Background. Gepotidacin (GEP) is a novel triazacaphenylbacterial type II topoisomerase inhibitor targeting both bacterial DNA gyrase and topoisomerase IV by a different mechanism from fluoroquinolone antibiotics. Although in vitro frequency of resistance to GEP in *Neisseria gonorrhoeae* (NG) is low, during a phase 2 trial, clinical resistance to gepotidacin in NG emerged in a subset of fluoroquinolone-resistant NG isolates that contained a pre-existing ParC D86N mutation by introduction of a new GyrA A92T mutation. The objective of this study was to evaluate the role of GyrA A92T and ParC D86N mutations in resistance to GEP.

Methods. We utilized the high frequency of natural transformation to introduce GyrA A92T and ParC D86N mutations, individually and in combination, into NG isolates containing GyrA S91F D95G mutations with wild type (WT) GyrB. GEP and others were selected on ciprofloxacin (CIP) or GEP to generate isogenic strains for susceptibility evaluation.

Results. Results are summarized in enclosed table. Overall, GyrA A92T and ParC D86N mutations alone did not confer a significant (>4-fold) increase in GEP MIC; whereas together they gave >16-fold increases in GEP MIC. Importantly, quinolone target mutations (GyrA S91F D95G and ParC D86N) together showed no significant effect on the GEP MIC; while they gave >1000-fold increase in CIP MIC. As expected, GyrA A92T and ParC D86N mutations alone or together in WT GyrA background had no significant effect on CIP susceptibility.

Conclusion. Our results indicated that unlike fluoroquinolones that primarily target DNA gyrase in NG, there is no obvious primary target for GEP supporting well-balanced dual targeting of DNA gyrase and topoisomerase IV by GEP in NG. Though, the pre-existing ParC D86N mutation is a potential risk marker for clinical resistance development, as this mutation compromises dual targeting of GEP; our studies provide insight for appropriate clinical dose selection to potentially suppress further resistance development in this subset of clinical isolates.

Disclosures. Pan Chan, PhD, GlaxoSmithKline (Employee, Shareholder) Karen Ingraham, MS, GlaxoSmithKline (Employee, Shareholder) Sharon Min, MS, GlaxoSmithKline (Employee, Shareholder) Nicole Scangarella-Oman, MS, GlaxoSmithKline plc (Employee, Shareholder) Steve Rittenhouse, PhD, GlaxoSmithKline (Employee, Shareholder) Jianzhong Huang, PhD, GlaxoSmithKline (Employee, Shareholder)

1250. Novel Boronic Acid Transition State Analogs (BATSI) with in vitro inhibitory activity against class A, B and C β-lactamases

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Session: P-58. Novel Agents

Background. Catalytic mechanisms of serine β-lactamases (SBL; classes A, C and D) and metallo-β-lactamases (MBLs) have directed divergent strategies towards in vivo inhibition. For SBLs the catalytic triad Ser, His and Glu is critical for the active site where the amine group of the serine is oriented. For metallo-β-lactamases, the metal ion plays a critical role in catalysis.

Methods. Exploratory compounds were synthesized using stereoselective homologation of (+) pinanidol boronates to introduce the amino group on the boron-bearing carbon atom, which was subsequently acylated with mercaptoacrylic acid. Representative SBL (KPC-2, ADC-7, PDC-3 and OXA-23) and MBL (IMP-1, NDM-1 and VIM-2) were purified and used for the kinetic characterization of the BATSI series. In vivo activity was evaluated by a modified time-kill curve assay, using SBL and MBL-producing strains.

