Scientists develop genetic 'monitors' that detect when genes are active

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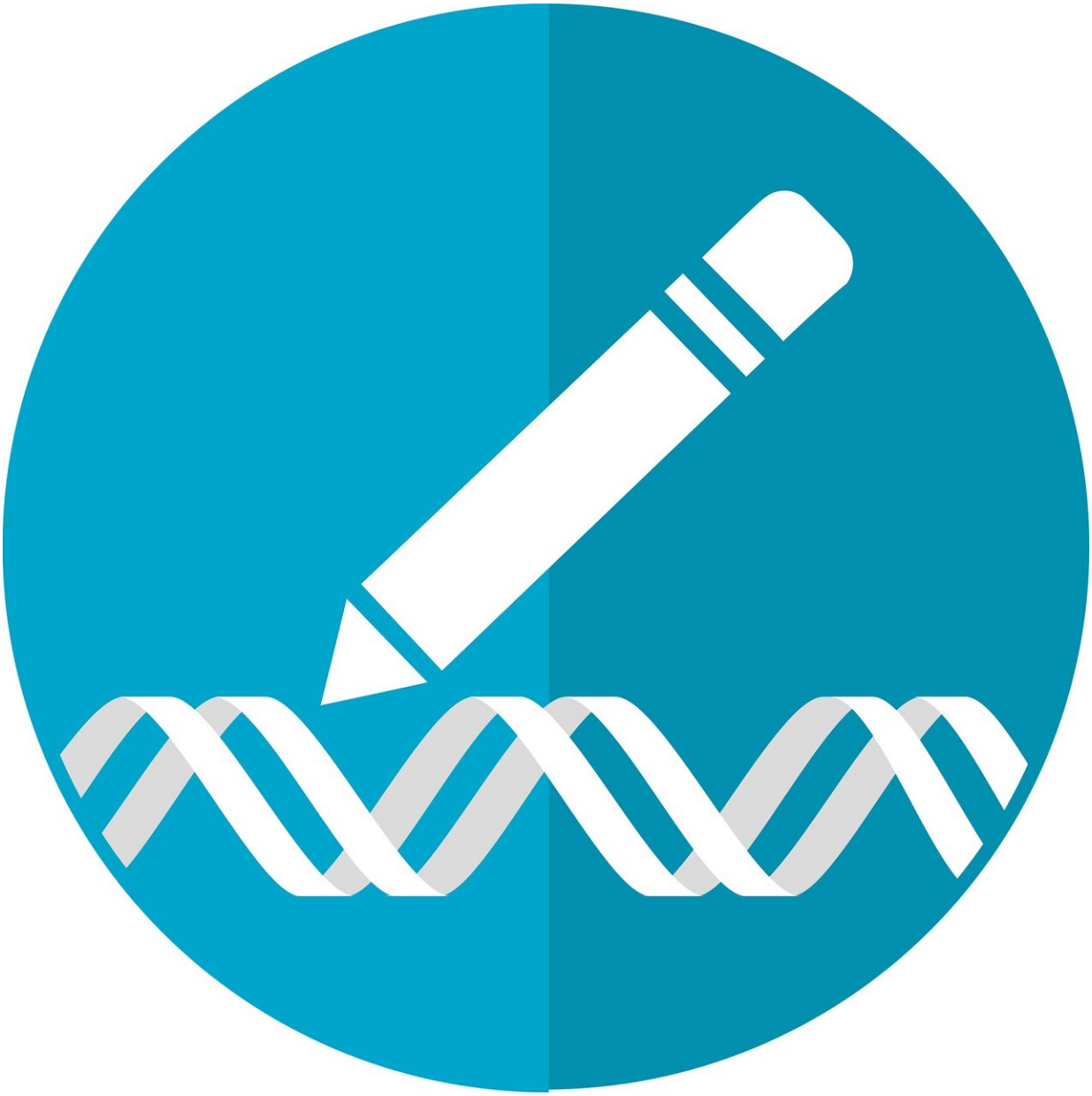

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Genetic sensors that can detect the activity from genes, rather than just the genes themselves, have been developed by a team led by University of Warwick scientists.

