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GENETIC ENGINEERING

# *Trans*-epigenetic modulation of target genes in acute kidney injury

Genome editing technologies have advanced multiple areas of biomedical research. However, a major barrier in the use of these technologies to correct genetic mutations is the need to create double-strand breaks (DSBs) in the targeted region, which can result in permanent, unwanted mutations. Now, Juan Carlos Izpisua Belmonte and colleagues describe a method that enables activation of endogenous target genes while circumventing the need to create DSBs. "Our modified CRISPR–Cas9 system does not alter the genetic code but instead activates endogenous genes at levels sufficient to provide therapeutic benefit in a process we call *trans*-epigenetic modulation," Belmonte explains.

To avoid the need for DSBs, the CRISPR–Cas9 system has previously been modified by fusing a transcriptional activation domain to Cas9, enabling the system to transcriptionally activate target genes using a single guide RNA (sgRNA). However, the need to fuse multiple transcriptional activation domains prohibits its use in gene delivery vectors. To overcome these issues, Belmonte and colleagues identified a combination of co-transcriptional activators and sgRNAs that can fit within a single adeno-associated virus (AAV) vector and induce efficient gene activation.

To assess the therapeutic potential of their system, they generated AAV vectors containing sgRNAs specific for *klotho* and *Il10* together with the transactivation machinery. Injection of the vectors into Cas9-expressing mice led to upregulation of *klotho* and *Il10* expression and ameliorated the effects of cisplatin-induced acute kidney injury. "Using our novel *in vivo* gene activation system, we could observe physiological phenotypes and ameliorate disease symptoms in mouse models of human conditions," says Belmonte.

*Susan J. Allison*

"We could observe physiological phenotypes and ameliorate disease symptoms"

**ORIGINAL ARTICLE** Liao, H.-K. *et al.* *In vivo* target gene activation via CRISPR/Cas9-mediated *trans*-epigenetic modulation. *Cell* http://dx.doi.org/10.1016/j.cell.2017.10.025 (2017)