

# Editorial on CRISPR Interference Module

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## Editorial

Bacteria and archaea have evolved an innovative adaptive defence system termed CRISPR-Cas as a result of their frequent exposure to foreign nucleic acids. The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) array, as well as CRISPR (cas)-associated genes, make up the system. Sophisticated machinery incorporates pieces of foreign nucleic acids from viruses and mobile genetic elements (MGEs) into CRISPR arrays in this system. The inserted segments (spacers) are transcribed and utilised as guide RNAs by cas proteins for target recognition and inactivation. Different types and families of CRISPR-Cas systems are made up of different adaptability and effector modules with somewhat independent evolutionary paths. The origin of the effector modules, as well as the mechanism of spacer integration and deletion, is less well understood. The influence of the CRISPR-Cas system on the physiology and ecology of prokaryotes, as well as the control of horizontal gene transfer events, is examined.

After being offered as a tool for plant and animal embryo editing, cancer therapy, antibiotic against dangerous bacteria, and even combatting the novel coronavirus SARS-CoV-2 this system gained prominence; hence, the most recent and prospective uses are also covered. CRISPR and CRISPRi systems have changed our biological engineering capabilities by allowing us to customise single guide RNA (sgRNA) sequences to modify and regulate practically any gene. The dCas9-sgRNA complex represses a target transcriptional unit in CRISPRi modules, which act as programmable logic inverters. As an alternative to the commonly utilised transcriptional regulators, they have been effectively used in bacterial synthetic biology to create information processing tasks. The transfer function of numerous model systems was explored and adjusted in this study, with a particular attention on the cell load induced by the CRISPRi logic inverters. To begin, a rationally designed expression cassette for dCas9 was created to meet the low-burden high-repression trade-off.

At varied levels of dCas9 and sgRNAs targeting three separate promoters from the popular tet, lac, and lux systems, put at diverse DNA copy numbers, a circuit collection was analysed. The low-burden qualities of the CRISPRi NOT gates were used to fix a high-resource-consuming circuit with a non-functional input-output characteristic, as well as to convert a transcriptional regulator-based NOT gate into a 2-input NOR gate. The results show that CRISPRi-based modules can be used as low-burden components in a variety of synthetic information processing

circuits. The rational design of new biological functions necessitates component toolkits for the engineering of desired host organisms, as well as circuit composition guidelines to ensure predictable behaviour when parts are interconnected. Such functionalities can be accomplished based on the sensing-logic-actuation stacking of synthetic circuits to attain the normal system design complexity in the engineering world. Decoupling the application-specific sensing and actuator layers, which provide interactions with the surrounding environment, from the logic layer, which permits the designing of complicated cellular functions, is a good way to handle complexity.

Transcriptional regulators are commonly employed to build increasingly complicated synthetic circuits and to supply various logic modules that can increase the information processing capabilities of modified cells. However, various factors like as biological noise, cell burden, retroactivity, component crosstalk, and growing environment have been shown to affect the predictable performance of synthetic circuits, limiting the real complexity that may be obtained. Another significant difficulty is the scarcity of orthogonal component toolkits, which limits the scalability of circuit layouts as well as the engineering of non-model organisms. To overcome these problems, the intrinsic modularity of transcription activator-like effectors (TALEs), zinc finger transcription factors (ZF TFs), and the CRISPR system with catalytically inactive dead-Cas9 (CRISPR/dCas9 or CRISPR interference—CRISPRi) have been proposed. Given the presence of a protospacer adjacent motif (PAM) essential for system performance, one of the key advantages of CRISPRi modules over traditionally used transcriptional regulator proteins is the straightforward programmability of sgRNAs to inhibit the expression of any gene of interest. TALEs and ZFTFs have a modular structure as well, but their overall designability is still inferior.

This study established the low-burden properties of sgRNA-based logic inverters for a wide range of repression values using a large number of model systems. Two synthetic circuits were successfully repaired and upgraded using such modules. The former was a three-gene transcriptional cascade that was rendered ineffective due to a resource-intensive transcriptional regulator, which was replaced by a specific sgRNA that provided the intended function. A transcriptional regulator-based NOT gate was converted to a NOR gate by programming a second input-controlled suppression. For sgRNAs, no relevant expression-dependent burden was detected in any of the model systems studied in this study. Nonetheless, burden from target protein-coding genes, dCas9 expression, and plasmid expression may potentially alter sgRNA-based circuits.

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