Using synergy to enhance pharmacodynamic properties of existing and emerging classes of antibiotic

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Introduction

- Any new class of antibiotic will be more successful if it can outperform existing antibiotics in activity, efficacy or speed of infection resolution
- Lower risk of resistance or cross resistance development is also desirable
- Most clinically relevant antibiotics are weakly bactericidal and the dose response that describes this activity is characterised by poor cooperativity – a property that is thought to increase risk of resistance developing – *can we use synergy to increase bactericidal killing rates and/or cooperativity?*
- In nature, a major contribution to protection against disease typically comes from families of host defence peptides (HDPs), of which a subset are potent antimicrobial peptides (AMPs) – *do AMPs have the properties we desire and what is the evolutionary benefit to producing a family of peptides?*

Pseudomonas aeruginosa

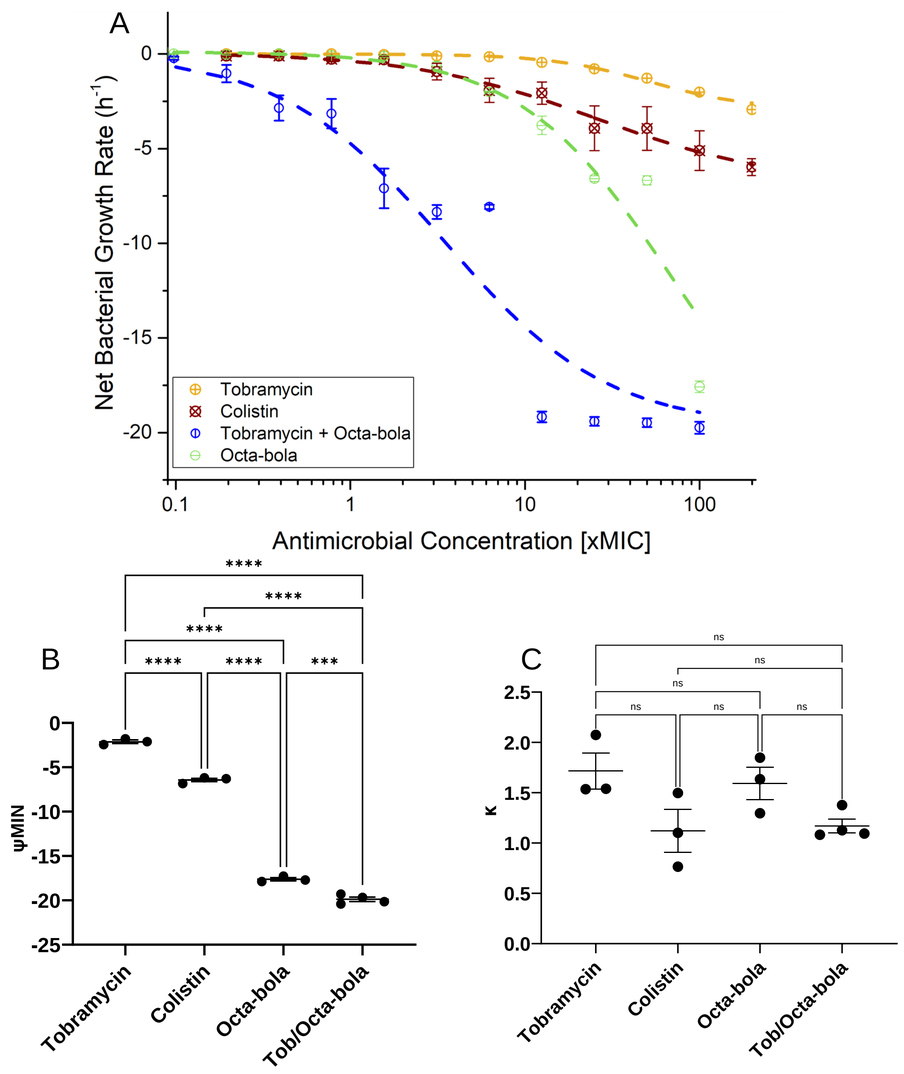

Figure 1: Synergy with a bolalipid enhances the bactericidal killing rate of tobramycin against *P. aeruginosa* RP73. Pharmacodynamic curves are an average fit of three independent repeated experiments (A). One-way ANOVA with Tukey post-hoc test multiple comparisons for ψ_{min} (B) and κ (C), highlight the differences in bactericidal rate but not cooperativity between the conditions. ns $p > 0.05$; *** $p < 0.001$; **** $p < 0.0001$.

