| MSSA | ATCC 25923[b] | 2 | 0.25 |
| HA-MRSA | ATCC 33591[b] | 1 | 0.125–0.25 |
| | SA 238[c] | 2 | 0.25–0.5 |
| | CM 05[d] | 8 | 0.25–0.5 |
| CA-MRSA | NRS 192[e] | 2 | 0.125–0.25 |
| | NRS 384 (US300)[e] | 2 | 0.25 |
| VISA | NRS 52[e] | 2 | 0.125 |
| VRSA | VRS 1[e] | 1–2 | 0.125–0.25 |
| | VRS 2[e] | 1–2 | 0.25 |
| animal MRSA | N7112046[f] | 2 | 0.125 |
| *Listeria monocytogenes* | | | |
| | EGD[g] | 1–2 | 0.125 |
| *Legionella pneumophila* | | | |
| | ATCC 33153[b] | 4–8 | 0.25–0.5 |

LZD$^R$, resistant to linezolid.
[a]Representative values of at least two determinations.
[b]From the American Tissue Culture Collection (Manassas, VA, USA).
[c]Provided by P. C. Appelbaum.[36]
[d]Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.
[e]From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN272200700055C); details on each strain are available at http://www.narsa.net/content/home.jsp.
[f]Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
[g]Provided by P. Berche, Hôpital Necker, Paris, France.[28]

Lemaire et al. JAC 2009; 64:1035–1043

# And even for *S. aureus* of different epidemiological origin…

AAC Journals.ASM.org
Antimicrobial Agents and Chemotherapy 2013 57 p. 2892–2895

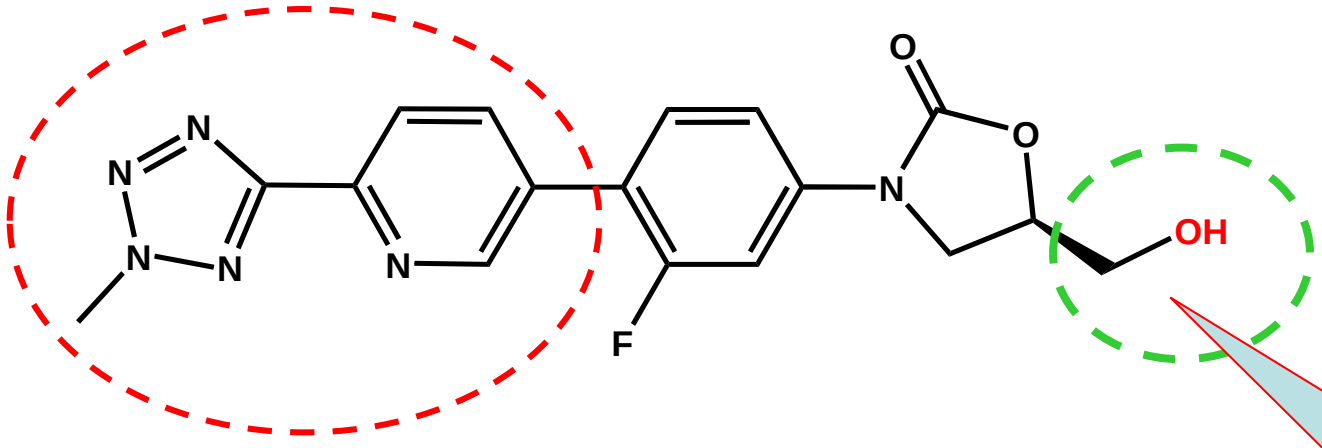
## Activity of Tedizolid (TR-700) against Well-Characterized Methicillin-Resistant *Staphylococcus aureus* Strains of Diverse Epidemiological Origins

**Kenneth S. Thomson, Richard V. Goering**
Creighton University, Omaha, Nebraska, USA

TABLE 1 Drug activity against all MRSA isolates and epidemiological groups[a]

| Isolate(s) | Drug(s) | MIC range (μg/ml) | $MIC_{90}$ (μg/ml) |
|---|---|---|---|
| All isolates ($n$ = 111) | Tedizolid | 0.12 to 0.5 | 0.5 |
| | Linezolid | 0.5 to 4 | 2 |
| | Trimethoprim/sulfamethoxazole | ≤0.5/9.5 to >2/38 | >2/38 |
| | Tigecycline | 0.06 to >1 | 0.5 |
| | Levofloxacin | 0.12 to >4 | >4 |
| | Clindamycin | 0.06 to >16 | >16 |
| | Vancomycin | ≤0.25 to 4 | 1 |
| | Daptomycin | ≤0.5 to 2 | ≤0.5 |
| | Oxacillin | 0.12 to >4 | >4 |
| | Erythromycin | 0.12 to >8 | >8 |
| | Gentamicin | ≤0.06 to >16 | >16 |

# Dong-A pharmaceuticals and tedizolid: step #2




| # | R | X | MIC (μg/mL) | | |
|---|---|---|---|---|---|
| | | | MSSA | MRSA | VRE |
| Linezolid | | | 2 | 2 | 1 |
| **11** | 2-Methyl-2*H*-tetrazol-5-yl | —OH | 0.5 | 0.5 | 0.125 |

2. replacing the **acetamido** by an **hydroxyl** maintains the increased activity *vs.* linezolid !

[a] Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
[b] Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

# Tedizolid and linezolid resistance

# Oxazolidinones: 1st mechanism of resistance

Chloramphenicol-florfenicol resistance (Cfr)

- First identified in several staphylococcal species (cattle, swine) (Schwarz 2000; Kehrenberg 2006)
- CM05 (Colombia) - first clinical isolate documented to carry the *cfr* gene (Toh 2007)
- C-8 methylation of ribosome target at A2503 (Kehrenberg 2005; Giessing 2009)
- $PhLOPS_A$ phenotype leads to cross resistance to 6 drug classes!
  - Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, Streptogramin A and 16 membered macrolides (Long, 2006; Smith & Mankin 2008)
- Tedizolid retains potency against *cfr* strains and demonstrates 8-fold better activity than linezolid (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)

full

to 16

# Activity against Cfr$^+$ resistant strains … (*cfr*$^+$ bacteria)

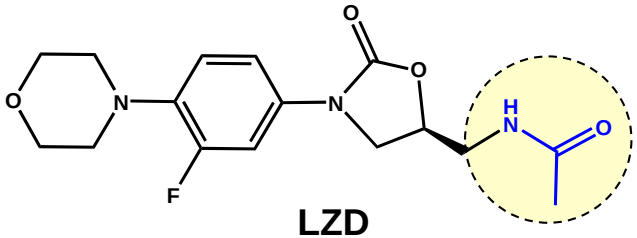
Oxazolidinone MICs for *S. aureus cfr* strains

| Strain | Reference | Presence of *cfr* | MIC (μg/ml)[a] | |
|---|---|---|---|---|
| | | | LZD | TR-700 |
| RN4220(pLI50) | 68 | − | 2 | 0.5 |
| RN4220(pLXM1)[b] | 68 | + | 8 | 0.5 |
| CM05Δ[c] | 44 | − | 2 | 0.5 |
| CM05[c] | 68 | + | 8 | 0.5 |
| 29213 | ATCC | − | 2 | 0.5 |
| 29213(p42262)[d] | 45 | + | 16 | 0.5 |
| 42262[e] | 51 | + | 16 | 0.5 |

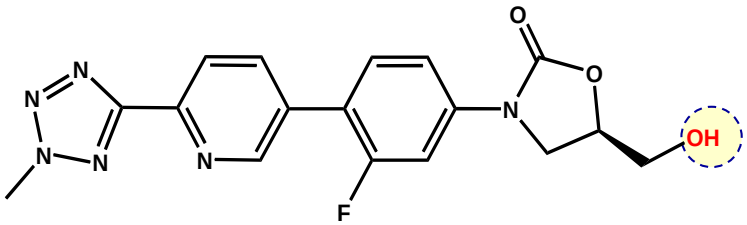
[a] MICs (broth microdilution: CLSI)
[b] The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.
[c] CM05Δ is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.
[d] 29213(p42262) was generated through transformation of ATCC 29213
[e] 42262 is a clinical *cfr*-positive isolate from a 2008 hospital outbreak in Madrid, Spain.

Locke et al. AAC 2010;54:5337-5343

# Why is tedizolid active against LZD$^R$ strains (*cfr*) ?




LZD




TR700

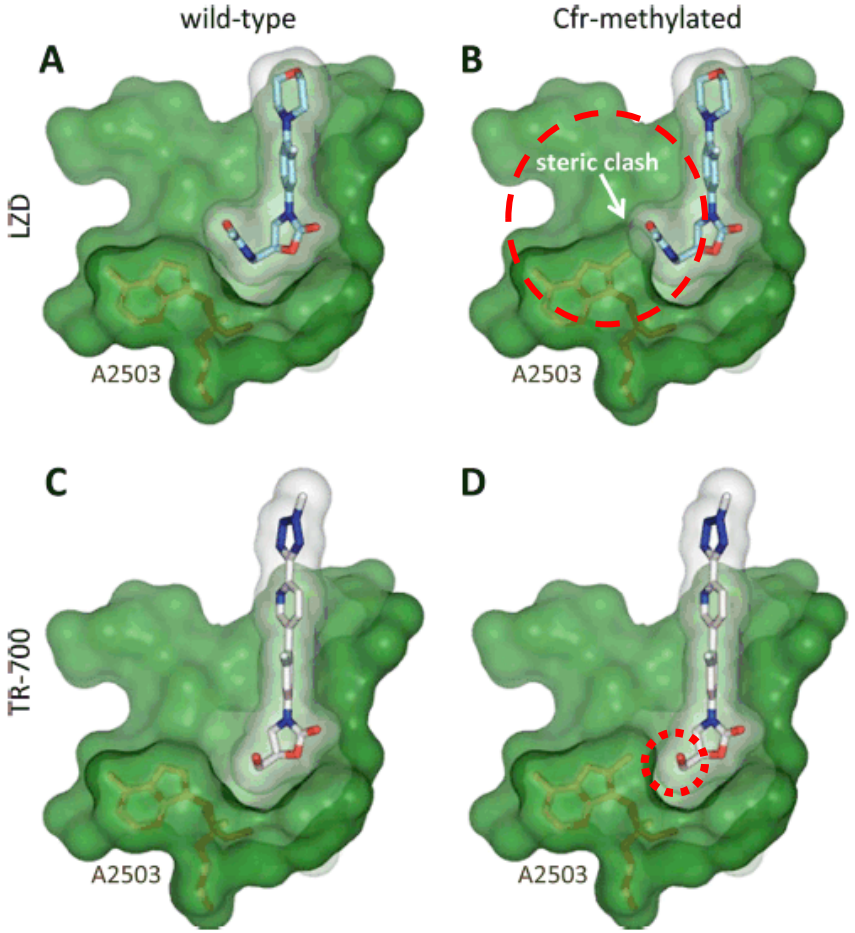
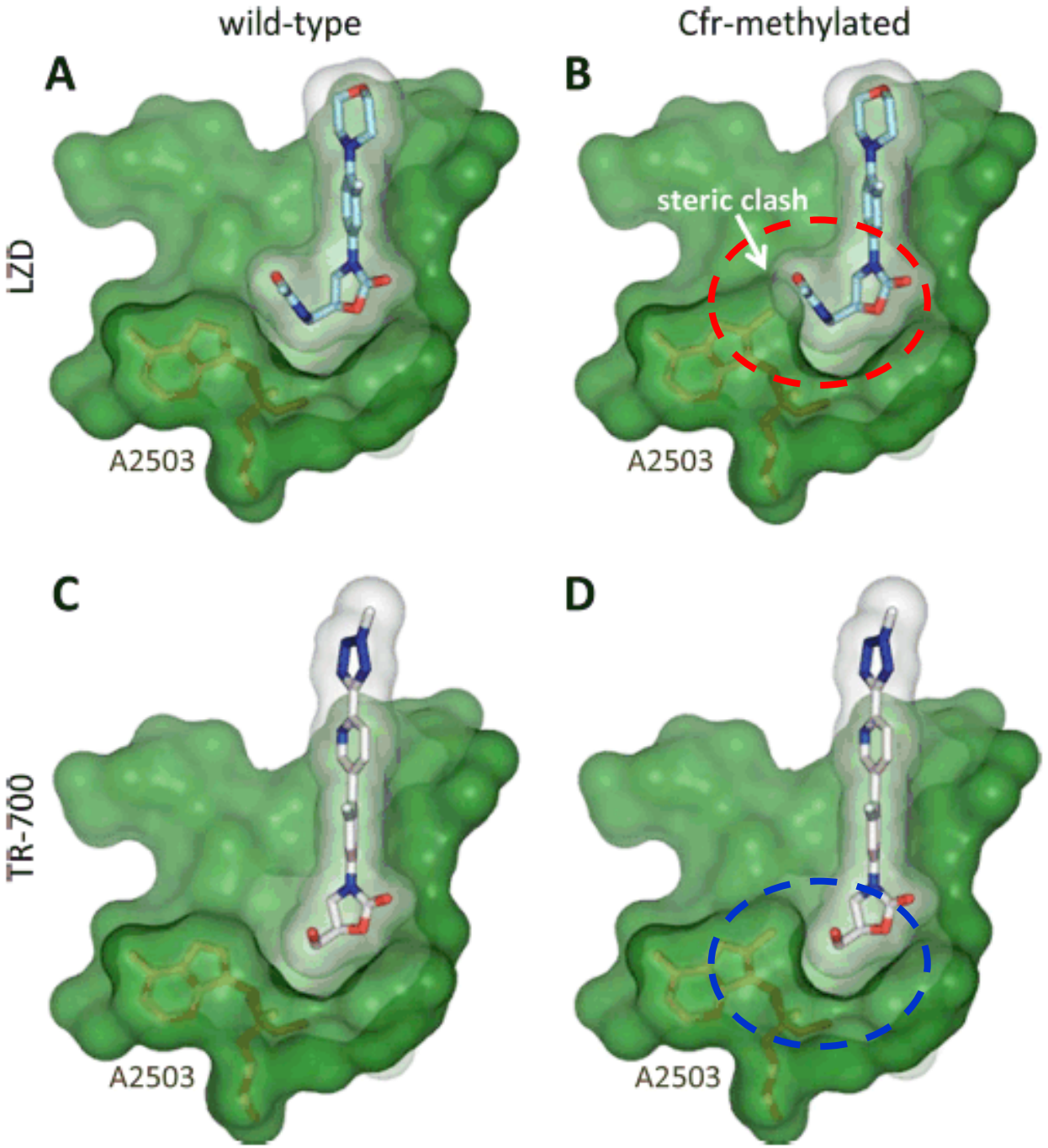



FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. Substantial steric hindrance between the LZD C-5 acetamide group and the 23S rRNA base A2503 carbon-8 methyl (bonds shown in brown) likely contributes to reduced binding affinity (B). As modeled, the TR-700 hydroxymethyl substituent does not display this steric clash with the A2503 methyl group (D), explaining its retained activity against *cfr* strains. A group of PTC bases were removed from the images to improve clarity. Images were generated with PyMOL (16).

Locke et al. AAC 2010;54:5337-5343

# Why is tedizolid active against LZD$^R$ strains (*cfr*) ?

Locke et al. AAC 2010;54:5337-5343



# Oxazolidinones: 2d mechanism of resistance

## Chromosomal 23S rRNA mutations

- Low frequency, but local outbreaks have been observed
- First clinical cases of resistant staphylococci and enterococci reported soon after linezolid approval in 2000 (Gonzales 2001; Tsiodras 2001)
- Tedizolid demonstrates 8-fold better potency against these strains (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)
- Mutations also observed in ribosomal proteins L3 and L4

**loses about 2 to 4-fold activity but still**

# Tedizolid and ribosomal mutations

TABLE 1. Oxazolidinone MICs for *S. aureus* ribosomal mutants

| Strain[a] | Source or reference | Resistance mechanism[b] | MIC (μg/ml)[c] | |
|---|---|---|---|---|
| | | | LZD | TR-700 |
| 29213 | ATCC | | 2 | 0.5 |
| 29213-1 | 43 | 23S (G2447T ×3) | 32 | 4 |
| 29213-2 | 43 | 23S (T2500A ×2) | 8 | 2 |
| 29213-3 | 43 | L3 (ΔPhe127-His146) | 8 | 2 |
| 33591 | ATCC | | 1 | 0.25 |
| 33591-1 | 43 | 23S (G2576T ×3) | 16 | 2 |
| 33591-2 | 43 | 23S (G2576T/T2571C ×3) | 16 | 2 |
| 33591-3 | 43 | L4 (Lys68Gln) | 2 | 0.5 |
| NRS127 | NARSA[d] | L3 (ΔSer145) | 8 | 1 |

[a] ATCC 29213 and ATCC 33591 isogenic mutant panels were generated through selection in the presence of LZD and/or TR-700. NRS127 is an LZD$^r$ clinical isolate.

[b] Mutations in 23S rRNA genes (and mutant allele copy number) or in the ribosomal protein L3 or L4 are shown.

