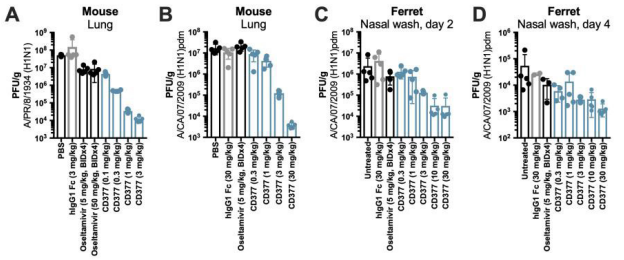
compared to PBS against influenza A/PR/8/1934 (H1N1) (Fig. 1A). In the same study, oseltamivir reduced viral lung burden only by 0.8 logs at both 5 mg/kg (HED) and 50 mg/kg. No significant reduction in lung burden was observed between negative controls, PBS and hIgG1 Fc. Similarly, CD377 demonstrated a dose-dependent, multi-log reduction in viral lung burden against influenza A/CA/07/2009 (H1N1)pdm (Fig. 1B). In ferrets, CD377 reduced viral load with dose dependency at days 2 (Fig. 1C) and 4 post-infection (Fig. 1D). CD377 at 3 mg/kg or higher dose was superior compared to oseltamivir at 4x HED on days 2 and 4 post-challenge.

Figure 1. CD377 demonstrates dose-dependent reduction in viral burden in mice (A, B) and ferrets (C, D).



Conclusion: CD377 demonstrated superior viral load reduction compared to oseltamivir in lethal influenza A (H1N1) mouse and ferret models. These data support further development of CD377 for prevention and treatment of influenza infection.

Disclosures: Simon Döhrmann, PhD, Cidara Therapeutics (Shareholder) Amanda Almaguer, Bachelors, Cidara Therapeutics, Inc. (Employee, Shareholder) Nicholas Dedeic, n/a, Cidara Therapeutics (Employee) Karin Amundson, BSc, Cidara Therapeutics (Shareholder) Thomas P. Brady, PhD Chemistry, Cidara Therapeutics (Employee) Alain Noncovich, PhD, Cidara Therapeutics (Shareholder) Grayson Hough, MS - Chemistry, Cidara Therapeutics (Employee) Allen Borchardt, PhD, Cidara Therapeutics (Employee) Jeffrey B. Locke, PhD, Cidara Therapeutics, Inc. (Employee, Shareholder) Jason Cole, PhD, Cidara Therapeutics (Shareholder) James Levin, PhD, Cidara Therapeutics (Shareholder) Les Tari, PhD, Cidara Therapeutics (Shareholder)

163. Enhancing the Immunogenicity of a Novel, Low-cost Ebola Vaccine

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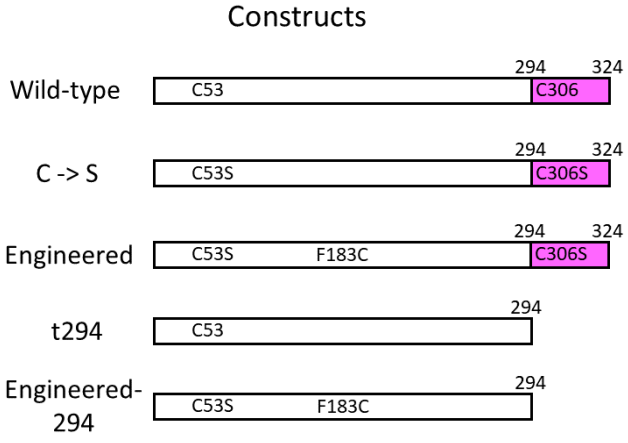
Session: O-31. Novel Vaccines and Antibodies

