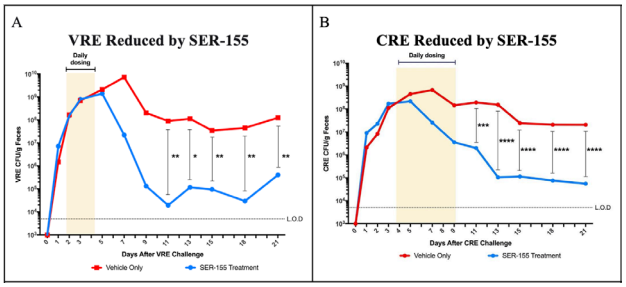

Figure 1. SER-155 Efficacy in Mouse Models of VRE and CRE Colonization.

The titers of VRE or CRE were quantified in fecal pellets by plating on selective agar at the indicated time-points. The median A) VRE and B) CRE CFU per gram of feces was calculated for each group and plotted on the line graph (n=6-10 per group). L.O.D., limit of detection. Data were analyzed using the Mann-Whitney t-test and significance was determined as a p-value of p< 0.05*, p<0.01**, p<0.001***, p<0.0001****.

Conclusion. SER-155 is an investigational cultivated microbiome therapeutic intended to reduce the risk of infection by engrafting human-commensal bacterial strains in adults undergoing allogeneic HSCT. Preclinical assessments *in vitro* and *in vivo* support the ability of SER-155 to reduce VRE and CRE carriage and restore colonization resistance in the gut. A Phase 1b study evaluating SER-155 in allogeneic HSCT patients is being planned.

Disclosures. **Elizabeth Halvorsen, PhD**, **Seres Therapeutics** (Employee, Shareholder) **Marin Vulic, PhD**, **Seres Therapeutics** (Employee) **Edward J. O'Brien, PhD**, **Seres Therapeutics** (Employee, Shareholder) **Jessica Byrant, PhD**, **Seres Therapeutics** (Employee, Shareholder) **Mary-Jane Lombardo, PhD**, **Seres Therapeutics** (Employee, Shareholder) **Christopher Ford, PhD**, **Seres Therapeutics** (Employee, Shareholder) **Matt Henn, PhD**, **Seres Therapeutics** (Employee, Shareholder)

131. Antiviral NL-CVX1 Efficiently Blocks Infection of SARS-CoV-2 Viral Variants of Concern (VOC)

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Session: O-27. Novel Antimicrobial Agents

Background. Using a computational approach, NL-CVX1 was developed by Neoleukin Therapeutics, Inc. to create a *de novo* protein that both blocks SARS-CoV-2 infection and is highly resilient to viral escape. In this study we evaluated the efficacy of NL-CVX1 against variants of the original SARS-CoV-2 strain, including important viral variants of concern (VOC) such as B.1.1.7, B.1.351, and P.1.

Methods. The relative binding affinity of NL-CVX1 to the SARS-CoV-2 viral spike protein of VOC was measured using biolayer interferometry (Octet). A competitive ELISA measured the ability of NL-CVX1 to compete with hACE2 for binding to the receptor binding domain (RBD) of the SARS-CoV-2 S protein from the original strain and VOC. The activity of NL-CVX1 in preventing viral infection was assessed by evaluating the cytopathic effects (CPE) of SARS-CoV-2 in a transmembrane protease, serine 2-expressing Vero E6 cell line (Vero E6/TMPRSS2) and determining the viral load using quantitative real-time reverse transcriptase polymerase chain reaction in infected cells. A K18hACE2 mouse model of SARS CoV-2 infection was used to study the dose-response of NL-CVX1 anti-viral activity *in vivo*.

Results. NL-CVX1 binds the RBD of different VOC of SARS-CoV-2 at low nanomolar concentrations (Fig 1; K_d < 1-~5 nM). When competing with hACE2, NL-CVX1 achieved 100% inhibition against hACE2 binding to the RBD of different VOC with IC50s values ranging from 0.7-53 nM (Fig 2). NL-CVX1 neutralized the B.1.1.7 variant as efficiently as the original strain in Vero E6/TMPRSS2 cells, with EC50 values of 16 nM and 101.2 nM, respectively (Fig 3). In mice, we found that a single intranasal dose of 100 µg NL-CVX1 prevented clinically significant SARS-CoV-2 infection and protected mice from succumbing to infection. Results from additional *in vitro* and *in vivo* experiments to be conducted this summer will be presented.

