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 hlgG1 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 Almague, 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.

Constructs

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

Relative binding to sGP & GP, & relative pseudovirion neutralization

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 pave 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 MIC₉₀s of 0.25-2 µg/mL against clinical isolates of *P. aeruginosa*, ABC, *S. maltophilia*, and BCC, including CarbNS subsets. MIC₉₀s 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 MIC₉₀ 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 MIC₉₀ 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.