# *In vitro* and *In vivo* Activities of LCB01-0648 & LCB01-0699 against Gram-positive Bacteria

International Conference on Medical and Clinical Microbiology 2017

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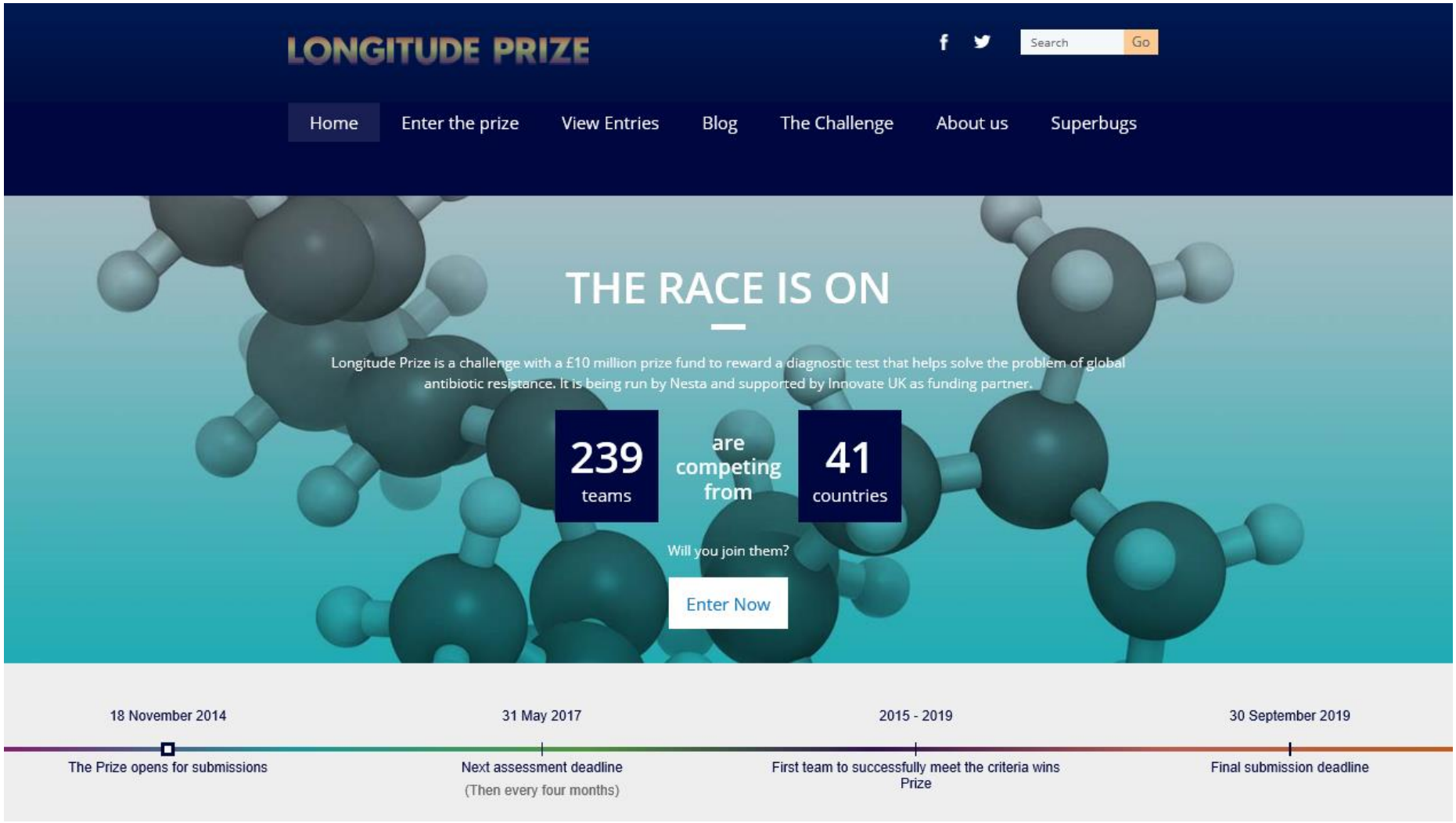
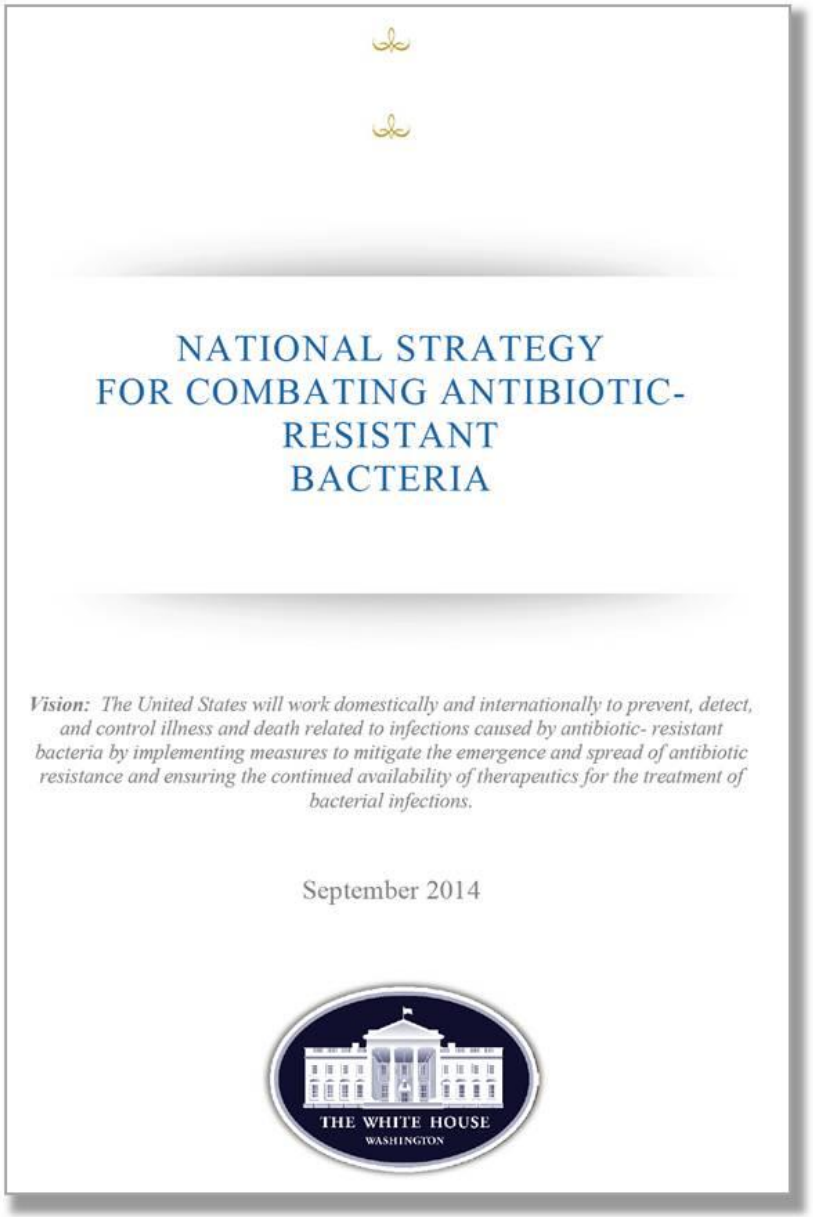
HANDONG GLOBAL UNIVERSITY