[c] MICs (broth microdilution; CLSI) were determined against the oxazolidinone panel

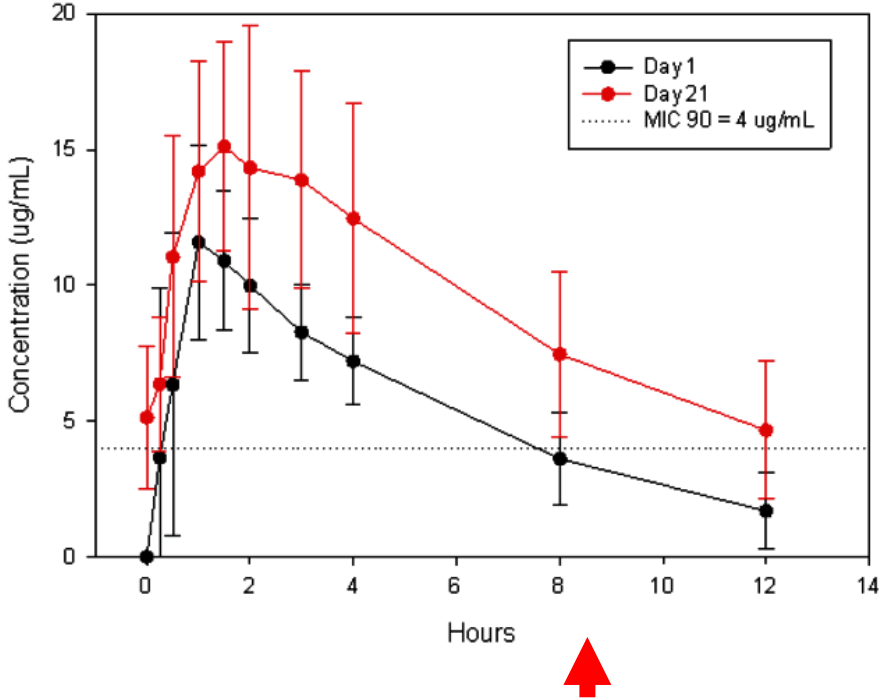
[d] Network of Antimicrobial Resistance in *Staphylococcus aureus*.

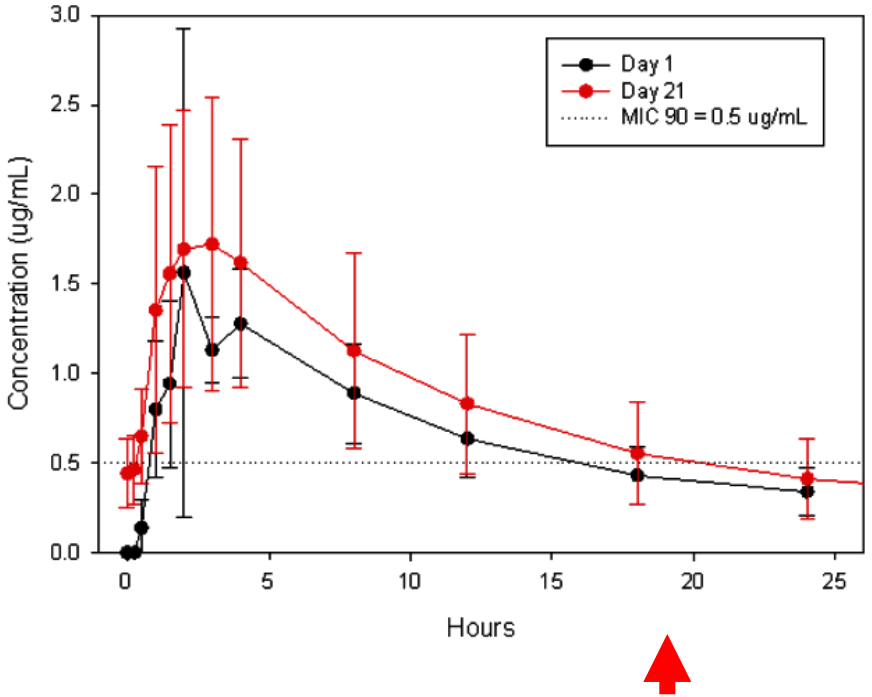
**TDZ MICs are 8x < than LZD but 2-4x > than for wild type bacteria**

Locke et al. AAC 2010;54:5337-5343

# Tedizolid vs Linezolid human pharmacokinetics:

## oral doses (200 mg TR-701 q24h *vs* 600 mg linezolid q12h for 21 days.




Tedizolid :

- mean $t_{1/2}$ > 2 x greater than linezolid
- longer initial presence at > 0.5 mg/L (vs. 4 mg/L for linezolid).

This allows for a once-a-day dosing

Muñoz et al. ECCMID 2010 P1594

# Manipulating dosages and schedules

TABLE 2. Calculated pharmacodynamic variables for 4 total daily dosages of TR-701 administered as one, two, or four equally divided doses over 24 h

| Total dosage (mg/kg/24 h) | Regimen[a] | $fC_{max}$/MIC ratio[b] | fAUC/MIC ratio[c] | $fT>$MIC (%)[d] |
|---|---|---|---|---|
| 10 | 10 mg/kg q24h | 2.62 | 13.19 | 21 |
| | 5 mg/kg q12h | 1.29 | 12.82 | 20 |
| | 2.5 mg/kg q6h | 0.64 | 12.26 | 0 |
| 20 | 20 mg/kg q24h | 5.16 | 26.03 | 31 |
| | 10 mg/kg q12h | 2.62 | 25.63 | 43 |
| | 5 mg/kg q6h | 1.29 | 24.51 | 50 |
| 36 | 36 mg/kg q24h | 9.29 | 46.88 | 39 |
| | 18 mg/kg q12h | 4.65 | 46.14 | 60 |
| | 9 mg/kg q6h | 2.32 | 44.12 | 87 |
| 72 | 72 mg/kg q24h | 18.59 | 93.76 | 49 |
| | 36 mg/kg q12h | 9.29 | 92.28 | 79 |
| | 18 mg/kg q6h | 4.65 | 88.24 | 100 |

[a] The first dose was administered 2 h after infection. All doses of TR-701 are provided as dose equivalents (mg/kg/day) of TR-700. Doses were given every 24 h (q24h), every 12 h (q12h), or every 6 h (q6h).

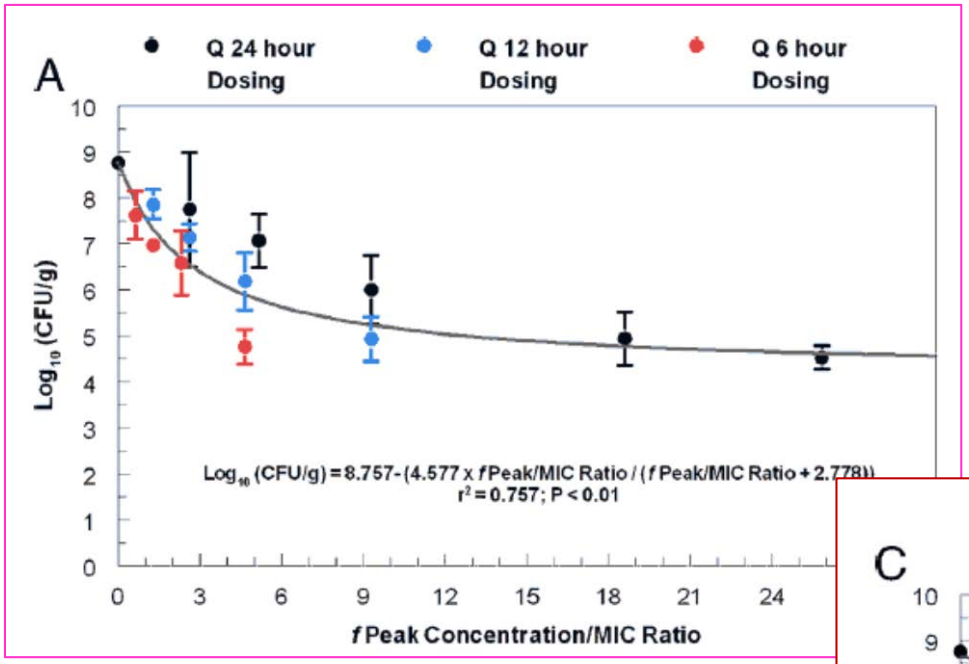
[b] $fC_{max}$/MIC ratio, maximum concentration of free drug in serum divided by the MIC. The MICs for the MRSA strain were 0.5 mg/liter in CA-MHB and 1 mg/liter in 80% mouse serum.

[c] fAUC/MIC ratio, area under the concentration-time curve over 24 h for the free, unbound fraction of a drug divided by the MIC.

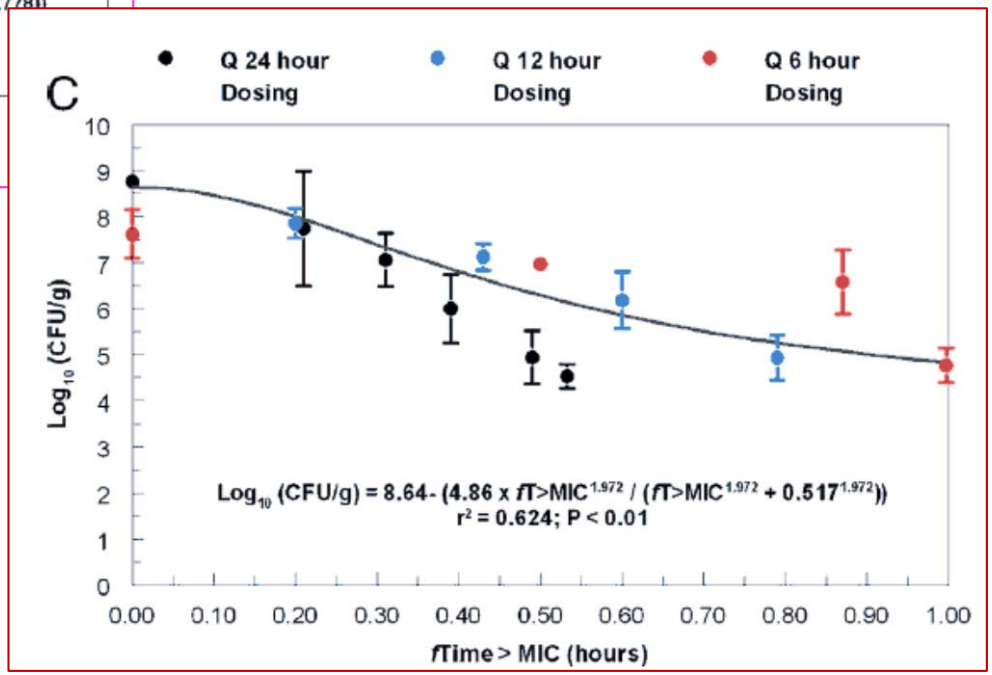
[d] $fT>$MIC, calculated cumulative percentage of a 24-h period that the concentration of the free drug exceeded the MIC under steady-state pharmacokinetic conditions (expressed as a percentage of the dosing interval).

Louie et al. AAC 2011; 55:3453-3460

# What do you see ?



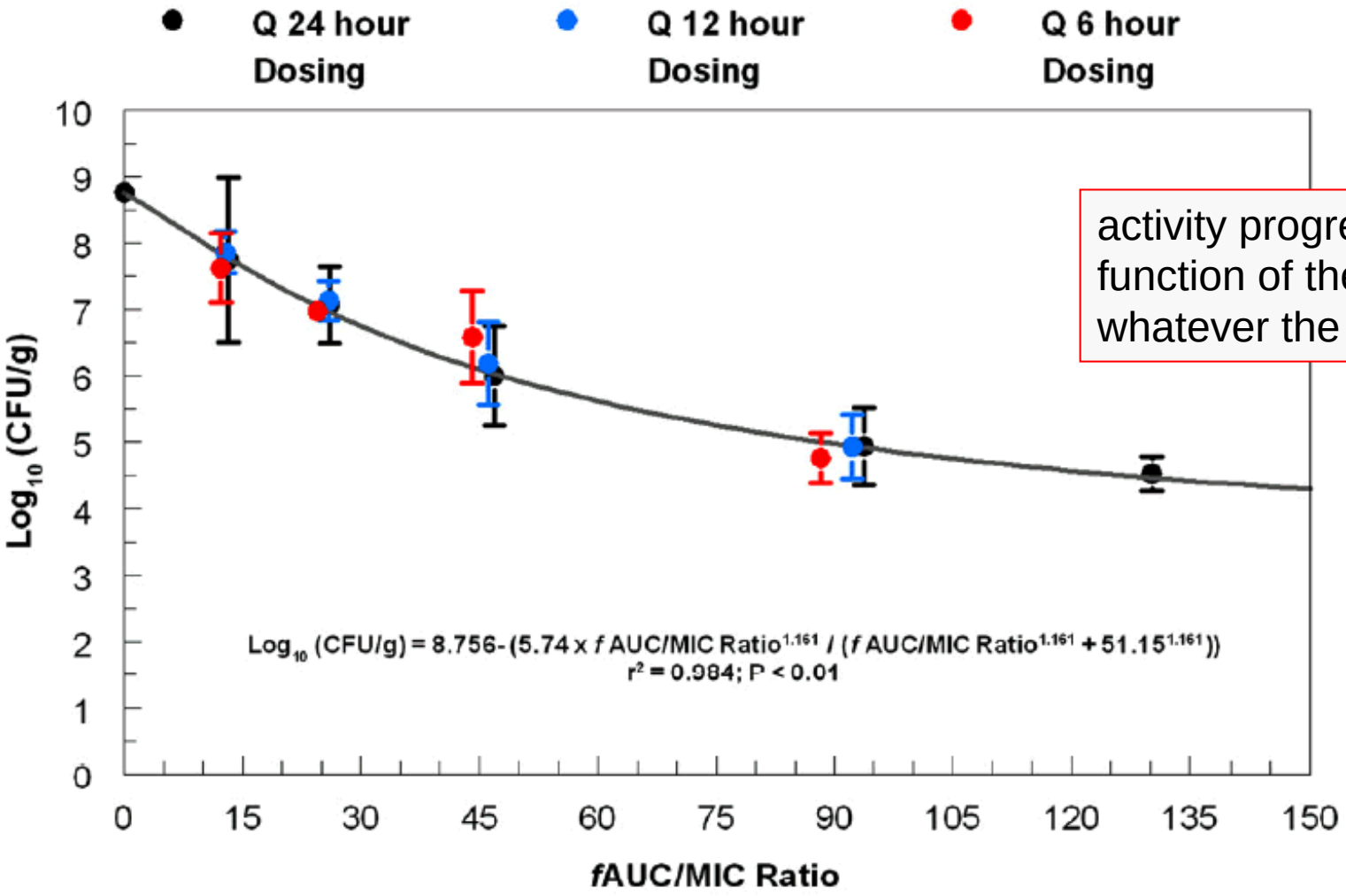

The correlation with
*f* $C_{max}$ is not excellent




The correlation with
*f* T > MIC is worse !

Louie et al. AAC 2011; 55:3453-3460

# $AUC_{24h}$ and activity tedizolid




activity progresses as a function of the AUC/MIC, whatever the schedule

Louie et al. AAC 2011; 55:3453-3460

# Tedizolid: a fast development…

ORIGINAL CONTRIBUTION

## Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

### The ESTABLISH-1 Randomized Trial

Philippe Prokocimer, MD
Carisa De Anda, PharmD
Edward Fang, MD
Purvi Mehra, MD
Anita Das, PhD

**Importance** Acute bacterial skin and skin structure infections (ABSSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgery and hospitalization. Increasingly, ABSSSIs are associated with drug-resistant pathogens, and many antimicrobial agents have adverse effects restricting their use. Tedizolid phosphate is a novel oxazolidinone in development for the treatment of ABSSSIs.

*JAMA. 2013;309(6):559-569*

**Design, Setting, and Patients:**

- Efficacy and Safety of
  - 6-day Oral Tedizolid (200 mg once-daily) *vs*
  - 10-day Oral Linezolid Therapy (600 mg twice daily)
- Intent-to-treat analysis from 667 adults (tedizolid: n=332; linezolid: n=335).

