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In Vivo Characterization of the Peptide Deformylase Inhibitor LBM415 in Murine Infection Models[▽]

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LBM415 is an antibacterial agent belonging to the peptide deformylase inhibitor class of compounds. It has previously been shown to demonstrate good activity in vitro against a range of pathogens. In this study, the in vivo efficacy of LBM415 was evaluated in various mouse infection models. We investigated activity against a systemic infection model caused by intraperitoneal inoculation of *Staphylococcus aureus* (methicillin [meticillin] susceptible [MSSA] and methicillin resistant [MRSA]) and *Streptococcus pneumoniae* (penicillin susceptible [PSSP] and multidrug resistant [MDRSP]), a thigh infection model caused by intramuscular injection of MRSA, and a lung infection produced by intranasal inoculation of PSSP. In the systemic MSSA and MRSA infections, LBM415 was equivalent to linezolid and vancomycin. In the systemic PSSP infection, LBM415 was equivalent to linezolid, whereas against systemic MDRSP infection, the LBM415 50% effective dose (ED_{50}) was 4.8 mg/kg (dosed subcutaneously) and 36.6 mg/kg (dosed orally), compared to 13.2 mg/kg for telithromycin and >60 mg/kg for penicillin V and clarithromycin. In the MRSA thigh infection, LBM415 significantly reduced thigh bacterial levels compared to those of untreated mice, with levels similar to those after treatment with linezolid at the same dose levels. In the pneumonia model, the ED_{50} to reduce the bacterial lung burden by >4 $\log_{10}$ in 50% of treated animals was 23.3 mg/kg for LBM415, whereas moxifloxacin showed an ED_{50} of 14.3 mg/kg. In summary, LBM415 showed in vivo efficacy in sepsis and specific organ infection models irrespective of resistance to other antibiotics. Results suggest the potential of peptide deformylase inhibitors as a novel class of therapeutic agents against antibiotic-resistant pathogens.

With the emergence of pathogens resistant to current clinically used antibiotics, the need for new therapies has become of paramount importance. A novel class of antibacterial agents to emerge from research in this field is the peptide deformylase (PDF) inhibitors. PDF is a highly conserved metalloenzyme which deformylates the initial *N*-formyl methionine of newly synthesized bacterial polypeptides. This is an important step in bacterial protein synthesis, thus making it an attractive antibacterial target. The role of PDF and its attractiveness as an antibacterial target have previously been reviewed (10, 11, 15, 16).

LBM415 is one of the first compounds of the PDF inhibitor class to advance to clinical trials for the oral (p.o.) and parenteral treatment of respiratory tract and skin and skin structure infections caused by susceptible gram-positive and -negative organisms. LBM415 has been evaluated previously in vitro in comparison with other antibiotics and demonstrated potent activity against clinical strains of staphylococci, streptococci, enterococci, *Moraxella catarrhalis*, *Legionella pneumophila*, and *Haemophilus influenzae* (2, 5, 6, 9, 13, 14). There was no difference in activity against strains classified as being susceptible or resistant to other classes of antibiotics. LBM415 also displayed activity against a collection of other gram-positive species, including *Aerococcus* spp., *Bacillus* spp., *Corynebacterium* spp., *Gemella* spp., *Lactobacillus* spp., *Lactococcus* spp., *Leuconostoc* spp., *Listeria* spp., *Micrococcus* spp., *Nocardia* spp., and *Stomatococcus* spp. (9). In the present study, the in vivo efficacy of LBM415 was evaluated in mice against systemic infections caused by *Staphylococcus aureus* (methicillin [meticillin] susceptible [MSSA] and methicillin resistant [MRSA]) and *Streptococcus pneumoniae* (penicillin susceptible [PSSP] and penicillin resistant [PRSP]). Furthermore, the therapeutic efficacy of LBM415 was evaluated using a mouse thigh infection and a mouse pneumonia lung infection model.