The Longitude Prize 2014 is an inducement prize contest offered by Nesta, a British lottery funded charity, in the spirit of the 18th-century Longitude prize. The prize was announced by the Prime Minister of the United Kingdom, David Cameron, in 2012, and a shortlist of six challenges to be put to a public vote was announced at Broadcasting House in May 2014. It was announced on 25 June 2014 that the prize will be awarded for **antibiotics.**

# Executive Order – Combating Antibiotic-Resistant Bacteria

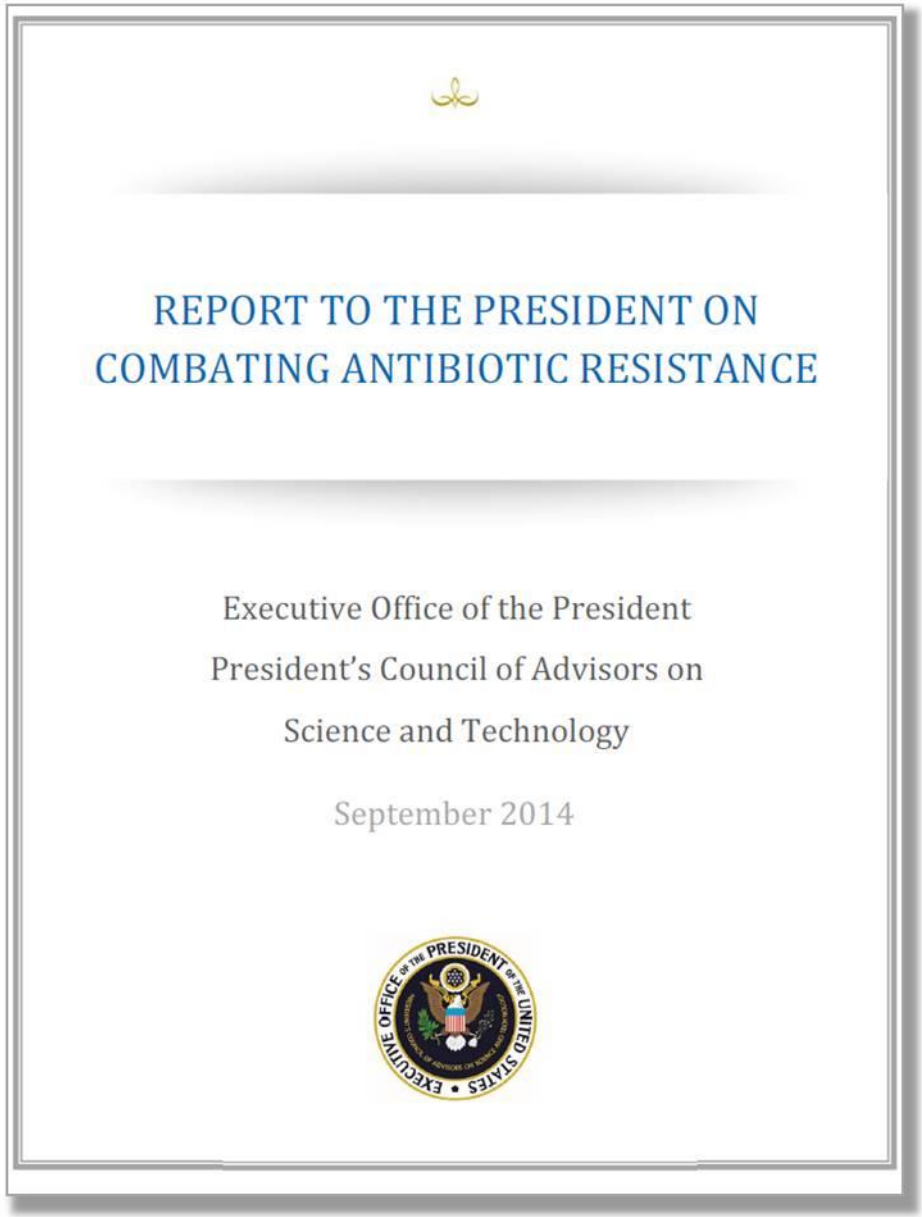


NATIONAL STRATEGY
FOR COMBATING ANTIBIOTIC-
RESISTANT
BACTERIA

***Vision:*** *The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic- resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.*