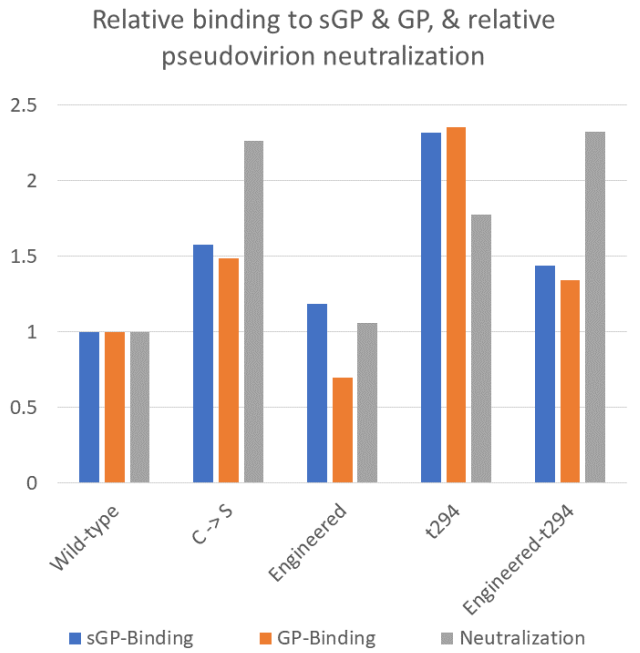
Background: Ebolaviruses cause viral hemorrhagic fever with high mortality rates. Nearly all Ebola vaccines in development use Ebola glycoprotein (GP) as the immunizing antigen. GP is present on the viral membrane and functions in cell entry by binding the cellular receptor and mediating membrane fusion; antibodies to GP induce protective immunity. Ebola also produces sGP: a smaller, secreted form of GP containing the receptor-binding domain; it is also able to induce protective immunity. sGP naturally refolds after thermal denaturation and thus may be more stable than GP, and may also be more cost effective as it is produced easily in high quantities. sGP is a homodimer that is covalently linked by a cysteine near its C-terminus. In this work, we explored how modifications to sGP that affect its ability to dimerize also alter its immunogenicity.

Methods: sGP mutants were generated in the pCAGGS mammalian expression plasmid, and injected into mice as a DNA vaccine. Mouse sera was tested by ELISA against sGP and GP proteins, and in a neutralization assay against GP-typed pseudovirions.

Results: We generated 4 different mutants of sGP that had altered abilities to form inter-protomer disulfide bonds. All had a mutated or deleted cysteine at position 306; two had disulfide-bonding restored by introduction of an engineered inter-protomer disulfide bond. Mice were immunized with a DNA vaccine encoding either an sGP mutant or wild-type sGP, and sera were collected. We found that sera from sGP mutants with reduced interprotomer disulfide bonds had significantly higher antibody titers to sGP and GP than sera from our wild-type sGP and engineered-disulfide sGP immunized mice. Antibody titers were similar between sGP and GP; these titers correlated with neutralization ability.



Relative binding to sGP & GP (by ELISA OD) & relative % neutralization of pseudovirions at 1:10 dilution



Conclusion: Immunogenicity of Ebola sGP was enhanced significantly when mutations were introduced to reduce its ability to covalently dimerize. Immunogenicity correlated with induction of neutralizing antibodies, implying that our mutants may outperform wild-type sGP when used as a vaccine *in vivo*. This work helps paves the way for an alternative Ebola vaccine that has the potential to be more cost-effective and heat-stable than the currently-licensed vaccine.

Disclosures: Samuel D. Stampfer, MD/PhD, Gilead (Shareholder)

164. *in Vitro* Antibacterial Activity of Cefiderocol Against Non-fermenter Clinical Strains Collected in North America and Europe from Multinational Surveillance Studies SIDERO-WT-2014–2018

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Session: O-32. Novel agents

Background: Non-fermenting Gram-negative bacilli (NFGNB), such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*-complex (ABC), *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*-complex (BCC), are recognized as difficult-to-treat organisms due to acquired and intrinsic antimicrobial resistance. This study evaluated the *in vitro* activity of cefiderocol (CFDC), a novel parenteral siderophore cephalosporin, and comparator agents against NFGNB clinical isolates collected in 2014–2018 as part of the multinational SIDERO-WT surveillance program.

