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New technique allows researchers to fine-tune gene editing

Taking advantage of advanced microscopy techniques, a team of University of Wisconsin–Madison engineers has developed a highly efficient method for more precisely editing genes in populations of cells and viewing how individual cells change, in real time. The method could increase researchers' ability to target genetic defects while leaving the rest of the genome alone.

"The ways we've been doing gene editing have been at the cell population level, without really watching how the nuclease is delivered and gets into individual cells: we typically only monitor what happens to these single cells after they get edited," says [Kris Saha](#), an assistant professor of [biomedical engineering](#) at UW–Madison. "This type of platform could potentially allow greater levels of control over how the nuclease gets in, when it is activated, which cells are the best ones to respond to nuclease treatment, maybe filtering out the cells that are responding improperly."

Saha and his collaborators published details of the advance on Jan. 12, 2016, in the [paper](#) "High-content analysis of CRISPR–Cas9 gene-edited human embryonic stem cells," in the journal *Stem Cell Reports*. They describe ArrayEdit, a highly efficient method of editing cell populations that allows for high-content imaging and analysis.

The advanced microscopy techniques provide a window into the highly complex gene editing process. Researchers can watch changes as they happen in high resolution, which opens up new possibilities for the future of gene editing.

Improved insight into gene-editing processes enables researchers to determine which editing strategies are most effective for certain stem cell populations, given how stem cells' potential, self-renewal and differentiation abilities may change after their genes have been edited. These properties often can be compromised if imprecise editing alters the genetic sequences at sites other than the defective ones. "What we're all hoping for is to go in and only correct genetic defects that we know are problematic, and leave the rest of the genome untouched," says Saha.

The CRISPR–Cas9 gene-editing tool enables researchers to disrupt a genome sequence with high precision. The tool consists of the protein Cas9 and a single-guide RNA, which work together like a scalpel to cut a target sequence within a cell's genome. ArrayEdit transforms this tool, using multiwell plates that each contain transcribed single-guide RNAs that allow researchers to separate edited cell populations. The multiwell plates rely on surface chemistry techniques developed in the Wisconsin Institute for Discovery by Saha's colleague [Randolph Ashton](#), an assistant professor of biomedical engineering at UW–Madison.

"The platform allows us to spatially localize edited cells on a surface, such that we can come back to that same cell, cell aggregate or embryonic structure many times using a microscope," Saha says. "That allows us to watch the process unfold, of not only the gene editing but also effects on a cell's phenotype—its observable characteristics—after editing. It's powerful because it allows us to quickly ascertain changes in cell behavior from a very specific gene editing event."

He and his collaborators used a gene called laminin- α -5 as a template to test the efficacy of ArrayEdit. These genes were targeted by the single-guide RNAs in the multiwell plates, which are meant to disrupt the genes' functionality.

"The editing disrupted both copies of that gene at very high levels, so about a third of the colonies that we isolated had both copies of laminin- α -5 disrupted," he says. "That type of efficiency has not been seen before."

The paper was also authored by graduate students Jared Carlson–Stevermer, Benjamin Steyer and Arezoo Muvaghar, as well as undergraduate assistants Madelyn Goedland, Meng Lou, Lucille Kohlenberg and Ryan Prestil. An [additional paper](#) also published in January 2016, "High content analysis platform for optimization of lipid mediated CRISPR–Cas9 delivery strategies in human cells," in the journal *Acta Biomaterialia*, used the platform to find new biomaterials that could promote gene editing.

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Assistant Professor Kris Saha