September 2014

THE WHITE HOUSE
WASHINGTON



REPORT TO THE PRESIDENT ON
COMBATING ANTIBIOTIC RESISTANCE

Executive Office of the President
President's Council of Advisors on
Science and Technology

September 2014

EXECUTIVE OFFICE OF THE PRESIDENT OF THE UNITED STATES

# Antibiotics Currently in Clinical Development

As of March 2016, an estimated 37 new antibiotics[1] with the potential to treat serious bacterial infections are in clinical development for the U.S. market. The success rate for clinical drug development is low; historical data show that, generally, only 1 in 5 infectious disease products that enter human testing (phase 1 clinical trials) will be approved for patients.* Below is a snapshot of the current antibiotic pipeline, based on publicly available information and informed by an external expert. It will be updated periodically, as products advance or are known to drop out of development. Because this list is updated periodically, footnote numbers may not be sequential. Please contact abxpipeline@pewtrusts.org with additions or updates.

| Drug name | Development phase[2] | Company | Drug class | Expected activity against resistant Gram-negative ESKAPE pathogens?[3] | Expected activity against a CDC urgent threat pathogen?[4] | Potential indication(s)?[5] |
|---|---|---|---|---|---|---|
| WCK 4873[15] | Phase 1 | Wockhardt Ltd. | Second-generation ketolide | No | No | Bacterial infections |
| MGB-BP-3 | Phase 1[10] | MGB Biopharma Ltd. | DNA minor groove binder | No | Yes | *C. difficile* infections |
| OP0595 (RG6080) | Phase 1[10] | Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc. (Roche licensee) | Beta-lactamase inhibitor | Possibly | Possibly | Bacterial infections |
| BAL30072 | Phase 1 | Basilea Pharmaceutica Ltd. | Monosulfactam | Yes | Yes | Multidrug-resistant Gram-negative bacterial infections[6] |
| CRS3123 | Phase 1 | Crestone Inc. | Methionyl-tRNA synthetase (MetRS) inhibitor | No | Yes | *C. difficile* infections |
| LCB01-0371 | Phase 1[10] | LegoChem Biosciences Inc. | Oxazolidinone | No | No | Bacterial infections |
| TD-1607 | Phase 1 | Theravance Biopharma Inc. | Glycopeptide-cephalosporin heterodimer | No | No | **Acute bacterial skin and skin structure infections,[6] hospital-acquired pneumonia/ventilator-associated bacterial pneumonia,[6] bacteremia[6]** |
| WCK 2349[15] | Phase 1 | Wockhardt Ltd. | Fluoroquinolone (WCK 771 pro-drug) | No | No | Bacterial infections |
| WCK 771[15] | Phase 1 | Wockhardt Ltd. | Fluoroquinolone | No | No | Bacterial infections |
| Zidebactam+Cefepime (WCK 5222)[15] | Phase 1 | Wockhardt Ltd. | Novel beta-lactamase inhibitor+beta-lactam | Possibly | Possibly | Complicated urinary tract infections,[6] hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia[6] |

# LCB01-0371 is in clinical development

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 5359–5362 Vol. 54, No. 12
0066-4804/10/$12.00 doi:10.1128/AAC.00723-10


## *In Vitro* and *In Vivo* Activities of LCB01-0371, a New Oxazolidinone[▽]

Ji-Woong Jeong,[1] Sung-Ji Jung,[1] Hyun-Hee Lee,[1] Yong-Zu Kim,[2] Tae-Kyo Park,[2] Young-Lag Cho,[2] Sang-Eun Chae,[2] Sung-Yoon Baek,[2] Sung-Ho Woo,[2] Hyang-Sook Lee,[2] and Jin-Hwan Kwak[1]*

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**LCB01-0371 is a new oxazolidinone with cyclic amidrazone. *In vitro* activity of LCB01-0371 against 624 clinical isolates was evaluated and compared with those of linezolid, vancomycin, and other antibiotics. LCB01-0371 showed good activity against Gram-positive pathogens. *In vivo* activity of LCB01-0371 against systemic infections in mice was also evaluated. LCB01-0371 was more active than linezolid against these systemic infections. LCB01-0371 showed bacteriostatic activity against *Staphylococcus aureus*.**

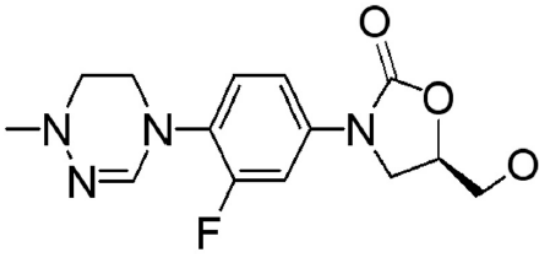


FIG. 1. Chemical structure of LCB01-0371.

# Novel Oxazolidinones

- **LCB01-0648**
  - LCB01-0648 is one of novel antibacterial agents in oxazolidinone class.
  - LCB01-0648 has antibacterial activity to drug-susceptible or resistant gram positive cocci in *in vitro* system.
- **LCB01-0699**
  - Phosphate monoester prodrug of LCB01-0648.