MATERIALS AND METHODS

Antimicrobial compounds. LBM415 is an *N*-alkyl urea hydroxamic acid with the chemical name (*S*)-1-{(*R*)-2-[formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrroli-dine-2-carboxylic acid (5-fluoro-1-oxy-pyridin-2-yl)-amide (Fig. 1) and was synthesized by Novartis. It was formulated in ethanol–20% hydroxypropyl-β-cyclodextrin (CD) (1:20 [vol/vol]) (catalogue no. 33259; Aldrich). Further dilutions were made with CD. Linezolid was purchased as the commercial drug product (Zyvoxid; Pharmacia) and was suspended in 0.5% sodium carboxymethylcellulose (Sigma). Telithromycin was extracted from tablets (Ketek; Aventis) and prepared in 0.5% sodium carboxymethylcellulose with 1% Tween 80. Vancomycin hydrochloride (Eli Lilly), clarithromycin lactobionate (Abbott), amoxicillin (amoxicilline), oxacillin, penicillin G, and penicillin V (all from Sigma) were formulated in distilled water.

Bacterial strains and inoculum preparation. Three *Staphylococcus aureus* strains, ATCC 49951, ATCC 13709, and NB01021, and three *Streptococcus pneumoniae* strains, ATCC 6301, ATCC 6303 and ATCC 700677, were investigated. NB01021 is a clinical isolate from the Novartis bacterial (NB) collection and is an MRSA strain, while ATCC 49951 and ATCC 13709 are MSSA strains. ATCC 6301 and ATCC 6303 are PSSP strains, while ATCC 700677 is a multidrug-resistant *S. pneumoniae* strain. For the inoculum preparation, ATCC 49951 and NB01021 were prepared from an overnight culture in Mueller-Hinton broth,

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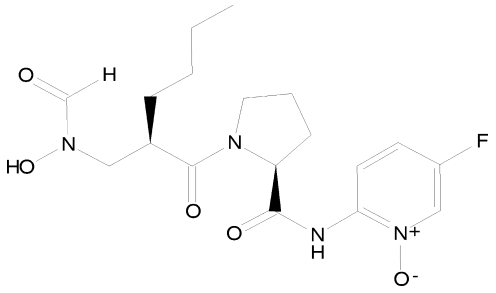

FIG. 1. Chemical structure of LBM415.

while ATCC 13709 was prepared from an overnight culture in tryptic soy broth. ATCC 6301 was prepared from an overnight culture on Trypticase soy agar, whereas ATCC 6303 and ATCC 700677 were prepared from a 5-hour log culture with Todd-Hewitt-Broth–30% horse serum. For ATCC 700677 and NB01021, inocula were suspended in 5% hog gastric mucin. For the other four strains, inocula were made with 0.86% NaCl. In each experiment, the infecting dose (CFU/mouse) was confirmed by agar plating.

Antimicrobial susceptibility testing. The MICs for LBM415 and standard antibiotics against the study organisms were determined by broth microdilution methods according to the Clinical and Laboratory Standards Institute (CLSI) recommended guidelines for susceptibility testing (4).

Animal infection models. All animals experiments were approved by and conducted in accordance with the guidelines of the Animal Care and Use Committee of Novartis Institutes for BioMedical Research, Inc. Death was not used as an endpoint in these studies, animals were observed for clinical signs, and based on a scoring system, moribund animals were preemptively euthanized.

Pharmacokinetics of LBM415 in mice. To investigate the pharmacokinetics of LBM415, the compound was administered p.o. at 20 mg/kg and intravenously at 5 mg/kg to CD1 mice. The first collection point after intravenous dosing was 0.083 h and after p.o. dosing was 0.25 h, with the last sample taken 24 h after dosing. Plasma was removed after centrifugation at 10,000 rpm for 10 min at 4°C and stored at −80°C prior to analysis. Analysis of drug concentrations in plasma was carried out using liquid chromatography/mass spectrometry. Blood samples were collected from three mice at each time point. The mean value from the animals at each collection point was plotted against time to give a plasma concentration time course. Pharmacokinetic parameters were determined using WinNonlin (Pharsight, CA) pharmacokinetics software with noncompartment modeling.