Methods: 12,293 non-fermenter clinical isolates, including 5310 from North America and 6983 from Europe, were tested for antimicrobial susceptibility. Minimum inhibitory concentrations (MICs) were determined for CFDC, cefepime (FEP), ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), meropenem-vaborbactam (MVB), meropenem (MEM), ciprofloxacin (CIP), colistin (CST), and trimethoprim-sulfamethoxazole (SXT) by broth microdilution according to Clinical Laboratory and Standards Institute (CLSI) guidelines. MICs for aztreonam-avibactam (ATM/AVI; ATM in the presence of 4 µg/mL AVI), MVB, and SXT were determined only for SIDERO-WT 2018 strains. As per CLSI guidelines, CFDC was tested in iron-depleted media, and carbapenem-non-susceptible (CarbNS) isolates were defined as non-susceptible to MEM.

Results: CFDC demonstrated *in vitro* activity with MIC_{90}s of 0.25–2 µg/mL against clinical isolates of *P. aeruginosa*, ABC, *S. maltophilia*, and BCC, including CarbNS subsets. MIC_{90}s of CFDC against CarbNS *P. aeruginosa* (N=1416), CarbNS ABC (N=2274), *S. maltophilia* (N=1565), and CarbNS BCC (N=80) were 1, 2, 0.5, and 2 µg/mL, respectively, which were the lowest among the tested compounds (Table). The MIC_{90} differences between all isolates and CarbNS subsets were ≤2-fold for *P. aeruginosa* and ABC, showing that CFDC is active against CarbNS subsets as well as carbapenem-susceptible isolates. However, an 8-fold MIC_{90} difference between all isolates and CarbNS subsets was observed for BCC.

Conclusion: In 4 years of consecutive multinational surveillance studies, CFDC was the most active agent among antimicrobials tested against a wide range of NFGNB, including CarbNS strains.

Table. Activity of cefiderocol and comparators against non-fermenting Gram-negative bacilli											
	N	MIC_{90}[a] (μg/mL)									
		CFDC	FEP	CZA	C/T	CIP	CST	MEM	MVB[b]	ATM/AVI[b]	SXT[a,b]
Non-fermenters	12293	1	64	64	64	>8	2	>64	64	>8	-
P. aeruginosa	6213	0.5	16	8	2	>8	2	16	8	>8	NT
CarbNS *P. aeruginosa*	1416	1	64	64	>64	>8	2	64	8	>8	NT
A. baumannii complex	4185	2	>64	>64	>64	>8	2	>64	>64	>8	NT
CarbNS *A. baumannii* complex	2274	2	>64	>64	>64	>8	>8	>64	>64	>8	NT
S. maltophilia	1565	0.5	>64	>64	>64	8	>8	>64	8	8	1
B. cepacia complex	265	0..25	>64	8	32	>8	>8	16	8	8	NT
CarbNS *B. cepacia* complex	80	2	>64	16	>64	>8	>8	16	8	8	NT
[a]MVB, ATM/AVI, SXT were only included in SIDERO-WT-2018; [b]SXT was only tested against *S. maltophilia*; NT not tested.											

Disclosures: Yuuta Ukai, MSc, Shionogi & Co., Ltd. (Employee) Rio Nakamura, BSc, Shionogi & Co., Ltd. (Employee) Merime Oota, BSc, Shionogi & Co., Ltd. (Employee) Roger Echols, MD, Shionogi Inc. (Consultant) Miki Takemura, MSc, Shionogi & Co., Ltd. (Employee) Yoshinori Yamano, PhD, Shionogi & Co., Ltd. (Employee) Daniel F. Sahm, PhD, IHMA (Employee)Pfizer, Inc. (Consultant)Shionogi & Co., Ltd. (Independent Contractor)

165. Cefiderocol Treatment for Serious Infections Caused by Carbapenem-resistant Bacteria: Post-hoc Analysis of Outcomes by Pathogen in the CREDIBLE-CR Study

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Session: O-32. Novel agents

Background: The efficacy and safety of cefiderocol (CFDC), a novel siderophore cephalosporin, for the treatment of serious infections due to carbapenem-resistant (CR) Gram-negative pathogens was assessed in the CREDIBLE-CR study. The current analysis evaluated clinical and microbiological outcomes by baseline CR pathogen.

