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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.

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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).

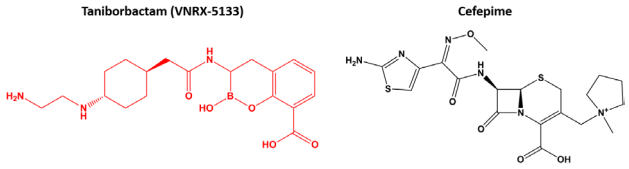

Figure 1. Structures of taniborbactam and cefepime. The β-lactamase inhibitor is in red and the β-lactam antibiotic is in black.

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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134. KRP-A218, an Orally Active and Selective PI4KB Inhibitor with Broad-Spectrum Anti-Rhinovirus Activity, Has Potent Therapeutic Antiviral Activity *In vivo*

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Session: O-27. Novel Antimicrobial Agents

Background. Rhinovirus (RV) is a major respiratory virus that poses a threat to immunocompromised people and those with underlying disease. However, there are no approved therapies. Moreover, RV infection cannot be prevented by a vaccine because there are over 100 serotypes. Here we report the pharmacological profile of a novel small-molecule host-targeted antiviral (HTA), KRP-A218 (A218). A highly potent and selective inhibitor of phosphatidylinositol 4 kinase beta (PI4KB), a key host factor of RV replication, A218 is undergoing clinical study.

Methods. *in vitro* antiviral activities of A218 and Vapendavir (Vap), a virus-targeted antiviral, were examined by inhibition of CPE, viral load, or replication. *in vivo* antiviral activity and pathological analysis of A218 were examined in coxsackievirus B3 (CVB3; belong to the genus enterovirus as with RV)-infected mice as a surrogate model of RV infection as CVB3, unlike RV, replicates very well in both mouse and human tissue. Daily oral dosing of A218 (1-10 mg/kg) was started 2 days post intraperitoneal infection with CVB3. Tissue viral load, pancreas pathological change at 4 days post infection, and survival rate up to 14 days were evaluated. PI4KB heterozygous kinase-dead mice (PI4KB KD) were established by a CRISPR-Cas9 system. Viral load and survival rate following viral infection were evaluated in these mice.

Results. A218 showed broad antiviral activity for RV and enteroviruses (Table) and has a higher barrier to drug resistance than Vap. These results are consistent with expectations for HTAs. Repeated dosing of A218 starting 2 days post infection decreased viral load and improved acute pancreatitis, accompanied by decrease of inflammatory and pancreatitis markers in plasma. Moreover, therapeutic dosing of A218 improved survival rate in a CVB3-infected lethal mouse model (Figure). These results show the first evidence that a PI4KB inhibitor has potent therapeutic efficacy in a severe viral infection model. Similar effects were observed in PI4KB KD, supporting the on-target effect of A218.

Table. Antiviral activity of A218 and Vap against RV/EV infection

Antiviral activity

Virus types		EC_{50} (nM)	
		A218	Vap
Rhinovirus	RV-A1B	63	3.6
	RV-A16	44	37
	RV-A39	45	3.2
	RV-A45	42	> 1,000
	RV-B14	73	30
	RV-B52	77	34
	RV-B69	43	33
	RV-C15	19	> 10,000
Enterovirus	EV-A71	41	7,300
	CV-A6	66	340
	CV-B3	53	> 10,000
	CV-B4	25	4,000
	EV-D68	60	210

Antiviral activity (CPE assay) against RVs and EVs except for RV-C15 (replicon assay).