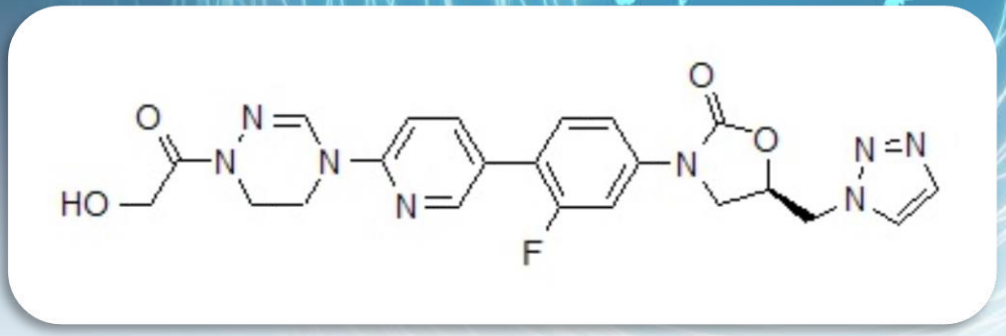


**Figure 1. Chemical structure of LCB01-0648**

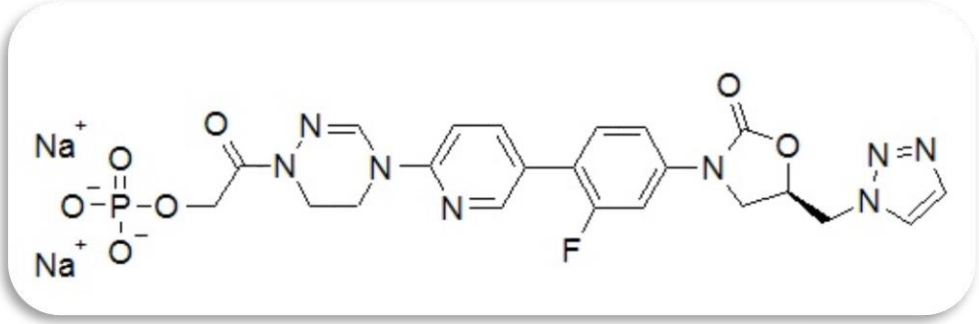


**Figure 2. Chemical structure of LCB01-0699**

molecules

MDPI

Article

# In Vitro Activities of LCB 01-0648, a Novel Oxazolidinone, against Gram-Positive Bacteria

**Sang-Hun Oh [1], Josep Kim [1], Sung-Yoon Baek [2], Sang-Eun Chae [2], Hee-Soo Park [3], Young-Lag Cho [2] and Jin-Hwan Kwak [1,*]**

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**Abstract:** Oxazolidinones are a novel class of synthetic antibacterial agents that inhibit bacterial protein synthesis. Here, we synthesized and tested a series of oxazolidinone compounds containing cyclic amidrazone. Among these compounds, we further investigated the antibacterial activities of LCB01-0648 against drug-susceptible or resistant Gram-positive cocci in comparison with those of six reference compounds. LCB01-0648 showed the most potent antimicrobial activities against clinically isolated Gram-positive bacteria. Against the methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS) isolates, LCB01-0648 showed the lowest $MIC_{90}$s (0.5 mg/L) among the tested compounds. In addition, LCB01-0648 had the lowest minimum inhibitory concentrations (MICs) against the four linezolid-resistant *S. aureus* (LRSA) strains (range 2–4 mg/L). The results of the time–kill studies demonstrated that LCB01-0648 at a concentration 8× the (MIC) showed bactericidal activity against methicillin-susceptible *Staphylococcus aureus* MSSA or MRSA, but showed a bacteriostatic effect against LRSA. These results indicate that LCB01-0648 could be a good antibacterial candidate against multidrug-resistant (MDR) Gram-positive cocci.

**Keywords:** LCB01-0648; oxazolidinone; MICs; linezolid-resistant *S. aureus*

# Comparative *in vitro* activities of LCB01-0648 against clinical isolates

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| MSSA (74) | **LCB01-0648** | **0.25~0.5** | **0.5** | **0.5** |
| | Linezolid | 2~2 | 2 | 2 |
| | Oxacillin | 0.06~4 | 0.25 | 0.5 |
| | Erythromycin | 0.125~>64 | 0.25 | >64 |
| | Ciprofloxacin | 0.06~>64 | 0.25 | 0.5 |
| | Sparfloxacin | 0.015~8 | 0.06 | 0.125 |
| | Moxifloxacin | 0.015~8 | 0.06 | 0.125 |
| | Gemifloxacin | 0.008~8 | 0.015 | 0.06 |
| | Vancomycin | 0.25~2 | 1 | 1 |
| | Quinupristin-dalfopristin | 0.125~0.5 | 0.25 | 0.5 |

*MSSA, methicillin-susceptible *S. aureus*

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| MSCNS (19) | **LCB01-0648** | **0.125~0.5** | **0.25** | **0.5** |
| | Linezolid | 1~2 | 1 | 2 |
| | Oxacillin | 0.03~1 | 0.125 | 1 |
| | Erythromycin | 0.06~>64 | 0.25 | >64 |
| | Ciprofloxacin | 0.06~8 | 0.125 | 8 |
| | Sparfloxacin | 0.03~8 | 0.125 | 4 |
| | Moxifloxacin | 0.03~4 | 0.125 | 4 |
| | Gemifloxacin | 0.008~0.5 | 0.015 | 0.5 |
| | Vancomycin | 1~4 | 2 | 4 |
| | Quinupristin-dalfopristin | 0.125~1 | 0.25 | 1 |

*MSCNS, methicillin-susceptible coagulase-negative staphylococci

MICs of LCB01-0648, linezolid, oxacillin, erythromycin, ciprofloxacin, sparfloxacin, Mmoxifloxacin, gemifloxacin, vancomycin, and quinupristin-dalfopristin against clinical isolates of Gram-positive organisms.