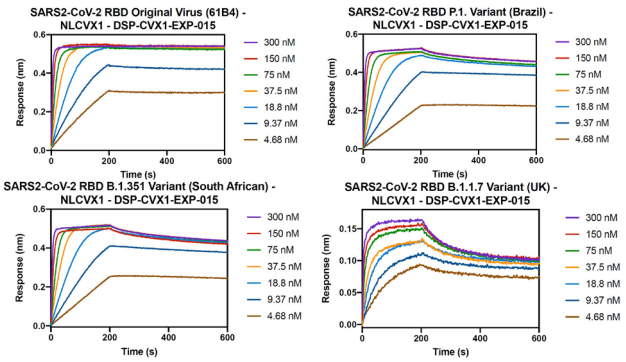

Figure 1. NL-CVX1 binds the RBD from multiple strains of SARS-CoV-2 at low nanomolar concentrations.

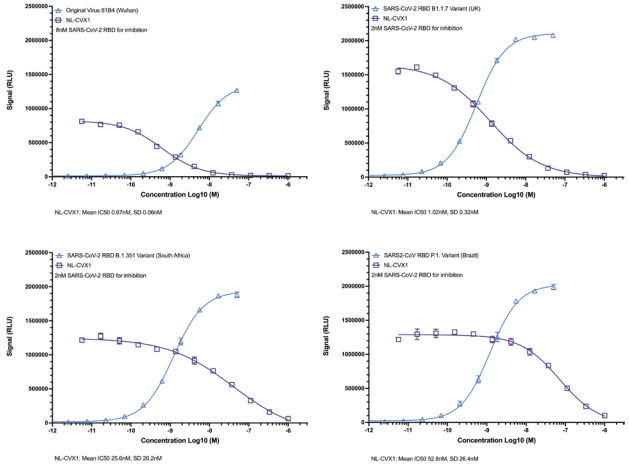

Figure 2. NL-CVX1 achieves 100% inhibition against all strains tested, including SARS-CoV-2 VOC.

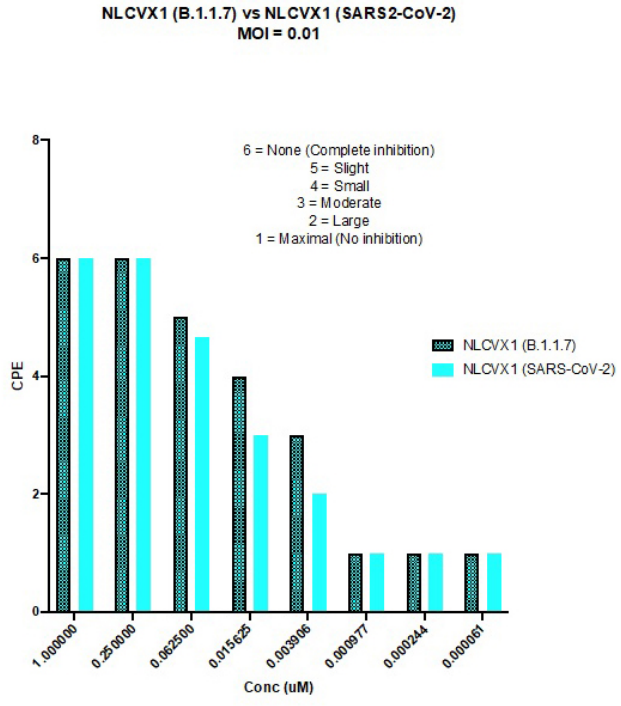

Figure 3. NL-CVX1 neutralizes the B.1.1.7 variant as efficiently as the original SARS-CoV-2 strain.

Conclusion. *In vitro* and *in vivo* data (Fig 4) demonstrate that NL-CVX1 is a promising drug candidate for the prevention and treatment of COVID-19. As a hACE2 mimetic, it is resilient to antibody escape mutations found in SARS-CoV-2 VOC. NL-CVX1 further demonstrates the power and utility of *de novo* protein design for developing proteins as human therapeutics.

