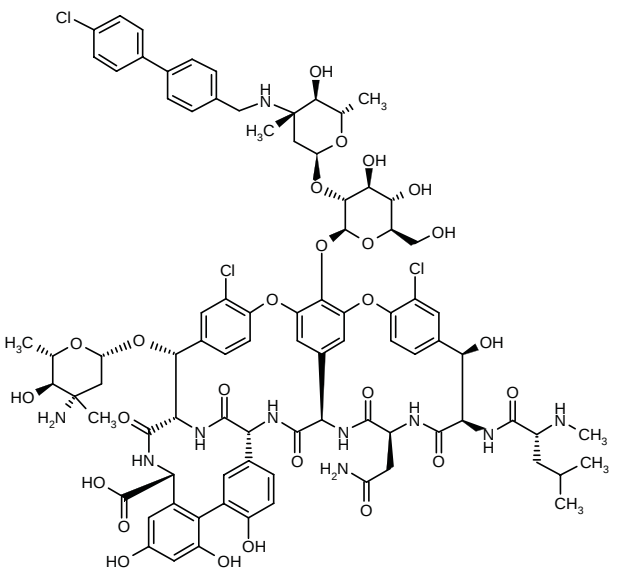
Drugs of the Future 1998, 23(1): 17-23

LY-333328

Glycopeptide Antibiotic

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-22-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-mannopyranosyloxy)-3-(carbamoylmethyl)-10,19-dichloro-44-[2-*O*-[3-(4'-chlorobiphenyl-4-ylmethylamino)-2,3,6-trideoxy-3-*C*-methyl-α-L-mannopyranosyl]-β-D-glucopyranosyloxy]-7,28,30,32-tetrahydroxy-6-(*N*^{2}-methyl-D-leucylamido)-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-1*H*,22*H*-8,11:18,21-dietheno-23,26-(iminomethano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiacyclotetracosine-26-carboxylic acid

(4''*R*)-22-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-*N*$^{3''}$-(4'-chloro[1,1'-biphenyl]-4-ylmethyl)-vancomycin



$C_{86}H_{97}Cl_3N_{10}O_{26}$ Mol wt: 1793.12

CAS: 171099-57-3

EN: 226450

Synthesis*

LY-333328 was synthesized by reductocondensation of the glycopeptide antibiotic A82846B (I) with 4'-chlorobiphenyl-4-carboxaldehyde (II) by means of sodium cyanoborohydride in refluxing methanol (1-3). Scheme 1.

Introduction

LY-333328 is a semisynthetic *N*-alkylated derivative of LY-264826 (formerly A82846B), a naturally occurring structural analog of vancomycin (1-11). LY-333328 contains a chlorodiphenyl side chain and is a member of the glycopeptide class of antibacterial compounds (1). This developmental antibiotic has reported activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci.

The enterococci and staphylococci are responsible for many of the nosocomial infections acquired annually worldwide. These bacteria are multidrug resistant and glycopeptide antibiotics generally are the only effective therapy. This rapidly emerging resistance has appeared both in the United States (12, 13) and in Europe (14-16). The emergence of enterococci resistant to the currently marketed glycopeptide antibiotics, vancomycin and teicoplanin, and reports of MRSA with decreased teicoplanin suceptibility indicate a distinct need for the rapid development of new antibacterial drugs.

This article represents a review of the current published literature on LY-333328, a novel glycopeptide antibacterial compound.

