RP557 Exhibits Broad Empiric Activity Against MDR Bacterial and Fungal Wound Pathogens Including *P. aeruginosa* and *A. baumannii*

MHSRS-26-4614
MHSRS Conference 2026

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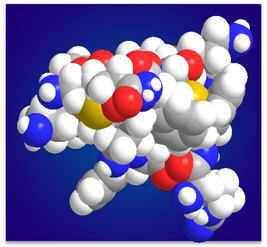
Background

Combat-related trauma and prolonged field care increasingly involve infections caused by multidrug-resistant (MDR) Gram-negative pathogens, particularly *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which drive morbidity, delayed evacuation, osteomyelitis, and limb-threatening complications. Treatment is limited by widespread antibiotic resistance, including the emergence of colistin-resistant strains, despite colistin's toxicity-restricted role as a last-line agent. New empiric, field-relevant antimicrobials are urgently needed.

Methods

RP557 is an engineered antimicrobial peptide with broad-spectrum activity against Gram-positive and Gram-negative bacteria, fungi, and biofilm.[1-4] RP557 has demonstrated efficacy in multiple infection models, including polymicrobial full-thickness porcine burns, resistant MRSA ABSSSI,[1] vulvovaginal candidiasis,[2] and MRSA biofilm-infected diabetic wounds,[4] with reduced inflammation and accelerated healing. To further support empiric treatment, RP557 was evaluated against 20 clinical isolates each of *A. baumannii* and *P. aeruginosa*. MICs were determined by CLSI-standard broth microdilution.[5-6] Comparator agents included colistin, levofloxacin, meropenem, and tobramycin.



RP557 is an amphipathic 17-amino acid α-helical peptide rationally designed from three iterative designed cycles, including pathogen cytotoxicity and safety evaluation. RP557 is conformationally locked by two disulfide linkages that are integral to its enhanced activity and stability. RP557's physicochemical features selectively perturb the barrier function of the predominantly anionic pathogen membrane, ensuring that bacterial resistance is less likely to develop.

Results

Potent RP557 Activity Against MDR Gram-Negative Pathogens

Activity Summary (μg/mL) of RP557 & Comparators

Organism	Test Agent	MIC Range	MIC_{50}	MIC_{90}	%S	%R
P. aeruginosa	RP557	0.25 – 4	1	1	NA	NA
	Colistin	0.25 – >16	0.25	0.5	95%	5%
	Levofloxacin	0.25 – >16	>16	>16	20%	80%
	Meropenem	0.25 – >16	16	>16	20%	80%
	Tobramycin	0.25 – >16	8	>16	40%	50%
A. baumannii	RP557	0.5 – 4	1	2	NA	NA
	Colistin	0.06 – >16	0.25	4	80%	20%
	Levofloxacin	0.06 – >16	16	>16	5%	90%
	Meropenem	0.5 – >16	>16	>16	5%	95%
	Tobramycin	0.25 – >16	>16	>16	30%	60%

MIC, minimum inhibitory concentration. MIC_{50}, concentration inhibiting 50% of isolates. MIC_{90}, concentration inhibiting 90% of isolates. NA, not applicable: %S, percentage of isolates that are susceptible according to established CLSI breakpoints. %R, percentage of isolates that are resistant according to established CLSI breakpoints.

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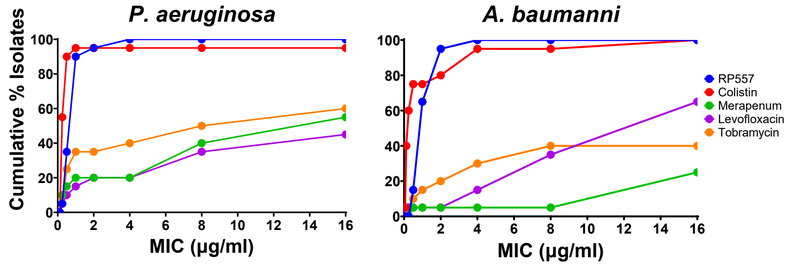
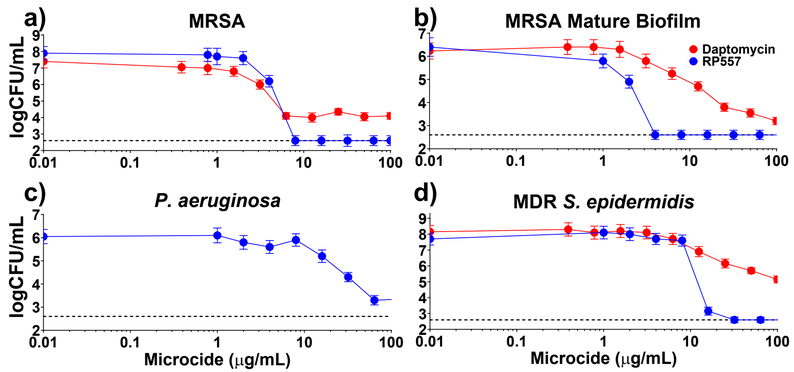
RP557 is Potent against MDR *A. baumannii* & *P. aeruginosa*

