1507. Vancomycin (VAN) Combinations with B-Lactams (BLs) against Methicillin-Resistant *Staphylococcus aureus* (MRSA), Heterogeneous Intermediate-Level Resistance to Vancomycin (hVISA) and Vancomycin-Intermediate *Staphylococcus aureus* (VISA)

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Background. *Staphylococcus aureus (S. aureus)*, especially Methicillin-resistant *S. aureus* (MRSA) remains a major cause of serious infection and is associated with increased morbidity and mortality. Vancomycin (VAN) has been the mainstay of therapy for MRSA infections. However, decades of selective pressure have led to increasing concerns regarding the efficacy of VAN against MRSA. *In vitro* data suggest the potential for potent synergy between several B-lactams (BLs) and VAN. The objective of this study is to further explore the synergistic effect between BLs and VAN against MRSA strains with varying susceptibility to VAN.

Methods. Fifty randomly selected clinical MRSA strains from the Anti-Infective Research Laboratory library with varying susceptibility to VAN were evaluated for VAN alone and VAN in combination with Cefazolin (CFZ), Cefepime (FEP), Ceftaroline (CPT), and Nafcillin (NAF) minimum inhibitory concentration (MIC) by microdilution in duplicate. The potential for synergy was assessed by 24 hours time-kills (TK). Synergy was defined as >2 $\log_{10}$ CFU/mL difference between combination and the most active single agent at 24 hours.

Results. BLs reduced VAN MIC values against all strains (4–16 fold reduction). In TK studies against MRSA, all BLs demonstrated a similar extent of killing at 24 hours and showed synergy with VAN against all strains. Each combination was superior to any single agent alone, and each was bactericidal (3.42 ± 0.26 $\log_{10}$ CFU/cm^2 reduction, $P < 0.001$ for all comparisons). All single agent exposures demonstrated no activity at 24 hours.

Phenotype (Number of Strains)	VAN MIC Range (μg/mL)	VAN MIC Range with CFZ	VAN MIC Range with FEP	VAN MIC Range with CPT	VAN MIC Range with NAF
MRSA (15)	0.5 – 2	0.0625 – 0.25	0.0625 – 1	0.0625 – 0.25	0.125 – 0.5
hVISA (20)	0.5 – 2	0.125 – 0.5	0.0625 – 0.5	0.0625 – 0.5	0.125 – 1
VISA (15)	4 (all)	0.0625 – 0.5	0.5 – 2	0.0625 – 0.25	0.125 – 1

Conclusion. The combination of VAN and BLs significantly improved antibacterial activity against MRSA, hVISA, and VISA compared with any agent alone, supporting the potential use of Vancomycin/BL combination therapy in infections caused by MRSA. Further clinical research is warranted to investigate the synergistic activity of vancomycin against these Staphylococcus strains.

Disclosures. **M. J. Rybak**, Allergen: Scientific Advisor, Consulting fee

1508. SCY-078 Demonstrates Significant Tissue Penetration in Rats and Mice Following Oral or IV Administration

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Background. The ability of a pharmacologic agent to reach target organ(s) in therapeutically-meaningful concentrations is one of the fundamental considerations when developing effective, anti-infective treatments. SCY-078 is a novel, oral and intravenous (IV), triterpenoid glucan synthase inhibitor with activity against *Aspergillus* and *Candida*, currently in clinical development for the treatment of invasive fungal infections. Tissue distribution studies were conducted in rats and mice to evaluate the distribution profile of SCY-078 following oral or IV administration.

Methods. Sprague-Dawley rats were given single oral doses of ^{3}H-SCY-078 at 5 mg/kg. Han Wistar and Long Evans (pigmented) rats were given single oral doses of ^{14}C-SCY-078 at 15 mg/kg or IV at 5 mg/kg. Mice were orally-dosed at 3, 6.25, 12, 25, 50, 100 mg/kg BID for seven days.

Results. SCY-078 distributed rapidly into tissues following administration. In rats, T_{max} in whole blood, plasma and tissues following oral dosing was 4 hours. Blood to plasma ratio was < 1.0 indicating low partitioning into erythrocytes. The tissue distribution profile in rats was generally consistent between IV and oral routes and between pigmented and non-pigmented strains. High concentrations were noted in pituitary, spleen, liver, adrenals, lymph nodes, thyroid, bone marrow, thymus, lungs, kidneys and vagina. Tissue:blood ratios in rats ranged from approximately 15- to 50-fold, indicating appreciable penetration characteristics. In mice, kidney concentrations were approximately 20-fold greater than plasma at all doses studied, and the kidney:plasma ratio increased in a dose-related fashion indicating enhanced tissue distribution from greater unbound fractions in plasma. In lungs, exposures in epithelial lining fluid were generally 4-fold greater than plasma and the epithelial lining fluid:plasma ratio increased as much as 13-fold. Concentrations in vaginal tissue and secretions also exceeded those in plasma, and increased as much as 10-fold.

