Using CRISPR to create a cell 'black box' to record cell life events

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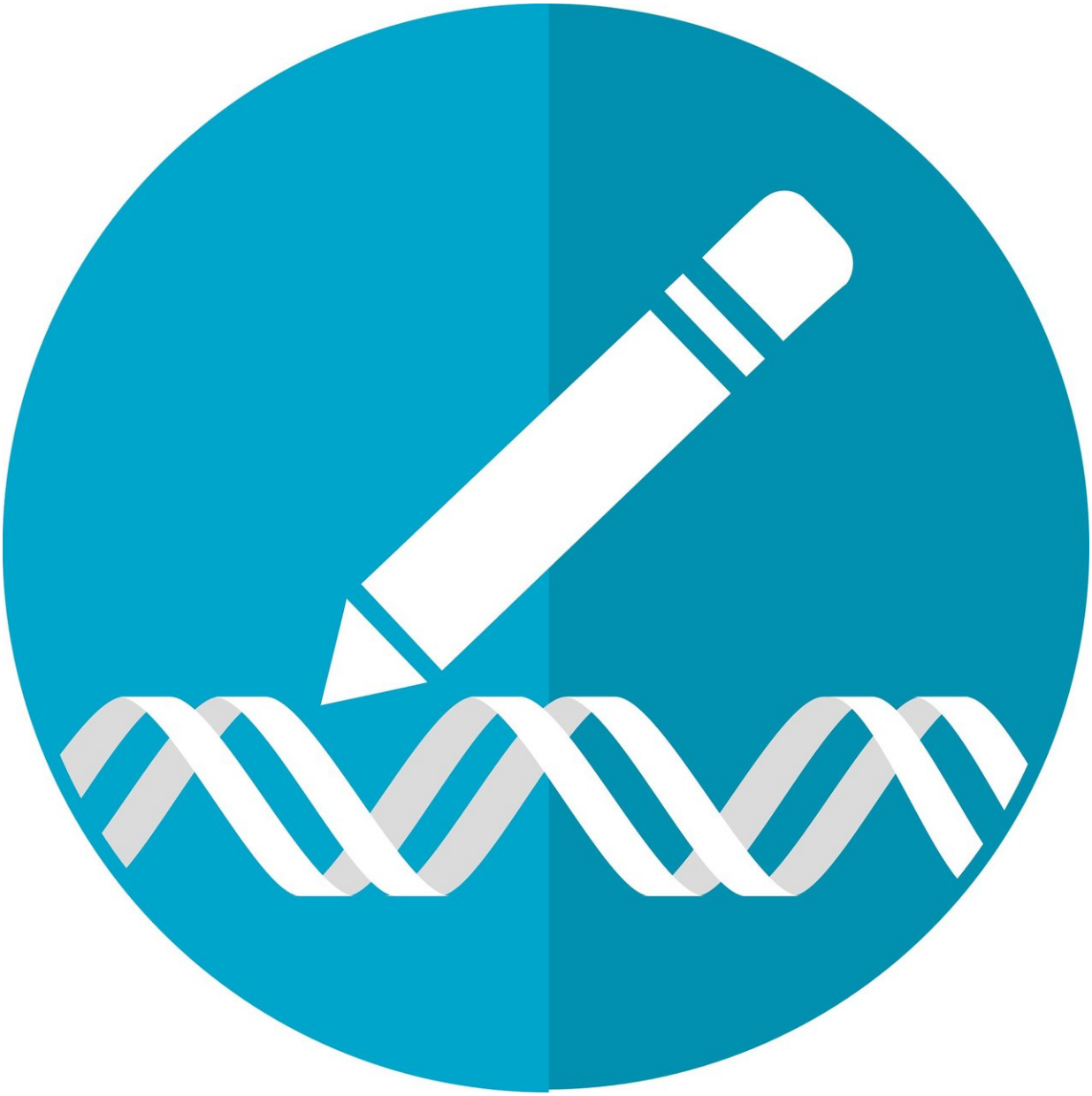

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A pair of researchers with the Broad Institute of MIT and Harvard has developed a technique that uses CRISPR to create cell event recording systems. In their paper published in the journal *Science*, Weixin Tang and David Liu describe the technique and the two recording systems they developed using it. Jon Cohen, staff writer for *Science*, also offers a look at the work done by the team in the same issue.

Scientists realized a long time ago that in order to understand how cell components work at their most basic level, they needed a way to note cell changes as they occur, along with a possible an explanation of what caused the changes to come about. In short, they needed a "black box" to record all of the events occurring over the life of a cell. Scientists have been working to develop such a black box, but so far, the results have not been encouraging. In this new effort, the researchers report on a technique they have developed called the CRISPR-mediated analog multi-event recording apparatus (CAMERA), which they have used to create two types of cell recording systems.

In the first, called CAMERA 1, the pair injected two plasmids into bacterial cells that were slightly different from one another and then used CRISPR-Cas9 to cut one of the plasmids during exposure to desired stimuli, inducing the cell to create another to replace it. Doing so created a record of the events as they occurred. This technique allowed the researchers to record how cells react to stimuli such as nutrients or antibiotics.

In the second, called CAMERA 2, the pair used base editors to change individual genetic code letters when desired signals occurred in the cell. Using this technique, they recorded how a cell reacted when exposed to

such things as viruses, nutrients and antibiotics. The technique, they report, was used successfully in both bacterial and human cells.

The next challenge for the team, as Cohen notes, will be to show that the CAMERA technique can work when engineered into the cells of a living test animal.

More information: Weixin Tang et al. Rewritable multi-event analog recording in bacterial and mammalian cells, *Science* (2018). DOI: 10.1126/science.aap8992

Abstract
We present two CRISPR-mediated analog multi-event recording apparatus (CAMERA) systems that use base editors and Cas9 nucleases to record cellular events in bacteria and mammalian cells. The devices record signal amplitude or duration as changes in the ratio of mutually exclusive DNA sequences (CAMERA 1), or as single-base modifications (CAMERA 2). We achieved recording of multiple stimuli in bacteria or mammalian cells, including exposure to antibiotics, nutrients, viruses, light, and changes in Wnt signaling. When recording to multi-copy plasmids, reliable readout requires as few as 10-100 cells. The order of stimuli can be recorded through an overlapping guide RNA design and memories can be erased and re-recorded over multiple cycles. CAMERA systems serve as "cell data recorders" that write a history of endogenous or exogenous signaling events into permanent DNA sequence modifications in living cells.