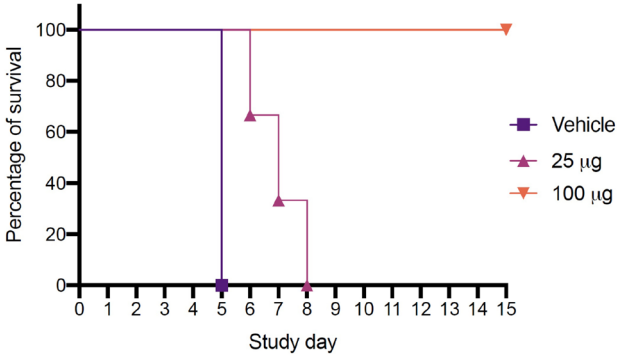

Figure 4. NL-CVX1 is effective in preventing clinically significant SARS-CoV-2 viral infection in a K18hACE2 mouse model.

Disclosures. **Matthew Walker, PhD, Neoleukin Therapeutics, Inc.** (Employee, Other Financial or Material Support, Ownership options and stock.) **Laurie Tatalick, DVM, PhD, DACVP, Neoleukin Therapeutics, Inc.** (Consultant, Other Financial or Material Support, Ownership options and stock.) **Marianne Riley, BS, Neoleukin Therapeutics, Inc.** (Employee, Other Financial or Material Support, Ownership options and stock.) **Kevin Yu, BS, MS, Neoleukin Therapeutics, Inc.** (Employee, Other Financial or Material Support, Ownership options and stock.) **Luis M. Blancas-Mejia, PhD, Neoleukin Therapeutics, Inc.** (Employee, Other Financial or Material Support, Ownership options and stock.) **Daniel-Adriano Silva, PhD, Neoleukin Therapeutics, Inc.** (Advisor or Review Panel member, Other Financial or Material Support, Ownership of Neoleukin options and stock) **David Shoultz, PhD, MBA, Neoleukin Therapeutics, Inc.** (Employee, Other Financial or Material Support, Ownership options and stock.) **Goncalo Bernardes, PhD, Neoleukin Therapeutics, Inc.** (Consultant, Advisor or Review Panel member, Shareholder) **Hui-Ling Yen, PhD, Neoleukin Therapeutics, Inc.** (Grant/Research Support)**Saiba AG** (Other Financial or Material Support, Received donation from Saiba AG)

132. Evaluation Phage Cocktails in Combination with Ciprofloxacin Against Multidrug-Resistant *Pseudomonas aeruginosa* Overexpressing MexAB-OprM Efflux Systems

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Session: O-27. Novel Antimicrobial Agents

Background. Multidrug-resistant (MDR) *Pseudomonas aeruginosa* infections are increasing in prevalence and cause significant mortality. The MexAB-OprM efflux system confers resistance to a wide range of drugs, including β-lactams, fluoroquinolones, tetracyclines, and macrolides. Obligately lytic bacteriophages (phages) are viruses that infect and kill bacteria. Phage therapy has been suggested as an alternative treatment option in combination with traditional antibiotics. The objective of this study was to determine the ability of a phage cocktail in combination with ciprofloxacin (CIP) to improve bacterial killing and/or prevent the emergence of phage resistance in MDR *P. aeruginosa*.

Methods. Initial bacterial susceptibility to phage was evaluated with three newly isolated phages (phages EM, LL, and A6) against ten clinical MDR *P. aeruginosa* isolates. Theoretical multiplicity of infection (tMOI) optimization was performed with two phages with the broadest initial susceptibility (tMOI: 1.0 chosen for further analysis). A preliminary evaluation was performed with *P. aeruginosa* R9316 (carbapenem-resistant clinical strain with MexAB-OprM overexpression, as determined previously by quantitative real-time PCR). Synergy for phage cocktail combinations ($\geq$ 2-$\log_{10}$ CFU/mL kill compared to most effective single agent at 24 h), bactericidal activity for all samples ($\geq$ 3-$\log_{10}$ CFU/mL reduction at 24 h compared to starting inoculum), and phage resistance development were evaluated in time kill analyses (TKA).

Results. R9316 is a MDR *P. aeruginosa* isolate with a CIP MIC of 2 mg/L. Phage cocktails as monotherapy had little impact on bacterial eradication (reduction: 1.19 $\log_{10}$ CFU/mL). However, the addition of CIP to phage cocktails of EM and LL phages led to synergistic and bactericidal effects (reduction: 3.92 $\log_{10}$ CFU/mL). Furthermore, phage resistance was observed in the phage monotherapy regimens. Whereas the addition of CIP was shown to prevent the emergence of phage resistance in some regimens.

Conclusion. Our results show synergistic activity and prevention of phage resistance with phage cocktail-antibiotic combinations against MDR *P. aeruginosa*. Further research is needed to determine the impact of phage cocktail therapy on additional strains and clinical outcomes.

