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ANTI-INFECTIVE INNOVATIONS: HIGHLIGHTS FROM THE 49TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY (ICAAC)

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ABSTRACT

As one of the largest and most important annual conferences on infectious diseases, this year's 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in San Francisco on September 12-15, provides access to a wide range of the latest information on efforts to identify treatments for these diseases. Each year, researchers share their investigations into ways of overcoming and circumventing resistance, and how microorganisms are able to overcome and circumvent these efforts. Here we provide a summary of notable developments in the world of drug and vaccine discovery, focusing on potential treatments and prophylactics for HIV, other viral, bacterial and fungal infections, and on newly identified compounds.

INTRODUCTION

From bioterrorism to parasitology, diagnostics to mycology, the annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) provides a forum for physicians and researchers to share recent data from the many-sided front in the battle against infectious diseases. Of great interest are new treatments in the pipeline for these continually challenging diseases. This report is an attempt to capture the very latest news in drug and vaccine development, highlighting efforts aimed at viral, bacterial and fungal targets. This includes new data on previously disclosed compounds, as well as a special section devoted to new molecular entities presented at the congress.

VIRAL DISEASES

HIV

Several presentations at this year's ICAAC were focused on treatments for HIV, including three related to studies of the pharmacoenhancer **GS-9350**. Gilead investigators described the process by which they developed GS-9350, an agent without anti-HIV activity, after seeking a means of improving the pharmacokinetics of HIV protease inhibitors other than the use of ritonavir. GS-9350 is currently in phase II development. The agent was found to be a potent, mechanism-based CYP3A inhibitor, with no antiviral activity at concentrations up to 90 μM and reduced in vitro effects on adipocytes compared to ritonavir. GS-9350 can be formulated with other agents and it is hoped that it will be associated with fewer metabolic side effects compared to ritonavir (1).

Previously found to boost plasma exposures of midazolam and elvitegravir compared to ritonavir, GS-9350 has now been found to boost atazanavir exposure. Healthy subjects (N = 42) included in a crossover study were given atazanavir 300 mg for 10 days with GS-9350 100 or 150 mg or ritonavir 100 mg in the fed condition. Atazanavir exposures were bioequivalent when given with GS-9350 150 mg or ritonavir 100 mg. Most adverse events were mild, and none were serious or grade 3-4. An ongoing phase II trial in treatment-naïve HIV patients is comparing atazanavir/GS-9350 300/150 mg and atazanavir/ritonavir 300/100 mg, both in combination with emtricitabine/tenofovir disoproxil fumarate (2, 3).

A fixed-dose combination of elvitegravir/GS-9350/tenofovir disoproxil fumarate/emtricitabine has been developed, and the effects of food on the constituent pharmacokinetics were evaluated in 24 healthy volunteers. Volunteers received single doses of the combination (elvitegravir 150 mg, GS-9350 150 mg, tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg) with a light meal and then, after washout, with a high-fat meal. Food increased elvitegravir exposures, while tenofovir exposures were slightly increased. The high-fat meal lowered GS-9350 exposure but this did not adversely affect elvitegravir exposures (4).

Tobira Therapeutics' chemokine CCR5 antagonist **TBR-652** (formerly TAK-652), licensed from Takeda for development as an anti-HIV agent, has shown the potential to be combined with other antiretroviral agents in vitro and displayed favorable pharmacokinetics in a study in healthy volunteers. To test the interaction of TBR-652 and other anti-HIV agents in vitro, an infectious replicative assay was used, with CCR5-tropic virus exposed to 12 concentrations of TBR-652 (0-100 nM) and 8 concentrations of other inhibitors for 4 days. Weak synergy was seen with TBR-652 and lopinavir, atazanavir, darunavir and etravirine, while additive effects were seen with TBR-652 and tenofovir and raltegravir. No antagonism and no cytotoxicity were observed with any two-drug combination (5). For pharmacokinetic and safety assessment, a randomized, double-blind, placebo-controlled, multidose study was conducted in healthy volunteers who received 1 x 25 mg/day or 4 x 25 mg/day of one tablet formulation (F1) or 1 x 100, 2 x 100 or 1 x 25 mg/day of a second tablet formulation (F2). Tablets were administered for 10 days after a high-fat meal. TBR-652 was well tolerated at doses up to 200 mg/day for 10 days and achieved mean peak plasma concentrations in 4-6 h. For the dose range tested, the mean half-life was approximately 40 h. At 25 mg/day with either F1 or F2, plasma exposures were greater than the target therapeutic level of 2 ng/mL. There were no deaths or serious adverse events, and treatment-emergent adverse events were mostly mild (6).

Bevirimat dimeglumine, acquired earlier this year by Myriad Pharmaceuticals from Panacos, is a viral maturation inhibitor in phase II investigation for HIV infection. A novel 100-mg tablet formulation has now been evaluated in a study in 35 patients with HIV-1 infection who received doses of 200 mg b.i.d. fed or fasted, 300 mg q.d. fed or fasted or 400 mg q.d. fed or fasted for 15 days in addition to HAART. Pharmacokinetic and safety assessments were favorable. Most adverse events were mild, with diarrhea (20%), abdominal cramping (11%), headache (11%) and nausea (9%) being the most common. The one serious adverse event, hip fracture, was unrelated to bevirimat. Twice-daily dosing improved C_{min} values compared to daily dosing and maintained C_{min} values above the estimated EC_{90} (27 µg/mL). Food delayed t_{max} by 3-4 h but had little effect on bevirimat exposure (7).

Oral doses of **S/GSK-1265744** (Shionogi/GlaxoSmithKline), a next-generation HIV integrase inhibitor, were well tolerated in healthy and HIV-infected subjects in a double-blind, randomized, placebo-controlled, single- and multiple-dose-escalation trial. Two cohorts of 9 healthy subjects received alternating suspension doses of 5, 10, 25 and 50 mg, while 3 cohorts of 10 healthy subjects were treated with suspension doses of 5, 10 or 25 mg q.d. S/GSK-1265744 for 14 days. HIV-infected participants were given 30 mg S/GSK-1265744 q.d. for 10 days followed by a 3-drug antiretroviral therapy for 14 days. The majority of adverse events reported in this study were mild, with headache being the most common. In healthy volunteers, a dose-proportional pharmacokinetic profile was seen over the dose range under evaluation, with a median elimination half-life of 30-40 h. In HIV-infected patients, on day 11 of treatment with S/GSK-1265744, there was a mean decrease from baseline in plasma HIV-1 RNA of 2.34 $\log_{10}$ copies/mL, which indicated that once-daily doses of 30 mg or lower could achieve target therapeutic concentrations. Further evaluation of S/GSK-1265744 in HIV-infected subjects is planned (8).

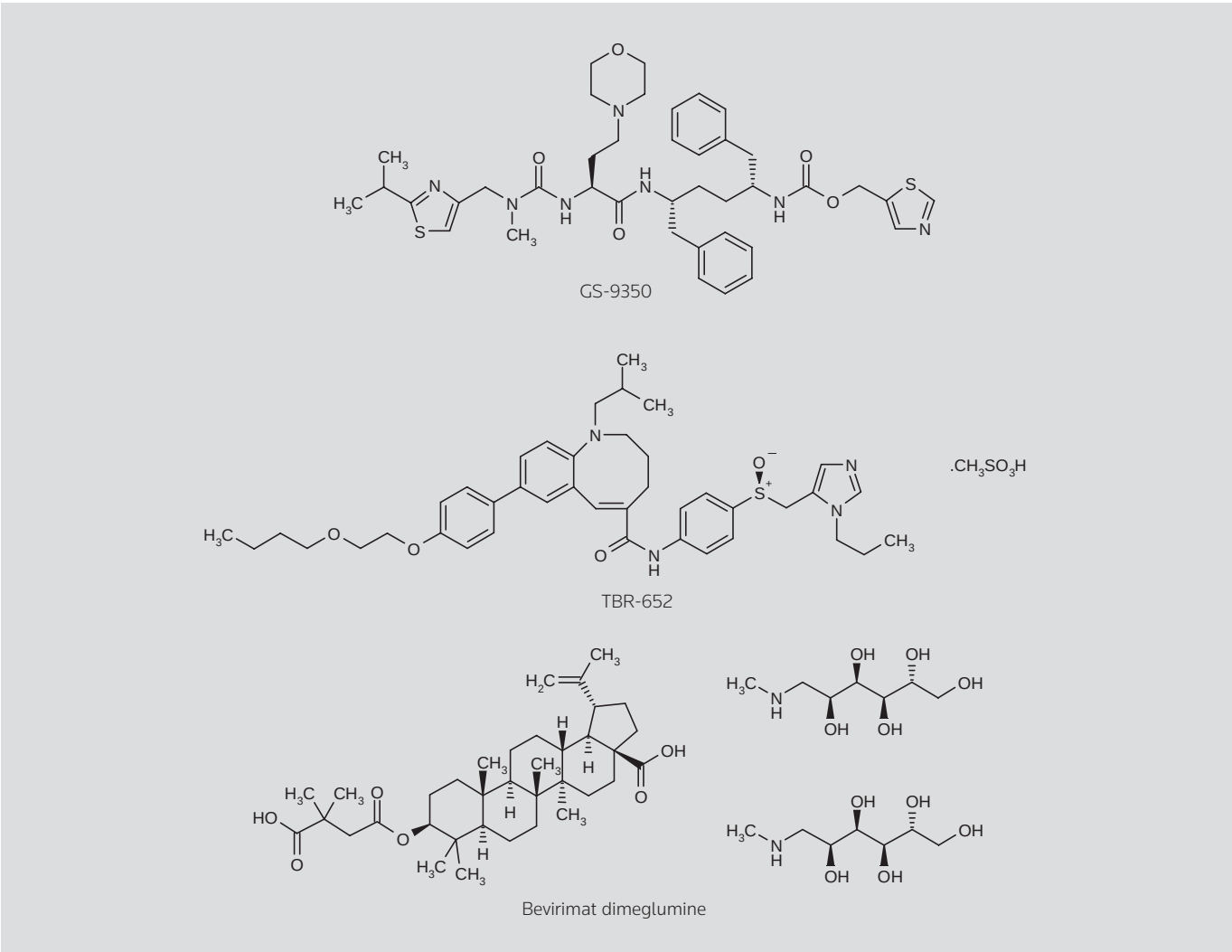
Several studies of the next-generation oral HIV integrase inhibitor **S/GSK-1349572** (Shionogi/GlaxoSmithKline) were discussed at the congress. S/GSK-1349572 was found to prevent HIV-1 NL432 virus replication at an initial concentration of 32 nM, whereas the same initial concentration of raltegravir permitted viral replication in passage studies. HIV-1 strains with integrase inhibitor resistance, such as E92Q, Q148H/K/R and N155H mutants, selected in the presence of 6.4 nM S/GSK-1349572 showed an inability to replicate at a concentration of 160 nM S/GSK-1349572 during passage. No additional mutations were observed during passage of N155H and E92Q under S/GSK-1349572; however, additional substitutions were seen in the presence of raltegravir. The possibility that S/GSK-1349572 may exhibit a higher genetic barrier to resistance compared to raltegravir is supported by in vitro data obtained in this study (9).

Clinical evaluation of the short-term safety of S/GSK-1349572 in healthy subjects and HIV-infected integrase inhibitor-naïve individuals was performed by meta-analysis of data obtained from seven phase II trials (six healthy subject trials and one HIV subject trial). A total of 183 participants were included in the meta-analysis; S/GSK-1349572 was given to 166 subjects, whereas 17 individuals received placebo. At single or repeated doses ranging from 2 to 100 mg, administered for up to 19 days, S/GSK-1349572 was well tolerated, with no clinically significant safety signals being identified following short-term dosing. The most frequent adverse events occurring in six or more subjects during treatment with S/GSK-1349572 were headache, diarrhea, nausea, dizziness and vomiting (16%, 7%, 5%, 4% and 4%, respectively) (10).

The effect of metal cation-containing products (such as an antacid and multivitamins) on the single-dose pharmacokinetics of S/GSK-1349572 (50 mg) was evaluated in 16 healthy subjects in an open-label, randomized, 4-period, crossover study in an effort to acquire guidance for possible concomitant use of these compounds in future clinical studies. The study concluded that S/GSK-1349572 may be administered concomitantly with multivitamins without prior dose adjustment; however, coadministration with an antacid should be avoided due to a 70% reduction in S/GSK-1349572 exposure seen in the presence of an antacid. All treatments in this trial were generally well tolerated with the incidence of only a few adverse events (11).

Coadministration of S/GSK-1349572 (50 mg) and tenofovir disoproxil fumarate (300 mg) in 15 healthy individuals was also well tolerated in an open-label, repeat-dose, 3-period study. The pharmacokinetic parameters of the combination were similar to those of each drug administered alone, which indicated no significant drug interaction. The study supports combined use of the compounds without the need for dose adjustment (12).

Results from an open-label, 2-period crossover study of S/GSK-1349572 (30 mg q.d.) given for 5 days followed by randomization to either lopinavir/ritonavir (LPV/RTV; 400/100 mg b.i.d.) or darunavir/ritonavir (DRV/RTV; 600/100 mg b.i.d.) coadministered with S/GSK-1349572 (30 mg q.d.) for 14 days in 30 healthy subjects revealed no serious drug-related adverse events. S/GSK-1349572 steady-state exposure was not affected by LPV/RTV coadministration, whereas DRV/RTV caused a reduction in S/GSK-1349572 exposure, albeit to a non-clinically significant extent. Combination therapy of S/GSK-1349572 with either LPV/RTV or DRV/RTV would require no dose adjustment according to this study (13).