# Tedizolid: a fast development…

ORIGINAL CONTRIBUTION

## Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

**Table 2.** Clinical Response at Early and Late Time Points

| Clinical Response | Tedizolid Phosphate (n = 332) | Linezolid (n = 335) | Absolute Treatment Difference (95% CI), % |
|---|---|---|---|
| At the 48- to 72-h assessment (ITT analysis set) | | | |
| Treatment responder, No. (%) [95% CI] | 264 (79.5) [74.8 to 83.7] | 266 (79.4) [74.7 to 83.6] | 0.1 (−6.1 to 6.2) |
| Cellulitis/erysipelas, No./total (%) | 101/135 (74.8) | 100/139 (71.9) | |
| Major cutaneous abscess, No./total (%) | 80/100 (80.0) | 84/98 (85.7) | |
| Wound infection, No./total (%) | 83/97 (85.6) | 82/98 (83.7) | |
| Treatment nonresponder or indeterminate, No. (%)[a] | 68 (20.5) | 69 (20.6) | |
| Treatment nonresponder | 27 (8.1) | 35 (10.4) | |
| Indeterminate | 41 (12.3) | 34 (10.1) | |
| Missing lesion measurements | 22 (6.6) | 24 (7.2) | |
| Missing temperature data | 37 (11.1) | 32 (9.6) | |

# Tedizolid: a fast development…

ORIGINAL CONTRIBUTION

## Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

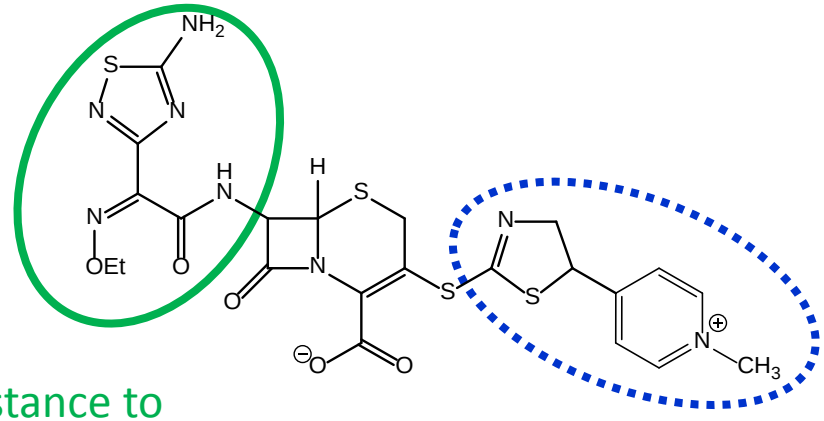
The ESTABLISH-1 Randomized Trial

**Table 2.** Clinical Response at Early and Late Time Points

| Clinical Response | Tedizolid Phosphate (n = 332) | Linezolid (n = 335) | Absolute Treatment Difference (95% CI), % |
|---|---|---|---|
| Sustained at the EOT assessment (ITT analysis set) | | | |
| Clinical success, No. (%) [95% CI] | 230 (69.3) [64.0 to 74.2] | 241 (71.9) [66.8 to 76.7] | −2.6 (−9.6 to 4.2) |
| Cellulitis/erysipelas, No./total (%) | 85/133 (63.9) | 84/135 (62.2) | |
| Major cutaneous abscess, No./total (%) | 72/100 (72.0) | 78/97 (80.4) | |
| Wound infection, No./total (%) | 73/99 (73.7) | 79/103 (76.7) | |
| Clinical treatment failure or indeterminate, No. (%) | 102 (30.7) | 94 (28.1) | |
| Clinical treatment failure | 60 (18.1) | 61 (18.2) | |
| Indeterminate | 42 (12.7) | 33 (9.9) | |
| Lost to follow-up | 14 (4.2) | 14 (4.2) | |
| Gram-negative infection | 4 (1.2) | 3 (0.9) | |
| Withdrew consent | 6 (1.8) | 2 (0.6) | |
| Indeterminate at the 48- to 72-h assessment | 33 (9.9) | 26 (7.8) | |
| Pregnancy | 1 (0.3) | 1 (0.3) | |
| Sustained at the EOT assessment (CE-EOT analysis set) | **(n = 273)** | **(n = 286)** | |

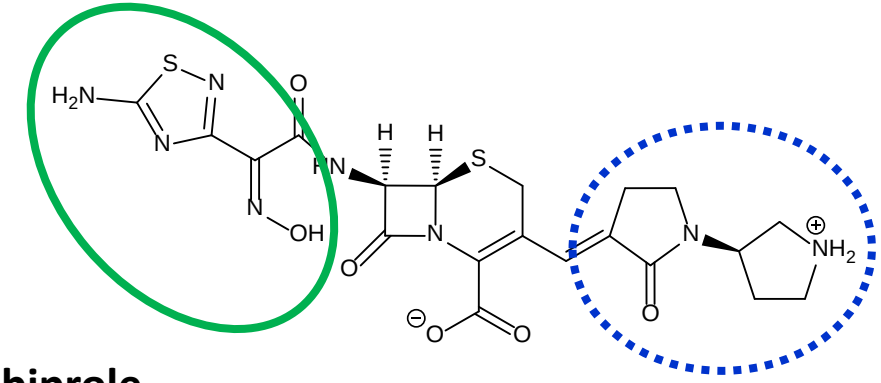
# ceftaroline and ceftobiprole

**ceftaroline**



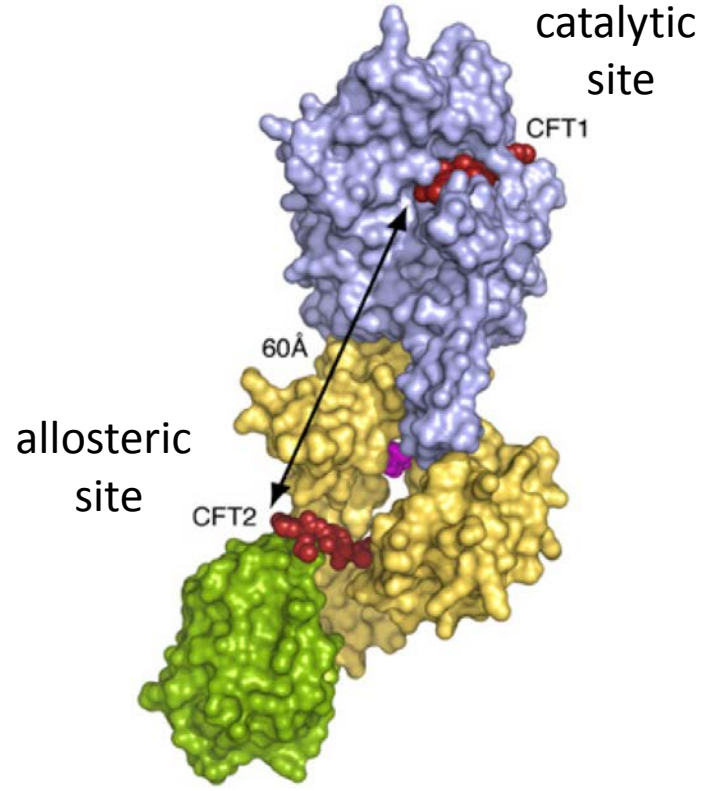
Resistance to β-lactamases

Binding to PBP2a



**ceftobiprole**

ceftaroline & PBP2a




*Otero et al, PNAS (2013) 110:16808–13*

# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Cempra | solithromycin | ketolide | Phase III<br>CAPB | ✓ | ✓ | |
| Melinta | delafloxacin | fluoroquinolone | Phase III<br>ABSSSI | ✓ | ✓ | |
| TaiGen | nemonoxacin | fluoroquinolone | Phase III<br>CAPB / ABSSSI | ✓ | ✓ | |
| Dong | zabofloxacin | fluoroquinolone | Phase III<br>CAPB | ✓ | ✓ | |
| Activis | avarofloxacin | fluoroquinolone | Phase II completed<br>CAPB / ABSSSI | ✓ | ✓ | |
| MerLion | finafloxacin | fluoroquinolone | Phase II<br>ABSSSI | ✓ | ✓ | |
| GSK | GSK2140944 | topoisomerase inhibitor | Phase II<br>respiratory / ABSSSI | ✓ | ✓ | |

*Constructed based on www.pewtrusts.org*

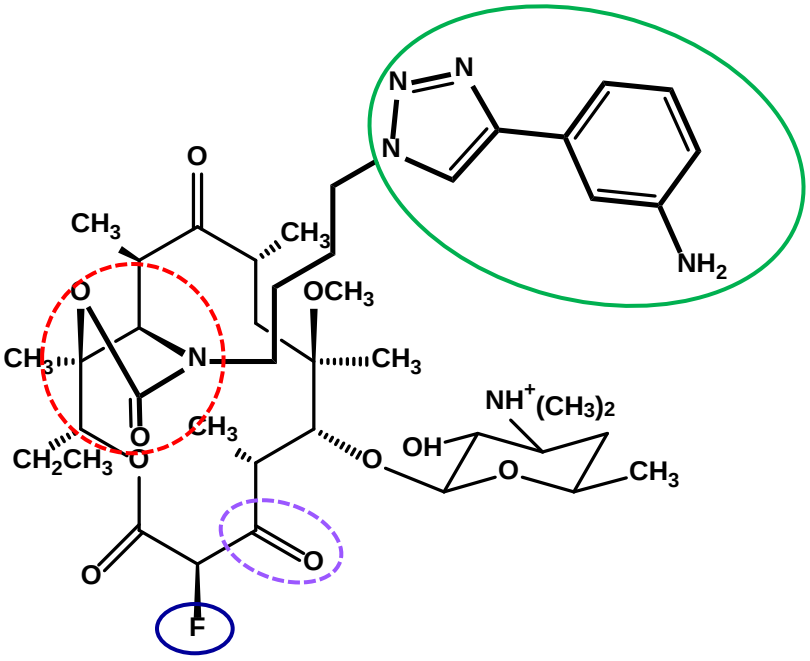
# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Cempra | solithromycin | ketolide | Phase III<br>CAPB | ✓ | ✓ | |
| Melinta | delafloxacin | fluoroquinolone | Phase III<br>ABSSSI | ✓ | ✓ | |
| TaiGen | nemonoxacin | fluoroquinolone | Phase III<br>CAPB / ABSSSI | ✓ | ✓ | |
| Dong | zabofloxacin | fluoroquinolone | Phase III<br>CAPB | ✓ | ✓ | |
| Activis | avarofloxacin | fluoroquinolone | Phase II completed<br>CAPB / ABSSSI | ✓ | ✓ | |
| MerLion | finafloxacin | fluoroquinolone | Phase II<br>ABSSSI | ✓ | ✓ | |
| GSK | GSK2140944 | topoisomerase inhibitor | Phase II<br>respiratory / ABSSSI | ✓ | ✓ | |

*Constructed based on www.pewtrusts.org*

# solithromycin vs telithromycin

lower interaction
with nicotinic receptor

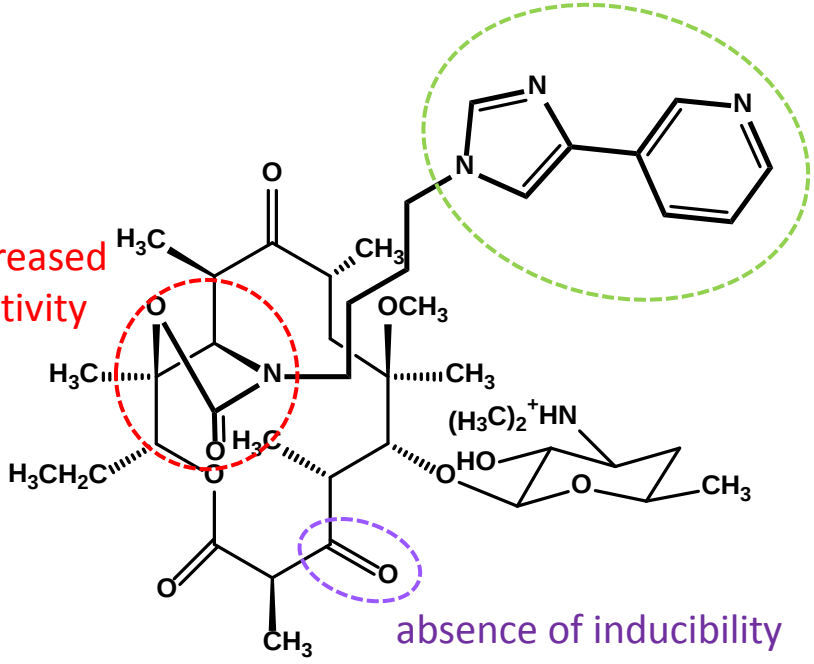



increased
activity

**solithromycin**

- binding to ribosomal domain II
- poor recognition by pneumococci efflux pumps

increased
activity



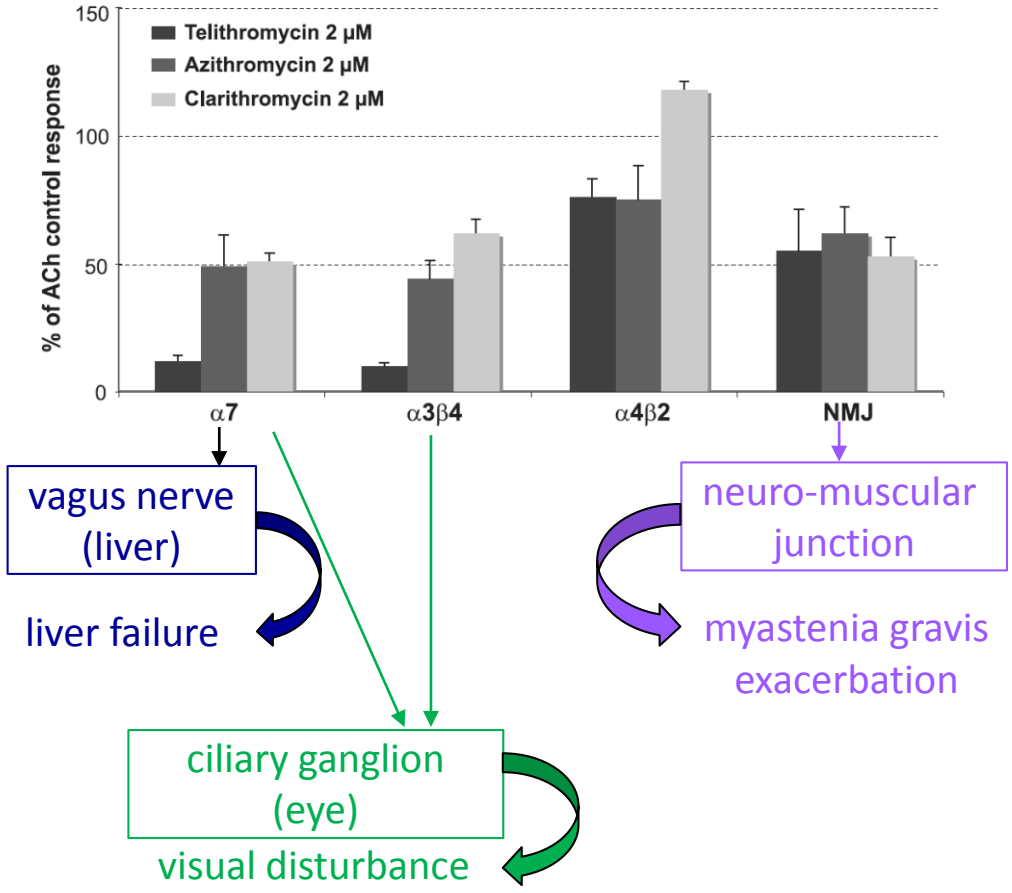

absence of inducibility
of $MLS_B$ resistance

**telithromycin**

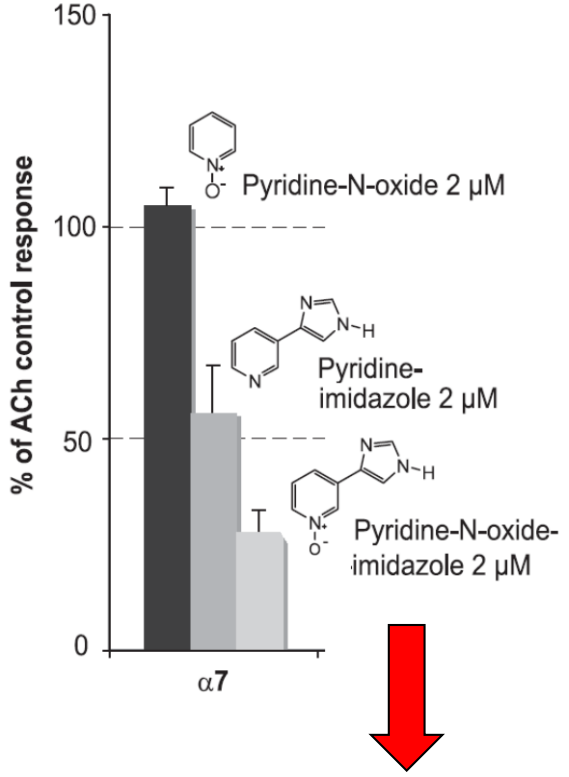
*Adapted from Van Bambeke, Ann. Med (2014) 46:512-29*

# telithromycin : structure-toxicity relationship

Inhibition of acetycholine nicotinic receptors




Role of telithromycin metabolites




Metabolites
NOT present for solithromycin

*Adapted from Bertrand et al, AAC (2010) 54:5399-42*

# solithromycin: ongoing clinical trials

| Study number & development Phase | Drugs and doses | Study title | Status |
|---|---|---|---|
| **NCT01966055; Phase I** | Solithromycin; dose not specified | Pharmacokinetics and Safety of Solithromycin Capsules in Adolescents | Recruiting |
| **NCT01168713; Phase II** | Oral solithromycin (800 mg QD day 1; 400 mg QD days 2-5) ; comparator: oral levofloxacin (750 mg QD days 1-5) | Efficacy and Safety Study of Oral CEM-101 Compared to Oral Levofloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia | Completed (2011) |
| **NCT01591447; Phase II** | Single dose solithromycin 1000 mg by oral route | Safety and Efficacy Study of Single-Dose Oral CEM-101 in Patients With Uncomplicated Urogenital Gonorrhea | Completed (2013) |
| **NCT01968733; Phase III** | Solithromycin (intravenous with the potential step-down to oral); comparator: moxifloxacin (intravenous with the potential step-down to oral); doses not specified | Efficacy and Safety Study of Intravenous to Oral Solithromycin (CEM-101) Compared to Intravenous to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-IV) | Recruiting |
| **NCT01756339; Phase III** | Solithromycin (800 mg orally on day 1 followed by 400 mg daily on days 2 through 5, followed by placebo on days 6 and 7); comparator: moxifloxacin (400 mg orally on Day 1 to 7) | Efficacy and Safety Study of Oral Solithromycin (CEM-101) Compared to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-ORAL) | Recruiting |

