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NON-GENETIC METHOD FOR CONTROLLING BIOSYNTHETIC GENE CLUSTER OPERATION

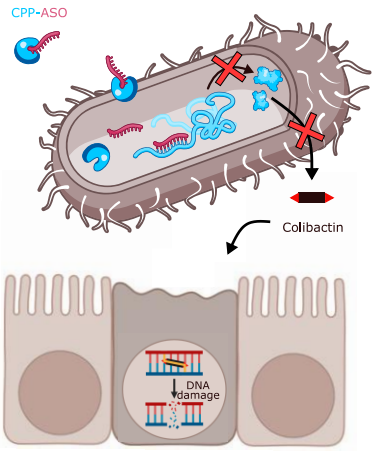
Keywords: antisense oligomers (ASOs), biosynthetic gene clusters (BGCs), secondary metabolites, colibactin, toxin suppression

INVENTION NOVELTY

Antibacterial antisense oligomers – referred to as asobiotics - have to date been primarily applied to kill pathogens by silencing mRNAs of essential bacterial genes, and more recently to target antibiotic-resistance genes, biofilm genes, or bacteriophages. The present example pioneers the use of ASOs to selectively suppress the production of bacterial secondary metabolites by targeting mRNAs of a biosynthetic gene cluster (BGC). While existing modulation strategies for BGCs rely on genetic knockouts or CRISPR-based tools that are limited to genetically tractable strains, this invention establishes ASO-mediated control as a non-genetic alternative. The targeted modulation of a transcription regulator within a cluster results in highly effective suppression, representing a conceptually new intervention principle distinct from prior art.

VALUE PROPOSITION

This technology enables precise, sequence-specific modulation of microbial metabolite output without killing host cells. Targeting non-essential genes allows the selective modulation of bacterial properties, such as toxin or metabolite production, without disrupting the overall composition of the microbiota. This could be particularly useful for the study of bacterial phenotypes or for controlling harmful commensals that contribute to host pathology under certain conditions. Applications span therapeutic suppression of toxins, silencing of virulence factors, and up-regulation of commercially valuable natural products such as antibiotics and antifungals. Because ASOs are programmable, rationally designed, and include clinically validated PMO chemistry, the technology offers broad licensing potential across therapeutics, functional genomics tools, and industrial bioproduction.



CPP-linked ASOs silence BGC expression and thereby suppress the associated genotoxic activity. © HZI

TECHNOLOGY DESCRIPTION

The method introduces one or more ASO-based constructs into a bacterial cell to modify the metabolite output of a BGC. ASOs based on peptide nucleic acid (PNA) or phosphorodiamidate morpholino oligomer (PMO) chemistry, with a length of 10 nucleobases, were conjugated to a cell-penetrating peptide (CPP) for bacterial uptake. A proof-of-concept study showed that ASO-mediated silencing of the colibactin *pks* cluster reduced BGC expression and the associated genotoxicity of the bacterium.

COMMERCIAL OPPORTUNITY

The technology has broad commercial potential in antibacterial applications, functional genomics and bioproduction. The technology is available for in-licensing and co-development.

DEVELOPMENT STATUS

Following successful proof-of-concept validation, the technology is being further developed to enhance ASO delivery and enable broader application.

PATENT SITUATION

A European patent application was filed in May 2026.

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