Viral diseases - HIV

Influenza

The recombinant sialidase fusion protein **DAS-181** (Fludase®; NexBio), which functions by removing viral receptor sialic acid from adjacent glycan structures, showed potent preclinical activity against H1N1, H5N1 and seasonal influenza virus. In one study, it was reported to significantly inhibit the replication of pandemic H1N1 2009 and seasonal influenza virus in vitro in MDCK cells and in differentiated primary human respiratory tract cultures, ex vivo in human bronchi tissue and in vivo in mice. DAS-181 also exhibited inhibitory activity against the oseltamivir-resistant influenza virus H274Y strain (14).

A second study presented at the meeting evaluated the in vitro and in vivo activity of DAS-181 against neuraminidase inhibitor-resistant strains of influenza virus. DAS-181-treated BALB/c mice previously infected with neuraminidase inhibitor-resistant A/Victoria/3/75(H3N2) exhibited significantly less weight loss, lower viral titers and increased survival ($P < 0.001$, $P < 0.001$ and $P < 0.0001$, respectively) compared to untreated animals. All of the 2004, 2007 and 2009 clinical isolates tested demonstrated sensitivity to DAS-181 (respective EC_{50} = 0.38, 0.25 and 0.23 μM) (15).

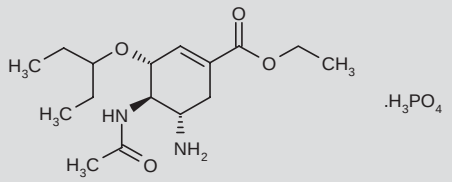
DAS-181-induced desialylation of both α2-6-linked and α2-3-linked sialic acid was shown to effectively protect human lung tissue and pneumocytes against the avian influenza virus H5N1 (A/Vietnam/3046/2004). Administration of two doses of DAS-181 at either 100 or 500 U/mL, given 12 h apart, efficiently blocked H5N1 infection in ex vivo lung tissue culture (16).

The safety, tolerability and systemic exposure of DAS-181 administered as dry powder via oral inhalation using a special device were evaluated in a phase I trial sponsored by NexBio and the National Institute of Allergy and Infectious Diseases (NIAID) conducted in healthy, nonsmoking adults. This randomized, double-blind, placebo-controlled, single-group assignment study, with primary outcome measures including safety and tolerability of a single DAS-181 dose (0.5, 1.0, 2.25 and 4.5 mg), was completed in January 2009 (17).

A study allowing advancement of the **NB-1008** vaccine into phase I clinical testing found intranasal administration of the vaccine to be safe in New Zealand White rabbits. NanoBio's NB-1008 is a W805EC-adjuvanted-Fluzone® vaccine. The animals were immunized with Fluzone® (2008-2009), phosphate-buffered saline (PBS), W805EC adjuvant or Fluzone® 15 or 30 µg total hemagglutinin (HA) mixed with 10 or 20% W805EC adjuvant. Two doses were administered, one on day 1 and one on day 15. No concerns were raised in clinical, laboratory, gross and histopathological examinations after administration of NB-1008. The maximum administered dose was considered the NOAEL (no observable adverse effect level). Robust immune responses were observed on day 16 to A/Brisbane (H3N2), and robust responses to all vaccine strains were seen on day 28. No immune responses were seen with Fluzone® alone or PBS alone (18). A randomized, controlled phase I study of NB-1008 involving 120 healthy human volunteers has been approved by the FDA.

A novel, fully synthetic influenza vaccine, designated **SFV2/NAM1**, comprising 5 immunogens and Variosite™ formulations that contain 16 peptide variants, accounting for past and future antigenic variation of the influenza virus in HA and nucleoprotein (NP), has been generated by scientists at Variation Biotechnologies using Variosite™ technology. The vaccine was evaluated in ferrets by intramuscular injection on days 0 and 28. Fourteen days after the initial vaccination, the animals were challenged with influenza A/Solomon virus. A reduction of viral load by 1 log was seen at day 2 post-vaccination with SFV2/NAM1, which was associated with a decrease in the magnitude and duration of fever. High titers of virus-specific serum IgG were detected and an induction of hemagglutination inhibition titers was observed. The vaccine was found to induce broadly reactive humoral and cellular immunity, which included the recently emerged pandemic H1N1/California isolate. The Variosite™ technology has provided a means to induce broadly reactive immunity necessary to confer protection against infection with variable influenza pathogens (19).

Various data dealing with **oseltamivir phosphate** (Tamiflu®; Roche, Gilead) and the emergence of resistance to the drug were presented. Among the presentations was an analysis of the emergence and evolution of influenza A/H1N1 viruses with H274Y mutations conferring resistance to oseltamivir. A pattern of nine H274Y-associated neuraminidase mutations which emerged in 2007 was identified, both with and without H274Y. The pattern with H274Y increased in prevalence between 2007 and 2008 and became dominant, indicating that the introduction of H274Y increased viral fitness. The authors concluded that a new H1N1 sequence pattern is likely to emerge through immune-driven antigenic drift (20).



Oseltamivir phosphate

An observational study in 760 patients with severe seasonal influenza treated at 2 Hong Kong hospitals found the rate of mortality to be 3.8% in those treated with oseltamivir (n = 395) compared to 6.0% in untreated patients. Oseltamivir treatment was associated with a reduced risk of mortality in a multivariate model (HR 0.38) (21, 22).

Data from 215 patients from 10 countries with virulent A H5N1 avian influenza found that the mortality rate was 88% in untreated patients while 53% of those given at least one dose of oseltamivir up to 8 days after symptom onset survived. Of those given oseltamivir within 2 days of symptom onset, five of seven survived (22).

A study in 391 healthy adults found high doses of oseltamivir (225 and 450 mg) to be well tolerated compared to placebo and standard-dose oseltamivir (75 mg). Treatments were given for 5 days. The most common adverse event was headache, with similar rates across treatment arms. The occurrence of nausea, vomiting and feeling hot/hot flushes increased with oseltamivir dose but these events did not lead to withdrawal. Dizziness was also more common in the higher-dose oseltamivir groups (23).

Lastly, the effect of oseltamivir on anticoagulation with warfarin was assessed in a crossover study in 20 volunteers who received daily warfarin (INR 2.0-3.5) for 2 weeks and then oseltamivir 75 mg b.i.d. for 4 days and 75 mg once on day 5 or warfarin alone. Oseltamivir had no clinically relevant effect on INR or on factor VIIa and did not affect warfarin pharmacokinetics (24).

Herpes

The novel helicase–primase inhibitor **ASP-2151** (Astellas Pharma) was shown to inhibit the replication of varicella zoster virus (VZV) with equal potency as herpes simplex virus HSV-1 and -2 in vitro. The helicase–primase complex plays a key role in DNA replication by catalyzing the unwinding of the DNA double helix and generating an RNA primer new strand synthesis initiation mediated by DNA polymerase. Unlike compounds such as aciclovir and valaciclovir, which inhibit viral DNA polymerase, ASP-2151 hampers the activity of the helicase–primase complex, thus inhibiting both viral DNA synthesis and viral growth. In plaque formation assays, ASP-2151 inhibited VZV and HSV growth at concentrations 3-76 times lower than those of aciclovir required to induce an equivalent level of inhibition (25).

In vivo, ASP-2151 was found to be orally effective and superior to valaciclovir at reducing HSV-1 pathology in a zosteriform spread mouse model. ASP-2151 (0.3, 1.0, 3.0, 10 and 30 mg/kg) or valaciclovir (3.0, 10, 30 and 100 mg/kg) was administered orally twice daily for 5 days to female mice which had been cutaneously inoculated with HSV-1 at 3 h postinfection. ASP-2151 exhibited a dose-dependent decrease in peak and overall disease scores (ED_{50} = 1.9 mg/kg), whereas valaciclovir decreased HSV-1 pathology with an EC_{50} value of 27 mg/kg. ASP-2151 (30 mg/kg b.i.d.) reduced disease symptoms to 87% in the vehicle group, while a 3.3-fold higher dose of valaciclovir (100 mg/kg b.i.d.) caused a 68% symptom reduction (26).

ANTIBACTERIALS

Carbapenems

Razupenem has been the subject of diverse investigations, as revealed at the meeting. The β-lactam antibiotic is being developed by Novartis and Protez Pharmaceuticals, with clinical studies reaching phase II, while in vitro and in vivo studies assessing the drug's activity also continue. Razupenem was tested against 103 strains of *Streptococcus pneumoniae*, including resistant strains. The drug was potent against all resistant phenotypes, with MICs of 0.5 µg/mL or less, and was bactericidal at 2 x MIC after 6 h against a multiresistant type 19A strain (27).

Against 108 *Haemophilus influenzae* strains, including resistant organisms, razupenem MICs were again 0.5 µg/mL or less, and the drug was bactericidal at 2 x MIC after 24 h against a non-β-lactamase-producing, ampicillin-resistant (BLNAR) strain (28).

MICs were 4 µg/mL or less against 102 methicillin-resistant *Staphylococcus aureus* (MRSA) strains, with bactericidal activity against two of three strains at 12 h in time-kill assays (29).

Against β-lactam-induced, vancomycin-resistant (BIVR) MRSA, the razupenem MIC range was 1-4 µg/mL, and against non-BIVR MRSA the range was 1-2 µg/mL. In BIVR, the combination with meropenem had additive effects, suggesting that razupenem can replace vancomycin in the vancomycin–meropenem combination, as this combination showed antagonism (30).

Experiments using an in vitro pharmacokinetic model of MRSA infection indicated that the time above MIC (T>MIC) for bacteriostatic effects up to 48 h was 5-10%, but such exposures were associated with a high risk of resistance. A T>MIC of 30-40% was thus set as a target (31).

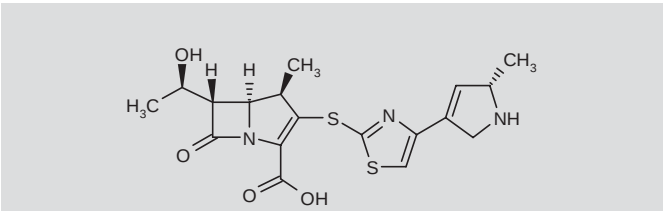
Against vancomycin-resistant *Enterococcus faecium* (VREF), razupenem MICs were 0.25-8 µg/mL and the drug showed stronger bactericidal activity against three strains than linezolid (LZD) and quinupristin/dalfopristin at 1, 4 and 16 x MIC in time-kill assays. In a murine VREF subcutaneous abscess model using four VREF strains, 10, 20 and 40 mg/kg s.c. razupenem showed significant therapeutic effects, with a superior effect seen with razupenem 40 mg/kg compared to the same dose of linezolid (32).

Razupenem was active against Gram-positive and Gram-negative pathogens in murine pneumonia models, with superior activity to imipenem against *S. aureus* and *S. pneumoniae*. Razupenem efficacy was greatly reduced against *Pseudomonas aeruginosa* in neutropenic mice (33).

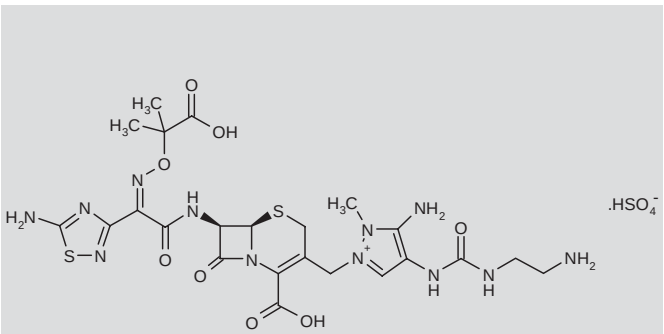
Cephalosporins

Several studies characterizing the in vitro activity and pharmacokinetics of Calixa Therapeutic's cephalosporin antibiotic **CXA-101** were presented at the meeting. The drug is in phase II development (34).

In vitro, CXA-101 was active against β-lactam-resistant *P. aeruginosa*, with good activity against AmpC-hyperproducing strains, including the highly resistant AmpD-PBP4 double mutant, and CXA-101 was the only β-lactam conserving full activity against the oprD-ampD and oprD-dacB double mutants (35).



Razupenem



CXA-101

Resistance to CXA-101 did not develop in wild-type, mucoid or hypermutable *P. aeruginosa* strains in either planktonic or biofilm growth, and potent activity was seen against these strains, making it a potential treatment option against chronic respiratory infection in cystic fibrosis (CF) patients (36).

Against isolates from chronically infected CF patients, the activity of CXA-101 was similar to meropenem and more potent than ceftazidime, imipenem, cefepime, piperacillin–tazobactam, levofloxacin and tobramycin, with activity against late CF isolates and against many isolates resistant to other antibiotics (37).

Against carbapenem-resistant *P. aeruginosa* isolates from a Spanish multicenter study, the CXA-101 MIC_{90} was 4 µg/mL, with activity seen against multidrug-resistant (MDR) strains (38). Against clinical *P. aeruginosa* isolates, the CXA-101 MIC range was 0.06-256 mg/L overall, with a low MIC against many ceftazidime-resistant isolates (39).

Assessment of the inhibition of penicillin-binding proteins (PBPs) of *P. aeruginosa* showed that CXA-101 was a potent PBP3 inhibitor, with greater potency than ceftazidime in terms of MIC, killing kinetics and binding affinity to essential PBPs (40).

In the neutropenic murine thigh infection model CXA-101 was shown to be potent against *P. aeruginosa* and Enterobacteriaceae (41).

Healthy volunteers received single i.v. doses of CXA-101 (250-2000 mg) or placebo in a phase I study, and CXA-101 was found to be generally safe and well tolerated. Pharmacokinetics were dose-proportional, with most drug eliminated through renal excretion (42). Data from two phase I studies were used to build a population pharmacokinetic model and to perform Monte Carlo simulations to aid dose and regimen selection. The results indicated that a

1000-mg dose given as a 1-h infusion every 8 h would be sufficient to treat target pathogens with an MIC of up to 8 μg/mL (43).

