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Universal Transcriptional Programming in a Bacteroides Consortium Creates a Foundation to Advance Living Therapeutics

Absence of universal programming framework and stable gut microbes limits living therapeutics

Synthetic biology endeavors to genetically reprogram microbes to perform beyond their inherent capabilities, allowing them to potentially function as diagnostic tools and living therapeutic devices or regulate a host's immune system. In the case of the human microbiome, certain limitations to genetic editing exist, including the lack of a universal programming framework and organisms that are receptive to genetic manipulation. Microbes currently used in living therapeutics research have limited value due to their instability and inadequate presence in the human colon.

Universal transcriptional programming framework creates viable living therapeutics

This biotic decision-making technology uses genetic circuit compression in a *Bacteroides* community. The consortium-based transcriptional programming structure uses species of *Bacteroides* that have a significant, lasting presence in the human gut microbiome.

The programming framework demonstrates sequential gain-of-function control in a consortium of five distinct *Bacteroides* species using complete sets of logical operations. It confirms control in both heterologous and endogenous genes by coupling the transcription program with clustered regularly interspaced short palindromic repeats (CRISPR) interference. In addition, this new technology can be deployed in consortia to display concurrent, asymmetric, and sequential decision making.

Unlike Cello circuits, the current approach in gene circuit design, consortium transcriptional programming shortens circuit-building time, offers a compact circuit footprint that allows more complexity, uses fewer endogenous cellular resources, and reduces cell communication time in the *Bacteroides* community.

While this innovation still requires demonstration in a host or equivalent model system, it provides an outstanding foundation for the next generation of living therapeutics and an advanced platform to greatly enhance the study of the *Bacteroides* genus.

Summary Bullets

- Consortium-based, universal transcriptional programming framework is a biotic decision-making technology using genetic circuit compression in a *Bacteroides* community.
- Compressed genetic circuit design shortens circuit-building time, offers a compact circuit footprint that allows more complexity, uses fewer resources, and reduces cell communication time.
- Has potential applications in living therapeutics, advanced biomanufacturing, and next-generation biosecurity.

Solution Advantages

- **Less expensive:** Circuit compression decreases the resources needed to build and execute a program in a *Bacteroides* (chassis) cell.
- **More advanced:** Compression technology minimizes the genetic circuit footprint, allowing the creation of a higher complexity program.
- **Flexible:** The universality of this invention allows the writing of any program desired as long as the resource limits of the cell type are not exceeded.
- **Adaptable:** This technology may confer complex decision-making capabilities to consortia in other biotic systems.

Potential Commercial Applications

This is a flexible platform technology with multiple applications in the biotechnology field, including:

- Living therapeutics
- Diagnostics
- Advanced biomanufacturing
- Next-generation biosecurity

Inventors

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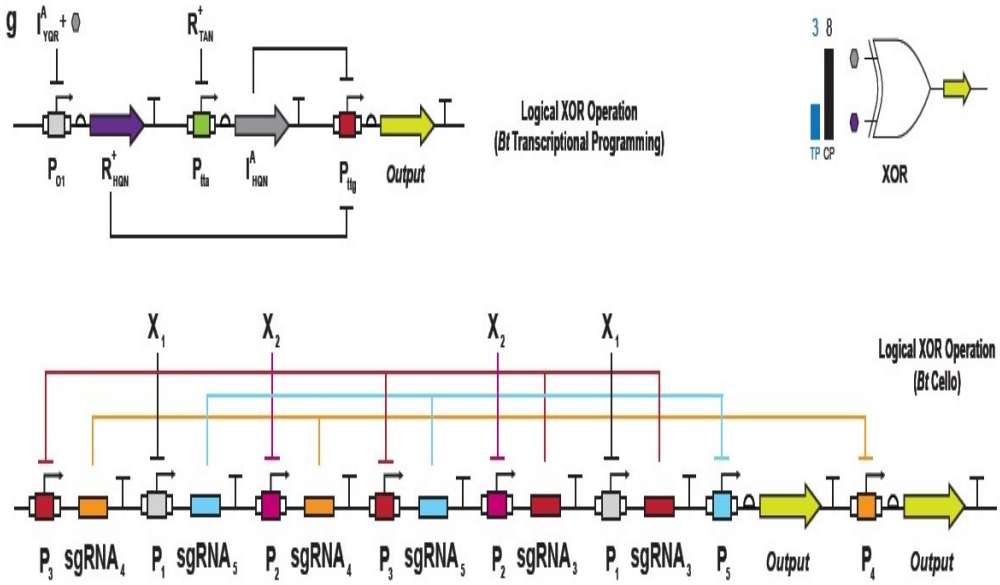
IP Status

Patent application has been filed : US63/482992

Publications

Performance Prediction of Fundamental Transcriptional Programs, ACS Synthetic Biology - March 19, 2023

Images



To illustrate circuit compression, the XOR gate is used as an example of the extent of gate compression that can be achieved via transcriptional programming, as the XOR logical operation represents the most direct comparison between Cello and transcriptional programming in the same chassis cell. In the figure, the wiring diagram for XOR construction using transcriptional programming (top) is compared to Bt Cello programming (bottom). The Cello XOR gate is composed of 8 regulated promoters and two output genes while the XOR gate constructed via transcriptional programming only requires 3 promoters and one output gene.

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