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Session: P-58. Novel Agents

Background. Gepotidacin (GEP) is a novel triazaacenaphthylene bacterial 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 & 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 either with GyrA S91F D95G mutations or with wild type (WT) GyrA by selection 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.

Susceptibility of isogenic NG strains to gepotidacin and ciprofloxacin

	Mutation in			MIC (ug/ml)/fold change from wt	
NG strain	GyrA	ParC	*mtrR*$_p$	GEP	CIP
FA1090	wt	wt	wt	0.063	0.004
FA1090-1	S91F D95G	wt	wt	0.063/1	0.5/128
FA1090-3	S91F A92T D95G	wt	wt	0.125/2	0.5/128
FA1090-2	S91F D95G	D86N	wt	0.125/2	4/1024
FA1090-4	S91F A92T D95G	D86N	wt	8/128	4/1024
FA1090E	wt	wt	*mtrR*$_{-79}$	0.25	0.004
FA1090E-1	A92T	wt	*mtrR*$_{-79}$	0.5/2	0.002/0.5
FA1090E-2	wt	D86N	*mtrR*$_{-79}$	0.25/1	0.004/1
FA1090E-3	A92T	D86N	*mtrR*$_{-79}$	4/16	0.002/0.5

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 mechanistic 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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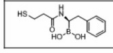
Background. Catalytic mechanisms of serine β-lactamases (SBL; classes A, C and D) and metallo-β-lactamases (MBLs) have directed divergent strategies towards inhibitor design. SBL inhibitors act as high affinity substrates that -as in BATSIs- form a reversible, dative covalent bond with the conserved active site Ser. MBL inhibitors bind the active-site Zn^{2+} ions and displace the nucleophilic OH^-. Herein, we explore the efficacy of a series of BATSI compounds with a free-thiol group at inhibiting both SBL and MBL.

Methods. Exploratory compounds were synthesized using stereoselective homologation of (+) pinandiol boronates to introduce the amino group on the boron-bearing carbon atom, which was subsequently acylated with mercaptopropanoic 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 BATSIs. *In vitro* activity was evaluated by a modified time-kill curve assay, using SBL and MBL-producing strains.

Results. Kinetic assays revealed that IC_{50} values ranged from 1.3 μM to >100 μM for this series. 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_{10}-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).

Table 1

Table 1. IC_{50} values and *in vitro* activity results for s08033 against selected SBLs and MBLs.

s08033	VIM-2	KPC-2	ADC-7	PDC-3
	IC_{50} = 2.8±0.3 μM log_{10} diff = 4	IC_{50} = 16±2 μM log_{10} diff = 5	IC_{50} = 13 ±2 μM log_{10} diff = 1.5	IC_{50} = 4.4±0.4 μM log_{10} diff = 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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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 acidified drinking water and treated with 30-, 15- and 7.5 mg/kg, IBX/BID. Control groups treatment included TMP-SMX (50/250 mg/kg QD) and vehicle. After 6 weeks, mice were sacrificed, and prevention was determined by organism burdens (asci and total nuclei). **Experiment 2**: Balb/c mice were immune-suppressed and infected as in Exp. 1. 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 6 wks after infection and immune suppression; 4) 15mg/kg BID for 8 wks; 5) 15 mg/kg BID for 6 wks then IBX was discontinued but with immune suppression; 6) untreated, vehicle control.

Results. **Experiment 1:** No *P. murina* nuclei or asci were observed after 6 weeks of treatment at a dose of 30 mg/kg/BID in the prophylaxis mouse model of PCP, similar to positive control, TMP/SMX. Some nuclei and asci were observed in the lower dose IBX groups. **Experiment 2:** To investigate whether any *P. murina* remained after different regimens of prophylaxis, treatment of IBX was withdrawn at both doses for an additional 3 wks of immune suppression to provoke the growth of any remaining fungi. Group 1 showed reduction in total nuclei and asci to undetectable. Group 2 did not result in any recrudescence of infection. Group 3 and 4 showed similar reduction in organism burden. Group 5 was similar to untreated control.