Acinetobacter baumannii

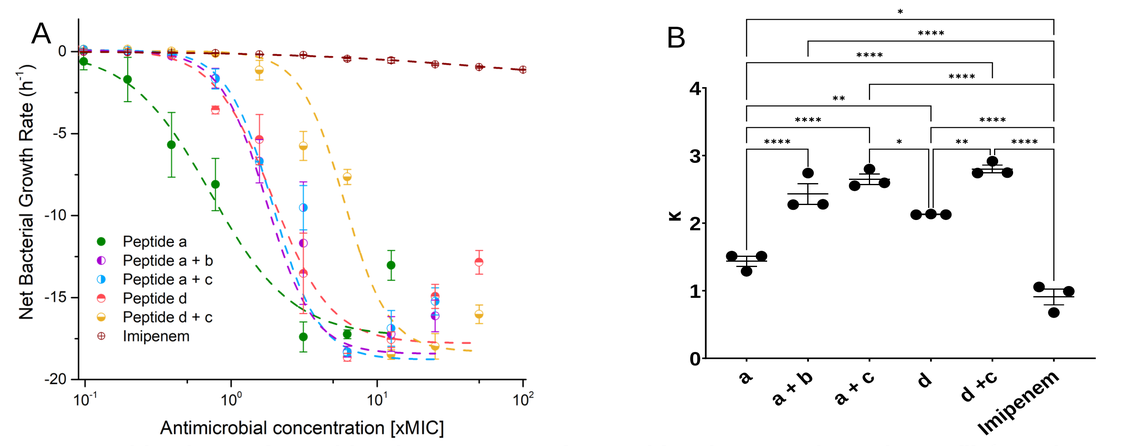

Figure 2: Combinations of peptides have a more favourable pharmacodynamic profile[1] against *A. baumannii* AYE than individual peptides and imipenem. Curves are an average fit of three independent repeated experiments (a). One-way ANOVA with Tukey post-hoc test multiple comparisons for κ (B) highlight the difference in cooperativity between the conditions. * < 0.05, ** p < 0.01, *** $p < 0.001$; **** $p < 0.0001$.

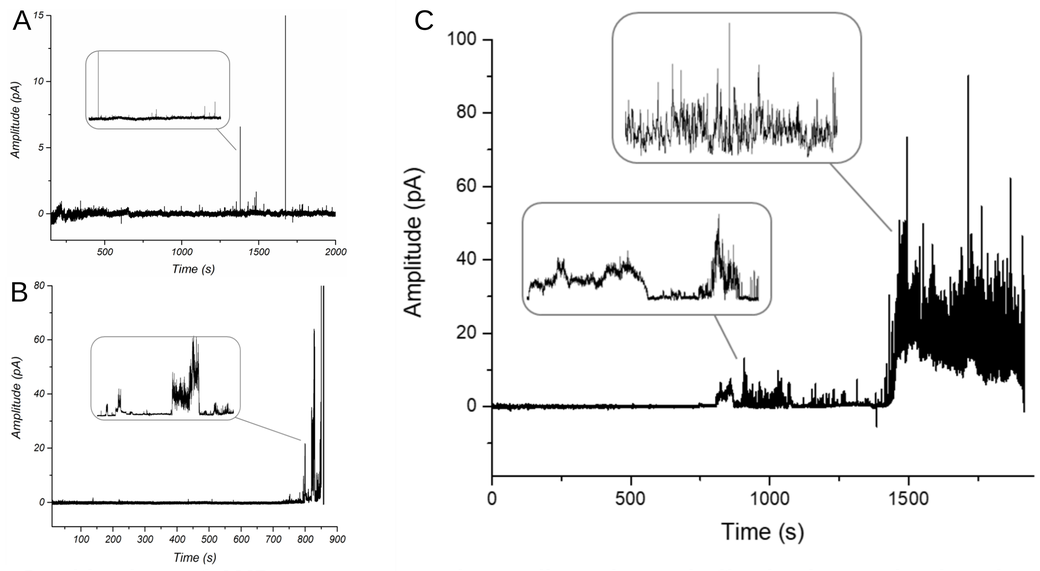

Figure 3: Combinations of AMPs are more membrane disruptive and effective in creating ion channels in models of bacterial membranes[2]. Traces are representative of 6 replicates of peptide *b* at 15 μM (A), peptide *a* at 7.5 μM (B) and a combination of peptides *b* at 5 μM and *a* at 3.75 μM (C) in DPhPEPG (60:40) membranes.

Conclusion

- Cooperative bactericidal action reduces the sub-inhibitory MIC range of drug that bacteria are exposed to which is hypothesised **to minimize development of antimicrobial resistance.**
- Synergism between a cationic bolalipid compound and tobramycin does not influence cooperativity of bacterial killing but rather effects a drastic improvement in the potency and rate of bactericidal activity.
- AMPs are highly bactericidal and are more cooperative at killing bacteria than conventional antibiotics.
- Combinations of AMPs exhibit an even **more cooperative** pharmacodynamic profile.
- Combinations of peptides are more **membrane damaging** in patch-clamp than individual peptides alone and at lower concentrations. This implicates the **synergistic membrane damaging** effect as responsible for the gain in potency and more favourable pharmacodynamic properties.

References

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2. Sekiya, Y., Sakashita, S., Shimizu, K., Usui, K., & Kawano, R. (2018). Channel current analysis estimates the pore-formation and the penetration of transmembrane peptides. *Analyst*, *143*(15), 3540–3543. https://doi.org/10.1039/c8an00243f
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