Mouse systemic infection model. Female NMRI mice weighing 21 to 25 g were used for infections with *S. aureus* strains ATCC 49951 and 13709 as well as *S. pneumoniae* ATCC 6301. For infections with *S. aureus* NB 01021 and *S. pneumoniae* ATCC 700677, female BALB/c mice (19 to 23 g) were used. Infections were induced by intraperitoneal injection of a freshly prepared bacterial suspension which was appropriately diluted in medium or 5% hog mucin (0.3 ml/mouse). The injected bacterial dose corresponded to 10 to 100 times the minimal lethal dose as determined from previous lethal dose titration studies. The inocula (CFU/mouse) used in the studies were as follows: ATCC 49951, 1.7×10^7 to 2.2×10^7; ATCC 13709, 7.3×10^7 to 2×10^8; NB01021, 2.1×10^7 to 2.8×10^7; ATCC 6301, 6×10^2 to 8×10^2; ATCC 700677, 1.5×10^7 to 2×10^7. The compounds were administered typically at three dose levels to groups of 5 to 6 mice each, and were dosed p.o. or subcutaneously (s.c.) Control mice received the corresponding vehicle. Against ATCC 49951 and ATCC 13709, treatment was administered 1 and 5 h postinfection, while for NB01021, treatment was administered 0, 4, and 23 h postinfection. In the *S. pneumoniae* infection model, a multiple-day treatment schedule was used. In our experience, we found that this approach was the most effective means of compound administration for the strains used in this model. Treatment for 1 day only generally was insufficient to clear the infection, leading to an increased mortality rate and therefore making it difficult to determine compound efficacy. Treatment against ATCC 6301 was administered 1, 5, 9, 25, 30, 35, 49, 54, 59, 73, 78, and 83 h postinfection (three doses per day for 4 days), while against ATCC 700677, the schedule was 1, 5, 17, 27, 42, and 51 h postinfection (two doses per day for 3 days). Following inoculation, the mice were observed for 8 days, and the 50% effective dose (ED_{50}), the dose providing protection to 50% of mice, and its 95% confidence intervals (95% CI) was calculated from the survival data at day 8 by probit analysis using the Systat program (SPSS Inc.).

Mouse pneumonia model. Pneumonia was established in anesthetized (ketamine/xylazine) female BALB/c mice (19 to 22 g) by intranasal inoculation of 50 μl of a log phase culture of *S. pneumoniae* ATCC 6303 (1.4×10^5 CFU per mouse). Oral therapy of pneumonia was started 16 h postinfection to groups of six mice and continued for 3 days (treatment was administered 16, 27, 40, 51, 64, and 75 h postinfection). Control mice received only the corresponding vehicle. One day after cessation of treatment, the lungs of surviving mice were harvested and homogenized, and the bacterial count was determined. After transformation to $\log_{10}$, data were expressed as CFU/lung. Mice that died from fatal infection during the study period were included for statistical purposes by allocating 9 $\log_{10}$ CFU/lung (highest determined CFU/lung in untreated control animals). Data on the bacterial count of lungs were analyzed using Kruskal-Wallis one-way analysis of variance on ranks with comparisons to the vehicle-treated control group performed by Dunn's method. A P value of <0.05 was considered to represent a statistically significant difference. ED_{50} values were calculated by the logistic dose response function after nonlinear curve fitting of data, using the program Origin 6.1. The ED_{50} value represents the dose that reduced the bacterial count on the $\log_{10}$ scale by 50% compared to controls.