Based on the CRISPR gene editing system, the scientists from Warwick and Keele universities have developed microscopic machines that use these sensors to detect when genes are 'on' or 'off' inside a cell, and react to those changes dynamically—making them a potentially ideal monitoring system.

These genetic sensors are detailed in a new paper published in The CRISPR Journal, where the scientists demonstrate a genetic device based on the CRISPR system inside a bacterial cell. The work is the first step in scientists developing genetic devices that can make changes to gene expression after sensing the existing gene activity within a cell.

Lead author Professor Alfonso Jaramillo from the School of Life Sciences at the University of Warwick said, "Currently, we don't know how to design novel genetic systems to see which genes are on or off inside a cell. In nature, there are proteins that do that, they can sense the status of the cell, and the best we can do is to take those from one organism and put them in another one.

"We wanted to approach a new way of doing this, from scratch, to ask how we can program a system to listen to whatever we want inside a cell.

"Cells contain a number of genes that are expressed to perform numerous functions, from sensing their environment and processing food. By having a sensor that can detect when those genes are active,

scientists could program a machine to react to a specific process, such as when the cell digests its food."

The researchers based their genetic device on the CRISPR system which is now broadly used for a variety of gene editing applications, including gene therapies. CRISPR molecules allow scientists to target and modify specific genomic sequences within cells. The advantage of the CRISPR system is its programmability, which allows it to be redirected to virtually any genetic targets, such as genetic mutations causing diseases.

To generate these novel genetic devices, the scientists used as a scaffold the programmable part of CRISPR which is also responsible for sequence recognition and binding, called guide RNA sequence (gRNA). They were able to redesign the gRNA sequence by introducing in it a sensor so that the CRISPR complex would be able to bind the DNA target only after being activated by a trigger signal, such as short segments of viral RNA sequences. The sensor can be triggered by any chosen RNA sequence and in this way it activates a CRISPR system at any point of the life cycle of a cell or virus.

The authors tested the genetic devices also in living Escherichia coli bacteria, by introducing a fluorescent gene that they could switch on or off only after interaction between the sensing device and the triggering molecule. They further validated their system to detect an RNA molecule deriving from the HIV virus, exemplifying its potential usability in medicine.

The scientists believe their system will be useful for many researchers looking to program cells with greater sophistication, for example to generate new synthetic circuits.

Dr. Jaramillo adds, "This is quite different from gene editing, where you simply modify the genome. This is about watching the behavior of the

genome. If you have a monitor of the cell's behavior then you can make the cell correct that behavior if you don't like it, you can suppress it, or you can exploit that to switch on other genes.

"The drive is to have a genetic device able to monitor the behavior of a cell. Monitoring the behavior allows us to reprogram the cell to respond to specific signals, this is the first step towards so many other things."

Co-lead author Dr. Roberto Galizi, from the School of Life Sciences at Keele University said, "Coupling a genetic sensor with CRISPR tools offers an unprecedented opportunity for researchers to take genetic editing technologies to a completely new dimension. Eukaryotic cells could be programmed to detect deleterious mutations that may arise within its own genes, or to respond when invaded by pathogens like bacteria naturally do against phages.

"One interesting feature is that we can program these molecular tools to sense any predesigned RNA molecule in a sequence-specific manner and, at the same time, target any desirable gene or genetic sequence to stimulate various genetic actions, all within the same cell.

"Even genetic technologies aimed to control vector-borne diseases could benefit of such innovation. For example, we could engineer mosquitoes to sense and counteract pathogen transmission, or even mutations that makes vector or pest insects resistant to insecticides."

More information: Roberto Galizi et al, Engineered RNA-Interacting CRISPR Guide RNAs for Genetic Sensing and Diagnostics, *The CRISPR Journal* (2020). DOI: 10.1089/crispr.2020.0029

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