Studies of the combination of CXA-101 and tazobactam were also presented. A phase I study of the combination has been initiated (34).

Among studies dealing with the combination of CXA-101 and tazobactam was one in which MIC checkerboards were prepared against β-lactamase-producing Enterobacteriaceae. Tazobactam concentration-dependently potentiated CXA-101 activity against ESBL- and AmpC-producing Enterobacteriaceae. Testing showed that a breakpoint of 8 + 8 mg/L could be active against more than 90% of ESBL- and AmpC-producing organisms (44).

The combination of CXA-101 and tazobactam demonstrated improved activity against ceftazidime-resistant Enterobacteriaceae compared with CXA-101 alone, particularly ESBL-producing strains (45).

Against *Escherichia coli*, *Klebsiella pneumoniae* and *P. aeruginosa* strains, CXA-101/tazobactam often displayed additive activity when combined with other antibiotics (amikacin, aztreonam, meropenem, levofloxacin and tigecycline) with some combinations showing synergy against certain strains and no antagonism detected (46).

The CXA-101/tazobactam combination had good activity against ESBL-producing *E. coli* and *K. pneumoniae* strains (susceptibility of at least 93%), with lower MIC_{90} values for the combination of CXA-101 and tazobactam 8 mg/L versus CXA-101 and tazobactam 4 mg/L (MIC_{90} = 1 mg/L vs. 2 mg/L) (47).

CXA-101/tazobactam displayed time-dependent and often bactericidal activity against *E. coli*, *K. pneumoniae* and *P. aeruginosa* strains, with in vitro killing activity > 2.5 $\log_{10}$ CFU/mL against PA9, PA12, PA13 and PA14 *P. aeruginosa* strains (48).

Testing by broth microdilution revealed potent activity for CXA-101 against *P. aeruginosa*, including β-lactam-resistant isolates, with activity broadened when combined with tazobactam to include ESBL *E. coli* and *K. pneumoniae*. Susceptibility testing by disk diffusion appeared feasible (49).

When tested against target Gram-positive and Gram-negative pathogens, the potency of CXA-101 was increased when combined with tazobactam against ESBL isolates, *Enterobacter cloacae* and *Citrobacter* spp. (50).

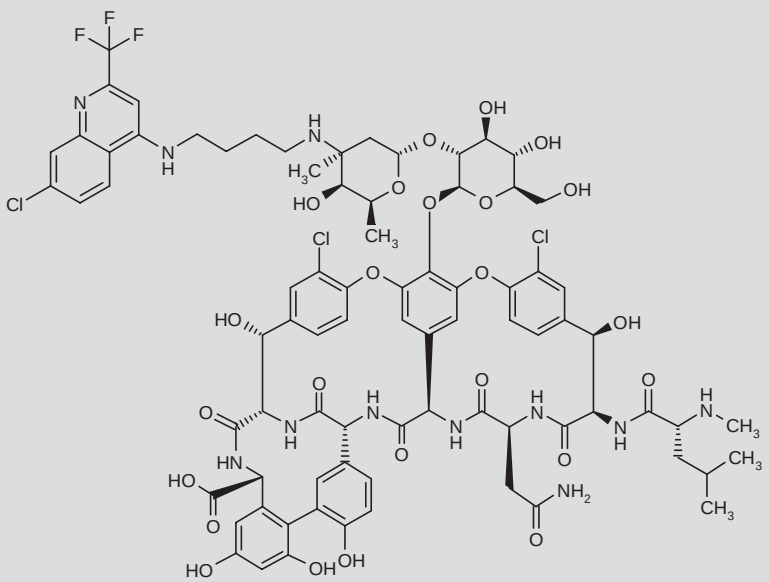
In mice with peritonitis due to ESBL-producing *E. coli* strains, CXA-101/tazobactam was as effective as ceftazidime against EC2 and EC3 strains and was more effective against the EC4 strain (51).

In a neutropenic mouse model of thigh infection due to Enterobacteriaceae-producing ESBL, the combination of CXA-101 and tazobactam exhibited potent bactericidal activity, a 2:1 ratio being most effective, with activity greater than that seen with CXA-101 alone (52).

In dogs, dose-linear pharmacokinetics were seen with CXA-101, tazobactam and their combination, and coadministration in a 2:1 ratio had little impact on the systemic exposure to either agent (53).

Glycopeptides

Palumed and the CNRS described a new hybrid antibacterial at the congress. Modification of vancomycin with an aminoquinoline yielded Vancomyquine® PA-1409 (**PA-1409**) for the treatment of infections due to MRSA. Investigations into in vitro activity yielded very low MIC values against MRSA, β-hemolytic *Streptococcus*, vancomycin-susceptible *Enterococcus* and vancomycin-resistant *Enterococcus* isolates. PA-1409 was bactericidal at lower concentrations than vancomycin, teicoplanin, LZD, daptomycin and telavancin and,



PA-1409

unlike comparators, displayed bactericidal activity against high inocula. The agent was selected for further preclinical development as a candidate for the treatment of nosocomial infections (54).

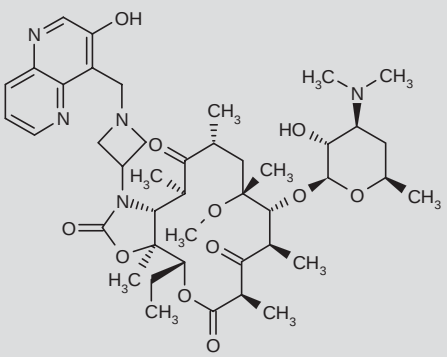
The pharmacokinetics of PA-1409 were compared to those of vancomycin in dogs, with the extent and persistence of exposure superior with PA-1409 after administration of a single i.v. bolus injection of 2.5 mg/kg. The half-life was 41.9 h and the AUC was 285 μg.h/mL. In vitro metabolism studies in which PA-1409 was incubated with liver microsomes from humans or CD1 mice indicated that the drug was not metabolized by the hepatic pathway (55).

Human monoclonal antibodies

A phase IIa study in 18 patients with ventilator-associated or hospital-acquired pneumonia caused by *P. aeruginosa* serotype O11 found **panobacumab** (KBPA-101; Kenta Biotech) to be safe and well tolerated and it could be detected in bronchoalveolar lavage (BAL) fluid. Study subjects received i.v. infusions of panobacumab 1.2 mg/kg on days 1, 4 and 7. Linear pharmacokinetics were measured, with a serum half-life of 77.8 h and a clearance rate of 0.048 L/h. The serum half-life was 70-95 h. The apparent volume of distribution was 4.67 L. Panobacumab could be detected in BAL samples collected at various time points from three of eight patients analyzed, indicating penetration of the drug into lung tissue. Signs of efficacy were seen, including 100% survival in patients receiving all three infusions, when mortality in these patients was predicted to be 22.4%. Three of five patients receiving only one infusion died. Most adverse events were self-limiting and most likely unrelated to the study drug (56).

Ketolides

A novel, orally active ketolide antibacterial agent, **PF-04287881**, has been developed by Pfizer for the treatment of infections caused by susceptible, MDR and atypical respiratory tract pathogens. Results from a recent study aimed at evaluating the in vitro and in vivo antibacterial activity of PF-04287881 and comparators against a range of geographically diverse recent bacterial clinical isolates were presented.



PF-04287881

PF-04287881 exhibited antibacterial activity against Gram-positive bacterial strains including *S. pneumoniae* (including macrolide-resistant, levofloxacin-resistant and serotype 19A), *Streptococcus pyogenes* (including macrolide-resistant) and *Streptococcus agalactiae* (MIC_{90} in the range of 0.06-1 μg/mL). Gram-negative and atypical bacteria such as *Moraxella catarrhalis*, *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Neisseria gonorrhoeae* were also included in the antibacterial spectrum of PF-04287881 (MIC_{90} in the range of 0.002-0.25 μg/mL). In vivo in a murine model of respiratory tract infection using a macrolide-resistant strain of *S. pneumoniae*, PF-04287881 displayed activity with a PD_{50} value of 33 mg/kg (57).

In a rat model of pulmonary infection using *H. influenzae*, treatment with PF-04287881 (dose range of 12.5-100 mg/kg b.i.d.) administered at 18 h postinfection for a period of 2 days demonstrated similar oral activity to comparator agents (telithromycin, azithromycin and clarithromycin; respective geometric mean MICs of 1.56, 0.78 and 6.25 μg/mL compared to 3.13 μg/mL for PF-04287881) (58).

PF-04287881 and telithromycin demonstrated almost equivalent MIC-normalized activity in three preclinical infection models; namely, a neutropenic mouse thigh infection model using *S. pneumoniae* 1056-02, a mouse respiratory infection survival model using *S. pneumoniae* 1095 and an in vitro static concentration time-kill assay. MIC values against *S. pneumoniae* 1056-02 and *S. pneumoniae* 1095 were 0.008 and 0.016 μg/mL, respectively, for PF-04287881 and 0.004 and 0.008 μg/mL, respectively, for telithromycin. The respective EC_{50} values for PF-04287881 and telithromycin were estimated at 19.5 and 14.9 ng/mL (59).

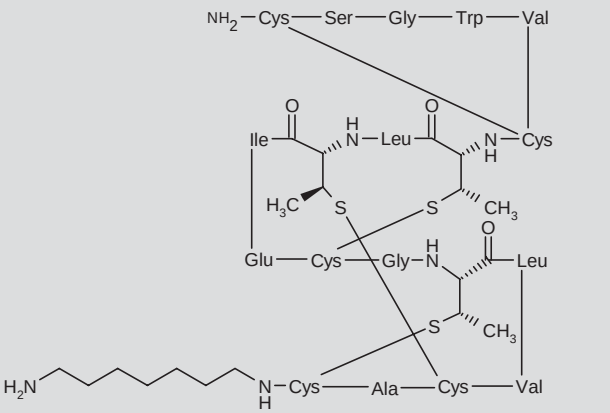
Preliminary broth microdilution quality control ranges for PF-04287881 versus reference strains, including *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49427, were estimated at 0.125-0.25, 0.06-0.125, 0.004-0.015 and 0.5-4.0 μg/mL, respectively. There was no significant lot-to-lot variability for PF-04287881 MICs in cation-adjusted Mueller-Hinton broth tests (60).

A safety and pharmacokinetic study of PF-04287881 in healthy adults sponsored by Pfizer is currently recruiting participants. The primary outcome of this randomized, double-blind, parallel-assignment phase I study is the evaluation of the safety and tolerability of PF-04287881 following a single oral dose (dose range 75-1500 mg). The estimated primary completion date was August 2009 (61).

Lantibiotics

Novacta presented preclinical data on its novel lantibiotic **NVB-302** in *Clostridium difficile* infection. The agent, a semisynthetic antibiotic derivative of deoxyactagardine B (DAB), demonstrated enhanced activity against *C. difficile* strains 37779 and 19126 compared to the parent compound (respective MIC values in the range of 0.5-2 μg/mL and 4-8 μg/mL for NVB-302 and DAB). NVB-302 retained the selectivity profile of DAB against *C. difficile* infection compared to enterococcal and staphylococcal infections, against which it exhibited MICs in the range of 4-> 32 μg/mL and 8-> 32 μg/mL, respectively (62).

The activity of NVB-302 against a number of *C. difficile* strains, including isolates with reduced metronidazole susceptibility, was



NVB-302

evaluated by agar incorporation (n = 91 strains) and broth macrodilution (n = 28 strains) in a separate study. The study reported that NVB-302 demonstrated equivalent MICs to metronidazole and vancomycin by agar incorporation in 69 metronidazole-susceptible strains (1.04, 1.16 and 0.77 mg/L, respectively) (63).

NVB-302 also exhibited selective activity against *C. difficile* (MIC values in the range of 0.5-2 µg/mL) compared to other normal gut flora (MIC values for *Bacteroides fragilis*, *Prevotella* spp. and *Porphyromonas* spp. of > 245, 64-256 and 2-64 µg/mL, respectively) (64).

NVB-302 was found to be stable in USP Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) over a clinically relevant period of 24 h and was excreted unchanged in feces following oral administration of 200 mg/kg for 7 days in rats. In the Syrian hamster cecitis model, NVB-302 (10 mg/kg) conferred protection against *C. difficile* 4013 strain, with similar efficacy to vancomycin at the same dose. The study supports the possibility of oral dosing of NVB-302 for the treatment of *C. difficile* infection without the need for the development of special enteric formulations. Further preclinical evaluation of NVB-302 in *C. difficile* infection is currently ongoing (65).

Mutilins

The novel synthetic pleuromutilin derivative **BC-7013** (Nabriva), which acts as an inhibitor of prokaryotic protein synthesis, was found to be active against a panel of the most prevalent Gram-positive pathogens implicated in the development of uncomplicated skin and skin structure infections in a recent study. The compound (≤ 0.03 µg/mL) inhibited 303 *S. aureus* isolates (MIC_{50} = 0.015 µg/mL), including MRSA. BC-7013 inhibited 100% of β-hemolytic streptococci tested in the study, including *S. pyogenes* and *S. agalactiae*, at a concentration of 0.06 µg/mL (66).

Another pleuromutilin derivative identified by Nabriva, **BC-3205**, displayed in vitro antimicrobial activity against skin pathogens (MIC_{90} values against *Staphylococcus* spp., including MRSA, and β-hemolytic streptococci of 0.06-0.12 and 0.06 µg/L, respectively). The compound also demonstrated potent activity against respiratory pathogens including *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, with respective MIC_{90} values of 0.12, 4.0 and 0.25 µg/mL (67). BC-3205 was found to be 16- to 32-fold more potent than LZD against *S. aureus* and 8-fold more active than either levofloxacin or LZD against penicillin-resistant *S. pneumoniae* (68).

