The titer 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 allo-HSCT. Preliminary 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 Vacular, PhD, Seres Therapeutics (Employee) Edward O'Brien, PhD, Seres Therapeutics (Employee, Shareholder) Jessica Byrant, PhD, Seres Therapeutics (Employee, Shareholder) Mary-Jane Lombardo, PhD, Seres Therapeutics (Employee) 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) Wen Su, PhD1; Matthew Walker, PhD2; Maria Rebele, PhD3; Cong Tang, MD, PhD4; Ana R. Coelho, PhD5; Laurie Tatalick, DVM, PhD, DACVP6; Marianne Riley, BS7; Kevin Yu, BS; MS8; Luis M. Blancas-Meja, PhD9; Daniel-Adriano Silva, PhD9; David Shoults, PhD, MBA2; Goncalo Bernardes, PhD3; Hui-Ling Yen, PhD10; The University of Hong Kong, Pokfulam, Not Applicable, Hong Kong; 'Neelkein Therapeutics, Inc, Seattle, Washington; 2Institute for Molecular Medicine, University of Lisbon, Lisbon, Lisbon, Portugal; 3University of Cambridge, Cambridge, England, United Kingdom; 4Laurie Tatalick Consulting, Richmond, Virginia

Session: O-27. Novel Antimicrobial Agents

Background. Using a computational approach, NL-CVX1 was developed by Neelkein 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 spike 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 transcription 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<sub>i</sub> < 1-5 nM). When competing with hACE2, NL-CVX1 achieved 100% inhibition against hACE2 binding to the RBD of different VOC with IC<sub>50</sub> values ranging from 0.7-53 nM (Fig 2). NL-CVX1 neutralized the B.1.1.7 variant as efficiently as the original SARS-CoV-2 strain. 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 transcription 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.

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.
132. Evaluation Phage Cocktails in Combination with Ciprofloxacin Against Multidrug-Resistant Pseudomonas aeruginosa Overexpressing MexAB-OprM Efflux Systems
Dana Holzer, PharmD, AAHVAP; Katherine Levine, MSc; Natasha Bhutani, MSc;1 Razieh Kebrizai, PhD;2 Taylor Morrisette, PharmD;3 Susan Lehman, PhD;3 Jose Alexander, MD;4 Michael J. Rybak, PharmD, MPH, PhD;4 Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan; 2Wayne State University, Detroit, Michigan; 3Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA, Silver Spring, Maryland; 4AdventHealth Orlando, Orlando, FL; 5Wayne State University / Detroit Medical Center, Detroit, Michigan
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. Bactericidal activity of infection (MOI) optimization was performed on two phages with the broadest initial susceptibility (MOI: 10.0 chosen for further analysis). A preliminary evaluation was performed with P. aeruginosa R3316 (carbapenem-resistant clinical strain with MexAB-OprM overexpression, as determined previously by quantitative real-time PCR). Synergy for phage cocktail combinations (≥ 2-log CFU/mL kill compared to most effective single agent at 24 h), bactericidal activity for all samples (≥ 3-log CFU/mL reduction at 24 h compared to starting inoculum), and phage resistance development were evaluated in time kill analyses (TKA).

Results. R3316 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 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 CFU/mL). Furthermore, phage resistance was observed in the phage cocktail regimens. 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).