**Improving antibiotics through a novel click-to-release unmasking mechanism at the infection site**

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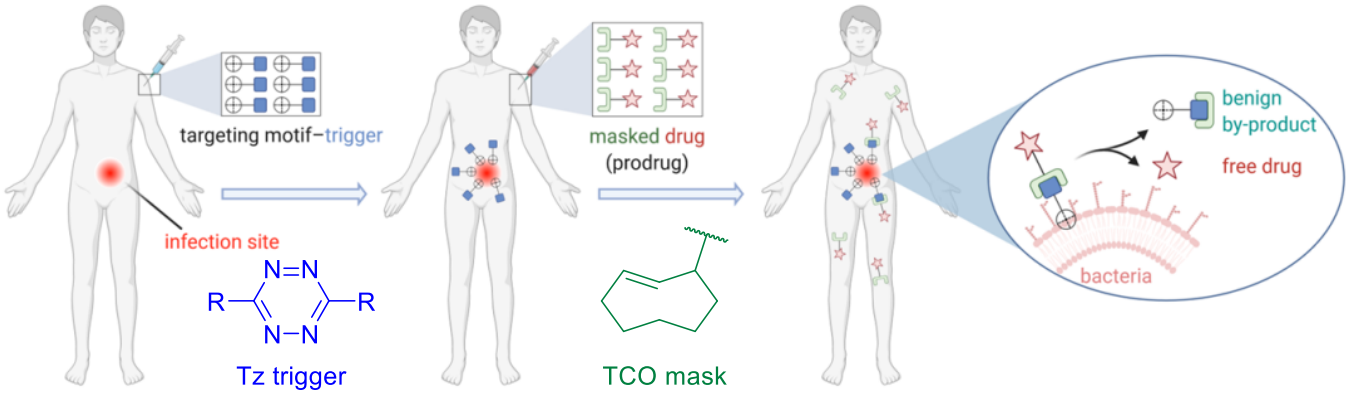
Antimicrobial resistance (AMR) is one of the greatest threats the world is currently facing. The lack of new classes of antibiotics prompted a revisit to last-resort antibiotics like colistin. While colistin is highly effective, it can produce severe adverse effects, including nephro- and neurotoxicity.[1] To reduce the side-effects, we are developing the "click-to-release" approach to only locally release an antibiotic from its masked form (i.e. a prodrug) at the infection site by employing a targeting exogenous trigger. Related variants of this concept have been established recently for tumour treatments but have not been applied in infectious diseases.[2,3]




A small library of bioorthogonal triggers and masks were generated for screening of their click-to-release kinetics. Regioisomeric mixtures of masked colistin were then synthesised and tested in an antibacterial assay against *E. coli* with their appropriate triggers. Based on the kinetic studies and the MIC assay results, the use of inverse-electron-demand Diels–Alder (IEDDA) reaction between a *trans*-cyclooctene (TCO) as the mask and a tetrazine (Tz) as the trigger provided the best results of restoring the antibacterial activity. Currently, we are optimising the toxicity profile of the TCO–colistin derivatives and investigating the use of ubiquicidin (29-41) peptide as the targeting motif, which we have previously utilised in our previous work.[4]

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