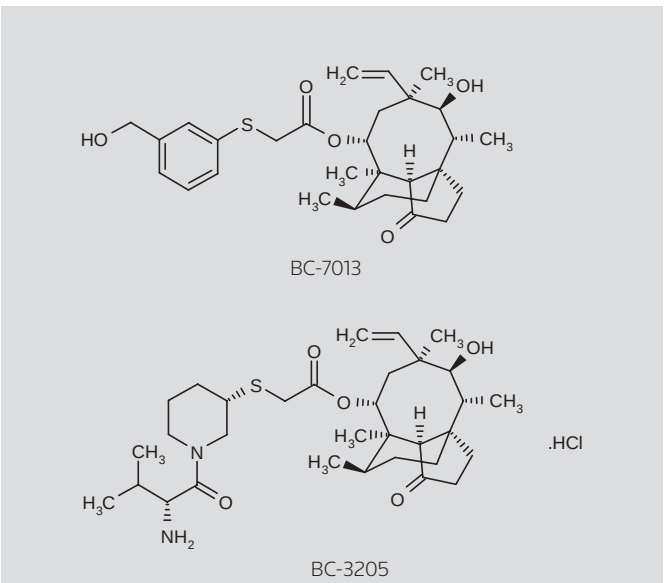
The in vivo pharmacodynamic activity of BC-3205 was evaluated against *S. aureus* and *S. pneumoniae* in neutropenic murine thigh and lung infection models. BC-3205 (10-160 mg/kg s.c.) appeared to induce time-dependent killing with prolonged postantibiotic effects (6 and 8 h, respectively, for *S. pneumoniae* and *S. aureus*). A 2-fold higher potency was observed in the lung compared to the thigh infection model (69).

Oxazolidinones

Several studies on TR-700 (**torezolid**) and its prodrug TR-701 (**torezolid phosphate**), under clinical development at Trius Therapeutics, were presented. Evaluation of 23S rRNA genes and ribosomal protein L3 and L4 sequences in two LZD-resistant clinical staphylococcal isolates revealed mutations in ribosomal protein L3, and although cross-resistance between TR-700 and LZD was seen, TR-700 was at least 8-fold more potent than LZD against both strains (70).

Against human epithelial cell lines HEp-2 and HeLa 229 infected with *Chlamydia pneumoniae* and *Chlamydia trachomatis* serovar D, TR-700 MICs were 1 and 4 µg/mL, respectively. MICs for LZD were 4 and 32 µg/mL, respectively. Neither drug was bactericidal in these studies (71).

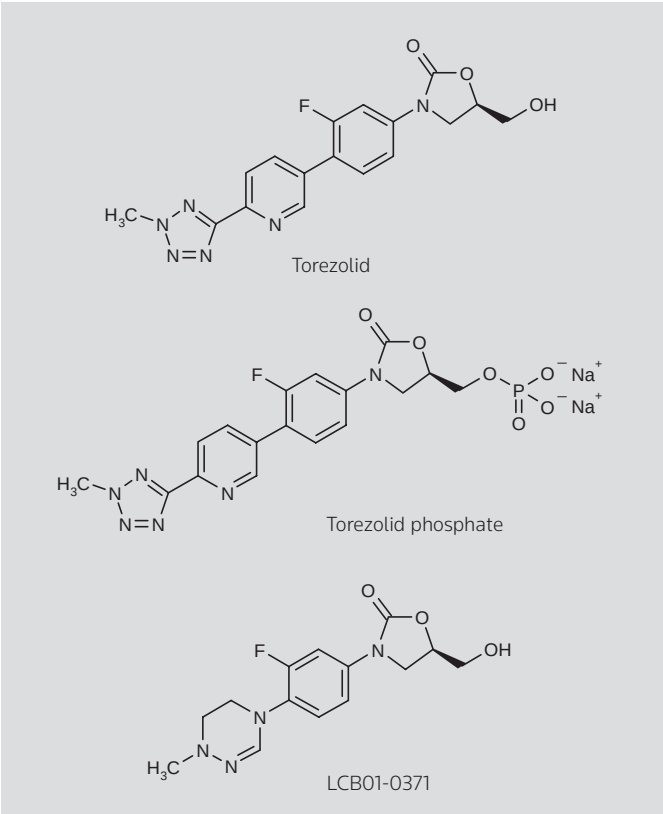
Against 660 staphylococcal blood isolates collected in Spain between 2004 and 2008, the MIC range for TR-700 was ≤ 0.03-4 µg/mL. TR-700 was more effective than LZD against MRSA, methicillin-resistant coagulase-negative staphylococci and LZD-nonsusceptible isolates (72).



BC-7013

BC-3205

Antibacterials - mutilins



Antibacterials - oxazolidinones

Against Gram-positive clinical isolates from patients with complicated skin and skin structure infections included in a phase II study, TR-700 was 4-fold more potent than LZD, with activity not altered against MRSA (MIC_{50} and MIC_{90} = 0.25 µg/mL against both MRSA and methicillin-susceptible *S. aureus*) (73).

TR-700 was tested against LZD-resistant MRSA mediated by the *cfr* gene isolated during an outbreak in a public hospital in Spain, yielding MICs of 0.5-1 mg/L and an MIC_{90} of 0.5 mg/L, with all tested strains susceptible to TR-700 (74).

Single-dose pharmacokinetic studies in a neutropenic and a non-neutropenic mouse model of thigh infection with MRSA with TR-700 and TR-701 showed that TR-700 has two major killing mechanisms, a direct effect on the organism and an indirect effect mediated through granulocytes. The results indicated that a 200-mg daily dose would be effective in humans (75).

The activity of TR-701 was assessed in a neutropenic pulmonary murine MRSA infection model, with the stasis and killing pharmacodynamic targets achieved at free-drug 24-h AUC/MIC values of approximately 10 and 25, respectively, with the targets not affected by resistance to other drug classes (76).

TR-701 15 mg/kg i.v. b.i.d. was administered to rabbits with aortic alve endocarditis caused by the MRSA strain COL, demonstrating actericidal efficacy similar to vancomycin 30 mg/kg i.v. b.i.d . but being slightly less effective than daptomycin 18 mg/kg i.v. o.d. (77).

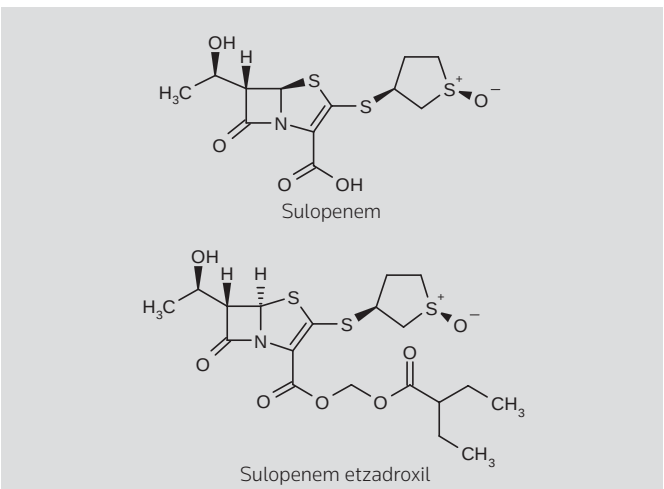
Twelve healthy volunteers received an oral 600-mg dose of TR-701 in fasting conditions, and microdialysis probes were implanted to evaluate the tissue distribution of TR-700. TR-700 was found to distribute well into the interstitial fluid of adipose and muscle tissues, with unbound TR-700 levels in plasma similar to those in muscle and adipose tissue; these three levels were well correlated (78).

Oral TR-701 was evaluated in a double-blind phase II study in which patients with severe complicated skin and skin structure infections were randomized to 200, 300 or 400 mg once daily for 5-7 days. With 200 mg, clinical cure rates at 7-14 days post-treatment in the clinically evaluable population were 100%, 100% and 91.7%, respectively, for abscess, wound and cellulitis lesion types. The respective rates were 94.7%, 75% and 100% for 300 mg and 92.9%, 100% and 100% for 400 mg. TR-701 was safe and well tolerated (79).

A wide variety of novel compounds falling outside the categories above are of interest, beginning with LegoChem Biosciences' novel cyclic amidrazone antibiotics. Seeking compounds with improved properties over oxazolidinone antibiotics such as LZD, LegoChem Biosciences investigators synthesized a series of oxazolidinone compounds containing cyclic amidrazone, leading to the identification of **LCB01-0371** as a preclinical candidate. Respective MIC_{90}s (µg/mL) against MSSA, MRSA, *S. pneumoniae, S. pyogenes, E. faecalis, E. faecium,* vancomycin-resistant *Enterococcus* (VRE), *H influenzae* and *M. catarrhalis* were 2, 2, 1, 2, 2, 2, 1, 16 and 8. For LZD, respective MIC_{90}s were 2, 2, 1, 2, 2, 2, 2, 16 and 8. In mice, the LCB01-0371 ED_{50} against MSSA was 4.53 mg/kg p.o. and against MRSA it was 2.96 mg/kg p.o., compared to 8.05 and 4.84 mg/kg p.o., respectively, for LZD (96).

Penems

Pfizer's broad-spectrum penem antibiotic **sulopenem** and its prodrug, **sulopenem etzadroxil**, have been evaluated in healthy volunteers. Sulopenem etzadroxil is in phase I development for bacterial infections and in phase II for community-acquired pneumonia (CAP). A semi-mechanistic pharmacokinetic (PK)/pharmacodynamic (PD) model was developed to describe this relationship with sulopenem, and Monte Carlo simulations were used to predict doses for a CAP



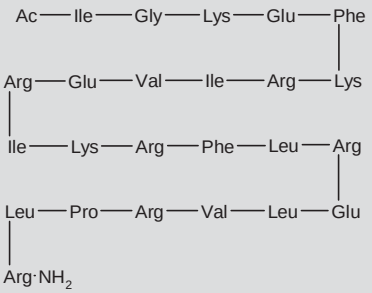
Antibacterials - penems

phase II trial. To this end, neutropenic mice infected with ESBL-producing *K. pneumoniae* were treated with four s.c. doses of sulopenem (4.69-300 mg/kg) and a semi-mechanistic model was developed. A population PK model was also built with data from healthy subjects from eight phase I studies (N = 132), and the mouse and human data were used in Monte Carlo simulations. As PD modeling was based on efficacy data from immunocompromised mice, net stasis at 24 h postdose was calculated: the percent target attainment for an sulopenem dose of 600 mg i.v. b.i.d. was 99.5% and that for a single 600-mg i.v. dose of sulopenem followed by oral sulopenem etzadroxil 1 g b.i.d. was 98.4% (80).

A study of the pharmacokinetics, safety and tolerability of multiple doses of sulopenem and sulopenem etzadroxil in healthy volunteers was also reported. In an intravenous study, 50 subjects were randomized to multiple sulopenem doses given twice daily: 800 mg over 3 h, 1200 mg over 1 and 2.5 h, 1600 mg over 1.5 h and 2000 mg over 1.5 h for 14 days. In an oral dosing study, 70 subjects were randomized to multiple twice- or thrice-daily doses of sulopenem etzadroxil, with sulopenem etzadroxil doses of 500 mg, 1 g and 1.5 g evaluated in the presence and absence of food and probenecid. Both i.v. and p.o. studies included a placebo arm, and the oral study included a cohort in which Augmentin® (amoxicillin and clavulanate) 875 mg was administered twice daily. In the i.v. study, doses up to 1600 mg were safe and well tolerated; severe nausea and vomiting at 2000 mg led to discontinuation. Exposure increased approximately proportionately at doses of 800-1600 mg, the mean half-life was approximately 0.9-1.2 h and the mean T>MIC of 1.0 μg/mL or more was 3.86-5.39 h. Gastrointestinal events were the most common side effects with oral dosing, but no discontinuations due to adverse events occurred. Sulopenem exposure increased approximately proportionately with the sulopenem etzadroxil dose under fed and fasted conditions. Exposure increased under fed versus fasted conditions with 1 g sulopenem etzadroxil, while T>MIC and the half-life were similar between states. Probenecid also increased exposure, T>MIC and the half-life compared to sulopenem etzadroxil given alone (81).

Polypeptides

Detailed results of a randomized, double-blind phase II study of **OP-145** (OctuPlus), a novel peptide product in development for otitis media, were reported at the congress. The study was to include 52 adults with chronic suppurative otitis media with perforated tympanic membrane who were to be treated with topical OP-145 0.5 mg/mL or vehicle given twice daily for 2 weeks. An interim analysis of the first 30 patients led to termination of the study after it was found that OP-145 was effective, with 47% of OP-145-treated subjects responding as compared to 6% of the vehicle group ($P = 0.017$). A response was evaluated by otoscopy and defined as an improvement of at least 2 points on a 4-point assessment scale. A difference in scores between groups was apparent from week 4. OP-145 was safe and well tolerated, with similar adverse events reported in the treatment groups. Most adverse events were disease-related; six were considered treatment-related (two in the OP-145 group and four in the placebo group). Serious adverse events were considered most likely unrelated to treatment. No specific antibodies to OP-145 were detected and there were no safety findings of clinical relevance in terms of physical examinations, laboratory values or audiometry assessments (82).



OP-145

Quinolones

The quinolone antibiotic **ozenoxacin** (GF-001001; Ferrer, Maruho) was the subject of several presentations covering in vitro, in vivo and phase I studies.

In vitro, ozenoxacin was active against Gram-positive bacteria that can cause skin and soft tissue infections, with greater activity than the other quinolones, LZD and daptomycin. MIC_{90} values (mg/L) against viridans group streptococci, β-hemolytic streptococci, MRSA, methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant *S. epidermidis* (MSSE) were 0.06, 0.03, 1, 0.008, 1 and 0.06, respectively (83).