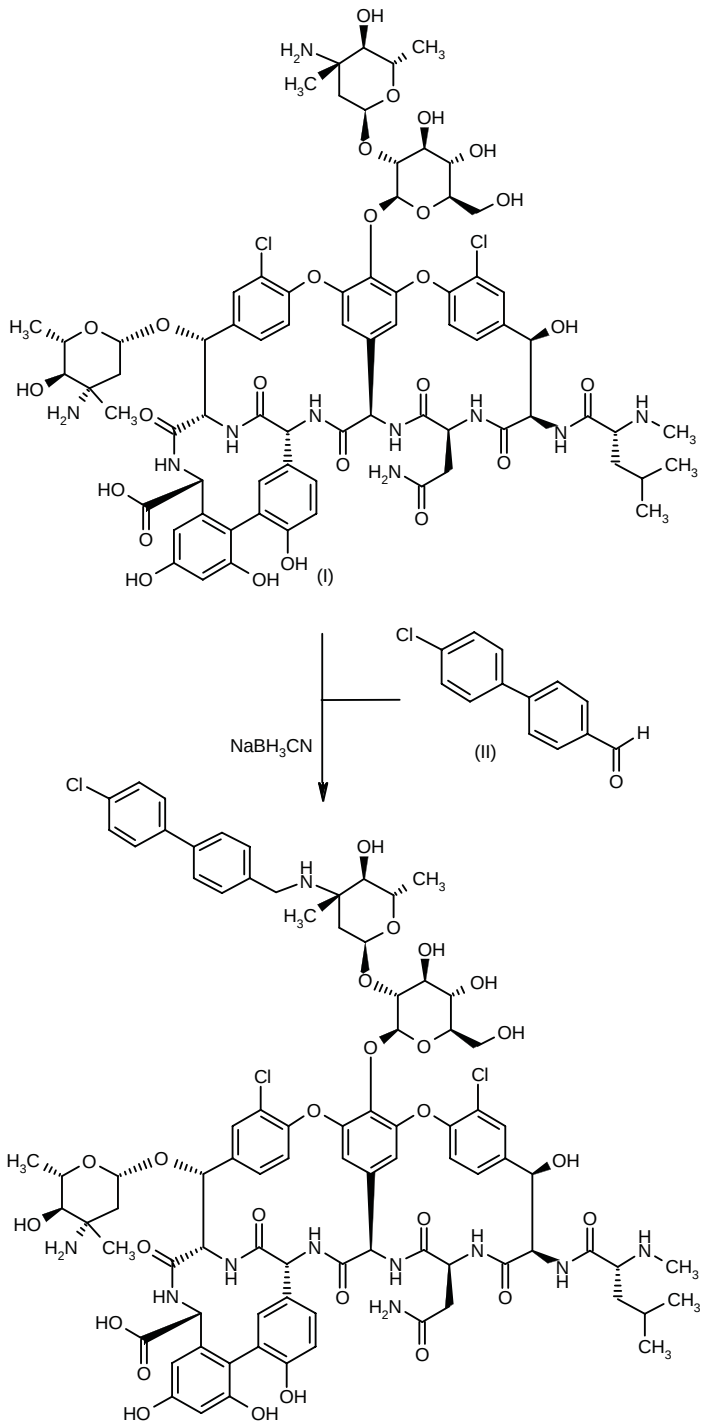
In Vitro Activity

The *in vitro* activity and pharmacodynamics of LY-333328 have been studied extensively with the first reports appearing in 1995 (4, 5). However, the first series of comprehensive studies was reported at the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy held in 1996 (17-28). The inhibitory and bactericidal activities of LY-333328, compared to leading antibiotics under a variety of *in vitro* test conditions, have been studied and reported by investigators internationally. The key data from many of these studies are summarized below.

The initial reports on the *in vitro* antibacterial activity of LY-333328 indicated that this new glycopeptide had potent activity against vancomycin- and teicoplanin-susceptible and -resistant isolates of enterococci, including *Enterococcus faecalis* and *Enterococcus faecium* (17-28). The potent bactericidal activity of LY-333328 was

Robert A. Fromtling, J. Castañer*. Regulatory Liaison-International, Merck Research Laboratories, P.O. Box 2000 (RY-33-208), Rahway, NJ 07065-0900, USA and Prous Science Publishers, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of LY-333328



demonstrated under several *in vitro* test and media conditions. Potent *in vitro* activity also was demonstrated against MRSA and streptococci (21, 22, 24), including activity against *Streptococcus pneumoniae* (27). Another study demonstrated that LY-333328 was highly protein bound (77% in rats), but that increasing the concentration to 8X the minimum inhibitory concentration value compensated for the binding effect (28). Overall, the initial

data indicated that LY-333328 was a potent new glycopeptide antibiotic with *in vitro* activity against important antibiotic-resistant Gram-positive bacteria. The initial panel of data supported further evaluation of this novel compound.