Methods: An open-label, prospective, randomised 2:1, Phase 3 study (CREDIBLE-CR; NCT02714595) was conducted in adult patients with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia, bloodstream infections or sepsis, and complicated urinary tract infections caused by CR Gram-negative pathogens. Patients received either intravenous (IV) CFDC 2g, q8h, 3-h infusion, or IV best available therapy (BAT: up to 3 drugs in combination), for 7–14 days (extendable to 21 days). Clinical and microbiological outcomes were assessed in the CR microbiological intent-to-treat (CR-MITT) population by CR pathogen, baseline MIC and by mechanism of carbapenem resistance at test of cure (TOC). Only summary statistics were collected.

Results: In the CR-MITT population (CFDC N=80; BAT N=38), *Acinetobacter baumannii* (46.3% and 44.7%), *Klebsiella pneumoniae* (33.8% and 31.5%), and *Pseudomonas aeruginosa* (15% and 26%) were the most frequent pathogens in CFDC and BAT arms, respectively. For all CR pathogens, clinical cure rates were achieved in 52.5% in the CFDC arm and 50.0% in the BAT arm at TOC; rates were similar between treatment arms by baseline CR pathogen (Table 1). Numerically higher clinical cure and microbiological outcomes were observed with CFDC for Enterobacterales (Table 1), especially against NDM-producing bacteria or those with porin-channel mutations (Table 1). CFDC MIC values ranged between ≤0.03 and 4 μg/mL, except for one pathogen (Table 2). Microbiological outcomes for CR *A. baumannii*, CR *K. pneumoniae*, and CR *P. aeruginosa* at TOC by baseline MICs of ≤4 μg/mL ranged between 0–40%, 0–100%, and 0–100%, respectively; at MIC ≤4 μg/mL, clinical and microbiological outcomes were equal (Table 2).

Table 1. Clinical and microbiological outcomes by most frequent baseline CR pathogens and CR mechanisms at test of cure (all infection sites) in the carbapenem-resistant microbiological intent-to-treat* population.

	Clinical cure rate		Microbiological eradication rate	
	Cefiderocol, (N=80) n/N (%)	BAT, (N=38) n/N (%)	Cefiderocol, (N=80) n/N (%)	BAT, (N=38) n/N (%)
Overall by patient	42/80 (52.5)	19/38 (50.0)	25/80 (31.3)	9/38 (23.7)
All non-fermenters	22/49 (44.9)	13/25 (52.0)	11/49 (22.4)	6/25 (24.0)
Enterobacterales	19/29 (65.5)	5/11 (45.5)	14/29 (48.3)	2/11 (18.2)
Mixed	1/2 (50.0)	1/2 (50.0)	0/2 (0)	1/2 (50.0)
Acinetobacter baumannii	18/37 (48.6)	9/17 (52.9)	10/37 (27.0)	5/17 (29.4)
Klebsiella pneumoniae	17/27 (63.0)	7/12 (58.3)	13/27 (48.1)	3/12 (25.0)
Pseudomonas aeruginosa	7/12 (58.3)	5/10 (50.0)	1/12 (8.3)	2/10 (20.0)
Resistance mechanisms				
NDM-producer (Enterobacterales)	6/8 (75.0)	0/4 (0)	5/8 (62.5)	0/4 (0)
KPC-producer (Enterobacterales)	8/14 (57.1)	4/7 (57.1)	5/14 (35.7)	2/7 (28.6)
Porin channel mutation (Enterobacterales)	10/15 (66.7)	5/9 (55.6)	7/15 (46.7)	1/9 (11.1)
MBL-producer** (non-fermenters or Enterobacterales)	12/16 (75.0)	2/7 (28.6)	7/16 (43.8)	1/7 (14.3)
OXA-producer (non-fermenters)	15/36 (41.7)	9/17 (52.9)	9/36 (25.0)	5/17 (29.4)

*CR status confirmed by central laboratory; **Includes IMP-, NDM-, VIM-producers; IMP: imipenemase metallo-β-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase; MBL: metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; OXA: oxacillinase; VIM: Verona integron-encoded metallo-β-lactamase.