# Comparative *in vitro* activities of LCB01-0648 against clinical isolates

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| *S. pneumoniae* (79) | **LCB01-0648** | **0.03~1** | **0.125** | **0.25** |
| | Linezolid | 0.5~1 | 1 | 1 |
| | Oxacillin | 0.008~>32 | 16 | 16 |
| | Erythromycin | 0.008~>64 | >64 | >64 |
| | Ciprofloxacin | 0.5~32 | 2 | 4 |
| | Sparfloxacin | 0.06~16 | 0.25 | 0.5 |
| | Moxifloxacin | 0.06~4 | 0.25 | 0.5 |
| | Gemifloxacin | 0.008~0.25 | 0.03 | 0.06 |
| | Vancomycin | 0.5~2 | 1 | 1 |
| | Quinupristin-dalfopristin | 0.5~4 | 1 | 2 |

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| *S. pyogenes* (21) | **LCB01-0648** | **0.125~0.5** | **0.25** | **0.25** |
| | Linezolid | 1~2 | 2 | 2 |
| | Oxacillin | 0.25~32 | 0.5 | 8 |
| | Erythromycin | 0.008~8 | 0.06 | 2 |
| | Ciprofloxacin | 0.5~4 | 1 | 2 |
| | Sparfloxacin | 0.125~1 | 0.25 | 0.5 |
| | Moxifloxacin | 0.125~0.5 | 0.125 | 0.25 |
| | Gemifloxacin | 0.03~0.125 | 0.03 | 0.06 |
| | Vancomycin | 0.5~4 | 1 | 1 |
| | Quinupristin-dalfopristin | 1~2 | 1 | 2 |

# Comparative *in vitro* activities of LCB01-0648 against clinical isolates

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| *E. faecalis* (108) | **LCB01-0648** | **0.125~0.5** | **0.25** | **0.5** |
| | Linezolid | 1~2 | 2 | 2 |
| | Oxacillin | 8~>64 | 16 | >64 |
| | Erythromycin | 0.125~>64 | >64 | >64 |
| | Ciprofloxacin | 0.06~>64 | 2 | 64 |
| | Sparfloxacin | 0.25~64 | 1 | 32 |
| | Moxifloxacin | 0.06~64 | 1 | 32 |
| | Gemifloxacin | 0.008~16 | 0.125 | 4 |
| | Vancomycin | 0.5~4 | 2 | 4 |
| | Quinupristin-dalfopristin | 0.25~16 | 4 | 16 |

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| *E. faecium* (29) | **LCB01-0648** | **0.25~0.5** | **0.25** | **0.5** |
| | Linezolid | 1~2 | 2 | 2 |
| | Oxacillin | 16~>64 | >64 | >64 |
| | Erythromycin | 0.125~>64 | >64 | >64 |
| | Ciprofloxacin | 1~64 | 4 | 64 |
| | Sparfloxacin | 0.5~32 | 4 | 32 |
| | Moxifloxacin | 0.25~>64 | 4 | 32 |
| | Gemifloxacin | 0.03~64 | 2 | 16 |
| | Vancomycin | 0.5~8 | 1 | 2 |
| | Quinupristin-dalfopristin | 0.25~32 | 0.5 | 4 |

# Comparative *in vitro* activities of LCB01-0648 against drug-resistant strains

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| MRSA (200) | **LCB01-0648** | **0.125~0.5** | **0.5** | **0.5** |
| | Linezolid | 1~2 | 2 | 2 |
| | Oxacillin | 8~>64 | >64 | >64 |
| | Erythromycin | 0.25~>64 | >64 | >64 |
| | Ciprofloxacin | 0.125~>64 | 32 | >64 |
| | Sparfloxacin | 0.06~>64 | 16 | >64 |
| | Moxifloxacin | 0.03~>64 | 4 | 64 |
| | Gemifloxacin | 0.008~>64 | 2 | 64 |
| | Vancomycin | 0.5~4 | 1 | 2 |
| | Quinupristin-dalfopristin | 0.125~1 | 0.5 | 1 |

*MRSA, methicillin-resistant *S. aureus*
*MRCNS, methicillin-resistant coagulase-negative staphylococci
*VRE, vancomycin-resistant enterococci

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| MRCNS (33) | **LCB01-0648** | **0.125~1** | **0.25** | **0.5** |
| | Linezolid | 1~2 | 1 | 2 |
| | Oxacillin | 2~>64 | >64 | >64 |
| | Erythromycin | 0.06~>64 | >64 | >64 |
| | Ciprofloxacin | 0.06~64 | 8 | 32 |
| | Sparfloxacin | 0.03~32 | 4 | 16 |
| | Moxifloxacin | 0.06~16 | 2 | 8 |
| | Gemifloxacin | 0.008~8 | 0.5 | 4 |
| | Vancomycin | 1~4 | 2 | 4 |
| | Quinupristin-dalfopristin | 0.125~8 | 0.25 | 2 |

| Organisms (no. of strains) | Antimicrobial agent | MIC (μg/mL) | | |
|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ |
| VRE (47) | **LCB01-0648** | **0.125~0.5** | **0.25** | **0.25** |
| | Linezolid | 1~2 | 2 | 2 |
| | Oxacillin | >64~>64 | >64 | >64 |
| | Erythromycin | >64~>64 | >64 | >64 |
| | Ciprofloxacin | 0.5~>64 | 64 | >64 |
| | Sparfloxacin | 0.25~64 | 32 | 64 |
| | Moxifloxacin | 0.25~32 | 16 | 32 |
| | Gemifloxacin | 0.015~32 | 16 | 32 |
| | Vancomycin | >64~>64 | >64 | >64 |
| | Quinupristin-dalfopristin | 0.25~4 | 0.5 | 2 |

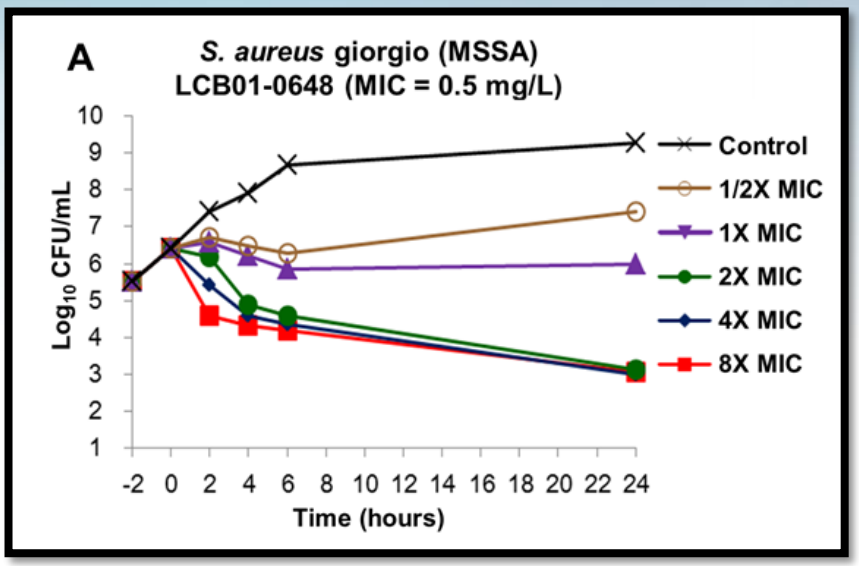
# *In vitro* activity of LCB01-0648, linezolid, and comparator drugs against linezolid-resistant *S. aureus* strains

