

Gene editing: from technologies to applications in research and beyond

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Cutting-edge gene editing technologies enable broadened genomic alternations and accelerate opportunities to use these tools in biomedicine, agriculture, and animal model development. In this issue, [Li et al. \(2022\)](#) reviews the tools of gene editing and highlights key technological developments and its broad applications in biomedicine, hoping to accelerate new discoveries and therapies in biomedicine.

The leap from reading to editing the genome offers immense opportunities toward bettering human health and improving the production of sustainable crops and animals. This technological advancement has also profoundly impacted biological research in the study of genotype-to-phenotype.

Steady progresses have been continually made to improve editing efficiency, control unintended off-target outcomes of editors, and explore different routes for delivery. One of the main obstacles limiting translational applications is the route of delivery of these large protein complexes, which affects the final therapeutic modality. In this issue, [Yin et al. \(2020\)](#) found that the co-delivery of a general AAV receptor (AAVR) increased AAV transduction efficiency, resulting in a substantial boost of indel and HR editing rates

in the correction of a single mutation in $\text{Pah}^{\text{R408W}}$ mice, which suggests an interesting approach to improve *in vivo* genome editing efficiency.

Improving the efficiency of delivery remains critically important for the application of gene editing technologies in biomedicine and agriculture. In particular, standard plasmid DNA delivery systems widely adopted in plants are restricted to only those plants that can regenerate. In this issue, [Qiu et al. \(2021\)](#) demonstrated that the transient expression of a complex of two growth regulators TaGRF4 and TaGIF1 (TaGRF4-TaGIF1) increased the regeneration and genome editing frequency in wheat plants. The use of mTaGRF4-TaGIF1 together with a cytosine base editor targeting *TaALS* resulted in a substantial increase in regeneration and transgene-free genome editing across multiple wheat cultivars, providing a valuable insight to the realization of advanced crop genome editing.

As a versatile genomic targeting platform, CRISPR-Cas systems have been repurposed for epigenome editing ([Qi et al., 2013](#)). Guide RNAs enable dCas9 effectors or dCas9 fused with gene-regulatory proteins to achieve transcriptional and epigenetic alterations in a DNA sequence-specific manner ([Nakamura et al., 2021](#)). In this issue, [Tang et al. \(2021\)](#) engineered a SunTag-based demethylation system to target a protein-coding gene in rice, leading to robust hy-

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pomethylation of the targeted gene. Importantly, the gene's hypomethylation and its resulting phenotypes were inheritable, providing an effective way to manipulate epigenetic regulation via CRISPR-Cas in rice. Since changes in DNA methylation can be transgenerationally inherited to generate stable epialleles, epialleles broaden genetic and phenotypic diversity, and can contribute to the regulation of important agronomic traits in crops, thus providing a new resource for crop breeding.

Animal models are great research tools for the study of human diseases and are essential for the validation of genome editing efficacies within a living organism. In this issue, [Yin et al. \(2020\)](#) established a phenylketonuria (PKU) mouse model carrying a pathogenic R408W mutation in the phenylalanine hydroxylase (Pah) gene via CRISPR-Cas9 genome editing. Phenylketonuria is one of the most common inborn errors of metabolism. Taking advantage of the AAVR co-injection approach, they successfully increased the site-specific insertion rate of a Pah cDNA, which results in decreased Phe levels and ameliorated PKU symptoms. The acquisition of multiple beneficial alleles in the genome has great value to breeders that seek to develop elite farm animals. In this issue, [Song et al. \(2022\)](#) evaluated the editing efficiency of four CBE variants, demonstrating that hA3A-BE3-Y130F and hA3A-eBE-Y130F had increased base-editing efficiency and low toxic effects during embryonic development. The use of direct zygote microinjection of the CBE system enabled the generation of pigs harboring multiple point mutations via a one-step approach, which enables the immediate introduction of multiple mutations in transgene-free animals that reflect favorable economic traits in pigs.

CRISPR-Cas has long been combined with genome-scale guide RNA libraries for phenotypic screenings ([Zhou et al., 2014](#)). This research method has driven many exciting biological findings that has significantly advanced the scope and accuracy of functional genomics with mechanistic insights. The outbreak of the novel coronavirus disease 2019 (COVID-19) has caused a global health crisis. In this issue, [Zhu et al. \(2021\)](#) developed an improved CRISPR activation screen

strategy to identify potentially novel host receptors besides ACE2 that are critical for SARS-CoV-2 entry and infections. The researchers discovered three new functional receptors, LDLRAD3, TMEM30A, and CLEC4G and confirmed their physiological roles in either neuronal or liver cells. These findings deepen our understanding of the entry mechanisms and the multiorgan tropism of the SARS-CoV-2 virus, potentiating the development of new countermeasures against COVID-19. These screening methods will deepen our understanding behind the link between genetic variants and functional phenotypes.

Compliance and ethics *The authors declare that they have no conflict of interest.*

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