More recent *in vitro* (29-38) and experimental *in vivo* (39-41) data on the activity of LY-333328 were presented at the 1997 Interscience Conference on Antimicrobial Agents and Chemotherapy in Toronto, Canada. These data and those summarized in a recent publication by Biavasco *et al.* (43) expand the key information available on this new glycopeptide antibiotic.

Muller-Serieys *et al.* (29) compared the *in vitro* activity of LY-333328 to that of vancomycin and teicoplanin against 124 clinical isolates and 5 reference strains of staphylococci and enterococci using a microtiter dilution assay and Mueller Hinton broth. Among the staphylococci, the *in vitro* activity of LY-333328 was similar to that of vancomycin against isolates of *S. aureus*, including decreased susceptibility to teicoplanin- and methicillin-resistant strains, with minimum inhibitory concentration (MIC) values ≤ 8 μg/ml. The MIC values of LY-333328 were similar to that of vancomycin against coagulase-negative staphylococci, and were 4-fold lower than that of teicoplanin against resistant strains. Among the enterococci, LY-333328 inhibited all strains tested at concentrations of ≤ 2 μg/ml. Overall, LY-333328 was the most active agent against drug-resistant strains and against glycopeptide-susceptible strains; the MIC_{50} and MIC_{90} values of LY-333328 and teicoplanin were not significantly different. In this study, vancomycin was slightly less active than LY-333328 and teicoplanin. Also, LY-333328 had higher inhibitory activity for tested vancomycin-resistant strains of enterococci, including VanA, VanB and VanC phenotypes. The investigators concluded that LY-333328 appears to be a new promising antibacterial agent against Gram-positive cocci.

Using the National Committee for Clinical Laboratory Standards (NCCLS) designed agar dilution assay, Mir *et al.* (30) studied the comparative *in vitro* activity and the inoculum effect of LY-333328 against vancomycin-resistant and -susceptible enterococcal isolates obtained from intensive care unit patients. The study included both vancomycin-susceptible and -resistant enterococci, and also determined the inoculum effect on the susceptibility testing of LY-333328 against 222 enterococcal isolates collected from the rectum, nose, oropharynx and tracheal aspirates from 139 intensive care unit patients. LY-333328 showed a higher intrinsic activity than vancomycin and teicoplanin against glycopeptide-resistant enterococcal isolates. The activity of LY-333328 against susceptible isolates was similar to the activities of vancomycin and teicoplanin. In this study an increment in inoculum size was associated with an increment in LY-333328 MIC values. Specifically, the results obtained with 45 enterococcal isolates (15 vancomycin-susceptible, 21 VanA isolates and 9 VanC isolates) clearly demonstrated that LY-333328 MICs were largely affected by an increase in inoculum, e.g., an increase in inoculum from 10^4 to 10^6 CFU/agar dilution spot yielded increased MIC values of LY-333328, vancomycin and teicoplanin by a factor of 11.4, 1.6, and 3.8, respectively. Therefore, in microbiological susceptibility studies with LY-333328 the inoculum size should be carefully monitored to avoid misinterpretation of susceptibility results.

Garcia-Garrote *et al.* (31) studied the *in vitro* activity of LY-333328 against 425 Gram-positive clinical isolates, including *S. aureus*, coagulase-negative *S. aureus*, *E. faecalis*, *E. faecium*, *S. pneumoniae*, *Streptococcus viridans* group, *S. pyogenes* and *S. agalactiae.* The NCCLS broth microdilution assay was used in this study. The investigators concluded that LY-333328 was uniformly active against all vancomycin-resistant enterococcci and all teicoplanin-resistant staphylococci. LY-333328 demonstrated activity that was superior to that of vancomycin and teicoplanin against *S. pneumonia* and the *S. viridans* group, including penicillin-resistant strains and against *S. agalactiae*, including erythromycin-resistant strains. Potency of LY-333328 was comparable to that of vancomycin and teicoplanin against methicillin-resistant staphylococci.

