Generating Novel E. coli Nissle Cells Using a Reprogrammable CRISPR-Cas12 System for Targeted Drug Delivery

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Commonly used cancer treatments are nonspecific and cytotoxic to healthy cells. As an alternative, bacteria can be exploited for the targeted delivery of therapeutics as some can associate to cancer cells. The natural probiotic Escherichia coli Nissle can thrive in hypoxic and harsh conditions found in tumors, making it ideal for the targeted delivery of drugs to colorectal cancer tumors. However, uncontrolled proliferation within the human body is a major concern. In this study, to adapt E. coli Nissle for therapeutic uses, it has been modified to inhibit undesirable proliferation using a novel built-in biocontainment system that allows for the retention of intracellular functions. A two-step process was used to develop the biocontainment system. The first step involves the removal of the two endogenous plasmids by inserting a CRISPR-Cas12 plasmid cassette. This step clears the intracellular environment, allowing for the insertion of new genetic material. The second step involves cloning two plasmids with the CRISPR-Cas12 system needed to shred the native genomic material. Out of 108 Nissle colonies used in this study, three colonies showed the removal of both endogenous and CRISPR-Cas12 containing plasmids, marking the efficiency of the four-plasmid removal protocol at 2.78%. A total of 12 clonings were completed, and the newly cloned plasmids contain the CRISPR array and Cas12 enzyme needed to induce fragmentation of the chromosomes. The CRISPR-Cas12 system can be adapted to other microorganisms. This research demonstrates a CRISPR-Cas12 system establishing a novel non-toxic platform for targeted drug delivery by generating chromosome-shredded Nissle cells.

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