*Van Bambeke, Ann. Med (2014) 46:512-29*

# solithromycin: ongoing clinical trials

| Study number & development Phase | Drugs and doses | Study title | Status |
|---|---|---|---|
| **NCT01966055; Phase I** | Solithromycin; dose not specified | Pharmacokinetics and Safety of Solithromycin Capsules in Adolescents | Recruiting |
| **NCT01168713; Phase II** | Oral solithromycin (800 mg QD day 1; 400 mg QD days 2-5) ; comparator: oral levofloxacin (750 mg QD days 1-5) | Efficacy and Safety Study of Oral CEM-101 Compared to Oral Levofloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia | Completed (2011) |
| **NCT01591447; Phase II** | Single dose solithromycin 1000 mg by oral route | Safety and Efficacy Study of Single-Dose Oral CEM-101 in Patients With Uncomplicated Urogenital Gonorrhea | Completed (2013) |
| **NCT01968733; Phase III** | Solithromycin (intravenous with the potential step-down to oral); comparator: moxifloxacin (intravenous with the potential step-down to oral); doses not specified | Efficacy and Safety Study of Intravenous to Oral Solithromycin (CEM-101) Compared to Intravenous to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-IV) | Recruiting |
| **NCT01756339; Phase III** | Solithromycin (800 mg orally on day 1 followed by 400 mg daily on days 2 through 5, followed by placebo on days 6 and 7); comparator: moxifloxacin (400 mg orally on Day 1 to 7) | Efficacy and Safety Study of Oral Solithromycin (CEM-101) Compared to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-ORAL) | Recruiting |

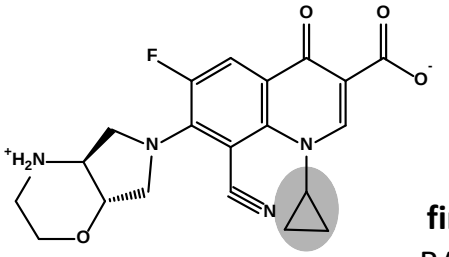
*Van Bambeke, Ann. Med (2014) 46:512-29*

# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

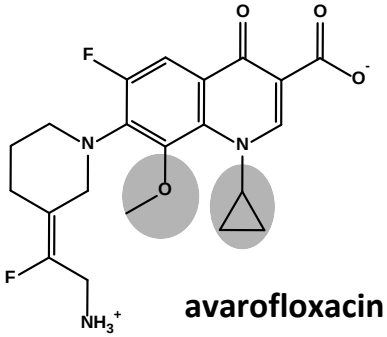
| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Cempra | solithromycin | ketolide | Phase III<br>CAPB | ✓ | ✓ | |
| Melinta | delafloxacin | fluoroquinolone | Phase III<br>ABSSSI | ✓ | ✓ | |
| TaiGen | nemonoxacin | fluoroquinolone | Phase III<br>CAPB / ABSSSI | ✓ | ✓ | |
| Dong | zabofloxacin | fluoroquinolone | Phase III<br>CAPB | ✓ | ✓ | |
| Activis | avarofloxacin | fluoroquinolone | Phase II completed<br>CAPB / ABSSSI | ✓ | ✓ | |
| MerLion | finafloxacin | fluoroquinolone | Phase II<br>ABSSSI | ✓ | ✓ | |
| GSK | GSK2140944 | topoisomerase inhibitor | Phase II<br>respiratory / ABSSSI | ✓ | ✓ | |

*Constructed based on www.pewtrusts.org*

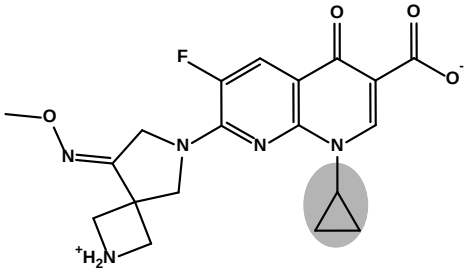
# new (fluoro)quinolones



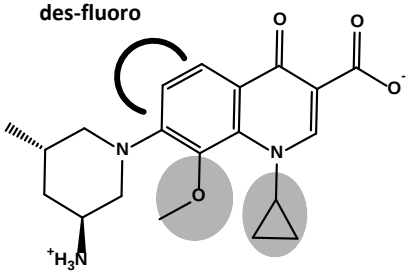
**finafloxacin**
BAY35-3377



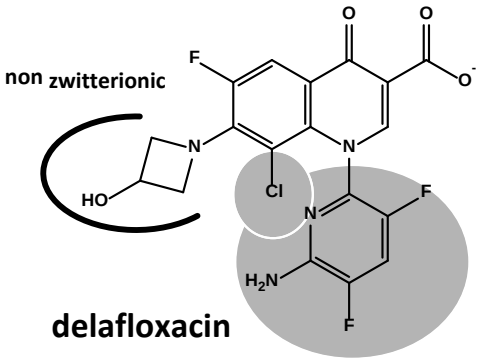
**avarofloxacin**
JNJ-Q2



**zabofloxacin**
DW-224a



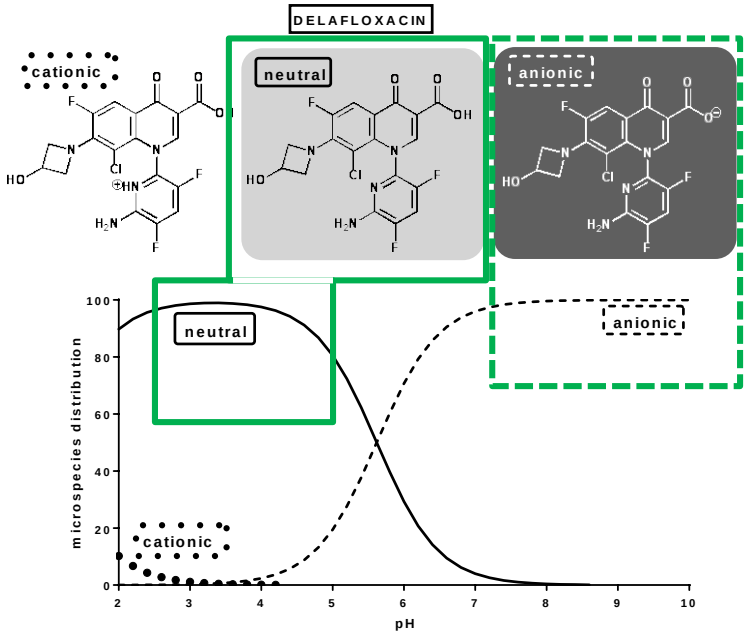

**nemonoxacin**
TG-873870

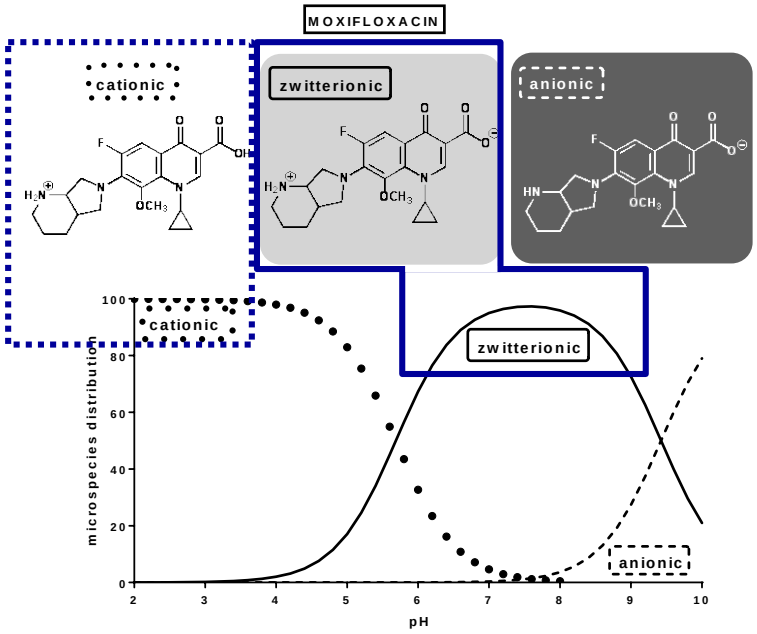



**delafloxacin**
WQ-3034; ABT-492; RX-3341

*Van Bambeke, Ann. Med (2014) 46:512-29*

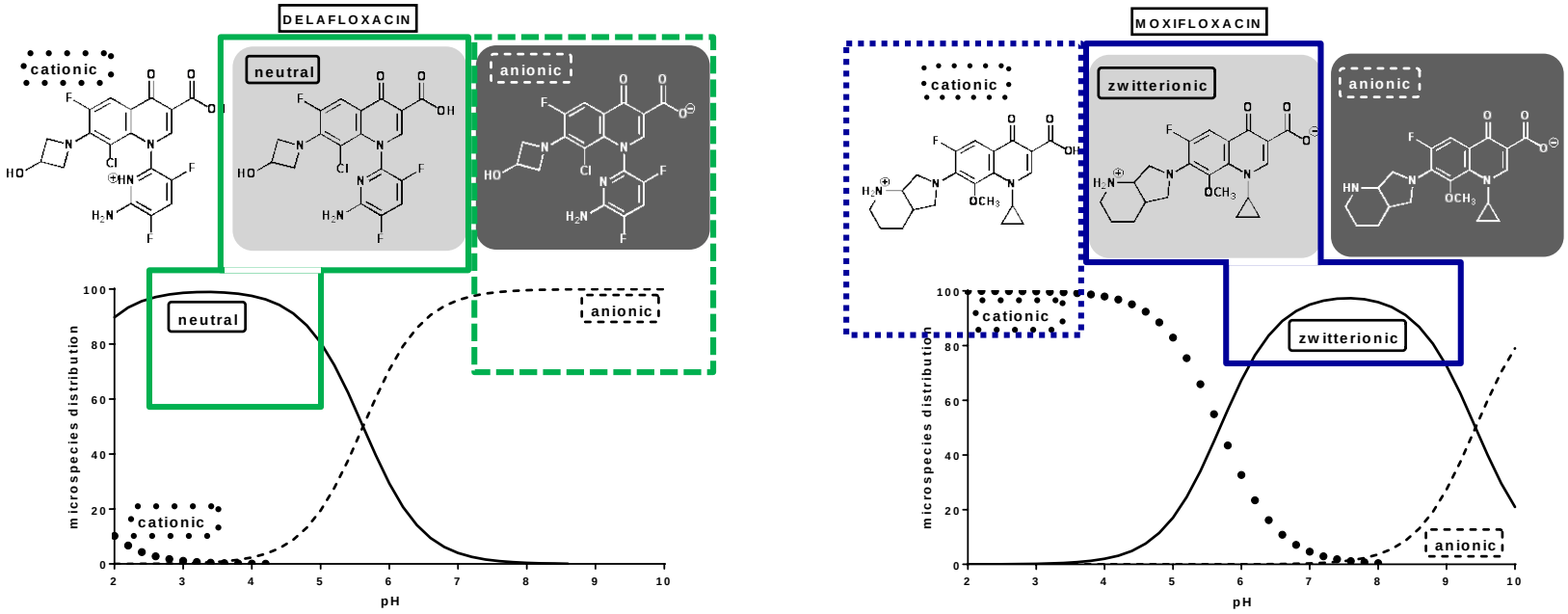
# Delafloxacin, the first “non-zwitterionic” quinolone



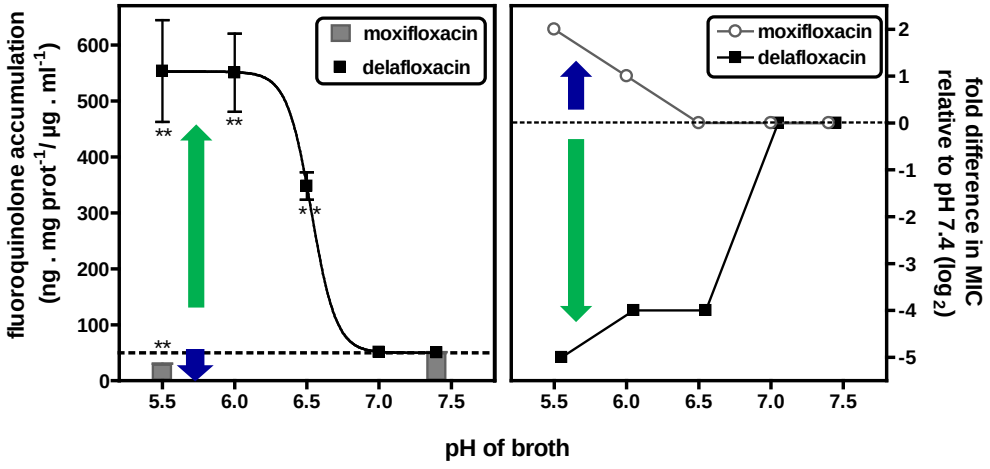

*Van Bambeke, Future Microbiol. (in press)*

# Delafloxacin, the first “non-zwitterionic” quinolone




Increased

- uptake by bacteria
- activity at acidic pH




*Van Bambeke, Future Microbiol. (in press); Lemaire et al, AAC (2011) 55:649-58*

# new (fluoro)quinolones: *in vitro* activity

Susceptibility of relevant pathogens to antibiotics in development and their comparators.

| Species | Phenotype | Antibiotic | $MIC_{50}$ (mg/L) | $MIC_{90}$ (mg/L) | MIC range (mg/L) |
|---|---|---|---|---|---|
| *S. aureus* | MRSA FQ-S | moxifloxacin | 0.06 | 0.12 | 0.06–0.25 |
| | | finafloxacin | 0.125 | 0.25 | 0.125–0.25 |
| | | zabofloxacin | 0.031 | 0.125 | 0.016–1 |
| | | avarofloxacin | ≤0.008 | ≤0.008 | ≤0.008–0.015 |
| | | nemonoxacin | 0.03 | 0.06 | ≤0.008–0.12 |
| | | delafloxacin | | | 0.008–0.03 |
| | MRSA FQ-R | moxifloxacin | 4 | 8 | 0.25–>16 |
| | | finafloxacin | 2 | 16 | 0.25–32 |
| | | zabofloxacin | 2 | 32 | 0.016–64 |
| | | avarofloxacin | 0.25 | 0.25 | 0.015–2 |
| | | nemonoxacin | 4 | 16 | 0.25–64 |
| | | delafloxacin | | | 0.5–2 |
| *S. pneumoniae* | all | moxifloxacin | 0.12 | 0.25 | 0.008–>8 |
| | | zabofloxacin | 0.063 | 1 | 0.008–4 |
| | | avarofloxacin | 0.008 | 0.015 | ≤0.004–1 |
| | S | moxifloxacin | 0.12 | 0.25 | 0.03–0.25 |
| | | zabofloxacin | 0.016 | 0.03 | ≤0.001–0.06 |
| | | nemonoxacin | 0.12 | 0.12 | 0.06–0.25 |

⇨as or more active ~ moxifloxacin, but cross resistance

*Adapted from Van Bambeke, Ann. Med (2014) 46:512-29*

# new (fluoro)quinolones: ongoing clinical trials

| Study number & development Phase | Drugs and doses | Study title | Status |
|---|---|---|---|
| **ZABOFLOXACIN** | | | |
| **NCT01081964; Phase II** | Zabofloxacin (400 mg orally QD for 3 or 5 days); comparator: levofloxacin (500 mg orally QD for 7 days) | Safety and Efficacy Study of Oral Zabofloxacin in Community Acquired Pneumonia | Completed (2012) |
| **NCT01658020; Phase III** | Zabofloxacin (400 mg orally QD); comparator: moxifloxacin (400 mg orally QD) | A Study to Evaluate Efficacy and Safety Profile of Zabofloxacin Tablet 400mg and Moxifloxacin Tablet 400mg (DW224-III-3) after Multi-dose Oral Administration in Patients With Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease. | Ongoing, not recruiting |

*Adapted from Van Bambeke, Ann. Med (2014) 46:512-29*

# new (fluoro)quinolones: ongoing clinical trials

| Study number & development Phase | Drugs and doses | Study title | Status |
|---|---|---|---|
| **NEMONOXACIN** | | | |
| **NCT00434291; Phase II** | Not provided | Safety and Efficacy Comparison of TG-873870 (Nemonoxacin) to Levofloxacin in Community-Acquired Pneumonia | Not provided |
| **NCT00685698; Phase II** | Nemonoxacin 750 mg, oral administration, once daily for 7±1 and 14±1 days | Safety and Efficacy Study of TG-873870 (Nemonoxacin) in Diabetic Foot Infections | Completed (2009) |
| **NCT01537250; Phase II** | Nemonoxacin (750 mg orally 2 tablets or 500 mg orally 3 tablets) ; comparator: levofloxacin (500 mg orally QD + placebo) for 7 days | Study to Assess the Efficacy and Safety of Nemonoxacin Malate in Treating Adult Patients With Community-acquired Pneumonia (CAP) | Completed (2010) |
| **NCT01944774; Phase II** | Nemonoxacin (500 mg or 650 mg QD IV for 7~14 days) ; comparator: moxifloxacin (400 mg QD IV for 7~14 days) | Study to Evaluate the Efficacy and Safety of Intravenous Infusion With TG-873870 (nemonoxacin) Versus Moxifloxacin in Treating Adult Patients With Community Acquired Pneumonia (CAP) | Recruiting |
| **NCT01529476; Phase III** | Nemonoxacin (500 mg orally) ; comparator levofloxacin (500 mg orally) for 7~14 days | Study to Evaluate the Efficacy and Safety of Oral Administration With Nemonoxacin and Levofloxacin in Patients With Community-acquired Pneumonia (CAP) | Completed (2012) |