Results. Kinetic assays revealed that IC<sub>50</sub> values ranged from 1.3 μM to >100 μM for these new agents. The best compound, s08033, demonstrated inhibitory activity against KPC-2, VIM-2, ADC-7 and PDC-3, with IC50 in the low μM range. Reduction of at least 1.5 log<sub>10</sub> fold of viable cell counts upon exposure to sub-lethal concentrations of antibiotics (AB) + s08033, compared to the cells exposed to AB alone, demonstrated the microbiological activity of this novel compound against SBL- and MBL-producing *E. coli* (Table 1).

| Mutations in | GEP | CIP | MIC (μg/ml)/fold change from WT |
|-------------|-----|-----|--------------------------------|
| FA1000      |     |     |                               |
| FA1000-1    |     |     |                               |
| FA1000-3    |     |     |                               |
| FA1000-4    |     |     |                               |
| FA1000     |     |     |                               |
| FA1000-2    |     |     |                               |
| FA1000-3    |     |     |                               |
| FA1000-4    |     |     |                               |
| FA1000     |     |     |                               |
| FA1000-2    |     |     |                               |
| FA1000-3    |     |     |                               |
| FA1000-4    |     |     |                               |

Conclusion. Addition of a free-thiol group to the BATSI scaffold increases the range of these compounds resulting in a broad-spectrum inhibitor toward clinically important carbapenemases and cephalosporinases.

Disclosures. Robert A. Bonomo, MD, Entasis, Merck, Venatorx (Research Grant or Support)

1251. Prevention of Pneumocystis Pneumonia by Ibrexafungerp in a Murine Prophylaxis Model

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Session: P-58. Novel Agents

Background. *Pneumocystis pneumonia* (PCP) is an opportunistic fungal infection that affects immunocompromised patients. Ibrexafungerp (IBX) is an oral and intravenous antifungal from a novel class of glucan synthase inhibitors, triterpenoids, and has shown activity against Candida, Aspergillus, and PCP in a murine therapy model.

We evaluated the ability of IBX to prevent PCP in a prophylaxis model of murine PCP.

Methods. Experiment 1: Balb/c mice (10 mice/group) were infected by intranasal inoculation with *Pneumocystis murina*, immune-suppressed with dexamethasone in acetic acid containing drinking water and treated with 30, 15- and 7.5 mg/kg IBX/BID. Control groups treated whiteno. At the completion of treatment groups included: 1) 30 mg/kg BID x 6wk; 2) 30 mg/kg/BID x 6wk followed by cessation of treatment with IBX but with immune-suppression for 3 additional weeks; 3) 15 mg/kg BID 1 week prior and 6wks after infection and immune suppression; 4) 15 mg/kg BID for 6 wks; 5) 15 mg/kg BID for 6 weeks then IBX was discontinued but with immune-suppression.

Results. Experiment 1: No *P. murina* were observed in any of the treatment groups at the completion of treatment. Overall, mice were sacrificed, and prevention was determined by organism burdens (asci and total nuclei).

Conclusion. These results demonstrate that 30 mg/kg BID IBX prevented PCP in a murine model. We suggest that IBX could be a viable option for preventing PCP in immunocompromised patients.

Disclosures. Katya Borroto-Esoda, PhD, SCYNEXIS, Inc. (Employee, Shareholder) Neechie Azie, MD, SCYNEXIS, Inc. (Employee, Shareholder) Alan Ashbaugh, PhD, SCYNEXIS, Inc. (Grant/Research Support) Melanie Cushion, PhD, SCYNEXIS, Inc. (Grant/Research Support) David A. Angulo, MD, SCYNEXIS, Inc. (Employee, Shareholder)

1252. In Vivo Activity of Cefiderocol Against Metallo-β-Lactamase-Producing Gram-Negative Bacteria Collected in North America and Europe Between 2014 and 2017: SIDERO-WT-2014–2016 Studies

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Session: P-58. Novel Agents

Background. Metallo-β-lactamases (MBLs; eg, NDM, VIM, and IMP) can inactivate most commonly-used β-lactam antibiotics, including carbapenems. Infections caused by MBL producers are difficult to treat due to their resistance to many antibiotics. Cefiderocol (CFDC) is a siderophore cephalosporin antibiotic approved in the USA in 2019, with potent activity against carbapenem-resistant Gram-negative bacteria (GBN), including both serine- and metallo-carbapenem-positive strains. These studies evaluated in vivo activity of CFDC and comparator agents against MBL-producing strains of GNB from North America and Europe in 3 years of consecutive surveillance studies (SIDERO-WT-2014–2016).