Conclusion. SCY-078 demonstrates significant tissue penetration, indicating an intrinsic ability to reach clinically meaningful levels in various potential target organs of importance, suggesting therapeutic benefit for both treatment and prophylaxis of invasive fungal infections.

Disclosures. **S. Barat**, Scynexis, Inc: Employee, Salary; **K. Borroto-Esoda**, Scynexis Inc: Consultant, Consulting fee; **D. Angulo**, Scynexis, Inc: Employee, Salary

1509. Efficacy of Lefamulin Against *Staphylococcus aureus*-Induced *Bacteremia* in a Neutropenic and Immunocompetent Murine Model

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Background. *S. aureus* (SA) is a major human pathogen that causes invasive, clinical infections including bacteremia. Lefamulin (LEF) is the first semi-synthetic, pleuromutilin antibiotic for IV and oral use in humans. LEF is currently in Phase 3 trials for the treatment of community-acquired bacterial pneumonia (CABP). LEF specifically inhibits bacterial protein synthesis by binding to the peptidyl transferase center (PTC) via four H-bonds and other interactions at the A- and P-site resulting in an "induced fit." LEF has been shown to be highly active against bacterial pathogens causing bacteremia, including SA. This study investigated the efficacy of LEF and comparators against SA in a neutropenic and immunocompetent murine bacteremia model.

Methods. Experimentally induced MSSA bacteremia (inoculum ~2 × 10^7 CFU/mouse) was established in immunocompromised and immunocompetent mice. Infected mice received a single subcutaneous dose of either LEF or comparator (Table 1) 1 hours post-inoculation, mimicking human therapeutic exposures. A control group of infected mice were sacrificed directly before treatment to establish a baseline CFU count and comparison with the bacterial load of treated animals 24 hours post drug administration.

Results. Irrespective of the immune status, LEF showed superior efficacy to linezolid (LZD) and tigecycline (TGC) against MSSA, reducing the bacterial burden more than 4 log^{10} CFU/mL within 24 hours (Table 1). A comparable reduction of bacterial burden was observed between LEF and daptomycin (DAP) or vancomycin (VAN) treatment.

Conclusion. LEF showed comparable therapeutic outcome to DAP or VAN in this acute experimental infection model, while showing superior killing as compared with LZD or TGC. The efficacy of LEF was maintained under neutropenic conditions with >4$\log_{10}$ ΔCFU/mL at clinically relevant exposures. This study supports continued evaluation of LEF for as a potential treatment of staphylococcal bacteremia.

Table 1: Efficacy of lefamulin and reference antibiotics against *S. aureus* (ATCC 49951)

Compound	Dose [mg/kg]	MIC [μg/ml]	*n*	Viable Counts [$\log_{10}$ CFU/ml] Mean ± SD	Δ$\log_{10}$ CFU/ml
non-neutropenic					
Early Control	-	-	24	5.58 ± 0.67	±0.00
LEF	70	0.06	32	1.08 ± 0.26 [a]	-4.50
VAN	160	1	16	1.00 ± 0.00 [a]	-4.58
LZD	80	2	16	3.61 ± 0.57 [ab]	-1.97
DAP	22.5	0.25	16	1.00 ± 0.00 [a]	-4.58
TGC	6.5	0.25	16	1.91 ± 0.68 [ab]	-3.67
neutropenic					
Early Control	-	-	24	6.12 ± 0.22	±0.00
LEF	70	0.06	32	1.98 ± 0.68 [a]	-4.14
VAN	160	1	16	2.33 ± 0.62 [a]	-3.79
LZD	80	2	16	5.75 ± 1.34 [b]	-0.37
DAP	22.5	0.25	16	1.86 ± 0.62 [a]	-4.26
TGC	6.5	0.25	16	3.21 ± 0.63 [ab]	-2.91

[a] $P < 0.05$ compared with Early Control (Dunnett´s method)
[b] $P < 0.05$ compared with lefamulin (Bonferroni t-test)

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1510. Evaluation of the *In Vitro* and *In Vivo* Antifungal Activity of APX001A/APX001 Against *Candida auris*

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Background. *Candida auris*, an emerging multidrug-resistant yeast, causes deadly invasive infections with high mortality. *C. auris* strains often show high MICs to fluconazole and amphotericin B, and some are resistant to all 3 major antifungal classes, limiting treatment options. We tested 16 *C. auris* strains from a wide geographical area (Germany, Japan, S. Korea, and India) against 10 antifungals including APX001A (APXA), an antifungal with a novel mechanism of action (inhibition of the Gwt1 fungal