Soft tissue infection model. Thigh infections were established by intramuscular injection of 50 μl of a freshly prepared bacterial suspension of *S. aureus* NB01021 (3.8×10^6 CFU/thigh) into the left hind thigh of immunocompetent female NMRI mice (20 to 23 g). Antibiotic therapy against thigh infections was performed for 2 days, starting immediately after injection of the bacterial inoculum. Treatments of 50, 16.7, or 5.6 mg/kg were administered p.o. three times daily (0, 4, 8, 24, 28, and 32 h postinfection). Control mice were treated with the corresponding vehicle. Eighteen hours after cessation of treatment, the mice were euthanized and the thighs aseptically excised. Thigh muscles were homogenized in 5 ml saline, and appropriate dilutions were plated onto blood agar plates to determine the number of viable bacteria per thigh. The detection limit was 100 CFU/thigh. Differences in the median values of the bacterial count per thigh between antibiotic treated mice and controls were analyzed by the Mann-Whitney rank sum test, using SigmaStat 2.03 (SPSS Inc.).

RESULTS

Antimicrobial susceptibility testing. The MICs for LBM415 and the standard compounds against the infecting organisms are shown in Table 1. *S. aureus* NB01021 and *S. pneumoniae* ATCC 700677 were shown to be penicillin resistant (MICs of 64 and 32 μg/ml, respectively). In addition, ATCC 700677 was also resistant to clarithromycin, with an MIC of 32 μg/ml.

Mouse pharmacokinetics. From the plasma concentration time course, the pharmacokinetics parameters that were determined were the peak concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC), bioavailability (F), concentration at time zero (C_0), clearance (CL), and volume of distribution at steady state (V_{ss}). With both dosing routes, it was possible to detect compound only up to 12 h after administration. The C_0 value was extrapolated from the intravenous plasma concentration time course plot and was

TABLE 1. In vitro activity of LBM415 and comparator antibiotics against the bacterial strains used in the mouse infection models

Compound	MIC (μg/ml)					
	S. aureus			*S. pneumoniae*		
	ATCC 49951	ATCC 13709	NB01021	ATCC 6301	ATCC 6303	ATCC 700677
LBM415	0.125	4	2	0.125	2	0.5
Linezolid	1	1	1	1	2	0.25
Vancomycin	1	1	1	0.5	0.5	≤0.125
Clarithromycin	1	0.5	>64	0.015	0.03	32
Penicillin	≤0.125	≤0.125	64	0.03	0.06	32
Amoxicillin	0.5	1	128	0.03	0.03	4
Telithromycin	0.25	≤0.125	>64	≤0.125	≤0.125	≤0.25
Moxifloxacin	0.06	≤0.03	1	0.5	0.5	≤0.06

TABLE 2. Efficacy of LBM415 and comparator drugs against acute systemic *S. aureus* and *S. pneumoniae* infections in mice