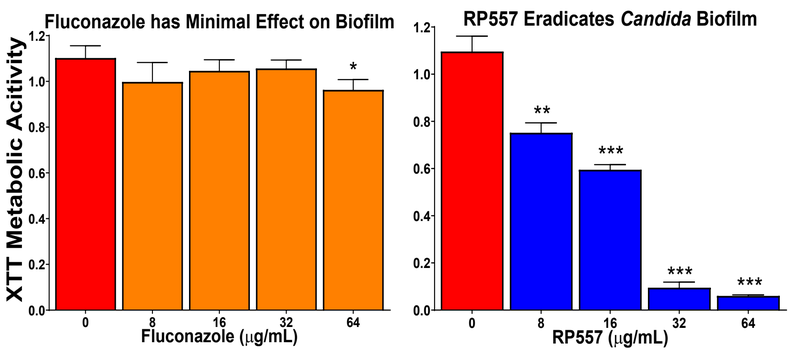


Finlandograms showing cumulative susceptibility to RP557 and clinical comparators. RP557 displayed a tight MIC range, including in colistin-resistant isolates, with no MIC increases in highly resistant phenotypes. Colistin's severe nephrotoxicity and neurotoxicity limit its last-line use, underscoring the need for safer agents.

RP557 Disrupts Preformed & Mature Biofilm

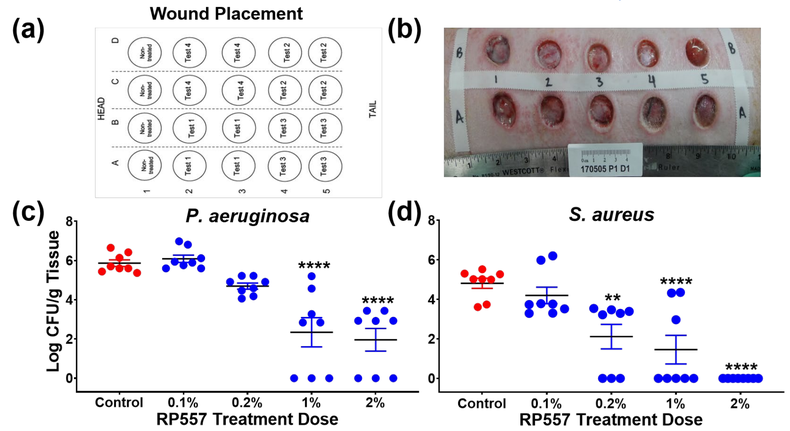


RP557 disrupts *P. aeruginosa*, MDR *S. epidermidis* and MRSA biofilms, including mature biofilm. Dose-dependent response of RP557 against 6 hr *P. aeruginosa* P14, MDR *S. epidermidis* 700578, MRSA 1556, and mature MRSA 1556 biofilms. Biofilms were established and then treated overnight and then CFUs evaluated.[1] Three technical replicates were performed for each condition tested. The dashed lines represent the lower limit of detection (LLOD) which is 2.6 logCFU/mL.



RP557 is a potent inhibitor of *Candida* biofilm. Fluconazole & RP557 were added to *Candida* 17-88 biofilm for 24 hrs & inhibition evaluated. Data represent the mean±SD of triplicate measurements and statistical significance, compared to Vehicle control, determined by one-way ANOVA followed by Dunnett's test (*p < 0.05, **p < 0.01, and ***p < 0.001).

Potent RP557 Bactericidal *In Vivo* Activity



RP557 topical treatment reduces polymicrobial infection in an infected porcine burn model. Full thickness wounds were created with a heated brass rod and a trephine on the back of anesthetized pigs followed by infection with 2:2:1 mixture of *S. aureus* ATCC 6538 and *P. aeruginosa* and *fusobacterium ssp*; **(a)** and **(b)**. After 3 hrs, 0, 0.1, 0.2, 1 or 2% RP557 was applied. After 24 hrs, wounds were sampled and *P. aeruginosa* **(c)** and *S. aureus* **(d)** bacterial counts, evaluated. Data expressed as mean±SE of 8 replicates. Statistical significance, compared to Vehicle, determined by one-way ANOVA followed by Dunnett's test (**p < 0.01, ****p < 0.0001).

Conclusions

RP557 has the following favorable characteristics to prevent & treat wound infections on the front line;

- ✓ Broad spectrum antimicrobial and antifungal activity,
- ✓ Effective against MDR Gram-negative and Gram-positive bacteria,
- ✓ Reduced likelihood of developing pathogen resistance,
- ✓ Able to eradicate biofilm, &
- ✓ Reduces infection in a polymicrobial thermal wound.

RP557 is a promising empiric therapeutic candidate for combat trauma, prolonged field care, and operational military settings.

References

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3. Woodburn KW, Jaynes JM, Clemens LE (2020) Designed antimicrobial peptides against trauma-related cutaneous invasive fungal wound infections. *J Fungi*. 6(3):184
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