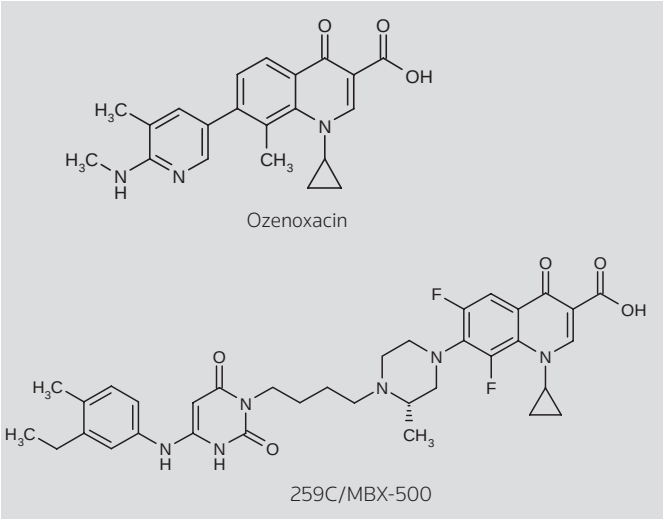
When tested against 428 bacterial strains, ozenoxacin was more active than other quinolones against anaerobes, respiratory pathogens and a group of "other" pathogens, but not against *P. aeruginosa* or Enterobacteriaceae (84).

Against ciprofloxacin-susceptible MSSA, ozenoxacin MICs were 0.0005-0.5 mg/mL, against ciprofloxacin-resistant MRSA the values ranged from 0.002 to 128 mg/mL and against *S. pyogenes* MICs ranged from 0.008 to 0.5 mg/mL. In a mouse model of *S. aureus* dermal infection, ozenoxacin 1% cream had a greater effect than mupirocin 2% and retapamulin 1% (85).

The in vivo tolerance and sensitization potential of ozenoxacin cream was evaluated in rabbits and in a murine local lymph node assay, respectively. In rabbits with abraded and intact skin, skin irritation was similar for ozenoxacin 2% cream and placebo and was classified as mild. Ocular irritation was classified as moderate in animals exposed to 2% cream, with no corneal or iridial irritation seen. Ozenoxacin 0.5%, 1% and 2% creams were not contact sensitizers in the murine local lymph node assay (86).

Systemic absorption of ozenoxacin was found to be negligible after topical administration of 1% and 2% creams in minipigs in vitro and in vivo in excised human skin (87).

In a randomized, double-blind, placebo-controlled, crossover phase I study, healthy male volunteers (N = 20) received 3 applications per



Antibacterials - quinolones

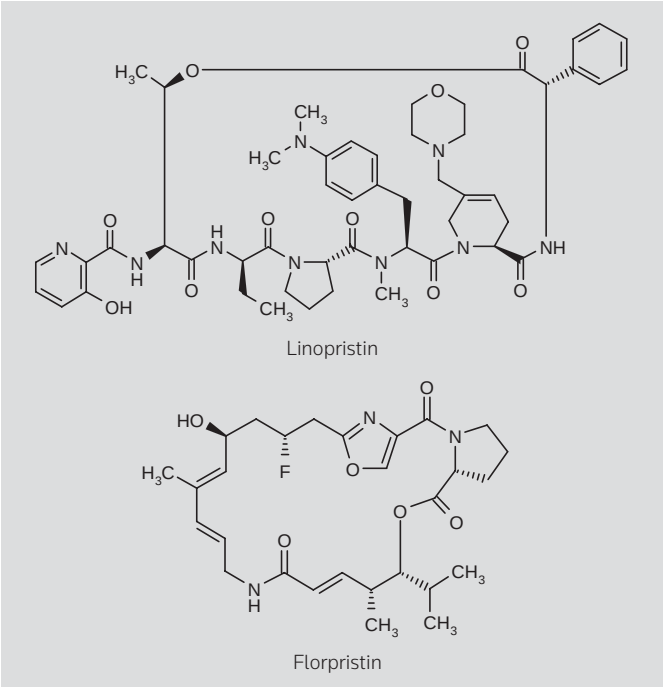
day of ozenoxacin 2% cream or placebo for 6 days and a single application on day 7. Plasma levels of ozenoxacin were undetectable pre-application each day and at various time points after day 7 of application. There were no adverse events or significant application-site reactions (88).

259C/MBX-500 (GLSynthesis, Microbiotix), a member of the AU-FQ class of antibacterial compounds comprising 6-anilinouracils (AU) connected via position 3 to the 7-piperazinyl group of fluoroquinolones (FQ), has demonstrated potent in vitro and in vivo activity against multiresistant Gram-positive bacteria. MIC_{50} values were in the range of 0.06-2 µg/mL and MIC_{90} values in the range of 0.12-4 µg/mL against clinical isolates, including methicillin-sensitive and MRSA, MSSE, MRSE, vancomycin-sensitive and -resistant *E. faecalis* and *E. faecium* (both VSE and VRE). Delivery challenges due to pH-dependent solution stability of the preclinical candidate 259C/MBX-500 have led to the development of a stable intravenous nanoemulsion formulation, designated F-20, using proprietary Nano-E™ technology. The F-20 formulation has enabled intravenous dosing of the compound with a high drug load (up to approximately 8 mg/mL) without any irritation at the site of injection. Pharmacokinetic analysis following administration of F-20 as a bolus injection at 40 mg/kg in the tail vein of Sprague-Dawley rats revealed a good PK profile (Cl = 0.0273 L/min; V_{ss} = 1.61 L/kg) and conversion of the compound to a single major metabolite, namely carboxyl glucuronide. F-20 liquid emulsions were found to be stable for at least 6 months at 2-8 °C, whereas reconstituted lyophilized versions were stable for a period of up to 6 months. Preclinical toxicity studies of F-20 emulsion (8 mg/mL) in rats have been initiated (89).

Streptogramins

Novexel's **NXL-103**, a combination of linopristin and flopristin in phase II development for community-acquired infections, is the focus of intense study, as the brief summaries below demonstrate.

Against strains of MRSA, NXL-103 MICs were 0.06-1 µg/mL, with MIC_{50s} of 0.12 and 0.5 µg/mL for community-acquired MRSA and hospital-acquired MRSA, respectively (90).



The results of an open, randomized, crossover study in 30 healthy male volunteers indicated that the optimal dose ratio of linopristin/flopristin in NXL-103 would be 250/350 mg. This ratio was associated with low PK variability, the least effect of the constituent agents on the other's PK and ex vivo bactericidal activity against *S. aureus* and *S. pneumoniae* strains (91).

A randomized, double-blind study was conducted in 43 healthy male volunteers given NXL-103 500 mg b.i.d., 750 mg b.i.d., 1500 mg o.d. or 1000 mg b.i.d. or placebo for 10 days. Most adverse events were gastrointestinal and dose-dependent, none were serious, and nausea/vomiting led to discontinuation in four subjects. A median t_{max} of 3 h was measured, with a mean half-life of 2.04-3.23 h. Pharmacokinetic/pharmacodynamic analysis indicated that the 500 mg b.i.d. dose would provide adequate exposure to treat pathogens with MICs of ≤ 0.5 µg/mL (92).

A population PK analysis utilizing data from 6 phase I studies in over 224 subjects revealed a significant effect of dietary conditions on the clearance of linopristin and flopristin. While dose and age influenced linopristin PK, dose, body weight and formulation influenced flopristin PK (93).

A single NXL-103 dose of 500 mg was given to 48 healthy subjects in a randomized, crossover study, with subjects studied in both the fed and fasted states. NXL-103 was generally well tolerated in the study population, consisting of young males, elderly males and post-menopausal females. Despite higher exposure in elderly subjects, dose adjustment did not appear necessary, and gender had no significant effect in the elderly. Food was found to increase exposure and decrease PK variability (94).

Lastly, NXL-103 was generally well tolerated in a randomized, double-blind, multicenter phase II study in 302 adults with commu-

nity-acquired pneumonia. Doses of 500 or 600 mg b.i.d. were compared to amoxicillin 1 g t.i.d., each given for 7 days. A clinical response was seen in 91.4%, 94.7% and 88.5% of these groups, respectively (95).

Other

The neoglycoside **ACHN-490**, a next-generation aminoglycoside identified in a focused medicinal chemistry campaign by Achaogen, has been described as a new antibacterial agent with potential to rejuvenate the aminoglycoside class of antibiotics. Synthesized from sisomicin in eight steps, ACHN-490 has displayed broad-spectrum, rapid bactericidal activity against Gram-negative (panel of 461 clinical isolates) and selected Gram-positive bacterial strains. The MIC_{90} values of ACHN-490 against aminoglycoside-resistant Enterobacteriaceae were 4 µg/mL or lower (except against *Proteus mirabilis* and indole-positive *Proteus* spp.; respective MIC_{90}s of 8 and 16 µg/mL). Aminoglycoside-resistant staphylococci were inhibited by ACHN-490 with an MIC_{90} of 2 µg/mL (97).

Evaluation of the activity of ACHN-490 (susceptibility testing) against 204 contemporary Gram-negative clinical isolates, including *P. aeruginosa*, *Acinetobacter baumannii*, *K. pneumoniae*, *E. coli* and *Enterobacter* spp. from 16 Brooklyn hospitals revealed that ACHN-490 displayed comparable activity to the antibiotic amikacin against *P. aeruginosa* and *A. baumannii*. It also demonstrated excellent antibacterial activity against *K. pneumoniae*, *E. coli* and *Enterococcus*, with respective MIC_{90} values of 1, 2 and 4 µg/mL compared to respective MIC_{90} values of 64, 16 and 16 µg/mL for amikacin.

ACHN-490 was also found to possess potent and rapid (1-4 h) bactericidal activity against aminoglycoside-resistant bacterial strains (MIC ≤ 2 µg/mL) irrespective of the presence of aminoglycoside-modifying enzymes such as acetyltransferases, phosphotransferases and nucleotidyltransferases (99). The presence of extended-spectrum β-lactamases, chromosomal or plasmid AmpC cephalosporinases, serine carbapenemases or metallo-β-lactamases showed no effect on ACHN-490 MIC values against a panel of 235 clinical isolates (100).

Combination of ACHN-490 with daptomycin at subinhibitory concentrations resulted in significant synergy against MRSA strains (15 and 22 strains exhibiting synergy at 3 and 24 h) (101).

ACHN-490 demonstrated activity against Gram-negative pathogens, *S. aureus* and *Staphylococcus saprophyticus*, which are described as leading causes of complicated urinary tract infections, even in strains resistant to current front-line antimicrobial agents (MIC_{90} range of 0.5-2 µg/mL) (102).

In vivo in neutropenic CD-1 mice inoculated with multidrug-resistant strains of *E. coli*, *K. pneumoniae* or MRSA, ACHN-490 reduced bacterial titers to below the initial bacterial load, with a ratio of ED_{50}/MIC comparable to that of gentamicin (103).

Pharmacokinetic profiling of ACHN-490 in CD-1 mice, Sprague-Dawley rats and beagle dogs following i.v. administration revealed a rapid renal clearance in rats and dogs ($t_{1/2}$ approximately 1 h). Dose-linear C_{max} and AUC were seen in rats up to a dose of 75 mg/kg. The compound was metabolically stable and unlikely to form drug–drug interactions. The use of high doses administered as once-daily short infusions was deemed possible based on PK data obtained in this study (104).

A double-blind, randomized, placebo-controlled, parallel-group, single- and multiple-dose-escalation trial of ACHN-490 in healthy individuals is currently ongoing. Dose-escalation (4 up to 15 mg/kg) will continue as long as the treatment is deemed safe. The primary outcome measure of the trial is the incidence and severity of adverse events, with an estimated final data collection date of November 2009 (105). Preliminary data from this trial suggest a dose-linear and dose-proportional PK profile. The most commonly seen adverse events were typical of phase I studies, described as mild to moderate and transient. There was no evidence of nephrotoxicity or ototoxicity in any of the study participants (106).

