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# E. coli's internal bomb may provide novel target for treatment strategy

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Bacteria's internal bomb, the so-called toxin-antitoxin (TA) system that is part of the normal bacterial makeup, may be triggered to make bacteria turn on themselves, providing a valuable target for novel antimicrobial approaches in drug design, according to research presented at the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID).

The TA system comprises genes that encode both a toxin and the toxin's antidote. Presenting author Dr Marcin Równicki from the Centre of New Technologies at the University of Warsaw, Poland demonstrated a potential means to stop the growth of *Escherichia coli* by targeting its TA system, called mazEF.

"Our findings suggest that mazEF toxin-antitoxin system is a potent and sensitive target or antisense peptide nucleic acids to inhibit *E. coli* growth," Równicki said. "The greatest strength of the proposed strategy is that it may work as a selective inhibitor and can precisely inhibit the growth of one type of bacteria. Also, the proposed strategy is universal and can be adapted to work on all bacteria with toxin-antitoxin systems."

Trylska's team, where Równicki works, tested two strategies for setting off this internal bomb. The first was to stop production of the antitoxin (mazE). The second was to interfere with a gene (thyA) that would indirectly trigger the toxin-antitoxin system. The team used the Mfold server, which is a bundle of software applications, to predict the secondary structures of mazE and thyA they hoped to target.

In order to activate the *E. coli* TA system, the researchers relied on antisense peptide nucleic acid (PNA) oligomers. PNAs are artificial polymers that act like DNA and can be used to alter the expression of genes. They bound the two PNAs, anti-mazE and anti-thyA, to a cell-penetrating peptide, or short-chain amino acid, which delivered the PNAs through the *E. coli*'s cell wall.

The team then examined the decay of messenger ribonucleic acid (mRNA), which carries genetic information copied from DNA, and watched for interactions between them and three antibiotics (polymyxin B, trimethoprim and sulfametoksazol). They found that both strategies resulted in concentration-dependent growth inhibition of the tested *E. coli*, which means the higher the concentration, the greater the effect on the bacteria. There was also a synergistic effect with two of the antibiotics, polymyxin B and trimethoprim.

"The antisense oligonucleotide can be designed to broaden the spectrum of activity and inhibit the growth of different types of bacteria simultaneously," Równicki explained. "Moreover, if mutations of the mRNA target appear, the sequence of the antisense oligonucleotide could be quickly redesigned to overcome resistance."

Most of the new antibiotics conform to already established classes and have the same cellular target, therefore are often subject to at least some of the same resistances observed in previous members of the class. For that reason, looking for new targets is fundamental in the antimicrobial development. Antisense-based drugs are part of a growing number of pharmaceutical and biotech programmes to treat not only infectious diseases but also some types of cancer.

"We have provided proof-of-concept for the exploitation of toxin-antitoxin systems in antibacterial strategies," Równicki said. "The proposed strategy may be important in the future when designing new

classes of antibiotics, but our research is in the early stage and further investigation is a must."

**More information:** Abstract no: O0250, Detonate an internal bomb. Bacterial toxin-antitoxin systems as a target for novel antimicrobials; New drugs and tricks against MDR bacteria, 16:30 - 18:30, Saturday, 21 April 2018, Hall L

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