Disclosures. **Michael J. Rybak, PharmD, MPH, PhD, Paratek Pharmaceuticals** (Research Grant or Support)

133. ARGONAUT-III: Susceptibility of Carbapenem-resistant *Klebsiellae* to Cefepime-Taniborbactam

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Session: O-27. Novel Antimicrobial Agents

Background. *Klebsiellae* are Gram-negative pathogens responsible for serious nosocomial and community-acquired infections. Carbapenem resistance, both intrinsic and acquired, complicates therapy. Taniborbactam (formerly VNRX-5133; Fig 1) is a bicyclic boronate β-lactamase inhibitor (BLI) that inhibits all four Ambler classes of β-lactamase enzymes, both serine- and metallo-, with the notable exception of class B IMP β-lactamases. Taniborbactam is currently undergoing phase 3 clinical trials in combination with cefepime (FEP; Fig 1) as part of the β-lactam-BLI (BL-BLI) combination FEP-taniborbactam (FTB).

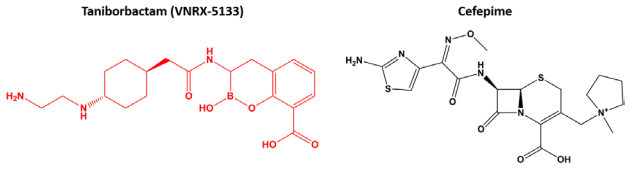

Figure 1. Structures of taniborbactam and cefepime. The β-lactamase inhibitor is in red and the β-lactam antibiotic is in black.

Methods. We determined the activity of FTB against 200 carbapenem-resistant *Klebsiellae* (CRK) strains collected as part of the Antibiotic Resistance Leadership Group (ARLG) Consortium on Resistance against Carbapenems in *Klebsiella* (CRACKLE) study. Among these strains, 193 expressed class A KPCs, one expressed a class B NDM, and six expressed class D OXA-48 or variants. Broth microdilution minimum inhibitory concentrations (MIC)s were determined using the ThermoFisher Sensititre system with custom assay panels. American Type Culture Collection strains were used for quality control. The susceptible-dose-dependent breakpoint for FEP was provisionally used for FTB, where taniborbactam was fixed at 4 μg/mL.

Results. Among the 200 *Klebsiella* strains tested, susceptibility for β-lactams alone ranged from 1% for ceftazidime (CAZ), 2.5% for meropenem, and 13.5% for FEP (Table 1). The addition of BLIs increased % susceptibility compared to BL alone to: 98% for CAZ-avibactam (CZA); 95.5% for MEM-vaborbactam (MVB); and 99.0% for FTB. MIC_{50} and MIC_{90} were in the susceptible and provisionally susceptible range for CZA and MVB, and in the provisionally susceptible range for FTB. Analyzing the CZA and MVB non-susceptible strains, 7 of 9 MVB non-susceptible strains and 2 of 4 CZA-resistant strains were provisionally susceptible to FTB.

	AMK	CST	CAZ	CZA	FEP	FTB	MEM	MVB	TGC
CLSI Susceptible Breakpoint	≤16	≤2*	≤4	≤8/4	≤8	≤8**	≤1	≤4/8	≤2
MIC_{50}	16	0.5	>16	1	>32	0.25	>4	≤ 0.03	1
MIC_{90}	32	>4	>16	2	>32	2	>4	1	4
%S	60	77	1	98	13.5	99**	2.5	95.5	88.5

Table 1. MIC50 and MIC90 values (μg/mL) and percent susceptibility for Klebsiella pneumoniae strains (n=200). AMK, amikacin; CST, colistin; CAZ, ceftazidime; CZA, ceftazidime-avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; MEM, meropenem; MVB, meropenem-vaborbactam; TGC, tigecycline. * The breakpoint for CST is intermediate, as no susceptible breakpoint is available. ** The susceptible-dose-dependent breakpoint for FEP alone was provisionally applied to FTB, where taniborbactam was fixed at 4 μg/mL. Breakpoints from CLSI M100, 31st ed, 2021.

Conclusion. The addition of taniborbactam restored susceptibility to FEP in 99.0% of CRACKLE isolates studied, comparable to CZA and MVB. Taniborbactam also restored FEP activity against some MVB- and CZA-resistant strains. FTB may provide a promising therapy for CRK infections.

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