Sloos *et al.* (32) studied the *in vitro* activity of LY-333328 against a panel of coagulase-negative staphylococci using NCCLS microbroth and agar dilution assays. Minimum bactericidal (MBC) activity also was determined. Among the 121 isolates tested, 17 were resistant to teicoplanin. The MIC and MBC values indicated that LY-333328 is a potent compound. The MBC/MIC ratio of all isolates tested was ≤ 8.0 μg/ml, indicating that LY-333328 is bactericidal. Among the clinical isolates tested, the MIC_{90} values of LY-333328 were 4.0 μg/ml using microbroth dilution and 8.0 μg/ml using agar dilution; the MBC_{90} value was 8.0 μg/ml irrespective of the methicillin susceptibility. Overall, LY-333328 was bactericidal against coagulase-negative staphylococci with activity similar to that observed for vancomycin. LY-333328 was highly active against teicoplanin-resistant organisms in this study.

Hoban *et al.* (33) studied the comparative *in vitro* activity of LY-333328 against 600 clinical isolates of *Enterococcus* species, including *Enterococcus gallinarum* and *E. casseliflavus* collected from patients in Canada. The investigators noted that the MIC_{90} value and percent of isolates susceptible to LY-333328 at a concentration of ≤ 8.0 μg/ml were: vancomycin-susceptible *E. faecium* (0.5 μg/ml; 100%), vancomycin-resistant *E. faecium* (2.0 μg/ml; 100%), vancomycin-susceptible *E. faecalis* (1.0 μg/ml; 100%), vancomycin-susceptible *E. gallinarum* (0.25 μg/ml; 100%), vancomycin-resistant *E. gallinarum* (1.0 μg/ml; 100%) and vancomycin-susceptible *E. casseliflavus* (0.25 μg/ml; 100%). Overall, this study demonstrated that LY-333328 had excellent *in vitro* activity against the enterococci studied, including those with resistance mechanisms to gentamicin, ampicillin or vancomycin.

Cheron and Boisivon (34) examined the *in vitro* bactericidal activity to LY-333328 against vancomycin-resistant and-susceptible isolates of *E. faecium* using a mac-

robroth dilution assay. Kill curves were assayed at 6, 24 and 48 h. The MIC values of LY-333328 were 4-fold higher for vancomycin-resistant isolates compared to vancomycin-susceptible isolates. At 24 h, however, a 3 $\log_{10}$ killing rate was observed at 16X the MIC value for both vancomycin-susceptible and -resistant isolates. At the 48 h time point, the MBC was obtained at 4-8X the MIC value. LY-333328 was more potent than vancomycin in bactericidal activity as the 16X MIC killing rates were 4-5 $\log_{10}$ and 1.9-2.3 $\log_{10}$, respectively.

Biavasco *et al.* (43) compiled an overview of the *in vitro* activity of LY-333328 against a broad panel of important bacterial pathogens. They studied 311 glycopeptide-susceptible isolates representing the genera *Staphylococcus*, *Enterococcus*, *Streptococcus*, *Aerococcus*, *Gemella*, *Lactococcus*, *Listeria*, *Corynbacterium* and the anaerobic genus, *Clostridium*. Additional strains tested included 56 clinical isolates of *Enterococcus* which were resistant or intermediate in activity against vancomycin and/or teicoplanin, and 32 clinical isolates of *Staphylococcus*, including *S. aureus*, *S. epidermidis* and *S. haemolyticus*. Other genera tested included *Leuconostoc*, *Pediococcus*, *Lactobacillus* and *Erysipelothrix*, genera not usually considered susceptible to vancomycin.

Overall, LY-333328 had potent activity against both glycopeptide-susceptible and -resistant isolates of staphylococci, enterococci and listeriae. Of additional interest was the observation of modest *in vitro* activity against most isolates of *Leuconostoc*, *Pediococcus* and *Erysipelothrix* with a MIC range of 1-8 μg/ml. Against *Lactobacillus* species LY-333328 was poorly active with MIC values ranging from 4-32 μg/ml, although MIC values for vancomycin and teicoplanin were > 256 μg/ml. Another important observation was the uniform bactericidal activity of LY-333328 against enterococcal isolates which were tolerant to vancomycin and teicoplanin in the same assays. LY-333328 had MBC to MIC ratios of 4-8 for most vancomycin-susceptible and -resistant isolates.

