Autoinducer-antibiotic conjugates - a Trojan horse approach to antibiotic resistance

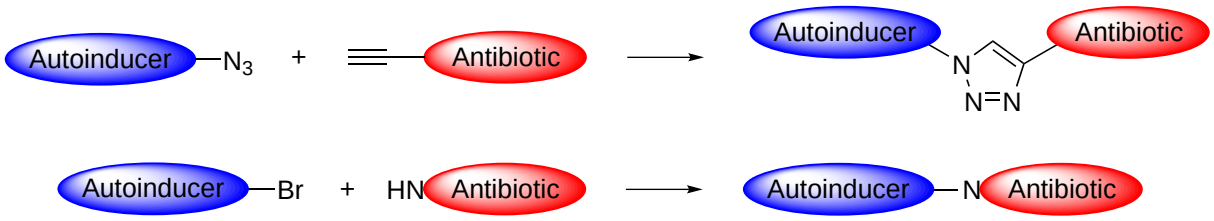
Lois M. Overvoorde[1], Ysobel R. Baker[2] and David R. Spring[1]

[1]University of Cambridge, [2]University of Oxford

Many bacteria use quorum sensing to coordinate behaviours such as swarming, virulence factor production and biofilm formation.[1] They communicate via the excretion and uptake of small molecules known as autoinducers.

With our library of autoinducer-antibiotic conjugates, we aim to hijack the autoinducer uptake apparatus to facilitate the influx of known antibiotics, in a strategy that has already successfully been employed with sideophore-antibiotic conjugates.[2]

We focus on the autoinducers produced by *Pseudomonas aeruginosa* as it is a significant human pathogen[3] which displays high resistance to many antibiotics[4] and uses quorum sensing to coordinate its group behaviours.[5] Derivatives of these autoinducers are coupled with derivatives of ciprofloxacin using either a copper(I)-catalysed azide-alkyne cycloaddition[6,7] or an S_N2 reaction. Ciprofloxacin was chosen as it is commonly used against *P. aeruginosa*[8] but resistance to it is developing.[9] It is hoped that the autoinducers will deliver the attached ciprofloxacin into the cell, thus potentially increasing its potency or even restoring its efficacy against resistant strains.



Funding sources

EPSRC PhD funding.

References

[1] C. M. Waters and B. L. Bassler. Quorum sensing: cell-to-cell communication in bacteria. *Annu. Rev. Cell Dev. Biol.*, 21:319–346, 2005.

[2] M. G. P. Page. Siderophore conjugates. *Ann. N. Y. Acad. Sci.*, 1277:115–126, 2013.

[3] G. P. Bodey, R. Bolivar, V. Fainstein and L. Jadeja. Infections caused by *Pseudomonas aeruginosa*. *Rev. Infect. Dis.*, 5(2):279–313, 1983.

[4] K. Poole. Efflux-mediated multiresistance in Gram-negative bacteria. *Clin. Microbiol. Infect.*, 10:12–26, 2004.

[5] J.-F. Dubern and S. P. Diggle. Quorum sensing by 2-alkyl-4-quinolones in *Pseudomonas aeruginosa* and other bacterial species. *Mol. Biosyst.*, 4(9):882–888, 2008.

[6] C. W. Tornøe, C. Christensen and M. Meldal. Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J. Org. Chem.*, 67(9):3057–3064, 2002.

[7] V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless. A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chemie Int. Ed.*, 41(14):2596–2599, 2002.

[8] A. P. Macgowan, M. Wootton and H. A. Holt. The antibacterial efficacy of levofloxacin and ciprofloxacin against *Pseudomonas aeruginosa* assessed by combining antibiotic exposure and bacterial susceptibility. *J. Antimicrob. Chemother.*, 43:345–349, 1999.

[9] H.-C. Su, K. Ramkissoon, J. Doolittle, M. Clark, J. Khatun, A. Secrest, M. C. Wolfgang and M. C. Giddings. The development of ciprofloxacin resistance in *Pseudomonas aeruginosa* involves multiple response stages and multiple proteins. *Antimicrob. Agents Chemother.*, 54(11):4626–4635, 2010.