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. Katyna Borroto-Esoda, PhD, SCYNEXIS, Inc. (Employee, Shareholder) Nkechi 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 Vitro 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 (GNB), including both serine- and metallo-carbapenemase positive strains. We evaluated the *in vitro* 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), ceftolozane-tazobactam (C/T), meropenem (MEM), cefepime (FEP), ciprofloxacin (CIP), and colistin (CST) was performed by broth microdilution according to CLSI guidance. CFDC was tested in iron-depleted medium. A total of 275 MBL-producing strains, consisting of 120 Enterobacterales (45 NDM; 75 VIM), 5 NDM-producing *Acinetobacter baumannii*, and 150 *Pseudomonas aeruginosa* (134 VIM; 16 IMP), identified among

4985 (654 Enterobacterales and 4331 non-fermenters) MEM non-susceptible (based on CLSI breakpoints) strains were used for the current analysis.

Results. The minimum inhibitory concentration (MIC) range and MIC_{90} for CFDC and comparators for each MBL-producing organism group are shown in the Table. Against NDM-producing Enterobacterales, of which 42% and 33% were isolated in Turkey and Russia, respectively, CFDC inhibited the growth of 84% of isolates tested at ≤4 µg/mL. CFDC MIC_{90} was 4 µg/mL for VIM-producing Enterobacterales (41% and 31% isolated in Greece and Italy, respectively), 1 µg/mL for VIM-producing *P. aeruginosa* (50% isolated in Russia), and 4 µg/mL for IMP-producing *P. aeruginosa* (88% isolated in Czech Republic). Other comparators (except for CST) were not active against these MBL producers.

Table. MIC range and MIC90 (µg/mL) for CFDC and comparators of MBL-producing organisms

Table. MIC range and MIC_{90} (µg/mL) for CFDC and comparators of MBL-producing organisms

	NDM-producing Enterobacterales (N=45)		VIM-producing Enterobacterales (N=75)		NDM-producing A. baumannii (N=5)		VIM-producing P. aeruginosa (N=134)		IMP-producing P. aeruginosa (N=16)	
Compounds	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}
CFDC	0.25–8	8	0.12–4	4	1–8	NC	0.008–4	1	0.12–4	4
CZA	1–>64	>64	4–>64	>64	>64	NC	2–>64	>64	>64	>64
C/T	>64	>64	32–>64	>64	>64	NC	0.5–>64	>64	>64	>64
MEM	4–>64	>64	2–>64	64	64–>64	NC	4–>64	>64	8–>64	>64
FEP	32–>64	>64	0.25–>64	>64	>64	NC	8–>64	>64	>64	>64
CST	≤0.25–8	1	≤0.25–>8	>8	≤0.25–0.5	NC	≤0.25–4	2	1–2	2
CIP	2–>8	>8	≤0.12–>8	>8	≤0.12–>8	NC	0.25–>8	>8	>8	>8

NC: MIC_{90} values were not calculated because the number of isolates was ≤10. IMP: imipenemase metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; VIM: Verona integron-encoded metallo-β-lactamase.

Conclusion. CFDC inhibited the growth of 100% of MBL-positive GNB at ≤8 mg/mL 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.

Disclosures. Miki Takemura, MSc, Shionogi & Co., Ltd. (Employee) Krystyna Kazmierczak, PhD, Shionogi & Co., Ltd. (Independent Contractor) Daniel F. Sahm, PhD, IHMA (Employee)Pfizer, Inc. (Consultant)Shionogi & Co., Ltd. (Independent Contractor) Roger Echols, MD, Shionogi Inc. (Consultant) Yoshinori Yamano, PhD, Shionogi & Co., Ltd. (Employee)

1253. *In Vitro* Activity of Omadacycline against 7000 Bacterial Pathogens from the United States Stratified by Infection Type (2019)

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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%), intraabdominal 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 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}, 1 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%S) 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 *Enterobacter cloacae* (MIC_{90}, 4 mg/L) and 89.7%-94.7% of *Klebsiella pneumoniae* (MIC_{90}, 4-8 mg/L) isolates from multiple infection types were S to OMC.