In Vitro Pharmacodynamics

Several investigators have conducted studies on the *in vitro* pharmacodynamic effects of this new glycopeptide. Zhanel *et al.* (37) studied the influence of human serum on the pharmacodynamic properties of LY-333328, teicoplanin and comparator agents against *S. aureus*. They concluded that human serum causes a significant reduction in the pharmacodynamic activity of LY-333328, as well as the activity of teicoplanin, cefazolin, ceftriaxone, cloxacillin and clindamycin, resulting in increased MIC and MBC values. Decreased killing and decreased postantibiotic effects against *S. aureus* is common for antibiotics that are greater than 80% protein bound. Further studies on protein binding are necessary to elucidate this issue.

Zelenitsky *et al.* (35) studied the pharmacodynamics of multidose LY-333328 against vancomycin-susceptible and -resistant *E. faecium* in an *in vitro* pharmacodynamic model. In addition, they compared the activities of LY-333328 *versus* LY-333328 plus once daily or 3 times daily gentamicin. The conclusions were that LY-333328 alone at 10X and 1X the MIC values resulted in net growth at 24 and 48 h. In contrast, LY-333328 at 0.1X and 1X the MIC value, plus either gentamicin at 18 μg/ml q24h or 6 μg/ml q8h, was synergistic with respect to kill rate and total bacterial kill at 24 and 48 h. LY-333328 plus gentamicin regimens were synergistic against both vancomycin-susceptible and -resistant *E. faecium*. In addition, there was no difference in the kill rate at 24 and 48 h between the regimens containing gentamicin q24h *versus* q8h.

Bauernfeind *et al.* (36) used a pharmacodynamic model to study the bactericidal effect of LY-333328 against staphylococci and enterococci. The investigators used both continuous and discontinuous infusion of LY-333328 into the test system in order to assess bactericidal activity. They concluded that LY-333328 has greater bactericidal activity when added continuously (complete kill of inoculum at 24 h for most isolates) at concentrations of 2.6X the MIC value for the target organism, as compared to discontinuous administration (5 $\log_{10}$ kill of inoculum, but with regrowth after 36 h).

In Vivo Activity

Several investigators have studied the *in vivo* activity of LY-333328 in various experimental animal models. Kundsen *et al.* (39) compared the effect of LY-333328 with teicoplanin and vancomycin against pneumococci in a mouse peritonitis model. *S. pneumoniae* is one of the most frequent pathogens isolated from patients suffering from pneumonia. Due to the worldwide increase in the incidence of pneumonia and the worldwide increase in antibiotic resistance, further knowledge of the pharmacokinetic and pharmacodynamic properties of alternative drugs to penicillin is desirable. Currently, the only class of antibiotics active against pneumococci without resistance problems is the glycopeptides. The purpose of this study was to compare the *in vivo* effects of LY-333328 with those of vancomycin and teicoplanin in a mouse peritonitis model against pneumococci using different treatment regimens. The data demonstrated that LY-333328 is highly active against pneumococci in a mouse peritonitis model with single-dose effective dose 50% (ED_{50}) values of 0.18 mg/kg. In comparison with teicoplanin and vancomycin, the weight potency of LY-333328 was 2-3 times greater, respectively, in all dosing regimens tested. The pharmacodynamic properties of LY-333328, teicoplanin and vancomycin were similar against pneumococci in this model. The efficacy of LY-333328 in this model correlated significantly with all pharmacokinetic parameters. Finally, this *in vivo* study revealed a probable protein binding of LY-333328 in mouse serum of approximately 95%.

Kaatz *et al.* (40) studied the comparative efficacy of LY-333328 and vancomycin in the therapy of experimental MRSA endocarditis in rabbits. The investigators concluded that LY-333328 was as efficacious as vancomycin in clearing bacteremia, reducing vegetation and tissue bacterial counts, and sterilizing all assayed sites in ani-

mals infected with a clinical isolate of MRSA. Further testing of the therapeutic efficacy of LY-333328 in experimental infections caused by other multidrug resistant Gram-positive organisms, such as *Enterococcus* species, would be appropriate. The authors speculated that if LY-333328 demonstrates good *in vivo* activity in animal models and has an acceptable toxicity profile in humans, it may serve as a viable alternative to vancomycin in human infections caused by these difficult-to-treat organisms.