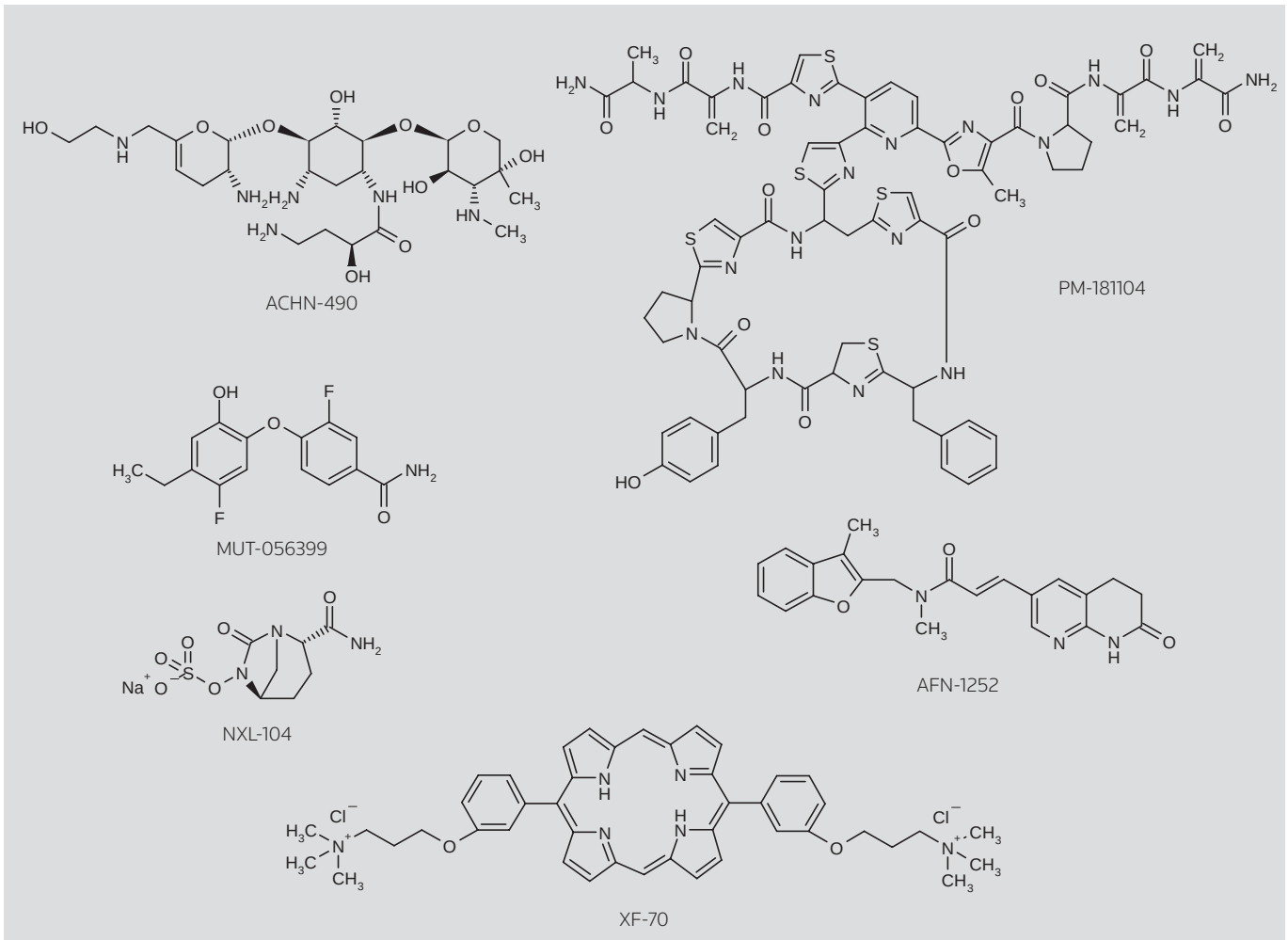
PM-181104, a novel antibiotic isolated from a marine sponge-associated bacterium by scientists at Piramal Healthcare in an in-house screen of natural product libraries, has displayed potent antibacterial activity against both MRSA and VRE. The compound demonstrated potent antimicrobial activity in three animal models of MRSA infection, including a mouse septicemia model (*S. aureus*; PD_{100} = 2.5 mg/kg i.v.), a murine lung infection model (*S. aureus*; 2-log reduction in bacterial burden at 20 mg/kg i.v.) and mouse skin abscess model (*S. aureus*; 1-log reduction in cfu count at 5 mg/kg i.v.). In a mouse septicemia model due to VRE infection, PM-181104 exhibited a PD_{100} value of 10 mg/kg i.v. and displayed a 1-log reduction in cfu count at 5 mg/kg i.v. in a VRE kidney infection model. Results from the animal models in this study support the therapeutic potential of PM-181104 for the treatment of Gram-positive bacterial infections (107).

FAB Pharma, a spin-off of Mutabilis, is developing **MUT-056399** (FAB-001) as an antibacterial agent for MSSA and MRSA infections. A phase I study began recruiting in September of this year and a second multiple-ascending-dose phase I study is expected to begin soon. Preclinical data were presented at the meeting.

Against community-acquired *S. aureus* strains MICs ranged from 0.03-8 µg/mL, against hospital-acquired *S. aureus* strains the range was 0.016-8 µg/mL and against hetero-vancomycin-intermediate *S. aureus* (hVISA), vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) strains MICs ranged from 0.016 to 4 µg/mL. Of the 200 strains tested, 198 were MRSA. MUT-056399 activity was greater than that of vancomycin, LZD, daptomycin and quinupristin/dalfopristin (108).

In further in vitro studies, MUT-056399 was bacteriostatic at 4 x the MIC against MSSA, MRSA, LZD-resistant and VISA strains. When tested against an *S. aureus* strain in combination with 13 antibiotics, synergy was observed with only 1: gentamicin. Pharmacokinetic studies in mice, rats and dogs showed a half-life of 3-5 h with i.v. MUT-056399, which was well distributed among tissues, without accumulation. In a mouse septicemia model with MSSA ATCC29213, the ED_{50} was 21.6 mg/kg with a single s.c. injection; against MRSA strains, the ED_{50} was 19.3-49.6 mg/kg. A mouse thigh infection model yielded a mean static dose of 44-55 mg/kg against MRSA with a single s.c. administration. Studies in mice, rats and dogs revealed no significant effects of the drug on central nervous system activity, respiratory function and cardiovascular function (109).

Affinium Pharmaceuticals is developing **AFN-1252**, an inhibitor of the bacterial fatty acid biosynthesis pathway, as a treatment for



Antibacterials - other

staphylococcal infections. The company reported data from phase 0 microdosing and phase I pharmacokinetic studies with the agent. In the phase 0 study, 4 healthy male volunteers received [^{14}C]-labeled AFN-1252 80 µg both p.o. and i.v. in a crossover design, while the phase I study was a single-ascending oral dose trial including 6 healthy subjects per dose. In the phase 0 study, absolute oral bioavailability was 82%, and data from both studies showed linear oral absorption from 80 µg up to 180 mg. The analysis found that microdosing PK could be used to predict human PK. An increased half-life at higher doses suggested a wide absorption window, and GastroPlus™ parameter sensitivity analysis of oral phase I exposures indicated that solubility was the dominant variable limiting absorption, while particle size had less effect. The findings were consistent with the Biopharmaceutics Classification System 2 classification (110).

This year's meeting featured numerous presentations on studies of Novexel's **NXL-104**, an agent in phase II development intended to enhance the spectrum of activity of β-lactam antibiotics.

CTX-M β-lactamase enzymes are associated with antibiotic resistance. To study the effects of NXL-104, the crystal structure of CTX-M15 in complex with NXL-104 was obtained, revealing no significant effects on active-site geometry and revealing displacement of the putative deacylation water molecule (111).

NXL-104 proved to be a potent inhibitor of the β-lactamase TEM-1, with activity characterized by high acetylation efficiency and covalent linking of the enzyme to NXL-104 (112).

The combination of ceftaroline and NXL-104 was potent against multidrug-resistant Enterobacteriaceae with high expression of genes encoding β-lactamases (KPC, CTX-M and AmpC). Rapid killing with no regrowth at 2-8 x MIC was seen (113).

The ceftaroline/NXL-104 combination was active in another evaluation of susceptibility in Enterobacteriaceae strains producing CTX-M, AmpC and KPC β-lactamases, while the activity of ceftaroline alone against *S. aureus* and *S. pneumoniae*, including resistant strains, was not enhanced by NXL-104 (114).

In two murine models of infection (septicemia and thigh infection) with *K. pneumoniae* strains harboring blaKPC, NXL-104 enhanced the susceptibility to ceftazidime and the combination proved efficacious (115).

Against 200 strains of Enterobacteriaceae including ceftazidime-resistant strains, the combination of ceftazidime and NXL-104 yielded improved MICs compared to ceftazidime alone, with activity against nearly all organisms with class A or class C β-lactamases (116).

NXL-104 improved the susceptibility of geographically diverse *P. aeruginosa* strains to ceftazidime, reducing the nonsusceptibility rate from 21% to 6% (117).

Against β-lactamase-producing anaerobic bacteria, ceftazidime/NXL-104 activity was poor against some *B. fragilis* strains but was good against the most predominant strains and against *Prevotella* species. The addition of metronidazole at half its MIC reduced ceftazidime/NXL-104 MICs by 1-2 dilutions (118).

NXL-104 enhanced the activities of ceftazidime, ceftriaxone and piperacillin against many anaerobes in tests against 316 strains, with the triple combination of metronidazole, ceftazidime and NXL-104 demonstrating potent activity against anaerobes representing most clinical species; this combination is being evaluated in phase II studies in patients with complicated intra-abdominal infections (119).

In mice infected with ceftazidime-resistant Enterobacteriaceae strains producing CTX-M, combination of ceftazidime and NXL-104 was efficacious, with ED_{50} values of 11-27 mg/kg s.c. (120).

In mice with pneumonia induced by AmpC-producing *K. pneumoniae*, lung bacterial counts were significantly reduced 48 h post-treatment with ceftazidime/NXL-104 compared to ceftazidime alone (121).

Finally, in a phase I study in 33 healthy subjects, a single i.v. infusion of NXL-104 500 mg was administered and was generally well tolerated. Pharmacokinetic analysis indicated that no dose adjustment is necessary based on age or gender (122).

Destiny Pharma's **XF-70** is a novel porphyrin antimicrobial, the activity of which has been evaluated against biofilms and slow-growing cultures and in a staphylococcal burn wound infection in vivo. A planktonic MIC for *S. aureus* SH1000 of 1 µg/mL was measured, along with a biofilm MIC of 1 µg/mL and a minimum biofilm eradication concentration of 2 µg/mL. XF-70 was highly active against slow-growing cells, with cold culture, stringent response and stationary phase cultures displaying at least a 5-log decline in viability within 2 h (123). To evaluate the treatment of burn infections, anesthetized mice received 15% total body surface area scald burns to the dorsum and, after inoculation with *S. aureus* HAS-1 and escharotomy 24 h later, mice were given one or two doses of XF-70 100 µg/wound or saline applied topically. Assessment of antistaphylococcal activity in punch biopsies taken after 24 h revealed a reduction in bacterial burden of 98.77% with a single XF-70 dose compared to saline-treated animals. *S. aureus* growth was reduced by 99.96% with two XF-70 doses. *S. aureus* dissemination was also significantly reduced with XF-70, as revealed by evaluation of growth in the spleen (124).

Lastly, we report on a study of **Hib-MenCY-TT** (GlaxoSmithKline), a combined *Haemophilus influenzae*, *Neisseria meningitides* serogroups C and Y and tetanus toxoid conjugate vaccine previously found to be immunogenic against *H. influenzae* type b (Hib) and meningitides (Men) C and Y, with an acceptable toxicity profile. The phase II study evaluated the antibody persistence and immune response to a fourth consecutive dose of Hib-MenCY-TT compared to the responses seen in infants primed with licensed MenC (LicMenC) and Hib conjugate vaccines. The study, conducted in 1,038 infants, found high levels of antibodies to MenC, MenY and Hib, which persisted until administration of the fourth dose of Hib-MenCY-TT in subjects primed with Hib-MenCY-TT. The fourth Hib-MenCY-TT dose, given to subjects 12-15 months of age, correlated with a higher immune response to MenC, MenY and Hib compared to the licensed Hib conjugate vaccine. There was no statistically significant difference between the Hib-MenCY-TT and licensed Hib vaccines in terms of immune responses to measles, mumps, rubella and varicella vaccination. The Hib-MenCY-TT vaccine displayed a clinically acceptable profile similar to that of the licensed Hib vaccine. The most frequently reported solicited symptoms, recorded during a period of 4 days postvaccination, were redness (60.9%, 50.5% and 78.1%, respectively, in the Hib-MenCY-TT, LicMenC and Hib groups at any injection site) and irritability (58%, 59.4% and 58.2%, respectively, in the Hib-MenCY-TT, LicMenC and Hib groups). The study supports the future development of the Hib-MenCY-TT vaccine for children < 2 years of age who are at the greatest risk of meningococcal disease (125).

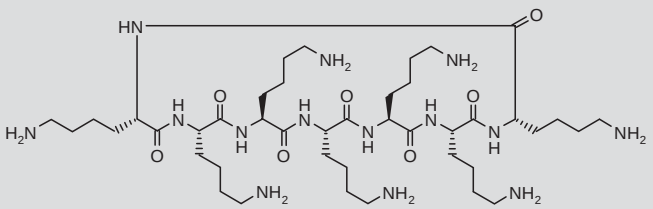
ANTIFUNGALS

Among data on antifungal agents under development presented at ICAAC were those supporting the clinical development of NovaBiotics' topical antifungal **NP-213** (Novexatin®). NP-213 has been evaluated in a first-in-man study in which good safety, tolerability and a lack of systemic exposure were seen in 12 patients with mild to moderate onychomycosis. A phase IIa component including 48 patients dosed daily for 28 days is under way.

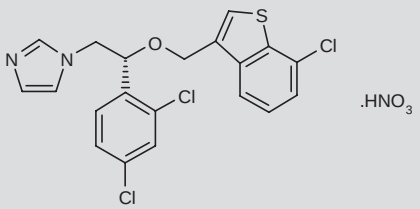
To evaluate fungicidal activity, excised human nail fragments were infected with *Trichophyton* spp. for over 2 weeks and were treated daily on the dorsal face with NP-213 and comparators. NP-213 demonstrated concentration-dependent fungicidal activity with a median MIC_{100} of 1 mM, killing *Trichophyton* spp. via membranolysis within 3 h. Nail fragments were cleared of fungi by 28 days. With transmission electron microscopy, fungicidal effects were noted deep with the nail matrix after NP-213 treatment (126).

In vitro tests of the cytotoxic and hemolytic potential of NP-213 revealed no toxicity at doses significantly above antifungal MICs. Single- and repeat-dose rodent and nonrodent studies were then undertaken with i.v., p.o. and dermal NP-213 administration. Safety margins for NP-213 in relation to the proposed clinical dose were 227 times in a pivotal 28-day repeat dermal exposure minipig study and over 400 times in a rat i.v. 28-day repeat exposure study. No sensitization was seen in minipig and rodent dermal challenge studies and rodent oral toxicology and eye irritation profiles were favorable. In a 28-day minipig toxicokinetics study of dermal daily application up to 50 mg/kg, there was no systemic exposure (127).