Conclusion. OMC demonstrated potent *in vitro* activity against Gram-positive and -negative bacterial pathogens from multiple infection types including SSSI and RTI and isolates displaying resistance to tetracycline, macrolides, and penicillin.

Table 1

		Omadacycline		Tetracycline	
Organism (no. of isolates)	Infection Type[a]	MIC_{90} (mg/L)	%S / %R[b]	MIC_{90} (mg/L)	%S / %R[c]
S. aureus (1,623)	ALL	0.25	98.3 / 0.2	≤0.5	95.0 / 4.0
S. aureus (736)	SSSI	0.12	99.0 / 0.1	≤0.5	94.3 / 4.3
S. aureus (396)	RTI	0.12	94.7 / 2.5[d]	≤0.5	94.9 / 5.1
MRSA (684)	ALL	0.25	96.5 / 0.4[e]	1	94.7 / 4.7
S. lugdunensis (26)	ALL	0.06	100 / 0.0[e]	≤0.5	96.2 / 0.0
E. faecalis (229)	ALL	0.25	100 / 0.0[e]	>16	29.3 / 70.7
E. faecalis (60)	SSSI	0.12	100 / 0.0	>16	21.7 / 78.3
S. pyogenes (68)	SSSI	0.12	98.5 / 0.0	>4	79.4 / 20.6
macrolide-R (15)	SSSI	0.12	93.3 / 0.0	>4	40.0 / 60.0
S. pneumoniae (380)	RTI	0.06	99.7 / 0.0	>4	77.1 / 22.6
tetracycline-R (86)	RTI	0.12	98.8 / 0.0	>4	0.0 / 100
penicillin-R (41)	RTI	0.06	100 / 0.0	>4	61.0 / 39.0
H. influenzae (291)	RTI	1	100 / 0.0	0.5	99.0 / 1.0
E. cloacae (219)	ALL	4	93.6 / 2.8[e]	16	85.4 / 11.4
E. cloacae (41)	SSSI	4	90.2 / 4.9	>16	83.3 / 11.9
K. pneumoniae (511)	ALL	4	93.2 / 3.5[f]	>16	78.9 / 18.6
K. pneumoniae (39)	SSSI	8	89.7 / 5.1	>16	66.7 / 30.8
K. pneumoniae (136)	RTI	4	90.4 / 5.1	>16	77.2 / 19.9
K. pneumoniae (113)	UTI	4	94.7 / 1.8[f]	>16	79.6 / 17.7

[a] ALL; all infection types, SSSI; skin and skin structure infection, RTI; respiratory tract infection, UTI; urinary tract infection.
[b] % susceptible (S) and % resistant (R) using US FDA breakpoint interpretive criteria.
[c] % S and % R using CLSI breakpoint interpretive criteria.
[d] US FDA breakpoints for CABP (MSSA only) applied for all *S. aureus*.
[e] US FDA breakpoint for ABSSSI applied.
[f] US FDA breakpoint for ABSSSI and CABP applied.

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1254. *In vitro* activity of sulbactam-durlobactam against recent global clinical *Acinetobacter baumannii-calcoaceticus* complex isolates

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Session: P-58. Novel Agents

Background. *Acinetobacter baumannii-calcoaceticus* complex (ABC) causes severe infections that are difficult to treat due to increasing resistance to antibacterial therapy. Sulbactam (SUL) has intrinsic antibacterial activity against ABC, but its clinical utility has been compromised by the prevalence of serine β-lactamases. Durlobactam (DUR, previously ETX2514) is a diazabicyclooctenone β-lactamase inhibitor with potent activity against Ambler classes A, C and D serine β-lactamases that effectively restores SUL activity against ABC isolates. SUL-DUR is an antibiotic designed to treat serious infections caused by *Acinetobacter*, including multidrug-resistant strains, which is currently in Phase 3 clinical testing. The potency of SUL-DUR against geographically diverse ABC isolates collected in 2018 was measured.