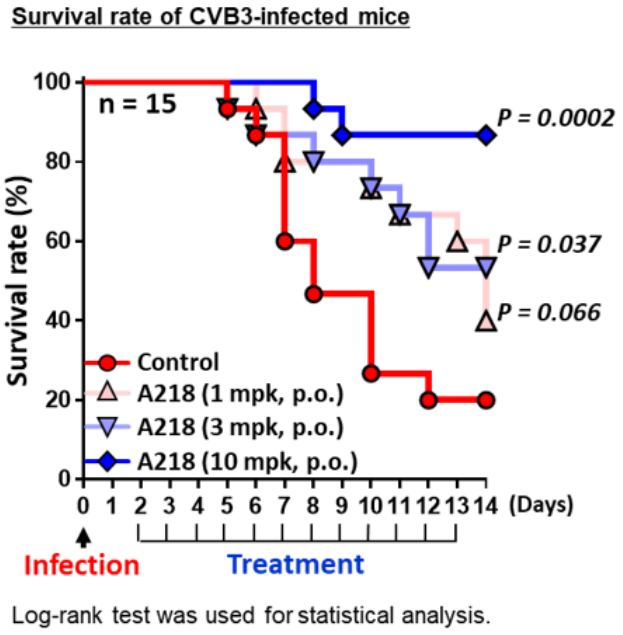

Figure. Therapeutic effect of A218 on survival rate in CVB3-infected mice

Conclusion. A218 is a promising therapeutic agent for improving the exacerbation of pathological conditions caused by RV infection. Nonclinical package including GLP-Tox also supports the ongoing first-in-human study of A218.

Disclosures. **Toshiyuki Matsui, MPharm**, **Kyorin pharmaceutical Co., LTD** (Employee) **Motomichi Fujita, PhD**, **Kyorin Pharmaceutical Co., Ltd.** (Employee) **Yuji Ishibashi, PhD**, **Kyorin Pharmaceutical co., ltd.** (Employee) **Tyzoon Nomanbhoy, PhD**, **ActivX Biosciences** (Other Financial or Material Support, Full time employee of ActivX, a wholly owned subsidiary of Kyorin Pharmaceuticals) **Jonathan S. Rosenblum, PhD**, **ActivX Biosciences** (Employee) **Michiaki Nagasawa, PhD**, **Kyorin Pharmaceutical Co., Ltd** (Employee)

135. Association Between Implementation of the Centers for Medicare & Medicaid Services Sepsis Performance Measure (SEP-1) and Outcomes in U.S. Hospitals

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CDC Prevention Epicenters

Session: O-28. Practice Issues

Background. In October 2015, CMS began requiring U.S. hospitals to report compliance with the Severe Sepsis/Septic Shock Early Management Bundle (SEP-1). We evaluated the impact of SEP-1 implementation on sepsis treatment patterns and outcomes using detailed clinical data from diverse hospitals.

Methods. We conducted a quasi-experimental interrupted time-series analysis of adults admitted to 114 hospitals in the Cerner HealthFacts dataset from October 2013-December 2017 with suspected sepsis (defined by blood culture orders, SIRS criteria, and acute organ dysfunction) within 24 hours of hospital arrival. The primary outcome was quarterly short-term mortality rates (in-hospital death or discharge to hospice). Secondary outcomes included lactate testing and administration of anti-MRSA or anti-Pseudomonal beta-lactam antibiotics within 24 hours of hospital arrival. Generalized estimating equations with robust sandwich variances were used to fit logistic regression models to assess for immediate SEP-1 impact and changes in quarterly trends after October 2015, adjusting for baseline characteristics and severity-of-illness.

Results. The cohort included 117,510 patients with suspected sepsis on admission. Lactate testing rates increased over the study period (61.9% pre-SEP-1 vs 77.9% post-SEP-1) with a significant immediate increase in risk-adjusted testing rates after SEP-1 (OR 1.34, 95% CI 1.04-1.74) (Figure 1). There was also an increase in utilization of anti-MRSA (20.6% pre vs 23.2% post-SEP-1) and anti-Pseudomonal antibiotics (30.1% vs 39.8%), %), but these trends began before SEP-1 implementation. Unadjusted short-term mortality was similar in the pre vs post-SEP-1 periods (20.3% vs 20.4%). SEP-1 was not associated with either an immediate change (OR 0.94, 95% CI 0.68-1.29] or quarterly trend change (OR 1.00, 95% CI 0.97-1.04] in risk-adjusted short-term mortality (Figure 2).