Strategies and Mechanisms of Precision Genome Engineering: From Gene Editing to Genome Writing

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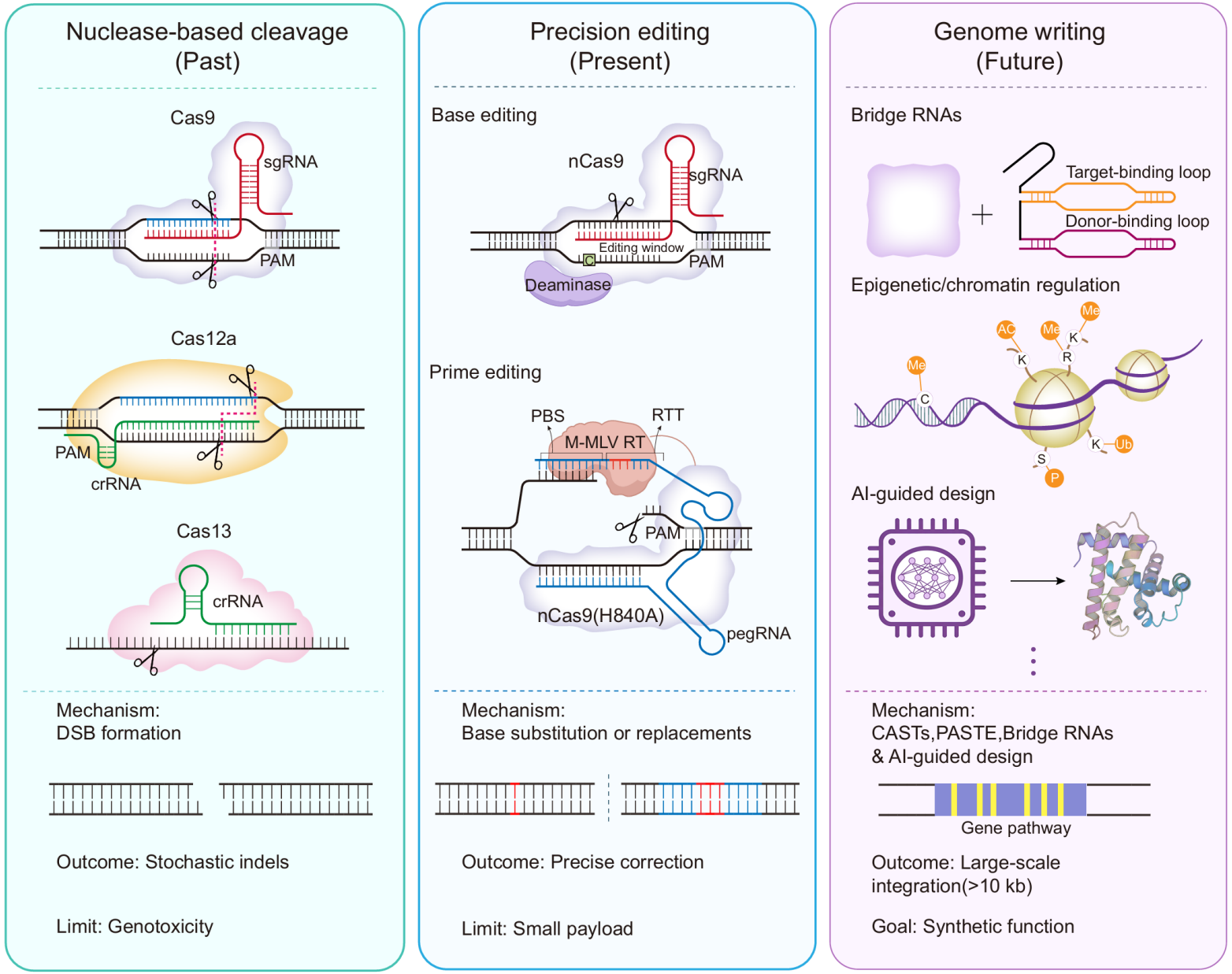
Introduction



Paradigm Evolution from Nuclease-Based Cleavage to Precision Editing and Genome Writing

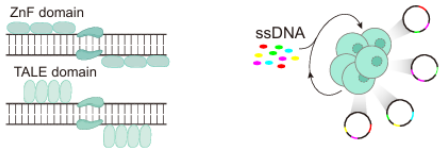
Highlights

- Genome manipulation is moving from nuclease-mediated, stochastic disruption toward deterministic, programmable genome writing.
- Precision technologies such as base and prime editors minimize genotoxicity by bypassing endogenous double-strand break repair.
- RNA-guided platforms, including CRISPR-associated transposases and bridge RNAs, enable seamless insertion of multi-kilobase modules, thereby overcoming cargo limitations.
- Generative Artificial Intelligence (AI), structural biology, and novel delivery architectures are revolutionizing the design of de novo synthetic effectors.
- These synergistic advancements are ushering in Generative Biology, transforming genomes into dynamically programmable media for synthetic design.