Methods. Susceptibility testing for CFDC, ceftazidime-avibactam (CZA), cefotaxime-tazobactam (C/T), meropenem (MEM), cefepime (FEP), ciprofloxacin (CIP), and tigecycline (TGC) was performed by both microdilution according to CLSI guidance. CFDC was tested in iron-depleted medium. A total of 275 MBL-producing strains, consisting of 120 Enterobacteriales (45 NDM; 75 VIM), 5 NDM-producing *Acinetobacter baumannii*, and 150 *Pseudomonas aeruginosa* (134 VIM; 16 IMP), identified among...
Activity against Gram-positive and Gram-negative bacteria. OMC was active against Streptococcus pyogenes isolates from SSSI (MIC$_{90}$ 0.12 mg/L; 93.3%-98.5%S) regardless of resistance to tetracycline or penicillin. Overall, 90.2%-93.6% of OMC was active against 99.0% susceptible [S] strains. OMC was also active against 100% of S. pneumoniae (MIC$_{90}$ 0.12 mg/L) and 98.5%-100% of S. aureus (MIC$_{90}$ 0.06 mg/L) and Haemophilus influenzae [MIC$_{90}$ 0.12 mg/L; 93.3%-98.5%S] including macrolide-resistant (R) strains. S. pneumoniae isolates from RTI were S to OMC (MIC$_{90}$ 0.12-0.25 mg/L; 91.4%-97.4%) and showed MIC$_{90}$ of 4 μg/mL against all 275 MBL producers, indicating that CFDC has high potential for treating infections caused by these difficult-to-treat strains.

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Session: P-58 Novel Agents

Background. Omadacycline (OMC) is a new aminomethylcycline antibacterial drug belonging to the tetracycline class, for intravenous or oral administration. It is well tolerated and has proven effective in the treatment of a variety of bacterial infections. OMC is active against bacterial strains expressing the most common clinically relevant tetracycline resistance mechanisms, namely efflux and ribosomal protection.

Methods. 7,000 clinical isolates were collected during 2019 in the SENTRY Surveillance Program from 31 medical centers in the United States (US). Isolates were obtained from bloodstream infection (23.8%), skin and skin structure infection (21.6%), pneumonia in hospitalized patients (22.7%), urinary tract infection (14.5%), intra-abdominal infection (6.2%), community-acquired respiratory tract infection (10.3%) and other infection types (0.9%). Identifications were confirmed by MALDI-TOF. One isolate/patient/infection episode was tested. Broth microdilution susceptibility testing was conducted according to CLSI M07 (2018) and M100 (2020) guidelines. Results were interpreted using US FDA and CLSI breakpoint criteria.

Results. OMC demonstrated potent in vitro activity against Staphylococcus aureus isolates representing multiple infection types (MIC$_{90}$ 0.12-0.25 mg/L; 94.7%-99.0% susceptible [S]) including MRSA (MIC$_{90}$ 0.25-5 mg/L; 96.5% S) (Table). All S. lugdunensis (MIC$_{90}$ 0.06 mg/L), Enterococcus faecalis (MIC$_{90}$ 0.12-0.25 mg/L), and Haemophilus influenzae [MIC$_{90}$ 0.12 mg/L] isolates were S to OMC. OMC was active against Streptococcus pyogenes isolates from SSSI (MIC$_{90}$ 0.12 mg/L; 93.3%-98.5%) including macrolide-resistant (R) strains. Similarly, S. pneumoniae isolates from RTI were S to OMC (MIC$_{90}$ 0.06-0.12 mg/L; 98.8%-100% S) regardless of resistance to tetracycline or penicillin. Overall, 90.2%-93.6% of OMC was active against 99.0% susceptible [S] including multidrug-resistant (MDR) strains which is currently in Phase 3 clinical testing. The potency of SUL-DUR against geographically diverse ABC isolates collected in 2018 was measured.