*Adapted from Van Bambeke, Ann. Med (2014) 46:512-29*

# new (fluoro)quinolones: ongoing clinical trials

| Study number & development Phase | Drugs and doses | Study title | Status |
|---|---|---|---|
| **NEMONOXACIN** | | | |
| **NCT00434291; Phase II** | Not provided | Safety and Efficacy Comparison of TG-873870 (Nemonoxacin) to Levofloxacin in Community-Acquired Pneumonia | Not provided |
| **NCT00685698; Phase II** | Nemonoxacin 750 mg, oral administration, once daily for 7±1 and 14±1 days | Safety and Efficacy Study of TG-873870 (Nemonoxacin) in Diabetic Foot Infections | Completed (2009) |
| **NCT01537250; Phase II** | Nemonoxacin (750 mg orally 2 tablets or 500 mg orally 3 tablets) ; comparator: levofloxacin (500 mg orally QD + placebo) for 7 days | Study to Assess the Efficacy and Safety of Nemonoxacin Malate in Treating Adult Patients With Community-acquired Pneumonia (CAP) | Completed (2010) |
| **NCT01944774; Phase II** | Nemonoxacin (500 mg or 650 mg QD IV for 7~14 days) ; comparator: moxifloxacin (400 mg QD IV for 7~14 days) | Study to Evaluate the Efficacy and Safety of Intravenous Infusion With TG-873870 (nemonoxacin) Versus Moxifloxacin in Treating Adult Patients With Community Acquired Pneumonia (CAP) | Recruiting |
| **NCT01529476; Phase III** | Nemonoxacin (500 mg orally) ; comparator levofloxacin (500 mg orally) for 7~14 days | Study to Evaluate the Efficacy and Safety of Oral Administration With Nemonoxacin and Levofloxacin in Patients With Community-acquired Pneumonia (CAP) | Completed (2012) |

*Adapted from Van Bambeke, Ann. Med (2014) 46:512-29*

# new (fluoro)quinolones: ongoing clinical trials

| Study number & development Phase | Drugs and doses | Study title | Status |
|---|---|---|---|
| **DELAFLOXACIN** | | | |
| **NCT00719810; Phase II** | Delafloxacin (300 mg or 450 mg IV BID) ; comparator: tigecycline (100 mg on day 1 then 50 mg IV BID) | Safety and Efficacy Study of a Fluoroquinolone to Treat Complicated Skin Infections | Completed (2008) |
| **NCT01283581; Phase II** | Delafloxacin (300mg IV BID) for 5-14 days; comparators: linezolid (600mg IV BID) and vancomycin (15mg/kg, up to 1250 mg, IV BID) for 5-14 days | A Study to Assess Objective Endpoint Measurements of Response in Bacterial Skin Infections | Completed (2011) |
| **NCT01811732; Phase III** | Delafloxacin (300 mg IV BID) for up 5-14 days; comparator: vancomycin (15mg/kg IV) + aztreonam (2g) BID | Delafloxacin Versus Vancomycin and Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections | Recruiting |
| **NCT01984684; Phase III** | Delafloxacin (300 mg IV BID 300mg iv BID for 3 days) followed by 450mg oral BID for up 5-14 days total; comparator: vancomycin (15mg/kg IV) + aztreonam (2g) BID | Delafloxacin vs Vancomycin and Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections | Not yet recruiting |

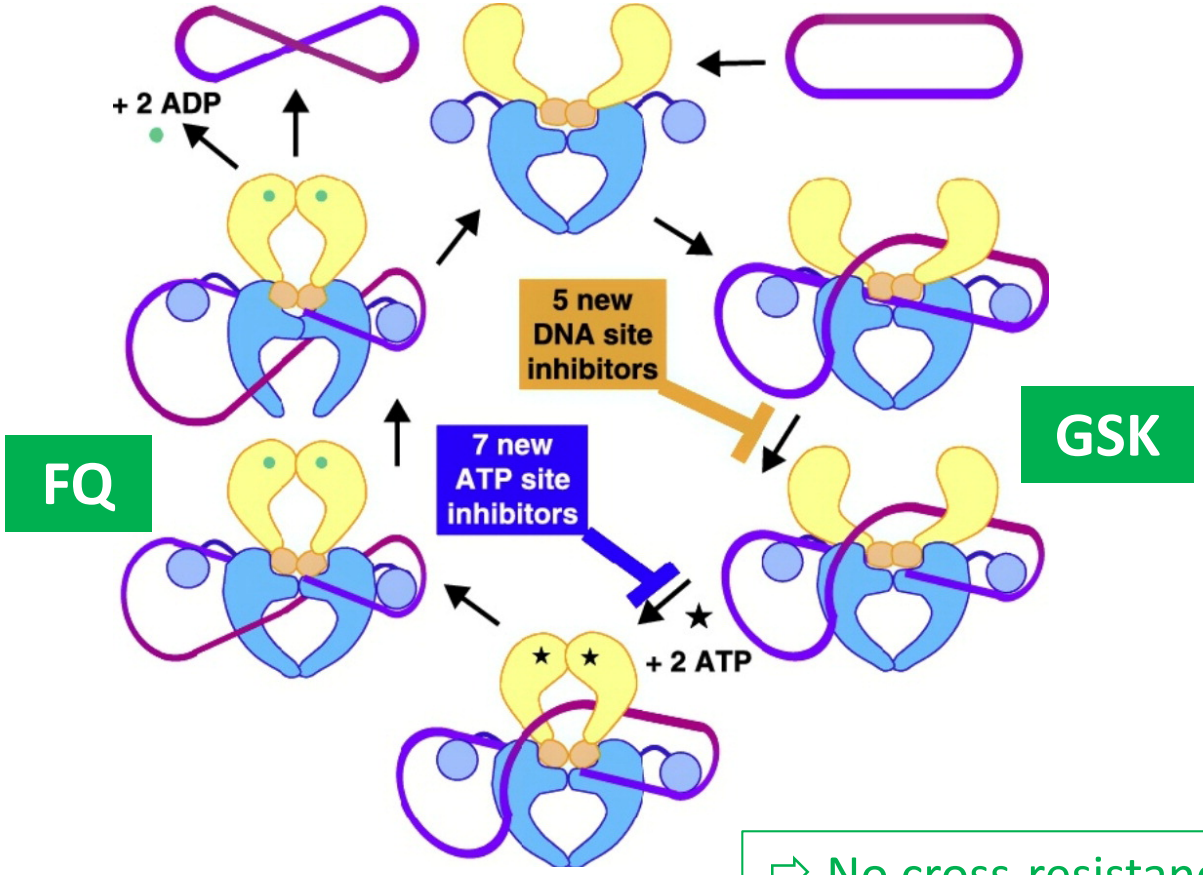
*Adapted from Van Bambeke, Ann. Med (2014) 46:512-29*

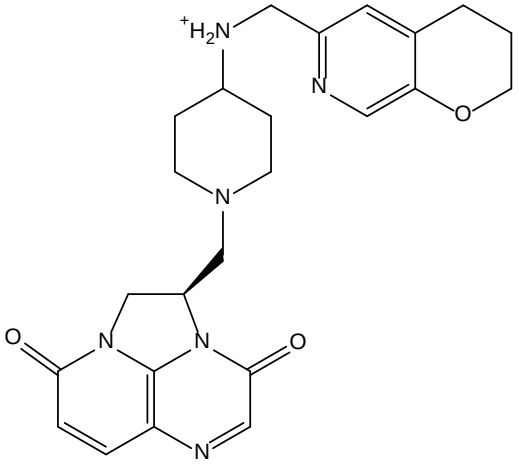
# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Cempra | solithromycin | ketolide | Phase III<br>CAPB | ✓ | ✓ | |
| Melinta | delafloxacin | fluoroquinolone | Phase III | ✓ | ✓ | |
| TaiGen | nemonoxacin | fluoroquinolone | Phase III<br>CAPB / ABSSSI | ✓ | ✓ | |
| Dong | zabofloxacin | fluoroquinolone | Phase III<br>CAPB | ✓ | ✓ | |
| Activis | avarofloxacin | fluoroquinolone | Phase II completed<br>CAPB / ABSSSI | ✓ | ✓ | |
| MerLion | finafloxacin | fluoroquinolone | Phase II<br>ABSSSI | ✓ | ✓ | |
| GSK | GSK2140944 | topoisomerase inhibitor | Phase II<br>respiratory / ABSSSI | ✓ | ✓ | |

*Constructed based on www.pewtrusts.org*

# GSK2140944 – topoisomerase inhibitor




⇨ No cross-resistance with fluoroquinolones

*Ehmann & Lahiri, Cur. Op. Pharmacol. (2014) 18:76–83*

# GSK2140944 – *In vitro* activity

Isolates Associated with Lower Respiratory Tract and Skin Infections

| Organism (N) | MIC Range | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|
| SA (1,008) | ≤0.06 - 2 | 0.25 | 0.5 |
| Methicillin-resistant SA (490) | ≤0.06-1 | 0.5 | 0.5 |
| Levofloxacin-resistant MRSA (375) | ≤0.06-1 | 0.25 | 0.5 |
| Spy (201) | 0.03-0.5 | 0.25 | 0.25 |
| Spn (549) | 0.03-1 | 0.12 | 0.25 |
| Levofloxacin-resistant Spn (22) | 0.06-0.5 | 0.25 | 0.5 |
| HI (n=981) | ≤0.015-8 | 0.5 | 1 |
| MC (n=158) | ≤0.06 - 0.12 | ≤0.06 | ≤0.06 |

*ICAAC (2013) F1216*

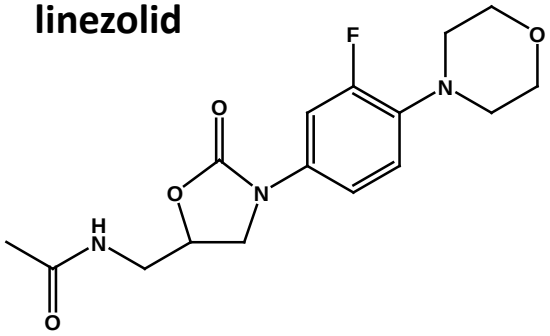
# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Melinta | radezolid | oxazolidinone | Phase II CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Paratek | omadacycline | aminomethyl cyclines | Phase III CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Cempra | fusidic acid | fusidane | Phase III ABSSSI | ✓ | | |
| Debiopharm | Debio1452 | FabI inhibitor | Phase II S. aureus ABSSSI | ✓ | | |
| Crystal-genomics | CG-400549 | FabI inhibitor | Phase II ABSSSI / osteomyelitis | ✓ | | |
| Theravance | TD-1792 | glycopeptide + cephalosporine | Phase II completed cSSSI | ✓ | ✓ | |
| Nabriva | lefamulin | pleuromutilin | Phase II completed ABSSSI /CABP/HA-VABP | ✓ | ✓ | ✓ |
| Cellceutix | brilacidin | defensin-mimetic | Phase II completed ABSSSI | ✓ | | ✓ |

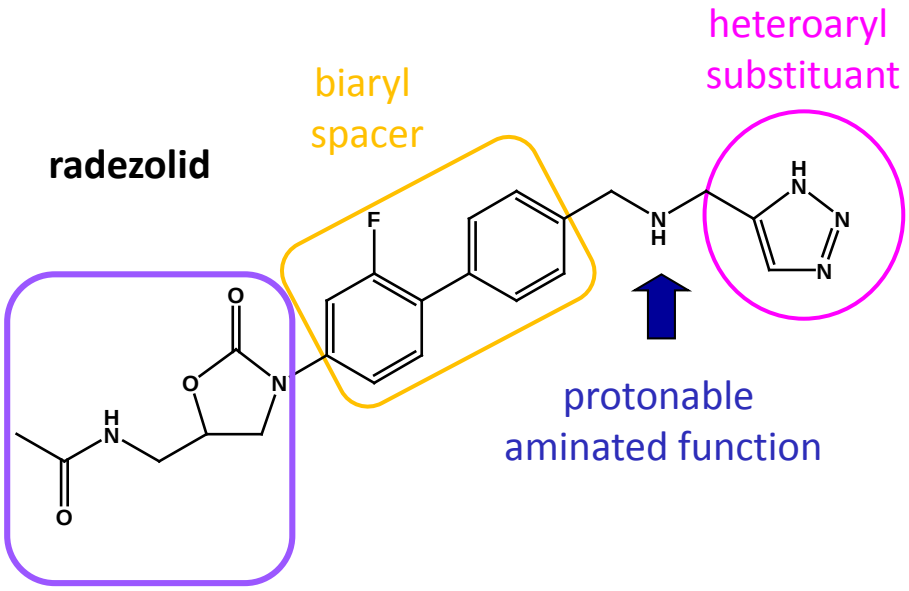
*Constructed based on www.pewtrusts.org*

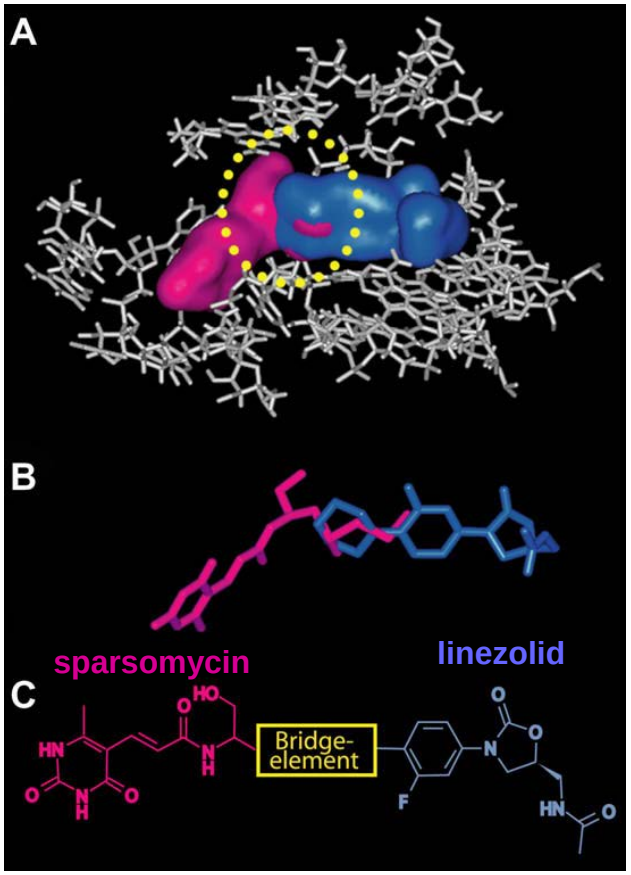
# radezolid vs linezolid

**linezolid**



**radezolid**




*Zhou et al., J. Bioorg. Med. Chem. Lett. (2008) 18:6179-83*

# Radezolid vs linezolid

Oxazolidinone MICs for *S. aureus* ribosomal mutants

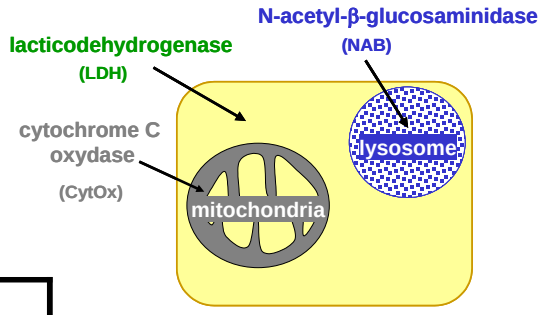
| Strain[a] | Source or reference | Resistance mechanism[b] | MIC (μg/ml)[c] | | |
|---|---|---|---|---|---|
| | | | LZD | TR-700 | RZD |
| 29213 | ATCC | | 2 | 0.5 | 1 |
| 29213-1 | 43 | 23S (G2447T ×3) | 32 | 4 | 4 |
| 29213-2 | 43 | 23S (T2500A ×2) | 8 | 2 | 4 |
| 29213-3 | 43 | L3 (ΔPhe127-His146) | 8 | 2 | 2 |
| 33591 | ATCC | | 1 | 0.25 | 0.5 |
| 33591-1 | 43 | 23S (G2576T ×3) | 16 | 2 | 2 |
| 33591-2 | 43 | 23S (G2576T/T2571C ×3) | 16 | 2 | 2 |
| 33591-3 | 43 | L4 (Lys68Gln) | 2 | 0.5 | 1 |
| NRS127 | NARSA[d] | L3 (ΔSer145) | 8 | 1 | 4 |

Oxazolidinone MICs for *S. aureus cfr* strains

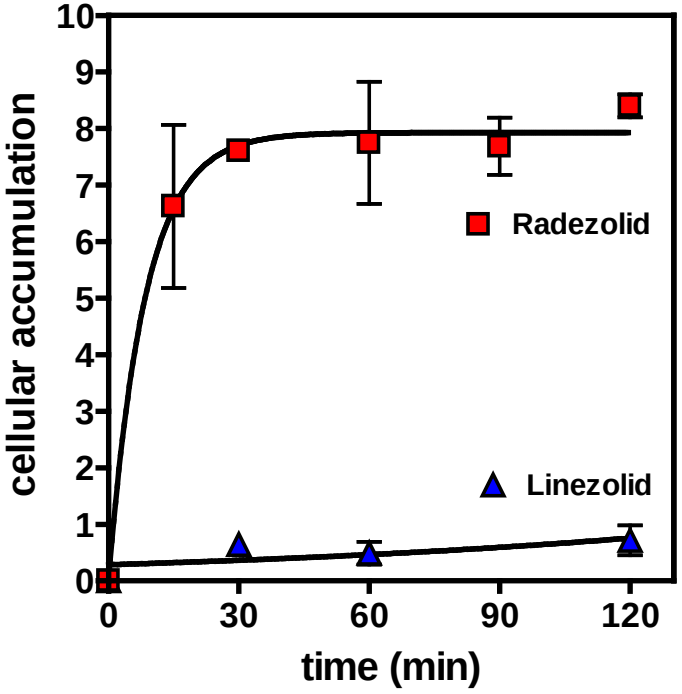
| Strain | Reference | Presence of *cfr* | MIC (μg/ml)[a] | | |
|---|---|---|---|---|---|
| | | | LZD | TR-700 | RZD |
| RN4220(pLI50) | 68 | − | 2 | 0.5 | 0.5 |
| RN4220(pLXM1)[b] | 68 | + | 8 | 0.5 | 1 |
| CM05Δ[c] | 44 | − | 2 | 0.5 | 1 |
| CM05[c] | 68 | + | 8 | 0.5 | 2 |
| 29213 | ATCC | − | 2 | 0.5 | 1 |
| 29213(p42262)[d] | 45 | + | 16 | 0.5 | 2 |
| 42262[e] | 51 | + | 16 | 0.5 | 4 |