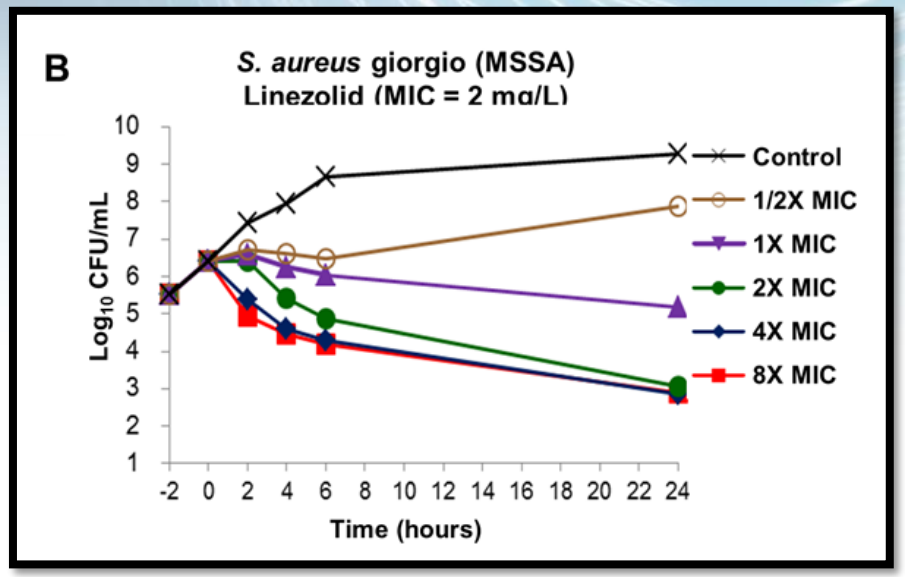
| Strain deriavtion[a] | Mutation | $MIC_{90}$ (mg/ml)[b] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **LCB01-0648** | LZD | OXA | ERY | CIP | SPX | MOX | GEM | VAN |
| **NRS119 MRSA** | G2576U | **4** | 64 | >64 | 1 | >64 | 16 | 4 | 8 | 1 |
| **NRS121 MRSA** | G2576U | **4** | 64 | >64 | 1 | >64 | 16 | 4 | 8 | 1 |
| **NRS127 MRSA** | Non-23S rRNA | **2** | 8 | 32 | 64 | >64 | >64 | 64 | 64 | 2 |
| **NRS271 MRSA** | G2576U | **2** | 64 | >64 | 1 | >64 | 16 | 16 | 16 | 0.5 |

[a] NRs strains were obtained from Samsung hospital, Seoul, Korea.
[b] LZD, linezolid; OXA, oxacillin; ERY, erythromycin; CIP, ciprofloxacin; SPX, sparfloxacin; MOX, moxifloxacin; GEM, gemifloxaxin; VAN, vancomycin.

# Time-kill curves of LCB01-0648 and linezolid against *S. aureus*

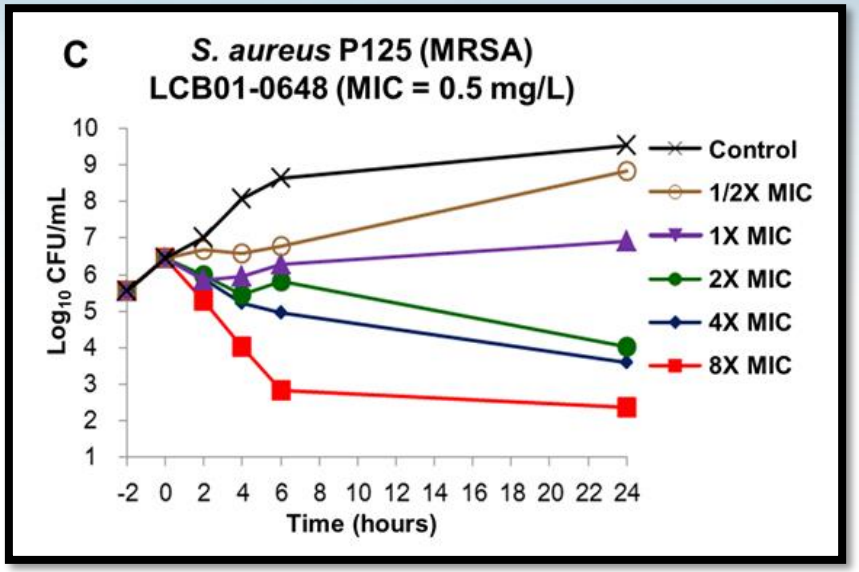
*S. aureus* giorgio(MSSA) exposed to LCB01-0648(A) or linezolid(B).