Saleh-Mghir *et al.* (41) studied the diffusion pattern of LY-333328 in cardiac vegetations in experimental endocarditis. The investigators concluded that, in their experimental model, the *in vitro* and *in vivo* activity of LY-333328 was not reduced against strains of *E. faecalis* with an acquired mechanism of resistance to vancomycin and teicoplanin. LY-333328 was the only glycopeptide tested that was active *in vivo* against the three study strains. However, the relatively moderate intensity of *in vivo* bactericidal activity might be related to pharmacokinetic parameters such as high protein binding and a heterogeneous pattern of diffusion within endocardiac vegetations. The investigators noted that no gradient of concentration was observed between the periphery and the core of the vegetation, so the optimal dosing regimen to overcome reduced diffusion in the vegetation remains to be determined.

Schwalbe *et al.* (42) used a neutropenic mouse model to characterize the activity of LY-333328 against vancomycin-resistant enterococci. In this study, LY-333328 was effective against all four enterococcal strains tested. By 48 h, the level of bacteremia was below the limit of detection, which was 100 CFU/ml for 52 of 53 treated mice. Vancomycin reduced bacteremia in mice challenged with vancomycin-susceptible enterococci, but the reduction was significantly less than that obtained with LY-333328. In addition, vancomycin was ineffective in reducing vancomycin-resistant enterococcal bacteremia.

Conclusions

LY-333328 is a new representative of the glycopeptide antibiotic class. This glycopeptide has potent i*n vitro* activity against Gram-positive bacteria and experimental *in vivo* activity against infections caused by antibiotic-susceptible and -resistant organisms. LY-333328 also has potent *in vitro* bactericidal activity against enterococci. Animal toxicology needs to be completed, and experimental and clinical pharmacokinetic data need to be collected to determine absorption, disposition, metabolism, excretion and potential plasma half-life. The data summarized in this overview support the further evaluation of LY-333328 as a novel glycopeptide antibiotic with activity focused on glycopeptide-resistant staphylococci and enterococci.

Manufacturer

Eli Lilly and Co. (US).

References

1. Cooper, R.D.G., Snyder, N.J., Zweifel, M.J. et al. *Reductive alkylation of glycopeptide antibiotics: Synthesis and antibacterial activity*. J Antibiot 1996, 49: 575-81.

2. Cooper, R.D.G., Huff, B.E., Nicas, T.I. et al. (Eli Lilly & Co.). *Glycopeptide antibiotic derivs.* WO 9630401.

3. Cooper, R.D.G., Huff, B.E., Nicas, T.I. et al. (Eli Lilly & Co.). *Glycopeptide antibiotic derivs*. EP 667353.

4. Lin, Y., Stratford, R.E., Zornes, L.L. et al. *Non-clinical pharmacokinetics of LY333328, a semisynthetic glycopeptide antibiotic active against vancomycin-resistant enterococci*. 35th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, San Francisco) 1995, Abst 254.

5. Boylan, C.J., Nicas, T.I., Preston, D.A. et al. *Efficacy of semisynthetic glycopeptides active against vancomycin-resistant enterococci in a mouse infection model.* 35th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, San Francisco) 1995, Abst 255.

6. Nagarajan, N. *Antibacterial activities and modes of action of vancomycin and related glycopeptides*. Antimicrob Agents Chemother 1991, 35: 605-9.

7. Nagarajan, N. *Structure-activity relationships of vancomycin-type glycopeptide antibiotics.* J Antibiot 1993, 46: 1181-95.

8. Nicas, T.I., Mullen, D.H., Klokowitsch, J.E., Preston, D.A., Snyder, N.J., Stratford, R.A., Cooper, R.D.G. *Activities of the semisynthetic glycopeptide LY191145 against vancomycin-resistant enterococci and other Gram-positive bacteria.* Antimicrob Agents Chemother 1995, 39: 2585-7.

9. Nicas, T.I., Mullen, D.H., Flokowitsch, J.E., Preston, D.A., Snyder, N.J., Zweifel, M.J., Wilkie, S.C., Rodriquez, M.J., Thompson, R.C., Cooper, R.D.G. *Semisynthetic glycopeptide antibiotics derived from LY264826 active against vancomycin-resistant enterococci.* Antimicrob Agents Chemother 1996, 40: 2194-9.