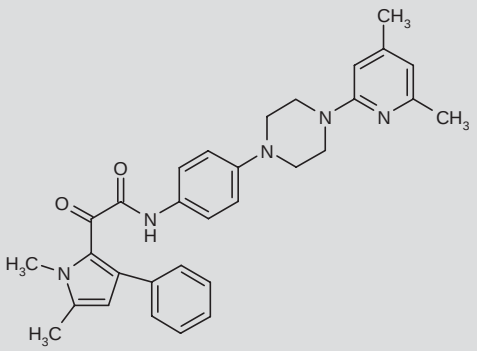
The Ferrer topical antifungal agent **arasertaconazole nitrate** (the [*R*]-enantiomer of sertaconazole) displayed potent and broad antimycotic activity in recent studies. A total of 157 strains (42 yeasts, 17 dermatophytes, 11 filamentous fungi, 11 *Malassezia* spp., as well as 76 bacterial strains) were used to assess the antifungal and antibacterial activities of the two enantiomers. The antifungal activity of (*R*)-



NP-213



Arasertaconazole nitrate



FG-3622

Antifungals

(–)-sertaconazole was found to be double that of the racemic form and 10-fold higher than the activity exhibited by (*S*)-(+)-sertaconazole. (*R*)-(–)-Sertaconazole also demonstrated antibacterial activity, with MIC_{90} and MIC_{50} values in the range of 1-4 mg/L (geometric mean) against opportunistic bacterial pathogens involved in secondary infections, including *S. aureus*, *S. pyogenes*, *S. epidermidis* and *E. faecalis* strains, among others. The mechanism of action of arasertaconazole nitrate was assessed by determining the IC_{50} values for inhibition of ergosterol biosynthesis in *Candida albicans*. Arasertaconazole nitrate inhibited ergosterol biosynthesis with an IC_{50} of 0.05 µM, whereas the IC_{50} values calculated for sertaconazole nitrate and (*S*)-(+)-sertaconazole nitrate were 0.09 and 0.66 µM, respectively. The anti-inflammatory activity of arasertaconazole nitrate was evaluated in a mouse ear edema model of irritant dermatitis. The compound displayed anti-inflammatory activity of approximately 40% at 0.4, 0.6, 0.8 and 1 µM. Arasertaconazole nitrate is currently under clinical development (128).

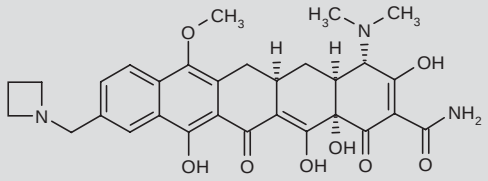
MethylGene researchers described the mechanism of action of the HOS2 fungal histone deacetylase (HD) inhibitor **MGCD-290**, along with phase I results in healthy volunteers. MGCD-290 is an orally available antifungal designed to synergize with azoles for the treatment of fungal infections. Susceptibility testing of fungal HD deletion mutants of *Saccharomyces cerevisiae* by broth microdilution and testing of the effect of MGCD-290 on HD activity of recombinant Hos2p showed the ΔHOS2 mutant to be more susceptible to azoles than other HD deletion mutants (ΔHOS1, ΔRPD3, ΔHDA1, ΔHOS3) and that MGCD-290 directly inhibited the activity of recombinant HOS2. Synergy between MGCD-290 and azoles was abolished in the ΔHOS2 mutant but not in the other mutants or their respective parent strains, further indicating that HOS2 mediates the synergy between MGCD-290 and azoles (129). The phase I studies included single-ascending-dose studies assessing oral MGCD-290 alone or with fluconazole, and data from 2 cohorts of a multiple-ascending-dose study of 14 days of dosing with MGCD-290 were also reported. Single ascending doses were 100-1000 mg in one trial and 300 and 450 mg with fluconazole 400 mg in another, while multiple ascending doses were 100 and 180 mg. Data to date show MGCD-290 to be well tolerated alone or with fluconazole, with no apparent drug–drug interactions. Single doses up to 1000 mg yielded no clinically significant adverse events, with C_{max} observed after 2 h, a mean half-life of 8 h and dose-proportional AUC values. Multiple-ascending-dose studies of MGCD-290 with fluconazole are planned (130).

Three presentations detailed the activity and pharmacokinetics of F2G's novel antifungal **FG-3622**. When tested against *Aspergillus* spp., MIC_{90}s of 0.03 mg/L were derived for *A. fumigatus*, *A. terreus* and *A. flavus*, while the MIC_{90} was increased slightly to 0.06 mg/L for *A. niger*. Seven isolates resistant to azoles were susceptible to FG-3622. Also susceptible were commonly resistant fungi such as *Scedosporium prolificans*, *Fusarium* spp., *Scopulariopsis brevicaulis* and *Paecilomyces variotii*, and FG-3622 was potent against dermatophytes and fungal species causing endemic mycoses (131). For in vivo evaluation of activity against disseminated aspergillosis, temporary or prolonged neutropenic CD-1 murine models were challenged with *A. fumigatus*. In the temporary model, dose-dependent survival was seen with FG-3622, with doses of 5 and 10 mg/kg/day p.o. yielding 80% and 90% survival, respectively, and 20, 30 and 40 mg/kg/day p.o. yielding 100% survival by day 12; 80% of vehicle-treated animals died by day 12. In the prolonged model, FG-3622 20 mg/kg p.o. b.i.d. was associated with 70% survival at day 12, while all untreated animals died by day 7 postinfection. Prolonged observation in the temporary model showed 10 mg/kg p.o. b.i.d. to be superior to 20 mg/kg p.o. once daily in terms of survival at day 18 (80% vs. 70%) (132). In pharmacokinetic studies, oral dosing was associated with an apparent bioavailability of 52% in mice, and excellent penetration into lung and kidney tissues was noted. Potentially therapeutic levels of FG-3622 were also detected in skin and brain after dosing of 20 mg/kg p.o. With i.v. administration in rats, high levels of unchanged drug were detected in fecal matter, suggesting biliary excretion (133). A phase I trial of oral FG-3622 was recently initiated, with plans to enroll 100 healthy volunteers.

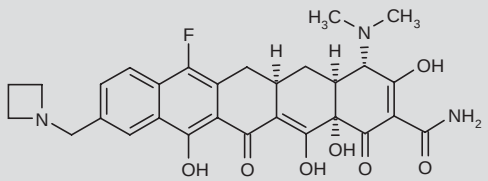
NEW MOLECULAR ENTITIES

The characteristics of several new molecular entities with anti-infective potential were described at this year's meeting. Among these was a new antimycobacterial discovered at Kitasato University as part of an effort to identify new treatments for tuberculosis. The investigators sought agents that selectively inhibit the growth of *Mycobacterium smegmatis*. A compound produced by the fungal strain *Mortierella alpina* FKI-4905 was found to have such activity and was isolated and its structure elucidated. The compound, named **calpinactam**, was active against *M. smegmatis* in the paper disk assay but was not active against 13 other species of microorganisms, including Gram-positive and Gram-negative bacteria, fungi and yeasts. Assessment of antimycobacterial activity by liquid microdilution yielded an MIC of 0.78 µg/mL against *M. smegmatis* and an MIC of 12.5 µg/mL against *Mycobacterium tuberculosis* (134).

Astellas Pharma researchers described a novel natural product isolated from the cultured broth of the fungus Capnodiaceae strain no. 339855 which may be a treatment for tinea pedis. MICs for **AS-2077715** against *Trichophyton mentagrophytes* FP2103 and *Trichophyton rubrum* FP596 were both 0.10 µg/mL, and fungicidal activity against *T. mentagrophytes* was seen within 2 h of administration in time-kill assays. AS-2077715 was found to be a potent inhibitor of complex III of *T. mentagrophytes*, but demonstrated weak inhibitory activity against mammalian complex III compared with the nonselective complex III inhibitor funiculosin. AS-2077715 reduced *T. mentagrophytes* burden on pedal skin in a guinea pig model of tinea pedis with oral administration of 10 and 20 mg/kg from 7 days after infection and continued for 10 days. The agent at 20 mg/kg was also active in this model when started 11 days after infection and given for 7 days (135).



[I]



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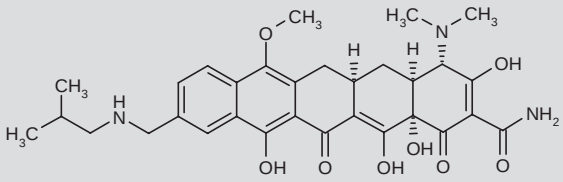

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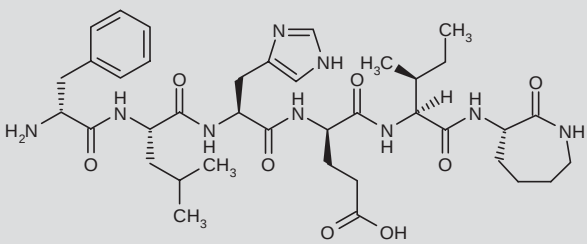
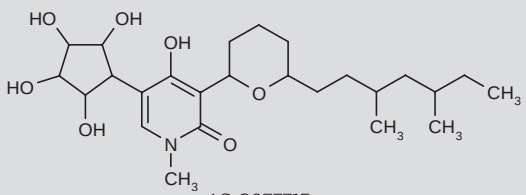
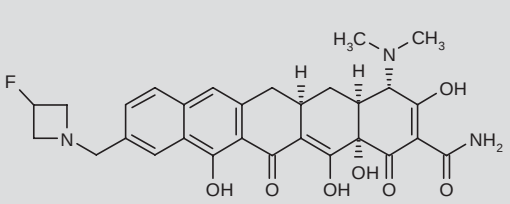


Calpinactam



AS-2077715

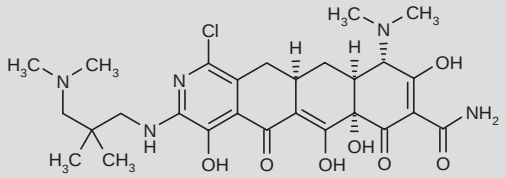


TP-038

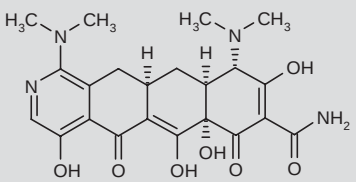
Tetraphase announced the disclosure of data for novel classes of antibiotics, identified via its breakthrough synthetic chemistry technology based on a process developed by Dr. Andrew Myers of Harvard University. Novel pentacycline analogues were synthesized from a key bicyclic AB precursor via a tandem Michael-Dieckmann reaction and were subsequently tested for susceptibility in vitro against strains expressing the ribosomal protection gene *tet(M)* or the efflux pump genes *tet(K)* and *tet(A)*. In vivo activity was evaluated in a mouse septicemia model against *S. aureus* ATCC13709 infection. Three representative compounds from this series, [**I**], [**II**] and [**III**], displayed antibacterial activities with MIC values in the range of 0.016-2 µg/mL against *S. aureus* strains, including methicillin- and tetracycline-resistant strains (136).

The novel synthetic pentacycline **TP-038** exhibited potent in vitro antibacterial activity against 13 MRSA strains with MIC values in the range of 0.125-0.25 µg/mL. In vivo in a mouse septicemia model, the compound displayed ED_{50} values of 0.36 and 12.2 mg/kg following i.v. and p.o. administration, respectively. In a neutropenic mouse model, TP-038 reduced *S. aureus* bioburden by 4.36 cfu/g of thigh following i.v. dosing. Pharmacokinetic profiling at a single 1 mg/kg i.v. dose or at 10 mg/kg p.o. in rats revealed favorable PK parameters and a bioavailability of 18% (137).