Bacterial strain	Compound	Treatment schedule[a]	Dosing route	ED_{50} (mg/kg/dose)	95% CI
S. aureus ATCC 49951	LBM415	1 and 5 h p.i.	s.c.	1.1	0.4–2.0
			p.o	2.3	1.6–3.3
	Linezolid	1 and 5 h p.i	s.c.	7.4	5.6–10.1
			p.o.	7.0	5.2–9.8
	Vancomycin	1 and 5 h p.i	s.c.	1.5	1.3–1.7
	Clarithromycin	1 and 5 h p.i	s.c.	1.2	0.4–2.4
			p.o.	7.7	4.5–14.4
S. aureus ATCC 13709	LBM415	1 and 5 h p.i.	p.o.	13.2	8.9–24.1
	Linezolid	1 and 5 h p.i	p.o.	10.3	6.3–15.3
	Vancomycin	1 and 5 h p.i	s.c.	2.8	1.9–4.5
	Clarithromycin	1 and 5 h p.i	p.o.	8.7	5.6–13.8
S. aureus NB01021	LBM415	0, 4, and 23 h p.i.	s.c.	0.7	0.3–1.2
			p.o.	5.9	3.2–15.7
	Linezolid	0, 4, and 23 h p.i.	p.o.	2	0.9–3.3
	Vancomycin	0, 4, and 23 h p.i.	s.c.	2.5	1.8–3.4
	Penicillin G	0, 4, and 23 h p.i.	s.c.	>135	
	Amoxicillin	0, 4, and 23 h p.i.	p.o.	>50	
S. pneumoniae ATCC 6301	LBM415	3× daily for 4 days	p.o.	6.4	5.1–11.6
	Clarithromycin	3× daily for 4 days	p.o.	2.1	1.3–3.2
	Linezolid	3× daily for 4 days	p.o.	5.6	2.9–8.2
S. pneumoniae ATCC 700677	LBM415	2× daily for 3 days	s.c.	4.8	2.3–7.3
			p.o.	36.6	16.9–87.9
	Clarithromycin	2× daily for 3 days	p.o.	>60	
	Penicillin V	2× daily for 3 days	p.o.	>60	
	Telithromycin	2× daily for 3 days	p.o.	13.2	8.3–26.1

[a] p.i., postinfection.

determined to be 5,361 ng/ml. LBM415 had an AUC concentration of 2,693 ng·h/ml, while CL was 1,851 ml/h/kg, and V_{ss} was 3,119 ml/kg. After p.o. dosing, LBM415 achieved a C_{max} of 4,250 ng/ml, with a T_{max} of 30 min. The AUC was 5,702 ng·h/ml. *F* was determined from the ratio of the dose normalized AUCs and was calculated to be 53%.

Mouse systemic infection model. The results of the systemic infection model are shown in Table 2, with the ED_{50} values for LBM415 in comparison to standard antibiotics shown for each strain tested. In the systemic MSSA infection, LBM415 performed as well as or better than the other compounds tested, with ED_{50} values of 2.3 mg/kg (p.o.) and 1.1 mg/kg (s.c.) compared to 7.0 mg/kg (p.o.) and 7.4 mg/kg (s.c.) for linezolid, 7.7 mg/kg (oral) and 1.2 mg/kg (s.c.) for clarithromycin, and 1.5 mg/kg for vancomycin (s.c. only). Against a second MSSA strain, the oral ED_{50} was higher but still comparable to those of linezolid and clarithromycin. Against systemic MRSA infection, LBM415 (p.o. ED_{50}, 5.9 mg/kg; s.c. ED_{50}, 0.7 mg/kg) was statistically comparable to vancomycin (s.c. ED_{50}, 2.5 mg/kg) and linezolid (p.o. ED_{50}, 2.0 mg/kg), whereas penicillin G and amoxicillin had ED_{50} values of >135 mg/kg and >50 mg/kg, respectively. In the systemic PSSP infection, the p.o. ED_{50} of LBM415 was 6.4 mg/kg, slightly less effective than clarithromycin but similar to linezolid (2.1 and 5.6 mg/kg, respectively). Against systemic multidrug-resistant *S. pneumoniae* infection, the ED_{50} of LBM415 was 4.8 mg/kg after s.c. dosing and 36.6 mg/kg when dosed p.o., compared to 13.2 mg/kg for telithromycin and >60 mg/kg for both penicillin V and clarithromycin (all dosed p.o.).

