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Probiotic delivery for antibiotic resurrection via programmable RNA-guided endonuclease inactivation of resistance genes

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We use bacterial cybergenetics to resurrect sensitivity to antibiotics in antimicrobial resistant (AMR) pathogens. Our "Nemesis Symbiotics", use a programmable RNAguided DNA endonuclease gene editing technology to target beta-lactamase (*bla*) resistance genes. By multiplexing guide RNA genes, we inactivate members of eight families of bla genes –VIM, OXA, NDM, CTXM, KPC, IMP, SHV and TEM (VONCKIST), so resurrecting sensitivity to a broad range of beta-lactam antibiotics. Transmids, our novel delivery vectors can be packaged in a bacteriophage coat to introduce Symbiotics by infection. Transmids also spread to other bacteria by plasmid conjugation. In a mouse model study, we show that Transmid delivery by conjugation from a probiotic donor strain introduced into the gut microbiome disarms a resident *E. coli* strain carrying a target AMR gene giving prophylactic applications in anticipation of opportunistic infections. Our experiments suggest that multi-functional gene targeting systems may obviate the need for prior diagnostic screens for antibiotic resistance and can be used generally as a companion biological therapeutic, together with well-established antibiotics, for both therapeutic treatment of infection as well as by prophylactic treatment in preventing the spread of AMR.

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