New azatetracycline analogues with a heterocyclic moiety were also designed, synthesized and tested by scientists at Tetraphase. Representative analogues, such as **TP-787** and **TP-120**, showed good in



TP-787

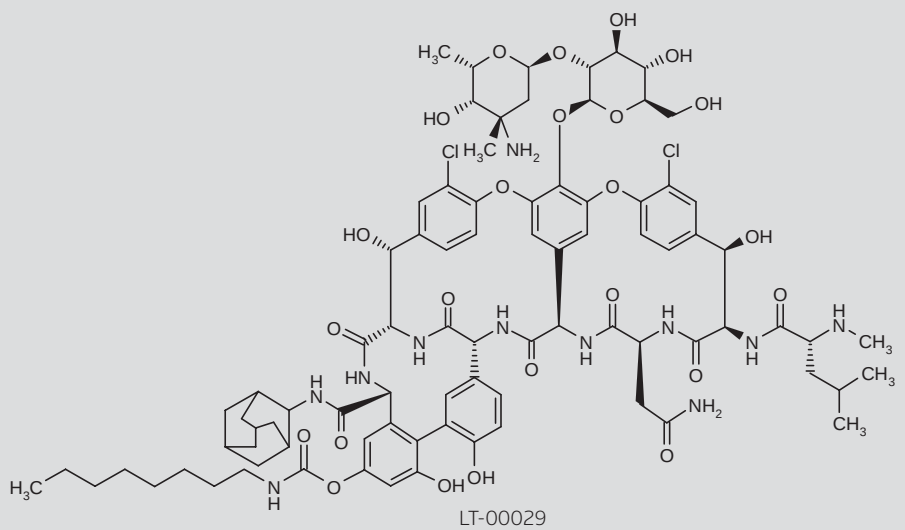


TP-120

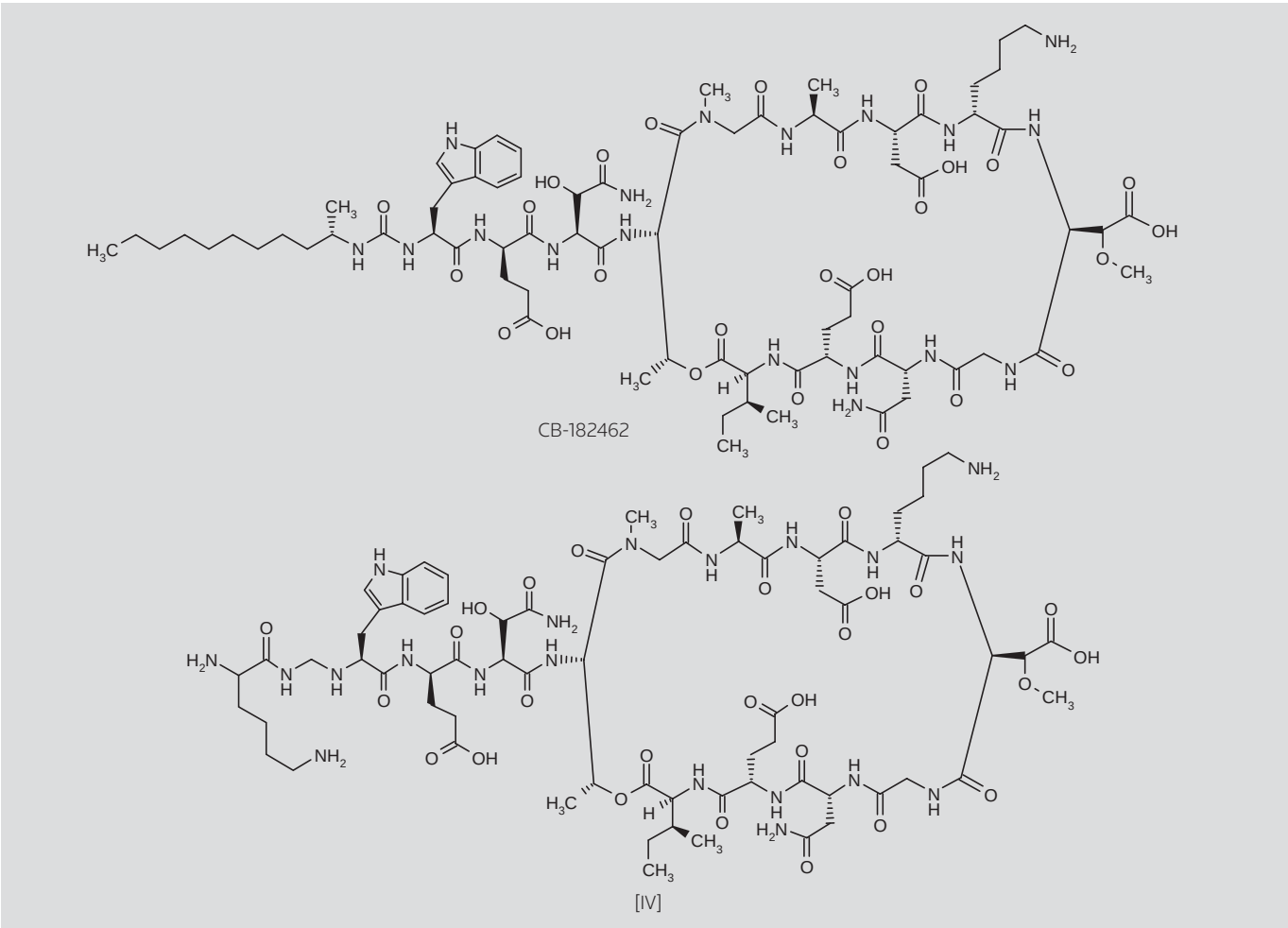
vitro and in vivo antibacterial activities against tetracycline-resistant strains with efflux- or ribosomal-mediated resistance (138). Susceptibility testing of TP-787 and TP-120 against 20 strains of *S. aureus*, 20 strains of *S. pneumoniae* and 12 strains of *H. influenzae* revealed respective MIC values in the range of 0.063-0.5, ≤ 0.016-0.063 and 0.25-2 µg/mL for TP-787, whereas the respective MIC values for TP-120 against these strains were within the range of ≤ 0.016-1, ≤ 0.016-8 and 0.063-4 µg/mL. In vivo, both compounds conferred protection against *S. aureus* ATCC13709 infection in a murine septicemia model following i.v. administration (MIC values of 0.25 and 0.5 µg/mL, respectively, for TP-120 and TP-787; PD_{50} values of < 0.30 and 0.36 mg/kg i.v., respectively, for TP-120 and TP-787) (139).

LEAD Therapeutics disclosed data on the synthesis and biological activity of a novel series of glycopeptide antibacterial agents. The lead compound from this series, **LT-00029**, a vancomycin carbamate derivative, displayed potent in vitro antibacterial activity against Gram-positive pathogens, including resistant strains such as MRSA, VISA and VRE. Pharmacokinetic profiling in mouse plasma following a 5 mg/kg i.v. dose revealed a C_{max} of 221 µg/mL, a half-life of 2.83 h and an AUC_{0-t} of 417 µg.h/mL. In vivo, LT-00029 demonstrated superior activity over vancomycin and telavancin in a mouse thigh infection model and in a neutropenic mouse pulmonary infection model, respectively. In the thigh infection model, LT-00029 (32 mg/kg i.v.) caused a 6.45 log_{10} cfu/mL reduction compared to 4.54 log_{10} cfu/mL seen with vancomycin in mice infected with MSSA. LT-00029 at 3.5, 4.5 and 9.7 mg/kg i.v. achieved 1, 2 and 3 log_{10} cfu reductions, respectively, whereas telavancin caused 1 and 2 log_{10} cfu reductions, respectively, at 4 and 17.7 mg/kg in the neutropenic mouse pulmonary infection model inoculated with MRSA VL-137. The study supports further evaluation of LT-00029 as an antibacterial agent (140).

Researchers at Cubist Pharmaceuticals described the discovery and activity of a number of novel antibiotics, including lead compound **CB-182462**. To target community-acquired pneumonia (CAP) caused by Gram-positive organisms, analogues of the cyclic lipopeptide A-54145, produced by *Streptomyces fradiae*, were prepared, with urea and carbamate analogues demonstrating improved MICs over A-54145D against *S. aureus* in vitro. In a murine *S. pneumoniae* lung infection model, the analogues were superior to daptomycin, A-54145D and semisynthetic acyl tail analogues. Overall, the urea series was superior to the carbamate series in vitro and in animal studies (141). One of the urea candidates, CB-182462, was selected for evaluation against *S. pneumoniae* lung infection in mice and rats, MRSA thigh infection in neutropenic mice, MSSA thigh infection and subcutaneous fibrin clots in rats. The agent was associated with dose-dependent decreases in bacterial cfu in all models, as well as in vivo antibacterial properties in rats and mice comparable to those seen with vancomycin and daptomycin. Pharmacokinetic analysis in rodents suggested the possibility of once-daily dosing in humans (142). As CB-182462 was found to lose potency in the presence of human serum albumin (HSA), novel lysine derivatives were prepared, several of which had improved activity in HSA without losing potency in the presence of surfactant. The respective cfu log reductions with one derivative (compound [**IV**]) in an *S. pneumoniae* lung infection model and in an MRSA thigh infection model were 3.5 and



LT-00029

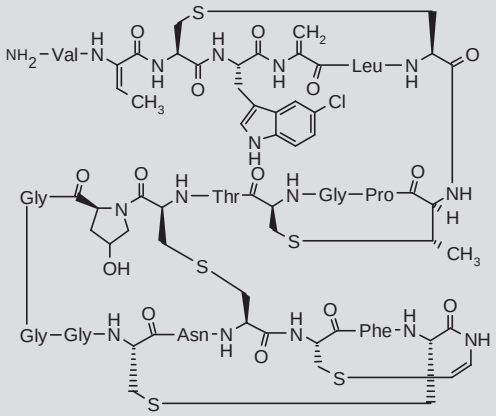


4.7 at 50 mg/kg s.c. These reductions were 4.0 and 4.1, respectively, with CB-182462 (143).

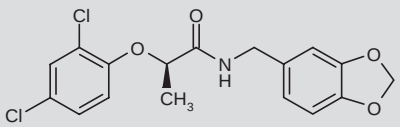
AdRem Biotech reported the development of **ABI-200** as a topical antimicrobial alternative to mupirocin. Peptidoglycan fusion proteins targeting multiple species may be an alternative to conventional antibiotics which face increased resistance. To this end, AdRem Biotech has developed ABI-200 (1401), a peptidoglycan fusion protein with four active lytic domains comprising LysK (a phage endolysin with two lytic domains), Lysostaphin (bacteriocin secreted by *Staphylococcus simulans*) and the streptococcal phage B30 endolysin. When evaluated against 13 MRSA strains including VISA, LZD- and tigecycline-resistant strains and USA100, 200, 300, 400 and 500 strains, ABI-200 displayed a mean MIC of 3.25 μg/mL and an MIC range of 1.22-9.76 μg/mL (144).

NanoBio disclosed promising preclinical data on the application of **NB-201**, a nanoemulsion-based topical lotion prepared with the NanoStat™ technology, for the treatment of burn wound infection and the attenuation of inflammation following thermal injury. Sprague-Dawley rats with 20% total body surface area scald burns (partial thickness burn injury model) were inoculated with 10^6-10^7 cfu of *P. aeruginosa* at 8 h postinjury and were subsequently treated with NB-201 nanoemulsion, placebo (NB-201 without benzalkonium chloride), 5% sulfamylon or 0.9% saline control at 16 and 24 h postinjury. Topical treatment with NB-201 correlated with a reduction in *P. aeruginosa* growth in the burn wounds by 3 log ($P < 0.001$) and caused a significant reduction in neutrophil sequestration compared to the control group as measured by a myeloperoxidase assay ($P < 0.001$). Marked decreases in the levels of the proinflammatory cytokines IL-1β and IL-6 were also seen following treatment with NB-201 compared to control, indicating an attenuation of the local dermal inflammatory response. The study supports the future development of NB-201 as a potential antimicrobial treatment for clinical burn wounds (145).

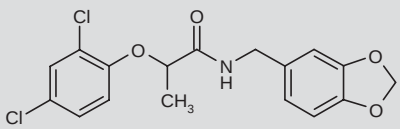
The novel lantibiotic **NAI-107** (Vicuron Pharmaceuticals, NAICONS) displayed a wide range of antibacterial activity targeting multidrug-resistant Gram-positive pathogens, such as MRSA, glycopeptide intermediate-resistant *S. aureus* (GISA) and VRE, in a recent study conducted by Italian scientists. MICs in the range of ≤ 0.125-2 mg/L, were calculated against all *S. aureus* isolates tested. *S. pneumoniae* and VRE isolates were inhibited with respective MICs in the range of ≤ 0.07-0.03 and 0.5-4 mg/L, respectively. Antibacterial activity was also reported against *Listeria monocytogenes*, *Lactobacillus* and Gram-positive anaerobes including *Clostridium* and *Propionibac-terium* spp., with respective MIC values of 0.125, ≤ 0.13-4, ≤ 0.13 and ≤ 0.004-4 mg/L. NAI-107 activity was not affected by pH or inoculum size and displayed synergistic effects with other cell wall synthesis inhibitors (146).



NAI-107



MBX-1684



MBX-1641

In vivo in immunocompetent mice infected by *S. pneumoniae*, NAI-107 (i.v. or s.c.) displayed superior bactericidal activity compared to LZD and penicillin (respective ED_{50} values for NAI-107 i.v., NAI-107 s.c., LZD and penicillin of 0.5, 1.1, 15.9 and 31.6 mg/kg). In acute infections induced by MRSA/GISA and VRE isolates (*E. faecalis* and *E. faecium*), i.v. NAI-107 was found to be more effective than LZD or vancomycin (ED_{50} values of 14.2, 22.4 and 17.8 mg/kg, respectively, for NAI-107, vancomycin and LZD against MRSA/GISA; i.v. NAI-107 ED_{50} values of 2.8 and 2.3 mg/kg vs. 22.4 and 5.1 mg/kg for LZD against *E. faecalis* and *E. faecium*). In the rat MRSA pouch granuloma model, i.v. NAI-107 displayed dose-proportional bactericidal activity, which was superior to vancomycin. NAI-107 may represent a promising antibiotic for the systemic treatment of multidrug-resistant Gram-positive bacterial infections (147).

The inhibition of the type III secretion system (TTSS) of *P. aeruginosa* with **MBX-1684** was described. The TTSS is a clinically important virulence mechanism in *P. aeruginosa* as it secretes and translocates protein toxin effectors into human cells, thus facilitating the establishment and dissemination of infection. The identification of *P. aeruginosa* TTSS inhibitors may potentially lead to the development of therapeutic treatments. Scientists at Microbiotix employed a bioluminescent transcriptional reporter primary screen followed by a chromogenic secreted reporter assay to isolate *P. aeruginosa* TTSS inhibitors in a high-throughput screening procedure. One such compound, **MBX-1641**, a racemic mixture of two stereoisomers, was found to inhibit TTSS-dependent secretion of an ExoS'-βLA fusion protein in a concentration-dependent manner (IC_{50} = 15 μM). TTSS-dependent intoxication of CHO cells by *P. aeruginosa* secreting ExoU was inhibited by MBX-1641 (IC_{50} = 20 μM). At a concentration of 50 μM, MBX-1641 induced the internalization of ExoT-secreting *P. aeruginosa* by HeLa cells to a level similar to that seen in the TTSS-defective *P. aeruginosa* strain δpscC. MBX-1684, the (*R*)-isomer of MBX-1641, was found to be twice as potent as the racemate (IC_{50} approximately 9 μM) in the ExoS'-βLA assay (148).

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