Mouse pneumonia model. Fig. 2 shows the efficacy of LBM415 in the lung infection model when tested in comparison with moxifloxacin. LBM415 dosed p.o. twice daily significantly reduced the bacterial counts when dosed at 80, 40, and 20 mg/kg to $\log_{10}$ 2.3 ± 1.4, <2.0 (detection limit of counting), and 5.1 ± 1.6, respectively, after infection of mice with 1.4×10^5 CFU/mouse (resulting in $\log_{10}$ 8.1 ± 1.5 CFU/lung in controls at day 4 postinfection). At the higher doses of 80 and 40 mg/kg of LBM415, bacteria were completely eradicated in 5/6 and 6/6 animals, respectively. The ED_{50} value for LBM415

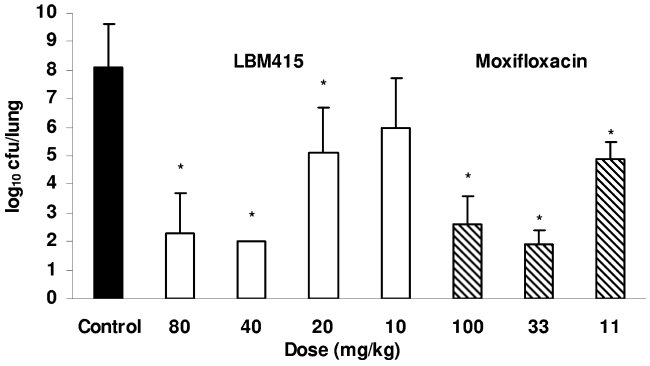

FIG. 2. Efficacy of LBM415 and moxifloxacin against lung infection in mice by *S. pneumoniae* ATCC 6303. Oral treatments were given twice daily for 3 days, starting 16 h postinfection; bacterial counts per lung ($\log_{10}$ CFU/lung) were plotted for each dose tested. *, $P < 0.05$ versus the control.

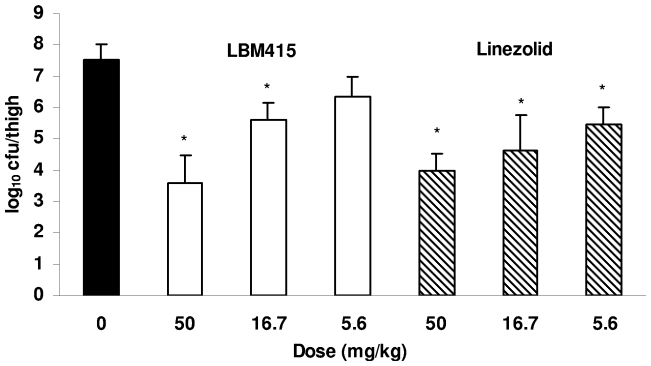

FIG. 3. Efficacy of LBM415 and linezolid against *S. aureus* NB01021 (MRSA) in a mouse soft tissue infection. Treatment was administered three times daily for 2 days, and bacterial counts per thigh ($\log_{10}$ CFU/thigh) were plotted for each dose tested. *, $P < 0.05$ versus the control.

was 23.3 mg/kg (95% CI, 14.8 to 36.0) while the comparator drug, moxifloxacin, had an ED_{50} of 14.3 mg/kg (95% CI, 4.6 to 25.7).

Mouse soft tissue infection model. Efficacy of LBM415 against thigh infections with *S. aureus* NB01021 is shown in Fig. 3. The CFU/thigh in control untreated mice reached 7.5 $\log_{10}$ CFU/thigh by the end of the study, and LBM415 significantly and dose-dependently reduced the bacterial count in thighs in comparison with this value. Bacterial counts after 2 days of treatment with 5.6, 16.7, and 50 mg/kg were 6.3 $\log_{10}$, 5.6 $\log_{10}$, and 3.6 $\log_{10}$ CFU/thigh, respectively. This compared well with linezolid, which had bacterial counts of 5.4 $\log_{10}$, 4.6 $\log_{10}$, and 4.0 $\log_{10}$ when mice were treated at equal dose levels.