10. Stack, D.R., Letourneau, D.L., Mullen, D.L., Butler, T.F., Allen, N.E., Kline, A.D., Nicas, T.I., Thompson, R.C. *Covalent glycopeptide dimers: Synthesis, physical characterization, and antibacterial activity.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F1.

11. Snyder, N.J., Zweifel, M.J., Cooper, R.D.G., Rodriquez, M.J., Nicas, T.I., Mullen, D.L., Butler, T.F. *New semisynthetic glycopeptide amides active against resistant enterococci.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F2.

12. Centers for Disease Control and Prevention. *Nosocomial enterococci resistant to vancomycin - United States*, 1989-1993. Morb Mortal Wkly Rep 1993, 42: 597-9.

13. Murray, B.E. *Editorial response: What can we do about vancomycin-resistant enterococci?* Clin Infect Dis 1995, 20: 1134-6.

14. Uttley, A.H.C., George, R.C., Naidoo, J., Woodford, N., Johnson, A.P., Collins, C.H., Morrison, D., Gilfillan, A.J., Fitch, L.E., Heptonstall, J. *High-level vancomycin-resistant enterococci causing hospital infections*. Epidemiol Infect 1989, 103: 173-81.

15. Manso, E., De Sio, G., Biavasco, F., Varaldo, P.E., Sambo, G., Maffei, C. *Vancomycin-resistant enterococci*. Lancet 1993, 342: 615-7.

16. Venditti, M., Biavasco, F., Varaldo, P.E., Macchiarelli, A., De Biase, L., Marino, B., Serra, P. *Catheter-related endocarditis due to glycopeptide-resistant Enterococcus faecalis in a transplanted heart.* Clin Infect Dis 1993, 17: 524-5.

17. Nicas, T.I., Mullen, D.L., Flokowitsch, J.E., Preston, D.A. *Bactericidal activity against enterococci of the semisynthetic glycopeptide LY333328*. 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F198.

18. Felmingham, D., Robbins, M.J. *In vitro activity of LY333328, a semi-synthetic glycopeptide active against glycopeptide-resistant enterococci, in various test media*. 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F199.

19. Zelenitsky, S., Karlowsky, J., Hoban, D., Kabani, A., Zechel, M., Zhanel, G. *Bactericidal activity of an investigational glycopeptide, LY333328, against vancomycin-sensitive and vancomycin-resistant Enterococcus faecium.* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18 New Orleans) 1996, Abst F200.

20. Baltch, A.L., Smith, R.P., Ritz, W. *Inhibitory/bactericidal activity of LY333328 against vancomycin-resistant Enterococcus faecium (VRE).* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F201.

21. Biavasco, F., Lupidi, R., Manso, E., Vignaroli, C., Facinelli, B., Varaldo, P.E. *In vitro activity of LY333328 against Gram-positive bacteria resistant or moderately susceptible to clinically available glycopeptides (GPs).* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F202.

22. Barrett, M.S., Erwin, M.E., Jones, R.N. *Antimicrobial activity of a new glycopeptide derivative, LY333328, tested against resistant Gram-positive organisms.* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F203.

23. Donabedian, S., Perri, M.B., Thal, L.A., Zervos, M.J. *Comparative in vitro and bactericidal activity of LY333328 against multi-drug resistant enterococci.* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F204.

24. Rouse, M.S., Piper, K.E., Patel, R., Cockerill, F.R., Wilson, W.R., Steckelberg, J.M. *In vitro activity of LY333328 against vancomycin resistant (vanA, vanB, vanC1, vanC2) enterococci*. 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F205.

25. Mercier, M.C., Houlihan, H.H., Rybak, M.J. *In vitro activity of a new glycopeptide, LY333328 (LY), alone and in combination with vancomycin (V), rifampicin (R), and gentamicin (G) against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus faecium (VREF) at standard (SI) and high inoculum (HI).* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F206.

26. Anzak, A., Mercier, R.C., Rybak, M.J. *In vitro activity of investigational antibiotics alone and in combinations against two strains of vancomycin-resistant Enterococcus faecium (VREF).* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F207.