*Locke et al, AAC (2010) 54: 5337–43*

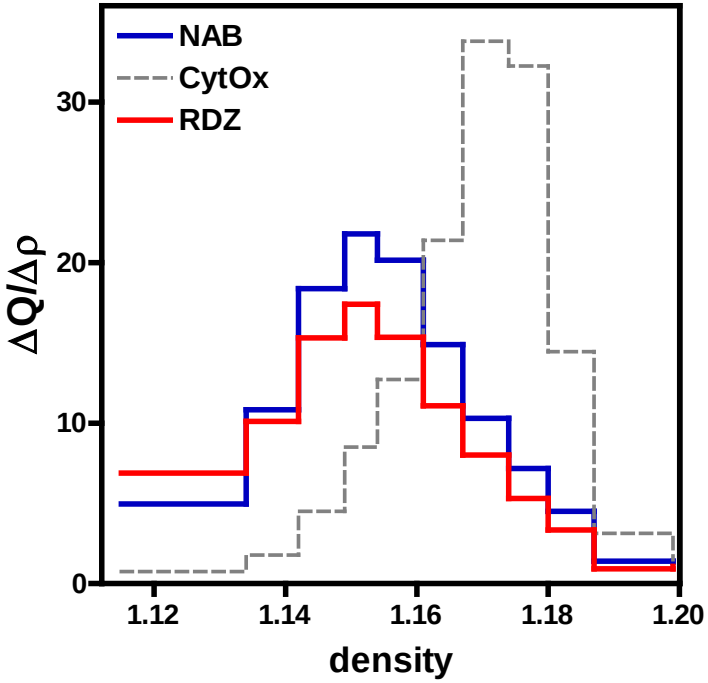
# Radezolid cellular pharmacokinetics in macrophages




Cellular accumulation




Subcellular distribution




⇨accumulation in acidic vacuoles

*Lemaire et al., AAC (2010) 54:2540-48*

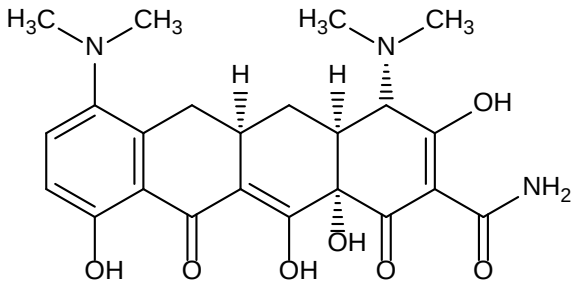
# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Melinta | radezolid | oxazolidinone | Phase II<br>CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Paratek | omadacycline | aminomethyl cyclines | Phase III<br>CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Cempra | fusidic acid | fusidane | Phase III<br>ABSSSI | ✓ | | |
| Debiopharm | Debio1452 | FabI inhibitor | Phase II<br>S. aureus ABSSSI | ✓ | | |
| Crystal-genomics | CG-400549 | FabI inhibitor | Phase II<br>ABSSSI / osteomyelitis | ✓ | | |
| Theravance | TD-1792 | glycopeptide + cephalosporine | Phase II completed<br>cSSSI | ✓ | ✓ | |
| Nabriva | lefamulin | pleuromutilin | Phase II completed<br>ABSSSI /CABP/HA-VABP | ✓ | ✓ | ✓ |
| Cellceutix | brilacidin | defensin-mimetic | Phase II completed<br>ABSSSI | ✓ | | ✓ |

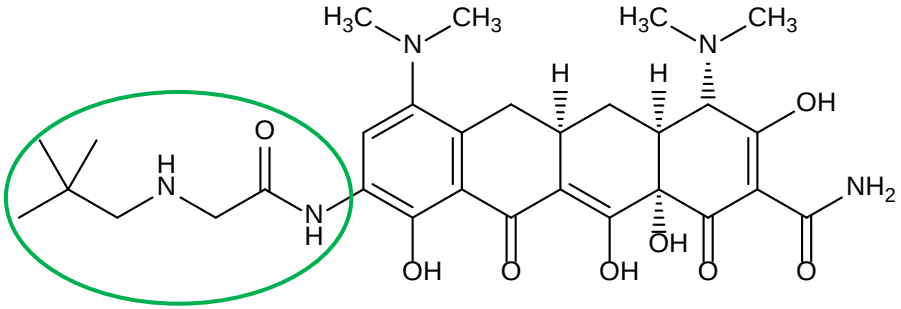
*Constructed based on www.pewtrusts.org*

# Omadacycline (PTK-0796) vs tigecycline

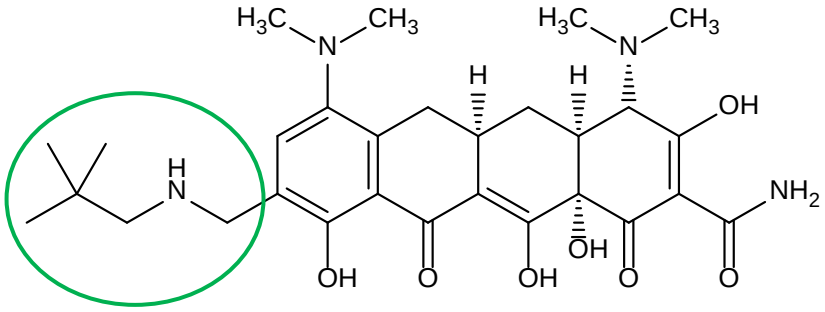
**minocycline**

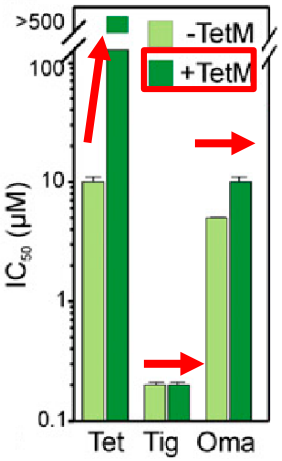


**tigecycline**



**omadacycline**

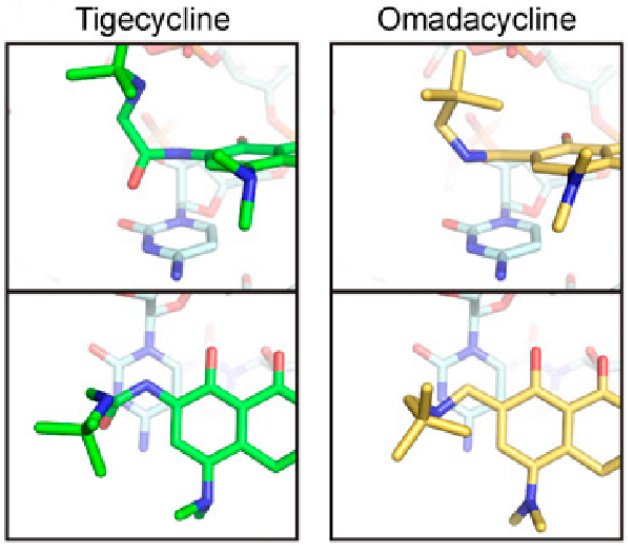





Active if

- ribosomal protection
- Tet-mediated efflux

Inactive if broad spectrum efflux (*P. aeruginosa*)




*Jenner et al., PNAS (2013) 110:3812-16*

# Omadacycline : CSSSI Phase II data

Omadacycline 100 mg [i.v.] QD; possible transition to 200 mg [p.o.] QD
linezolid 600 mg [i.v.] BID; possible transition to 600 mg [p.o.]y BID

TABLE 4 Rates of successful clinical response at test of cure by analysis population

| Population | Rate of clinical response (% [no. successful/total no.]) in patients given: | |
|---|---|---|
| | Omadacycline | Linezolid |
| Intent to treat | 88.3 (98/111) | 75.9 (82/108) |
| Modified intent to treat | 89.3 (75/84) | 75.6 (59/78) |
| Clinically evaluable | 98.0 (98/100) | 93.2 (82/88) |
| Subjects with no prior antibiotics[a] | 96.3 (53/55) | 95.2 (40/42) |
| Microbiologically evaluable | 97.4 (75/77) | 93.7 (59/63) |
| *S. aureus* | 97.2 (70/72) | 92.7 (51/55) |
| MRSA | 97.7 (43/44) | 93.8 (30/32) |
| Gram-positive bacterium other than *S. aureus* | 100 (3/3) | 100 (7/7) |
| Gram-negative bacterium | 100 (2/2) | 100 (1/1) |

[a] No prior antibiotic exposure 72 h before enrollment.

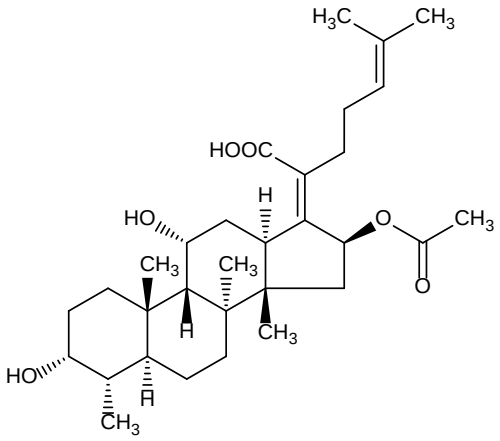
*Noel et al., AAC (2012) 56:5650-546*

# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Melinta | radezolid | oxazolidinone | Phase II CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Paratek | omadacycline | aminomethyl cyclines | Phase III CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Cempra | fusidic acid | fusidane | Phase III ABSSSI | ✓ | | |
| Debiopharm | Debio1452 | FabI inhibitor | Phase II S. aureus ABSSSI | ✓ | | |
| Crystal-genomics | CG-400549 | FabI inhibitor | Phase II ABSSSI / osteomyelitis | ✓ | | |
| Theravance | TD-1792 | glycopeptide + cephalosporine | Phase II completed cSSSI | ✓ | ✓ | |
| Nabriva | lefamulin | pleuromutilin | Phase II completed ABSSSI /CABP/HA-VABP | ✓ | ✓ | ✓ |
| Cellceutix | brilacidin | defensin-mimetic | Phase II completed ABSSSI | ✓ | | ✓ |

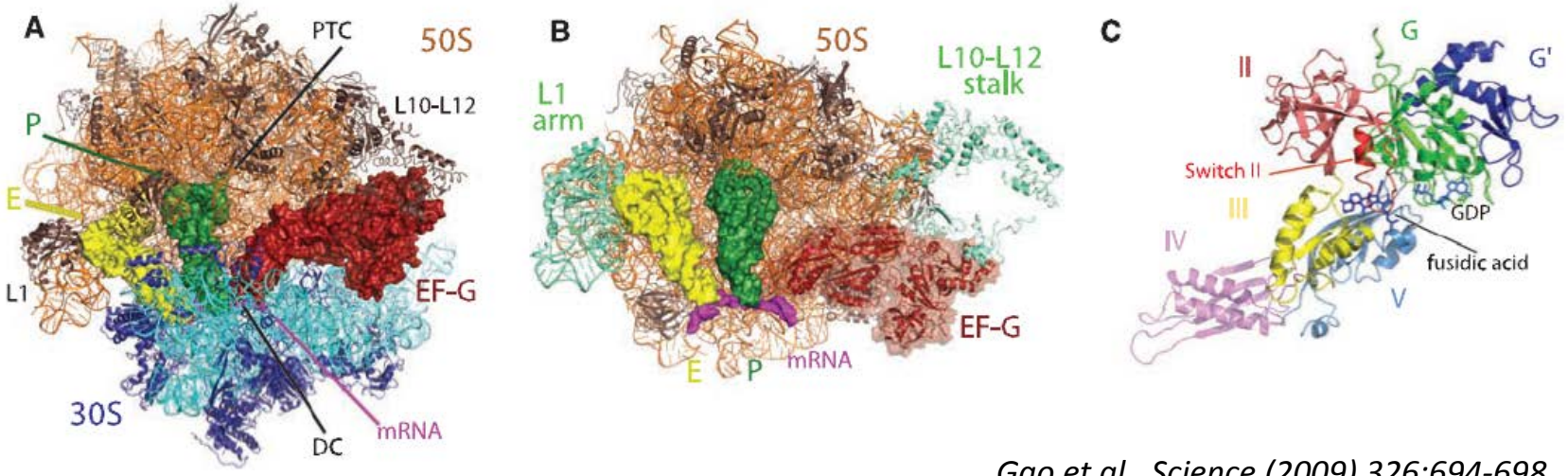
*Constructed based on www.pewtrusts.org*

# Fusidic acid




Elongation factor G = GTP-ase
~ translocation of tRNA-mRNA

Fusidic acid prevents EF-G release from the ribosome




*Gao et al., Science (2009) 326:694-698*

# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

| company | drug | class | status | MRSA | MDRSP | VRE |
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| Melinta | radezolid | oxazolidinone | Phase II CAPB / ABSSSI | ✓ | ✓ | ✓ |
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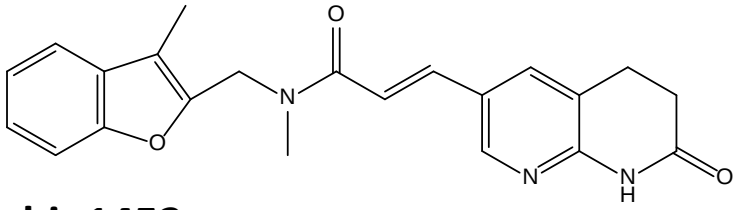
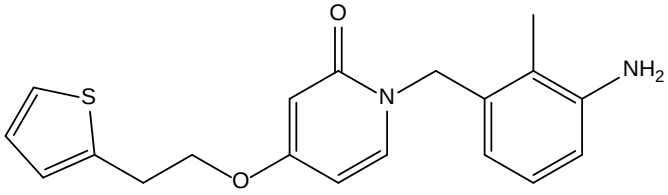
| Debiopharm | Debio1452 | FabI inhibitor | Phase II S. aureus ABSSSI | ✓ | | |
| Crystal-genomics | CG-400549 | FabI inhibitor | Phase II ABSSSI / osteomyelitis | ✓ | | |
| Theravance | TD-1792 | glycopeptide + cephalosporine | Phase II completed cSSSI | ✓ | ✓ | |
| Nabriva | lefamulin | pleuromutilin | Phase II completed ABSSSI /CABP/HA-VABP | ✓ | ✓ | ✓ |
| Cellceutix | brilacidin | defensin-mimetic | Phase II completed ABSSSI | ✓ | | ✓ |

*Constructed based on www.pewtrusts.org*

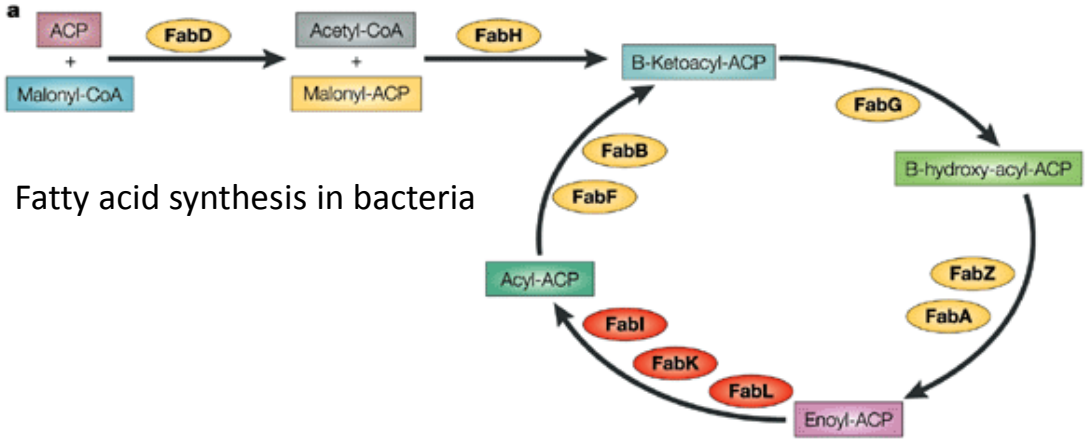
# FabI (Enoyl-[acyl-carrier-protein] reductase) inhibitors