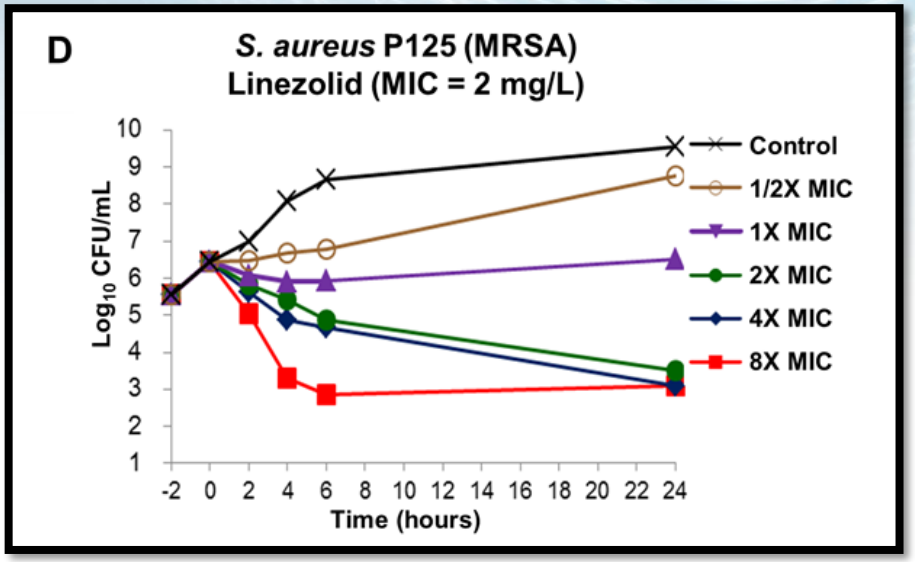


# Time-kill curves of LCB01-0648 and linezolid against *S. aureus*

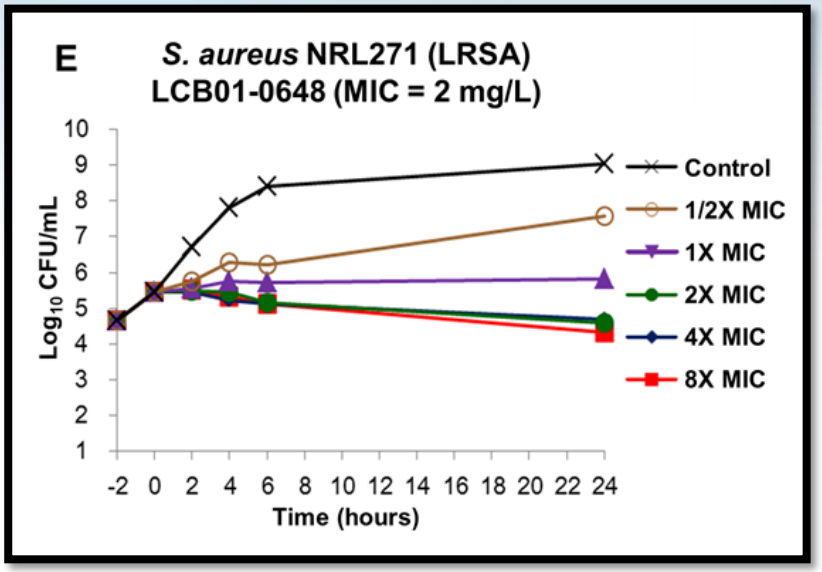
*S. aureus P125*(MRSA) exposed to LCB01-0648(C) or linezolid(D).

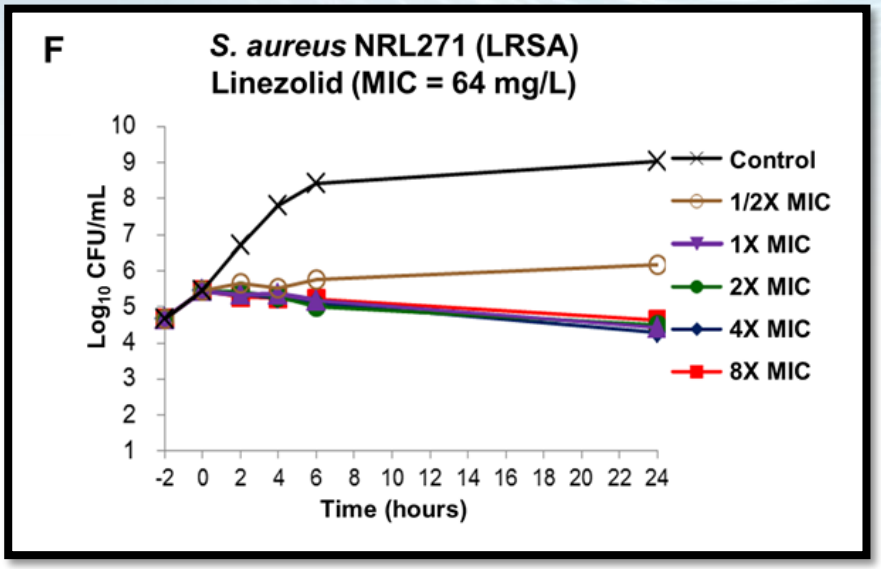


# Time-kill curves of LCB01-0648 and linezolid against *S. aureus*

*S. aureus* NRS271(LRSA) exposed to LCB01-0648(E) or linezolid(F).