DISCUSSION

S. pneumoniae is a leading bacterial cause of meningitis, community-acquired pneumonia, sepsis, and otitis media in the United States, with pneumococcal disease targeting especially young children and the elderly. Mortality in the elderly is about 20% for bacteremic pneumococcal infections (22). Effective treatment regimens have been affected by the emergence of penicillin- and multidrug-resistant *S. pneumoniae* strains. Surveillance studies have shown that penicillin and erythromycin resistance can be approximately 34% and 41%, respectively, among infants, with approximately 30% of *S. pneumoniae* strains tested being multidrug resistant (3, 12). Mathematical modeling using trends in *S. pneumoniae* resistance development predicts that multidrug resistance is developing faster than resistance to single drugs. (17). *S. aureus* is estimated to be responsible for approximately 16% of nosocomial infections in the United States (20). An issue of major and growing concern is that MRSA is now prevalent in hospitals and is appearing more frequently in the community as well (15). In the United States, approximately 60% of staphylococcal infections in intensive care units are now caused by MRSA (21). In U.S. hospitals, the total economic burden of *S. aureus* infection was estimated to be $14.5 billion for all inpatient stays and $12.3 billion for surgical patient stays, with a mortality rate of 5.6% (19). It is clear that antimicrobial resistance threatens the successful treatment of pneumococcal and *S. aureus* infections and highlights further the important need for new therapies against these pathogens.

PDF represents one of the most promising new targets for the development of novel antimicrobial chemotherapies. While human PDF has been identified and characterized (18), PDF inhibitors had no effect on different human cell lines, making it an attractive target for the development of new antibacterial agents. LBM415 is one of the most advanced compounds in this class of compounds and has previously been shown to have potent in vitro activity. In addition, LBM415 was active in vivo for the treatment of *Mycoplasma pneumoniae* pneumonia in a mouse model (7). *M. pneumoniae* is another major cause of community-acquired pneumonia. LBM415 was shown to have a microbiological effect and improve the lung histopathology, as well as reduce airway obstruction and immune response.

In this report, we further characterize the activity of LBM415 in vivo. A pharmacokinetic study showed this compound to have good bioavailability, and efficacy was demonstrated after p.o. and s.c. dosing in a number of animal models. We have shown that LBM415 is active in vivo against systemic infections caused by susceptible and resistant strains of *S. aureus* and *S. pneumoniae*. The systemic infection model is an important tool for demonstrating the in vivo effect of antibacterial agents against common human pathogens and is a valuable model for compound screening (8). The activity of LBM415 against MRSA and PRSP suggests that this compound could be a promising drug for the therapy of infections caused by multidrug-resistant staphylococci and streptococci. The mouse thigh soft tissue infection model was also used to show efficacy against MRSA infections. In addition, LBM415 was effective in vivo after p.o. administration against experimental pneumonia in mice induced by *S. pneumoniae*. The compound displayed dose-dependent activity and significantly reduced the bacterial count in lungs in comparison to that of vehicle-treated control animals. Activity of a compound against experimental pneumonia is considered to be predictive of the clinical efficacy and indicates that a compound penetrates sufficiently well into the infected lung tissues to attain microbiologically active concentrations (24). To the best of our knowledge, there has been only one other report on the efficacy of a PDF inhibitor in a mouse pneumonia model (1). In that report, survival rates of animals treated with the compound BB-83698 were higher than those of mice treated with erythromycin, amoxicillin, and ciprofloxacin. As strains of different virulence were tested, either immunocompetent or immunocompromised mice were used with therapy started 3, 6, 12, or 18 h after bacterial challenge, depending on the strain, and given 3, 6, or 9 s.c injections at 8, 12, or 24 h intervals.

In conclusion, LBM415 was shown to have activity against *S. aureus* and *S. pneumoniae* in both systemic infection and mouse thigh models. The compound was also active against experimental pneumonia after p.o. administration, indicating that it can penetrate into infected lung tissues. These results support further development of PDF inhibitors for the treatment of *S. pneumoniae* and *S. aureus* infections. However, any further development will need to take into consideration the recent discovery (23) of a clinical *S. aureus* isolate that exhibited preexisting resistance to LBM415 and other PDF inhibitors.

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