**Debio1452**

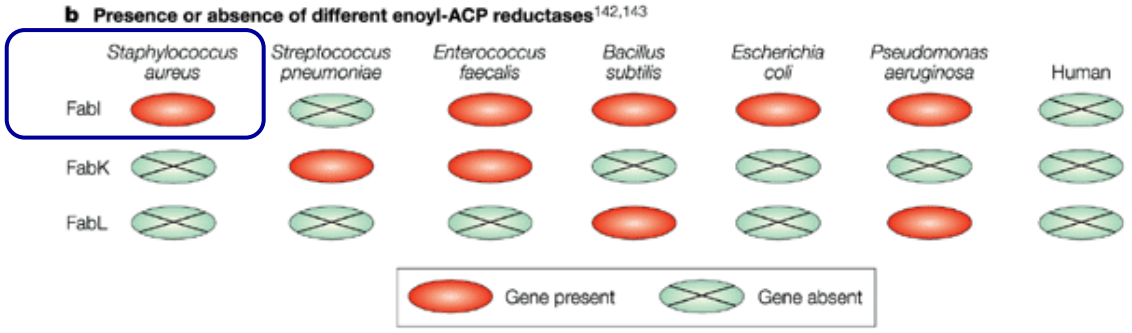


**CG-400549**




Fatty acid synthesis in bacteria

Specifically active on *S. aureus*




*Miesnel et al, Nature Rev. Gen. (2003) 4: 442-456*

# Debio (AFN) 1252 *in vitro* activity

| Species or isolate group (no. of isolates) | Agent | MIC (μg/ml) | | |
|---|---|---|---|---|
| | | 50% | 90% | Range |
| Methicillin-resistant *S. aureus* (127) | AFN-1252 | ≤0.008 | ≤0.008 | ≤0.008–0.06 |
| | Cefazolin | 64 | >128 | 32–>128 |
| | Ciprofloxacin | >16 | >16 | 0.25–>16 |
| | Clindamycin | >8 | >8 | ≤0.12–>8 |
| | Gentamicin | ≤0.5 | >32 | ≤0.5–>32 |
| | Linezolid | 2 | 4 | 0.25–4 |
| | Trimethoprim-sulfamethoxazole | ≤0.12 | 8 | ≤0.12–>8 |
| | Vancomycin | 1 | 1 | ≤0.25–2 |
| Methicillin-resistant *S. epidermidis* (9) | AFN-1252 | ≤0.008 | ≤0.008 | ≤0.008 |
| | Cefazolin | 64 | 128 | 32–128 |
| | Ciprofloxacin | >16 | >16 | 8–>16 |
| | Clindamycin | >8 | >8 | ≤0.12–>8 |
| | Gentamicin | 16 | >32 | ≤0.5–>32 |
| | Linezolid | 1 | 1 | 0.5–1 |
| | Trimethoprim-sulfamethoxazole | 4 | 8 | ≤0.12–>8 |
| | Vancomycin | 1 | 2 | 1–2 |
| *Streptococcus pneumoniae* (489) | AFN-1252 | >4 | >4 | 4–>4 |
| | Penicillin | 0.06 | 0.25 | ≤0.03–>8 |
| | Levofloxacin | 0.5 | 1 | ≤0.06–32 |
| | Ceftriaxone | ≤0.06 | 0.12 | ≤0.06–4 |
| | Linezolid | 0.5 | 1 | ≤0.12–2 |
| | Trimethoprim-sulfamethoxazole | ≤0.12 | 1 | ≤0.12–>8 |
| | Vancomycin | ≤0.25 | ≤0.25 | ≤0.25–0.5 |
| *Enterococcus faecalis* (81) | AFN-1252 | >4 | >4 | >4 |
| | Cefazolin | 32 | 128 | 0.5–>128 |
| | Ciprofloxacin | 2 | >16 | 0.25–>16 |
| | Clindamycin | >8 | >8 | ≤0.12–>8 |
| | Linezolid | 2 | 2 | 0.5–4 |
| | Trimethoprim-sulfamethoxazole | ≤0.12 | 0.25 | ≤0.12–>8 |
| | Vancomycin | 1 | 2 | 0.5–4 |

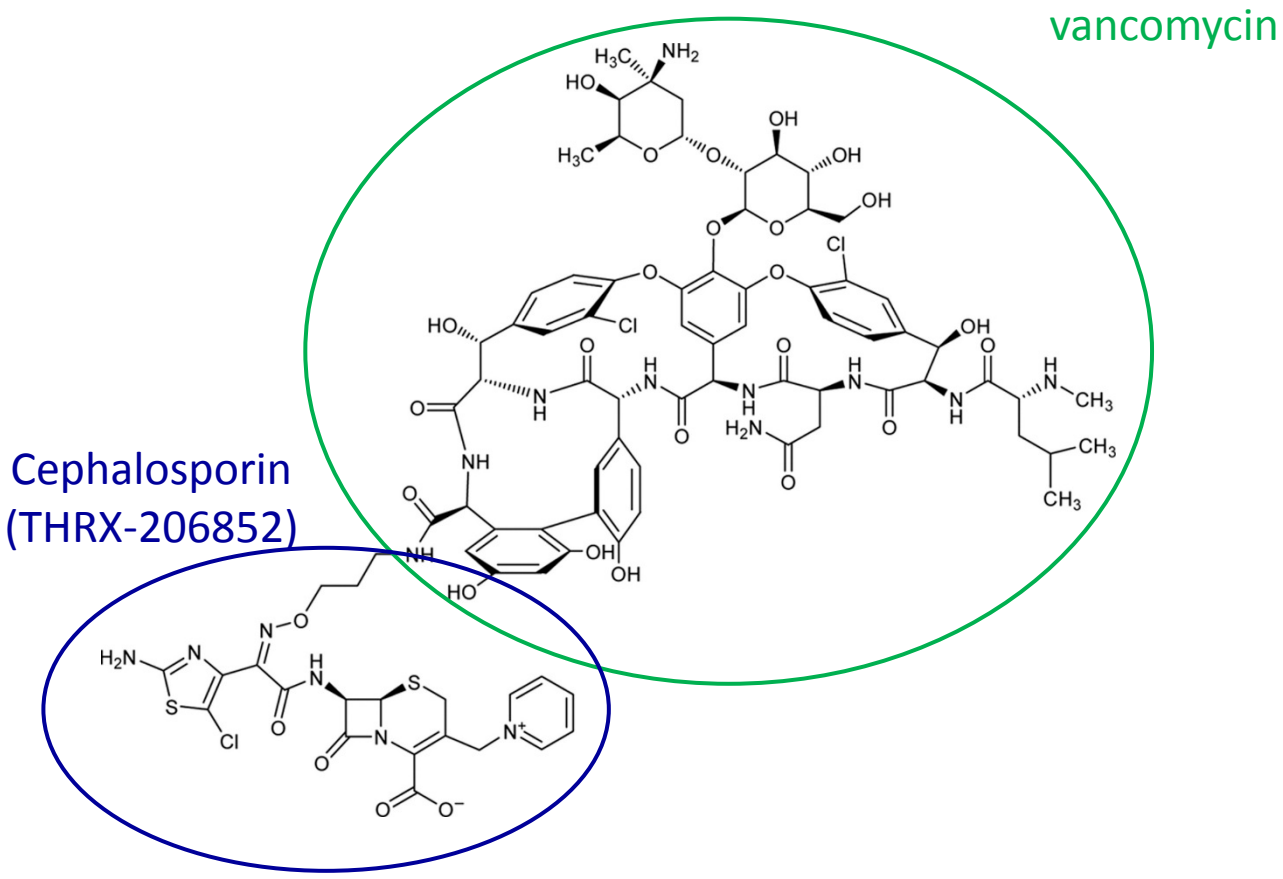
*Karlowsky et al, AAC (2009) 53: 3544-48*

# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Melinta | radezolid | oxazolidinone | Phase II CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Paratek | omadacycline | aminomethyl cyclines | Phase III CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Cempra | fusidic acid | fusidane | Phase III ABSSSI | ✓ | | |
| Debiopharm | Debio1452 | FabI inhibitor | Phase II S. aureus ABSSSI | ✓ | | |
| Crystal-genomics | CG-400549 | FabI inhibitor | Phase II ABSSSI / osteomyelitis | ✓ | | |
| Theravance | TD-1792 | glycopeptide + cephalosporine | Phase II completed cSSSI | ✓ | ✓ | |
| Nabriva | lefamulin | pleuromutilin | Phase II completed ABSSSI /CABP/HA-VABP | ✓ | ✓ | ✓ |
| Cellceutix | brilacidin | defensin-mimetic | Phase II completed ABSSSI | ✓ | | ✓ |

*Constructed based on www.pewtrusts.org*

# TD-1792



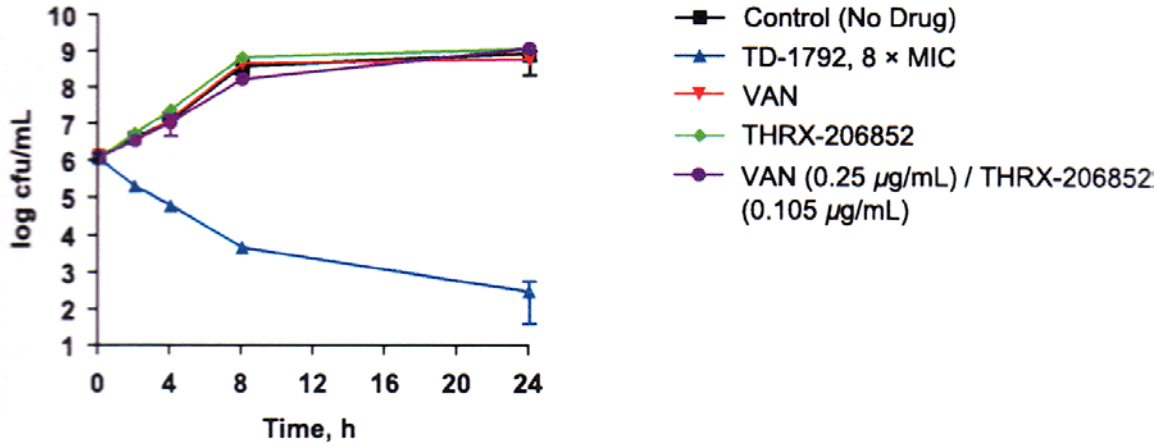

*Long et al, J. Antibiot. (2008) 61:603-14*

# TD-1792 : *in vitro* activity

## 1 In Vitro Activities of TD-1792 and Related Substructures

| Antimicrobial Agent | MIC, μg/mL | | |
|---|---|---|---|
| | MSSA | MRSA | VISA |
| TD-1792 | 0.015 | 0.03 | 0.03-0.06 |
| VAN | 1 | 1 | 8 |
| THRX-206852 | 2 | 16 | 16-32 |
| VAN / THRX-206852[a] | 1 / 0.42 | 1 / 0.42 | 4 / 1.68 |

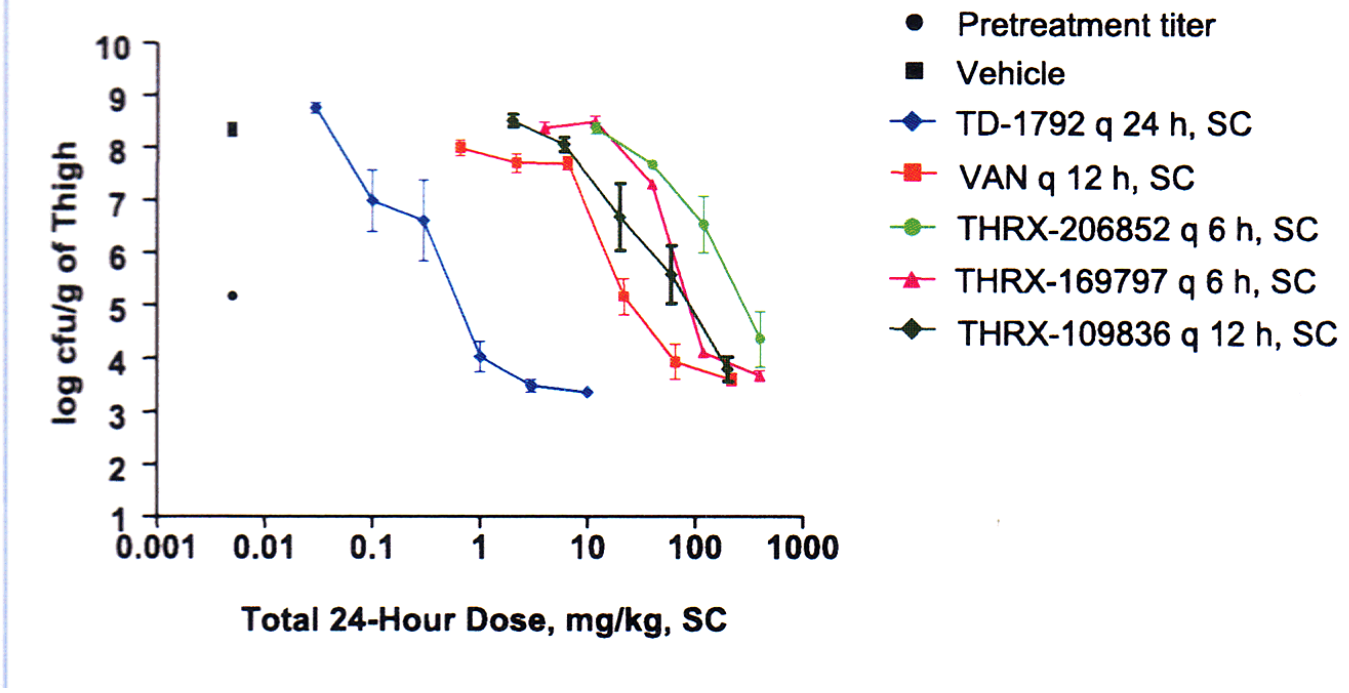
## 3 Bactericidal Activity of TD-1792 and Related Substructures Tested at 0.25 μg/mL Against MRSA




*ICAAC (2007) F1-2110*

# TD-1792 : *in vivo* activity

**4 Dose-Response Curve for TD-1792 and Related Substructures Against MRSA**




*ICAAC (2007)*

# TD-1792 : cSSSI Phase II data

TD-1792 : 2 mg/kg once daily vs vancomycin 1 g twice daily

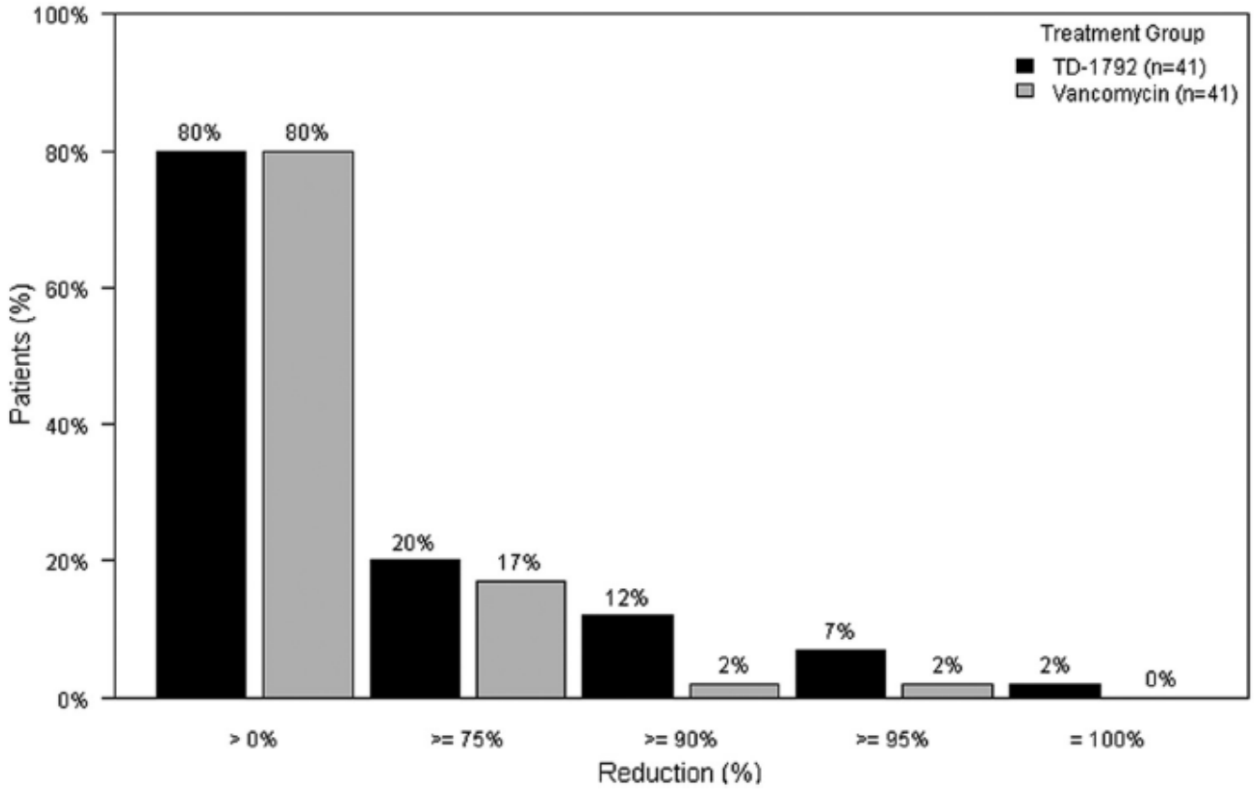



**FIG 1** Percentage of patients achieving cessation of spread or reduction of lesion size and temperature of <37.7°C at 72 h after initiation of treatment (early clinical endpoint). Only patients with baseline lesions ≥75 $cm^2$ and Gram-positive infection were included. Patients with missing percentage of change and/or missing temperature were excluded.