Table 2. Clinical cure and microbiological eradication rates by CR pathogen in the CR-Micro-ITT population in CFDC arm

	CR *A. baumannii* (N=37), n/N (%)		CR *K. pneumoniae* (N=27), n/N (%)		CR *P. aeruginosa* (N=12), n/N (%)	
	Clinical	Microbiological	Clinical	Microbiological	Clinical	Microbiological
Overall by pathogen	18/37 (48.6%)	10/37 (27.0%)	17/27 (63.0%)	13/27 (48.1%)	7/12 (58.3%)	1/12 (8.3%)
Cefiderocol MIC at baseline, μg/mL						
≤0.03	–	–	–	–	–	–
0.06	3/5 (60.0)	2/5 (40.0)	0/1 (0.0)	0/1 (0.0)	–	–
0.12	2/7 (28.6)	2/7 (28.6)	3/3 (100.0)	1/3 (33.3)	1/3 (33.3)	0/3 (0.0)
0.25	6/11 (54.5)	3/11 (27.3)	5/7 (71.4)	2/7 (28.6)	2/2 (100.0)	0/2 (0.0)
0.5	1/4 (25.0)	1/4 (25.0)	2/2 (100.0)	2/2 (100.0)	1/3 (33.3)	0/3 (0.0)
1	2/6 (33.3)	1/6 (16.7)	3/5 (60.0)	3/5 (60.0)	1/2 (50.0)	0/2 (0.0)
2	1/1 (100.0)	0/1 (0.0)	2/5 (40.0)	2/5 (40.0)	1/1 (100.0)	0/1 (0.0)
4	0/1 (0.0)	0/1 (0.0)	3/4 (75.0)	3/4 (75.0)	1/1 (100.0)	1/1 (100.0)
8	–	–	–	–	–	–
16	0/1 (0.0)	0/1 (0.0)	–	–	–	–
32	–	–	–	–	–	–
≥64	–	–	–	–	–	–
Unknown	1/1 (100)	1/1 (100)	–	–	–	–

Conclusion: CFDC, via a novel mechanism of entry and its stability against β-lactamases, was effective against serious infections caused by CR pathogens with various resistance mechanisms or baseline MIC values.

Disclosures: Yuko Matsunaga, MD, Shionogi Inc. (Employee) Mari Ariyasu, BPharm, Shionogi & Co., Ltd. (Employee) Miki Takemura, MSc, Shionogi & Co., Ltd. (Employee) Yoshinori Yamano, PhD, Shionogi & Co., Ltd. (Employee) Kiichiro Toyoizumi, PhD, Shionogi & Co., Ltd. (Employee) Masahiro Kinoshita, MPharm, Shionogi & Co., Ltd. (Employee) Roger Echols, MD, Shionogi Inc. (Consultant) Tsutae Den Nagata, MD, Shionogi & Co., Ltd. (Employee)

166. Activity of a Novel β-lactamase Inhibitor QPX7728 Combined With β-lactams Against st258 *klebsiella Pneumoniae* and st131 *escherchia Coli* Isolates Producing β-lactamases

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Session: O-32. Novel agents

Background: ST258 *K. pneumoniae* and ST131 *E. coli* clones are considered vectors for the global spread of multidrug resistance. We evaluated the activity of β-lactams in combination with QPX7728, a novel β-lactamase inhibitor active against all β-lactamase classes, against a collection of 210 isolates belonging to these clones collected from a worldwide surveillance study.

