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Engineered Miniature Cas Systems with Enhanced Activity

Researchers from Stanford developed dCasMIDAS, a structure-guided, engineered miniature CRISPR-dCas system with substantially enhanced activity, including gene activation, base editing, gene editing, multiplexing capability, and delivery compatibility compared to existing tools.

CRISPR-based gene editing and regulation have transformative potential in research and therapeutics, but most high-performing systems (e.g., SpCas9) are too large to package efficiently into size-constrained delivery vehicles such as adeno-associated virus (AAV), which has a payload limit below 4.7 kb. Smaller Cas variants, including the previously engineered CasMINI (based on Cas12f), have historically underperformed in mammalian cells.

To address these challenges, the inventors applied a dynamics-informed, structure-guided engineering strategy to develop novel Cas12f derivatives. Named dCasMIDAS, it contains mutations that strengthen its DNA-binding interactions and demonstrates robust gene activation and gene editing across multiple genomic loci, frequently outperforming the standard spCas9 in gene activation assays. The CasMIDAS activity has been validated in cell lines, primary cells, plants, and animals. RNA-seq analysis indicated that off-target perturbation is minimal. Additionally, it retains a substantially smaller protein footprint (~500 amino acids) compared with dCas9 or dCas12a, easing the challenge of viral vector-based delivery. Its small size facilitates multiplexed gene-regulation applications that require multiple effectors or additional payloads. These combined advantages make dCasMIDAS a powerful yet compact tool that addresses key limitations in delivery, activity, and multiplexing faced by larger CRISPR-Cas systems.

Stage of Development
Methods have been demonstrated in vitro

Applications

- Therapeutic gene regulation platforms
- Cell engineering services
- Research tools for gene function studies
- Diagnostic and Biosensing Platforms

Advantages

- Compact size for easier delivery
- Enhanced gene activation, base editing, and gene editing
- High specificity with minimal off-target effects
- Multitarget capability
- Validated in cell lines, primary cells, plants, and animals

Innovators

- Lei Qi
- Xiaoshu Xu

Licensing Contact

Mona Wan

Senior Licensing Manager for Special Projects

Email