Hybrid antibacterials:
A strategy to improve potency and spectrum

Shelley Parrott[1], Alastair Parkes[1], Martin Arthuis[1], David Corbett[1], Alain Dorali[1], Stephen East[1], Marta Pinto[1], Stephanie Sandiford[1], Peter Warn[1], Mark Whittaker[1], Helen Williams[1], Dan Kahne[2], Yuan Qiao[2], Marina Santiago[2], Veerasak Srisuknimit[2], Suzanne Walker[2], Alan Yang[2]

[1] Evotec (UK) Ltd, 114 Milton Park, Abingdon, OXON, OX14 4RZ, United Kingdom
[2] Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States
E-mail: Alastair.Parkes@evotec.com

This work aims to improve the antibacterial activity and enhance the spectrum of a series of bacterial peptidoglycan glycosyltransferase (PGT) inhibitors that currently only show moderate Gram-positive antibacterial activity. We reported in a recently published review that hybridisation of antibacterial compounds can affect their activity, particularly with regard to penetration of the outer envelope of Gram-negative bacteria.[1] Early results suggest that hybridisation of our small molecule antibacterial compounds with other small molecules can increase access to their targets in Gram-negative bacteria. We aim to expand on the promising results achieved thus far using a hybridisation strategy, by synthesising and testing a series of hybrids using different linkers and partner molecules.

Positive results of the work would be a better understanding of how to improve penetration of small molecules into Gram-negative bacteria. We also aim to produce several molecules with Gram-negative antibacterial activity but with distinct MOAs from those in currently available antibiotics.

References

[1] Alastair L. Parkes, Ian A. Yule, Expert Opinion on Drug Discovery, **Vol. 11, 7**, 665-680 (2016).