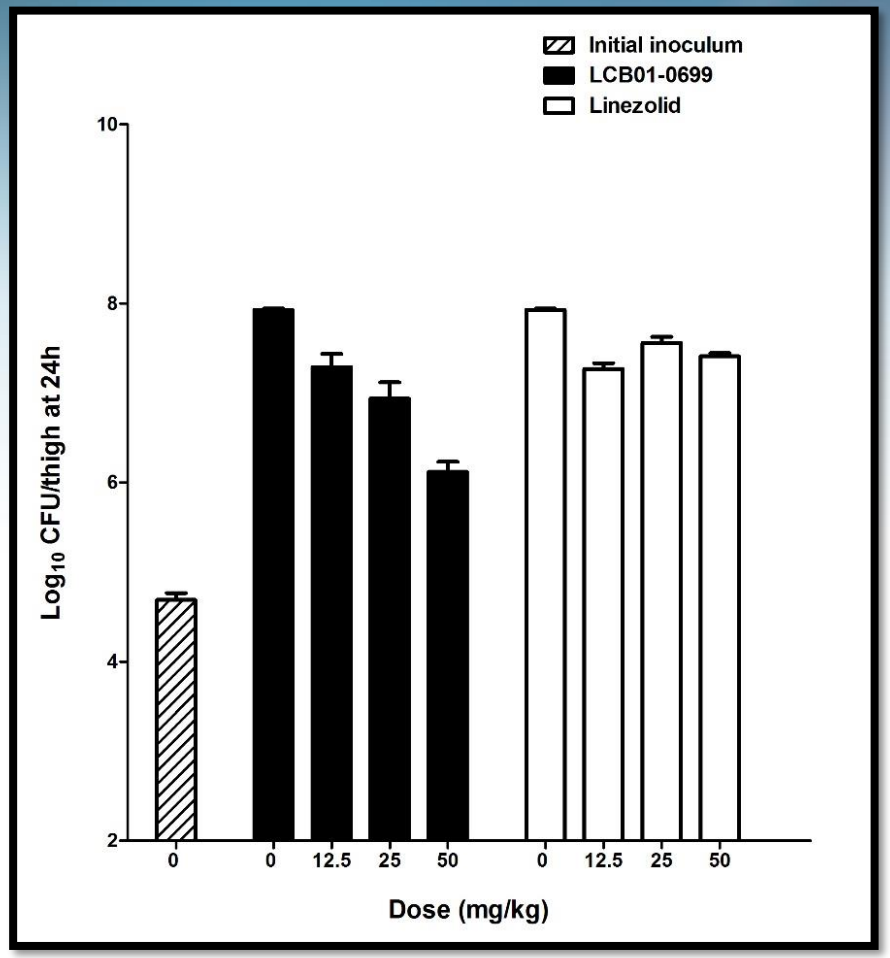



# *In vivo* Efficacy of LCB01-0699 against Systemic Infection Model in Mice

| Microorganism Inoculum (CFU/mouse) | Antimicrobial Agent [a,b] | MIC (μg/ml) | $ED_{50}$ (mg/kg) (95% confidence limits) |
|---|---|---|---|
| | | | p.o |
| *S. aureus* giorgio ($5\times10^7$) (MSSA) | LCB01-0699 | 0.5 | 6.20 (3.58~10.65) |
| | Linezolid | 2 | 7.07 (4.07~12.29) |
| *S. aureus* p125 ($5\times10^8$) (MRSA) | LCB01-0699 | 0.5 | 2.23 (0.94~5.28) |
| | Linezolid | 2 | 7.07 (4.07~12.29) |
| *S. aureus* NRS271 ($5\times10^7$) (LRSA) | LCB01-0699[b] | 2 | 2.74 (0.51~14.70) |
| | Linezolid | 64 | 5.27 (2.14~9.78) |

[a] Antimicrobial agents were orally administered at 1h and 4h post infection against *S. aureus* giorgio and *S. aureus* p125.
[b] Antimicrobial agents were orally administered at 1h, 4h, and 7h post infection against *S. aureus* NRS271.

# *In vivo* efficacy of LCB01-0699 against Thigh Infection Model in Mice




- *In vivo* activity of LCB01-0699 against thigh infection model caused by ***S. aureus* NRS271(LRSA)** in mice was compared with that of linezolid in Figure.

- **LCB01-0699** showed antibacterial activity in dose-dependent manner. However, **linezolid** was not active against *S. aureus* NRS271.

# New Antibiotics for New Super-bacteria

- New β-lactamase Inhibitor
- New Polymyxins
- Bacteriophages
- Genomic-driven Targets
- Identifying targets for antibiotic development using **omics technologies**
- Integrating **biophysics** with **HTS-driven drug discovery projects**

International Journal of Antimicrobial Agents

Available online 28 June 2017

In Press, Accepted Manuscript — Note to users

# Antimicrobial activities of LCB10-0200, a novel siderophore cephalosporin, against the clinical isolates of *pseudomonas aeruginosa* and other pathogens

Sang-Hun Oh[a, #], Hee-Soo Park[b, #], Hye-Shin Kim[a], Jeong-Yul Yun[c], Kyuman Oh[c], Young-Lag Cho[c], Jin-Hwan Kwak[a]

Show more

https://doi.org/10.1016/j.ijantimicag.2017.06.001



## Highlights

- LCB10-0200 is a novel siderophore–cephalosporin conjugate.
- LCB10-0200 shows potent antibacterial activity against *P. aeruginosa*, including β-lactamases-producing strains.
- LCB10-0200 has potent in vivo activity and is more effective than ceftazidime against *P. aeruginosa*.
- LCB10-0200 is a promising novel cephalosporin candidate for treating infections caused by *P. aeruginosa*.

## Abstract

Infections caused by multidrug-resistant bacteria, including *Pseudomonas aeruginosa*, are threating public health worldwide. Therefore, a novel antibacterial agent is needed for treating these infections. Here, we investigated the *in vitro* and *in vivo* activities of a novel siderophore-conjugated cephalosporin LCB10-0200 against the clinical isolates of Gram-negative baeria, including multidrug-resistant *P. aeruginosa*. *In vitro* susceptibility

# New Antibiotics under Clinical Development by Korean Companies

- **Factive®** (LG Biotech, Approved by FDA in 2003)
  - LB20304 → Gemifloxacin
- **Torezolid** (Dong-A, Approved by FDA in 2014)
  - TR-701 → Tedizolid → Torezolid (developed by Cubist)
- **Zabofloxacin** (DongWha) : DW-224a
- **CG-400549** (CrystalGenomics) : Ph-II
- **LCB01-0371** (LegoChem) : Ph-II
- **LCB10-0200** (LegoChem) : Ph-I
- **LCB01-0699** (LegoChem) : Back-up compound

# Acknowledgement