27. Fasola, E.L., Spangler, S.K., Ednie, L.M., Bajaksouzian, S., Jacobs, J., Appelbaum, P.C. *Antipneumococcal activity of LY333328, a new glycopeptide*. 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F208.

28. Mercier, R.B., Rybak, M.J. *Effect of protein and concentration on the pharmacodynamic properties of a new glycopeptide, LY333328 (LY).* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F209.

29. Muller-Serieys, C., Vallee, E., Pangon, B., Chachaty, E., Decre, D. *In vitro activity of LY333328, a new glycopeptide, against Gram-positive cocci.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F3.

30. Mir, N., Baquero, F., Sanchez, M., Luque, R., Lopez, B., Canton, R. *Comparative in vitro activity and inoculum effect of LY333328 against vancomycin resistant and susceptible enterococci isolates obtained from ICU patients.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F4.

31. Garcia-Garrote, F., Alcala, L., Cercenado, E., Bouza, E. *In vitro activity of the new glycopeptide LY333328 against Gram-positive clinical isolates.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F5.

32. Sloos, J.H., Van de Klunert, J.A.M., Seymonson, W.G., Van Boven, C.P.A. *Susceptibility of coagulase-negative staphylococci to a new glycopeptide (LY333328).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F6.

33. Hoban, D., Cox, L., Palatnick, L., Weshnoweski, B., Kabani, A., Zelenitsky, S., Karlowsky, J., Zhanel, G. *Comparative in vitro activity of LY333328, a new glycopeptide, against Enterococcus gallinarum and Enterococcus casseliflavus.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F7.

34. Cheron, M., Boisivon, A. *In vitro bactericidal effect of LY333328 against vancomycin resistant and susceptible E. faecium.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F8.

35. Zelenitsky, S., Booker, B., Karlowsky, J., Hoban, D., Laing, N., Kabani, A., Zeckel, M., Zhanel, G. *Synergistic activity of an investigational glycopeptide, LY333328, and once-daily gentamicin against vancomycin-resistant Enterococcus faecium (VRE) in a multiple dose in vitro pharmacodynamic model*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F9.

36. Bauernfeind, A., Eberlein, E., Jungwirth, R. *Bactericidal effect of LY333328 against staphylococci and enterococci in a pharmacodynamic model.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F14.

37. Zhanel, G., Kirkpatrick, I., Zelenitsky, S., Karlowsky, J., Kabani, A., Hoban, D. *The influence of human serum on pharmacodynamic properties of an investigational glycopeptide LY333328, teicoplanin and comparator agents against S. aureus.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F15.

38. Novelli, A., Mazzei, T., Fallani, S., Cassetta, M.I., Conti, S. *In vitro postantibiotic effect of the semisynthetic glycopeptide LY333328 on clinical Gram-positive pathogens.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F16.

39. Kundsen, J.D., Raber, S., Leggett, J., Fuursted, K., Espersen, F., Frimodt-Moller, N. *Comparison of effect of LY333328 with teicoplanin and vancomycin against pneumococ-*

ci in the mouse peritonitis model. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F10.

40. Kaatz, G.W., Seo, S.M., Aeschlimann, J.R., Houlihan, H.H., Mercier, R.C., Rybak, M.J. *Comparative efficacy of LY333328 [L] and vancomycin [V] in the therapy of experimental methicillin-resistant Staphylococcus aureus [MRSA] endocarditis in rabbits.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F11.

41. Saleh-Mghir, A., Lefort, A., Petegniff, Y., Vallois, J.M., Le Guludec, D., Fantin, B., Carbon, C. *Activity and diffusion of LY333328 in experimental endocarditis due to Enterococcus faecalis*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F12.

42. Schwalbe, R.S., Iarocci, T.R. *Establishment of a neutropenic mouse model to characterize activity of LY333328 against vancomycin-resistant enterococci.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F13.

43. Biavasco, F., Vignaroli, C., Lupidi, R., Manso, E., Facinelli, B., Varaldo, P.E. *In vitro antibacterial activity of LY333328, a new semisynthetic glycopeptide.* Antimicrob Agents Chemother 1997, 41: 2165-72.