*Stryjewski et al, AAC (2012) 56:5476-83*

# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Melinta | radezolid | oxazolidinone | Phase II CAPB / ABSSSI | ✓ | ✓ | ✓ |
| Paratek | omadacycline | aminomethyl cyclines | Phase III CAPB / ABSSSI | ✓ | ✓ | ✓ |
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| Crystal-genomics | CG-400549 | FabI inhibitor | Phase II ABSSSI / osteomyelitis | ✓ | | |
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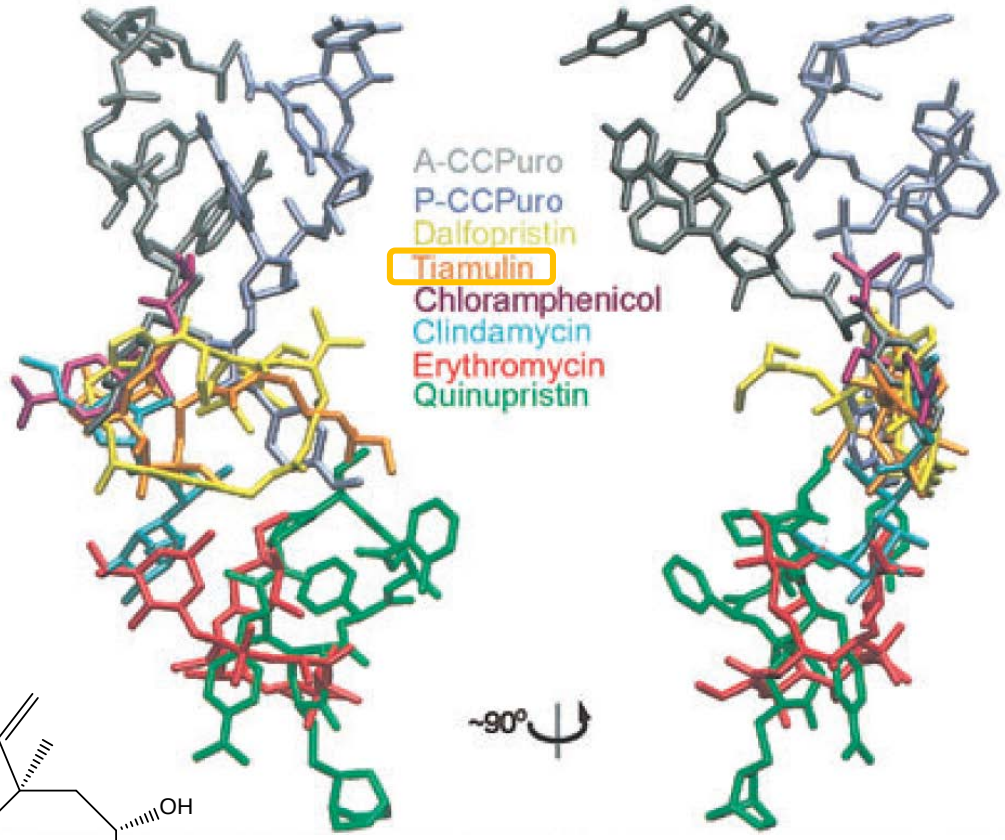
| Nabriva | lefamulin | pleuromutilin | Phase II completed ABSSSI /CABP/HA-VABP | ✓ | ✓ | ✓ |
| Cellceutix | brilacidin | defensin-mimetic | Phase II completed ABSSSI | ✓ | | ✓ |

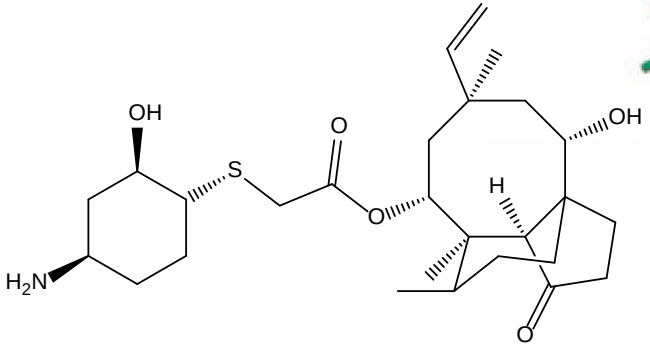
*Constructed based on www.pewtrusts.org*

# Lefamulin (BC-3781) vs retapamulin

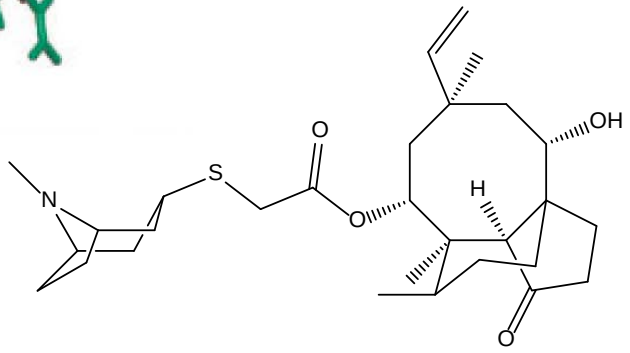
Antibiotic binding to peptidyl transferase center of 50S ribosome




**lefamulin**




**retapamulin**




*Schlünzen et al, Mol. Microbiol. (2004) 54: 1287–94*

# Lefamulin: ABSSSI Phase II data

## Microbiological Eradication and Clinical Success Rates at TOC by Baseline Pathogen

| Study Population | Pathogen | Treatment Arm: BC-3781 100 mg q12h | BC-3781 150 mg q12h | Vancomycin ≥ 1 g* q12h |
|---|---|---|---|---|
| **Microbiological Eradication Rate [%] at TOC [1,2]** | | | | |
| MITT | All pathogens | 80.0 | 84.3 | 82.4 |
| | *S. aureus* | 79.5 | 87.2 | 85.1 |
| | MRSA | 82.4 | 87.5 | 82.1 |
| ME | All pathogens | 84.8 | 90.7 | 95.0 |
| | *S. aureus* | 82.9 | 90.2 | 94.9 |
| | MRSA | 84.4 | 92.6 | 93.5 |
| **Clinical Success Rate [%] at TOC [1]** | | | | |
| CE | All pathogens | 90.0 | 88.9 | 92.2 |
| MITT | All pathogens | 82.0 | 82.4 | 82.4 |
| | *S. aureus* | 81.8 | 87.2 | 85.1 |
| | MRSA | 85.3 | 87.5 | 82.1 |
| | MRSA USA300 | 84.0 | 94.7 | 77.8 |
| ME | All pathogens | 87.0 | 88.4 | 95.0 |
| | *S. aureus* | 85.4 | 90.2 | 94.9 |
| | MRSA | 87.5 | 92.6 | 93.5 |
| | MRSA USA300 | 87.0 | 94.1 | 90.5 |

*ICAAC (2012) L1-1660*

# Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

| company | drug | class | status | MRSA | MDRSP | VRE |
|---|---|---|---|---|---|---|
| Melinta | radezolid | oxazolidinone | Phase II CAPB / ABSSSI | ✓ | ✓ | ✓ |
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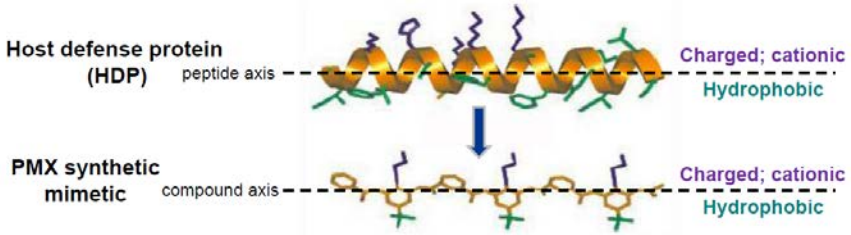
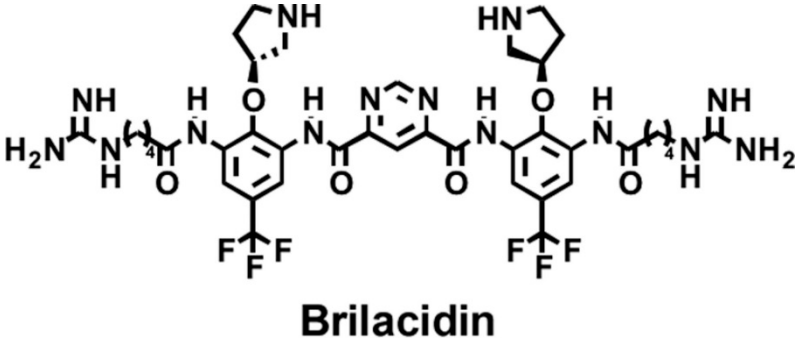
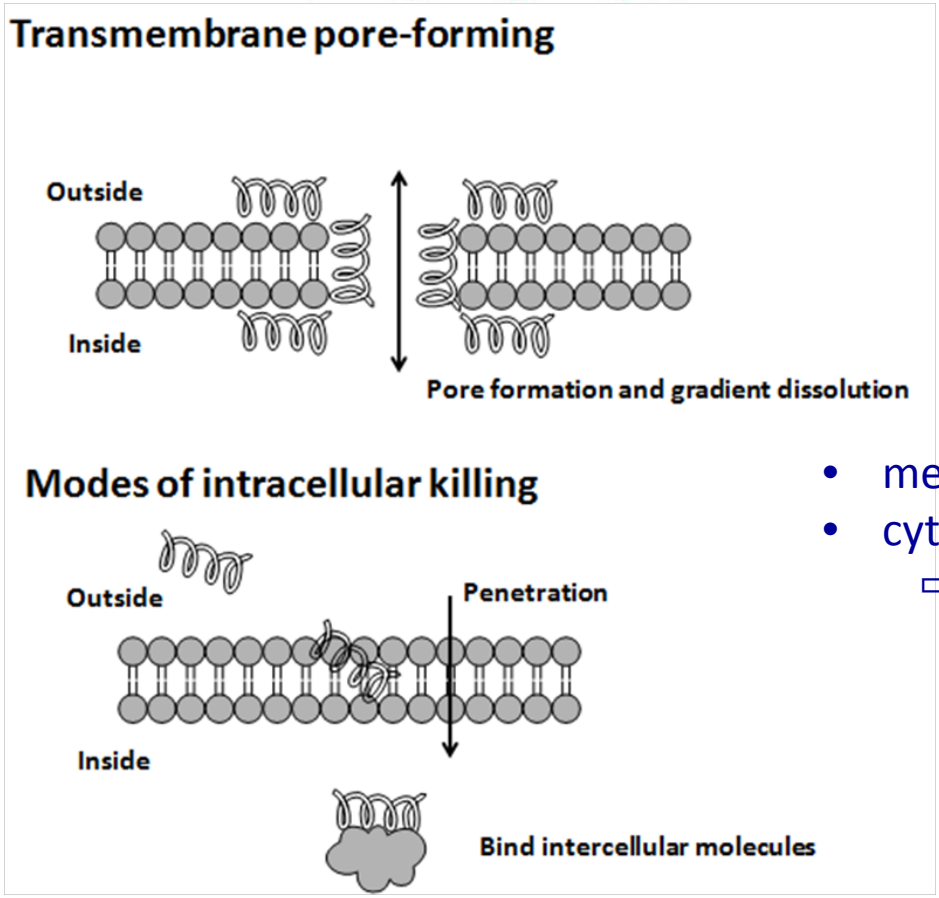
*Constructed based on www.pewtrusts.org*

# Brilacidin




- membrane depolarisation ~ daptomycin
- cytoplasmic protein misfolding
  - ⇨ upregulation of chaperones and proteases (genes involved in stress response) ~ defensins

*http://en.wikipedia.org/wiki/Antimicrobial_peptides*

*Mensa et al, AAC (2014) 58:5136-45*

# Brilacidin: phase II data

## Study CTIX-BRI-204 – Topline Results

**Proportions of Subjects with Early Clinical Response (Primary Efficacy Endpoint) - (≥20 % decrease in lesion area) at 48-72 Hours after the First Dose of Study Drug**

| | Brilacidin: 0.6 mg/kg single dose | Brilacidin: 0.8 mg/kg single dose | Brilacidin: 3-day regimen | Daptomycin 7-day regimen |
|---|---|---|---|---|
| Intent to Treat (ITT) Population, n assessed | n = 54 | n = 53 | n = 54 | n = 54 |
| ≥ 20% decrease in lesion area (%) | 47 (87.0) | 48 (90.5) | 51 (94.4) | 45 (83.3) |
| | | | | |
| All Treated / Safety Population, n assessed | n = 51 | n = 48 | n = 52 | n= 48 |
| ≥ 20% decrease in lesion area (%) | 47 (92.2) | 46 (95.8) | 51 (98.1) | 45 (93.8) |
| | | | | |
| MITT Population (pathogen isolated at baseline), n assessed | n = 29 | n = 30 | n = 28 | n = 36 |
| ≥ 20% decrease in lesion area (%) | 27 (93.1) | 30 (100.0) | 27 (96.4) | 34 (94.4) |

1

# Antibiotic pipeline: did you change your mind ?

- Large number of molecules in clinical development
  … much more in preclinical development

- More advanced molecules (Phase III) are new derivatives in existing classes with improved properties
  (MIC – resistance – PK- safety)

# Antibiotic pipeline: some work ahead

- Susceptibility Breakpoint harmonization

An example with MRSA …

| antibiotic | EUCAST | | CLSI/FDA | |
|---|---|---|---|---|
| | S ≤ | R > | S ≤ | R ≥ |
| rifampicin | 0.06 | 0.5 | 1 | 4 |
| azithromycin | 1 | 2 | 2 | 8 |
| doxycycline | 1 | 2 | 4 | 16 |
| vancomycin | 2 | 2 | 2 | 16 |
| linezolid | 4 | 4 | 4 | 8 |
| ceftaroline | 1 | 1 | 0.5 | 2 |
| telavancin | 0.125 | 0.125 | 0.125 | |
| dalbavancin | 0.125 | 0.125 | 0.125 | |

rule in Europe !

# Antibiotic pipeline: can we do better ?

- Equivalence to current options in comparative clinical trials

  ⇨ This will raise issues for reimbursement, especially against the generics of the comparators used in these studies

  ⇨ Need to design superiority trials and to focus pricing and reimbursement for documented cases of infection by resistant organisms

# Non-inferiority vs superiority trials ?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

## NON-INFERIORITY if NO evidence of spontaneous resolution rate (more effective than placebo)

Indications (and delta):

- Community-acquired pneumonia (-10%; more in PORT scores of IV-V)
- Hospital-acquired pneumonia and ventilator-associated pneumonia (less than ≤ -12.5%)
- Skin and soft tissue infections (-10%)
- Intra-abdominal infections (-12.5%)
- Urinary tract infections (-10 %)

→ DRUG/comparator trial

## SUPERIORITY if spontaneous resolution (placebo effective)

- Acute bacterial maxillary sinusitis
- Acute bacterial exacerbations of chronic bronchitis
- Acute otitis media
- Superficial skin infections (such as impetigo and minor wounds)
- Inhaled antibacterial agents (excl. CF)

→ Placebo/ DRUG/comparator trial

## LIMITED TRIALS

- Rare MDR organisms
- Few patients

→ DRUG non comparative trial

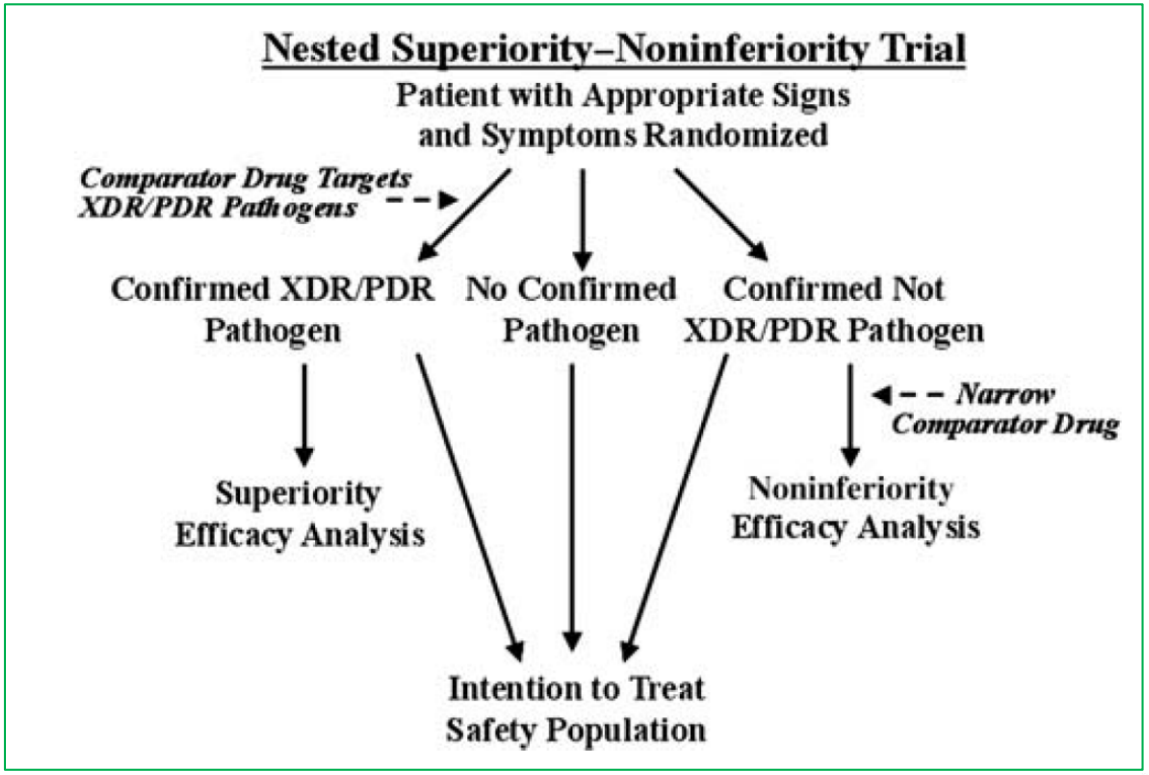
# Non-inferiority vs superiority trials ?

White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens

Clinical Infectious Diseases 2012;55(8):1031–46

IDSA PUBLIC POLICY

Infectious Diseases Society of America (IDSA)[a]



# What about the future ?