Methods: A total of 118 ST258 *K. pneumoniae* and 92 ST131 *E. coli* (single loci variant also included) were susceptibility tested by reference broth microdilution against various β-lactams ± QPX7728 and comparator agents. All isolates were screened for β-lactamases using whole genome sequencing analysis.

Results: All β-lactam agents had limited activity against 118 ST258 *K. pneumoniae* (1.7–7.6% susceptible). Among these, 104 carried carbapenemase-encoding genes: 66 KPC variants, 20 NDM and 17 OXA-48-like. One isolate carried 2 carbapenemases. The addition of QPX7728 at 4 mg/L or 8 mg/L lowered the MICs for cefepime ($MIC_{50/90}$, 0.25/1 mg/L and $MIC_{50/90}$, 0.12/0.5 mg/L), ceftolozane ($MIC_{50/90}$, 0.5/ > 32 mg/L and $MIC_{50/90}$, 0.25/16 mg/L), ertapenem ($MIC_{50/90}$, 0.12/2 mg/L and $MIC_{50/90}$, 0.06/0.5 mg/L), and meropenem ($MIC_{50/90}$, 0.06/0.5 mg/L and $MIC_{50/90}$, 0.03/0.12 mg/L; Table). QPX7728 at 4 mg/L reduced the ceftibuten ($MIC_{50/90}$, 0.25/8 mg/L) or tebipenem ($MIC_{50/90}$, 0.12/2 mg/L) MICs for ST258 isolates. *E. coli* ST131 carried mainly CTX-M variant (85 isolates), but 6 isolates harbored carbapenemases. Carbapenems were the only β-lactams displaying > 80.0% activity against ST131 *E. coli*, followed by piperacillin-tazobactam (79.3% susceptible). Only 5.4%and 41.3% ST131 isolates were susceptible to cefepime and ceftibuten, respectively. MIC_{50}/MIC_{90} values for these agents with QPX7728 were ≤ 0.015/≤ 0.015 mg/L for cefepime and ≤ 0.015/0.06 mg/L for ceftolozane with the inhibitor at 8 mg/L and ≤ 0.015/0.03 mg/L for ceftibuten with the inhibitor at 4 mg/L.

Conclusion: QPX7728 lowered the MICs for all agents tested to clinically achievable levels when tested against isolates multidrug resistant belonging to important clones responsible to the dissemination of KPC, CTX variants, and metallo-β-lactamases. The development of this broad β-lactamase inhibitor should be pursued.

Table 1

Agent/combination	ST258 *K. pneumoniae*			ST131 *E. coli*		
	MIC_{50}	MIC_{90}	% inhibited at 4 mg/L[a]	MIC_{50}	MIC_{90}	% inhibited at 4 mg/L[a]
Cefepime	>32	>32	4.2	32	32	15.2
Cefepime + QPX7728 at fixed 8 mg/L	0.12	0.5	99.2	≤0.015	≤0.015	100.0
Ceftolozane	>32	>32	2.5	16	>32	27.2
Ceftolozane + QPX7728 at fixed 8 mg/L	0.25	16	82.2	≤0.015	0.06	100.0
Ertapenem	>32	>32	5.1	0.03	0.5	94.6
Ertapenem + QPX7728 at fixed 8 mg/L	0.06	0.5	100.0	≤0.015	≤0.015	100.0
Meropenem	>32	>32	13.6	0.03	0.12	97.8
Meropenem + QPX7728 at fixed 8 mg/L	0.03	0.12	100.0	≤0.015	≤0.015	100.0
Ceftibuten	>32	>32	4.2	16	32	40.2
Ceftibuten + QPX7728 at fixed 4 mg/L	0.25	8	89.0	≤0.015	0.03	100.0
Tebipenem	4	32	52.5	1	8	95.7
Tebipenem + QPX7728 at fixed 4 mg/L	0.12	2	94.9	0.12	0.5	100.0
[a] 4 mg/L was used for comparison purposes only						

Disclosures: Mariana Castanheira, PhD, 1928 Diagnostics (Research Grant or Support)A. Menarini Industrie Farmaceutiche Riunite S.R.L. (Research Grant or Support)