inoculated intraperitoneally with lethal doses of one MSSA or one MRSA laboratory strain transformed with a plasmid containing the Lux operon (which confers bioluminescence). Photon emissions from living bioluminescent bacteria were imaged and quantified. The luminescence in saline-treated control mice either increased (neutropenic mice) or remained relatively unchanged (healthy mice). In contrast, by 2–3 hours after dosing, daptomycin resulted in a 90% reduction of luminescence of MSSA or MRSA in both healthy and neutropenic mice. The activity of daptomycin against both MSSA and MRSA strains was superior to that of nafcillin, vancomycin, and linezolid. In MSSA peritonitis, daptomycin showed greater and more rapid bactericidal activity than nafcillin or linezolid. Against MRSA peritonitis, daptomycin showed greater and more rapid bactericidal activity than vancomycin or linezolid (Mortin *et al.*, 2007).

Vancomycin and daptomycin were also compared in a rabbit ventriculitis model. Rabbits were treated with intraventricular vancomycin (30 or 120 μg) or daptomycin (7.5 μg). Single-dose intraventricular vancomycin did not lower *S. aureus* concentrations over 8 hours, whereas daptomycin did. Intraventricular half-lives were approximately 2.8 hours (maximum) for vancomycin and 4.5 hours for daptomycin. Thus, daptomycin achieved greater bactericidal activity, more rapid killing kinetics, and a longer half-life in the ventricle than vancomycin did in this model (Haworth *et al.*, 1990).

USING PHARMACODYNAMIC PRINCIPLES TO PREDICT THE EMERGENCE OF *IN VITRO* DAPTOMYCIN RESISTANCE

The MSW hypothesis has been tested using the pharmacodynamics of daptomycin and vancomycin by Firsov *et al.* (2006). The drugs' abilities to prevent the selection of resistant *S. aureus* were studied in an *in vitro* model. Two clinical isolates of *S. aureus* were exposed for 5 consecutive days to once-daily daptomycin (half-life, 9 hours) and twice-daily vancomycin (half-life, 6 hours) at a 24-hour AUC/MIC ratio that varied over a 16- to 30-fold range. The antistaphylococcal effect of the therapeutic doses of daptomycin (4 and 6 mg/kg) against a hypothetical *S. aureus* strain with MIC equal to the MIC_{90} (AUC_{24}/MIC_{90}, 380 and 570 hours for 4 and 6 mg/kg, respectively) was predicted to be similar to the effect of two 1-g doses of vancomycin given at a 12-hour interval (AUC_{24}/MIC_{90}, 200 hours). An AUC_{24}/MIC ratio that protects against the selection of resistant mutants was predicted at > 200 hours. This protective value is less than the AUC_{24}/MIC_{90} values provided by the 4 mg/kg dose of daptomycin and considerably less than the 6 mg/kg dose of daptomycin, but it is close to the AUC_{24}/MIC_{90} provided by two 1-g doses of vancomycin. These findings support the MSW hypothesis and suggest comparable antistaphylococcal effects of clinically achievable AUC_{24}/MIC_{90} values for daptomycin and vancomycin but slightly better prevention against the selection of resistant *S. aureus* by daptomycin (Firsov *et al.*, 2006).

Quinn *et al.* (2007) performed *in vitro* experiments comparing drug pharmacokinetics with MPC. Daptomycin MPC with *S. aureus* was below minimal plasma drug concentrations with approved doses, which is consistent with resistance to daptomycin arising rarely (Quinn *et al.*, 2007). The relationship of daptomycin to the development of resistance in *S. aureus* belonging to accessory gene regulator (agr) groups I and II was assessed by exposing isolates to varying concentrations of daptomycin simulating an *f*AUC/MIC of 30–239 in an *in vitro* pharmacodynamic model. At extremely low daptomycin exposures of *f*AUC/MIC of 22–66, an increase in MIC of two- to threefold up to a maximum of 0.75 mg/l was observed. However, this was independent of agr group and/or function and still within the susceptible range of daptomycin (Rose *et al.*, 2007).

In an *in vitro* pharmacokinetic/dynamic model with simulated endocardial vegetations, the daptomycin activity against *S. aureus* after vancomycin exposure over 8 days was studied. The emergence of daptomycin nonsusceptibility (12- to 16-fold MIC increase) was detected with an MSSA isolate with daptomycin, 6 mg/kg daily, for 4 days after vancomycin exposure. However, the bactericidal activity of daptomycin was maintained, and the MIC increases of these isolates, which had no mprF or yycG mutations, were unstable to serial passage on antibiotic-free agar. Subsequent regimens did not demonstrate nonsusceptibility to daptomycin. Daptomycin susceptibility seems to be a strain-specific and unstable event (Rose *et al.*, 2008b).

In the same model, sequential MSSA isolates collected from a patient with mitral valve endocarditis during persistent bacteremia on standard therapy and relapse after treatment with daptomycin were studied. An isolate obtained after 5 days of antimicrobial therapy but before exposure to daptomycin showed subtle physiological changes in response to daptomycin, with significant regrowth in the daptomycin killing assay compared with the treatment-naive strain. Once daptomycin was started, the population became more heterogeneous and tested as nonsusceptible. These organisms were examined in a simulated vegetation *in vitro* pharmacodynamic model, which confirmed progressive decreases in killing with daptomycin concentrations that simulate those attained in humans treated with 6 mg/kg once daily (Sakoulas *et al.*, 2008).

The prevention of resistance in enterococci, specifically mutations in genes encoding proteins associated with cell envelope homeostasis (*yycFG* and *liaFSR*) and phospholipid metabolism (cardiolipin synthase and cyclopropane fatty acid synthetase), was simulated in an endocardial vegetation pharmacokinetic/pharmacodynamic model over 14 days by using doses from 4–12 mg/kg/day. Two strains were used: *E. faecium* (S447) and *E. faecalis* (S613). Peak/MIC and AUC_{0-24}/MIC ratios associated with resistance prevention were 72.1 and 780 for S447 and 144 and 1561 for S613, respectively. Daptomycin doses of 10 mg/kg/day may be required to prevent daptomycin resistance in serious enterococcal infections (Werth *et al.*, 2014b).

ASSESSMENTS OF SYNERGY

Synergy *in vitro* was explored among daptomycin and 18 other antibiotics against 19 strains of high-level VRE (vancomycin