1. Evolution of Genome Manipulation Technologies

Nuclease-based cleavage

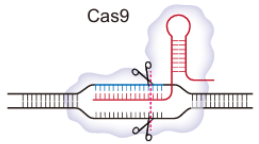
<2012 — ZFNs/TALENs & MAGE (2009)



Complex protein engineering; accelerated evolution.

ZFN/TALEN

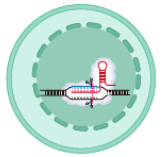
2012 — CRISPR-Cas9 characterization



sgRNA-programmed cleavage; conformational switch.

CRISPR-Cas9

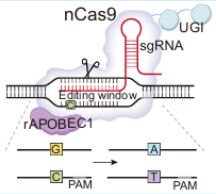
2013 — CRISPR revolution & mammalian editing



Ease of design; NHEJ reliance (error-prone).

Precision editing

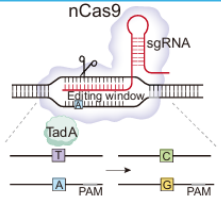
2016 — Cytosine base editors (CBEs) & anti-CRISPRs



C-G to T-A conversion (no DSBs); temporal control.

Base editors

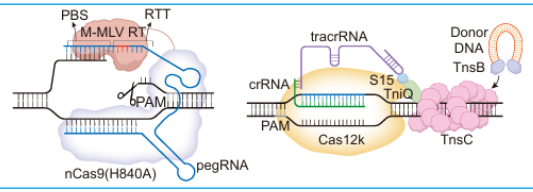
2017 — Adenine base editors (ABEs)



A-T to G-C conversion via evolved TadA.

Prime editors

2019 — Prime editing & CASTs

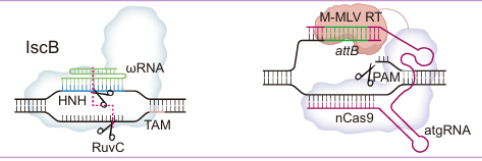


Template-directed substitutions/insertions; multi-kb RNA-guided integration.

Large-scale genome editors

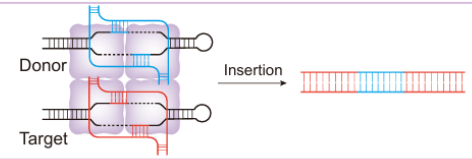
Genome writing

2021-2022 — OMEGA (2021) & PASTE (2022)



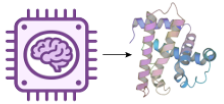
Cas9 ancestor identified; large-scale payload integration.

2023-2024 — Bridge RNAs & clinical validation



Programmable recombination (IS110); SCD therapy approved.

2025 — AI-designed editors

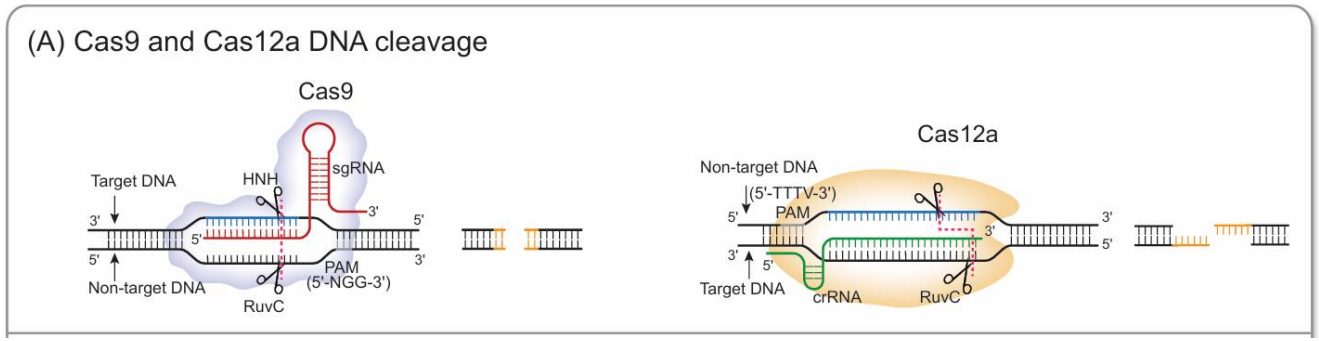


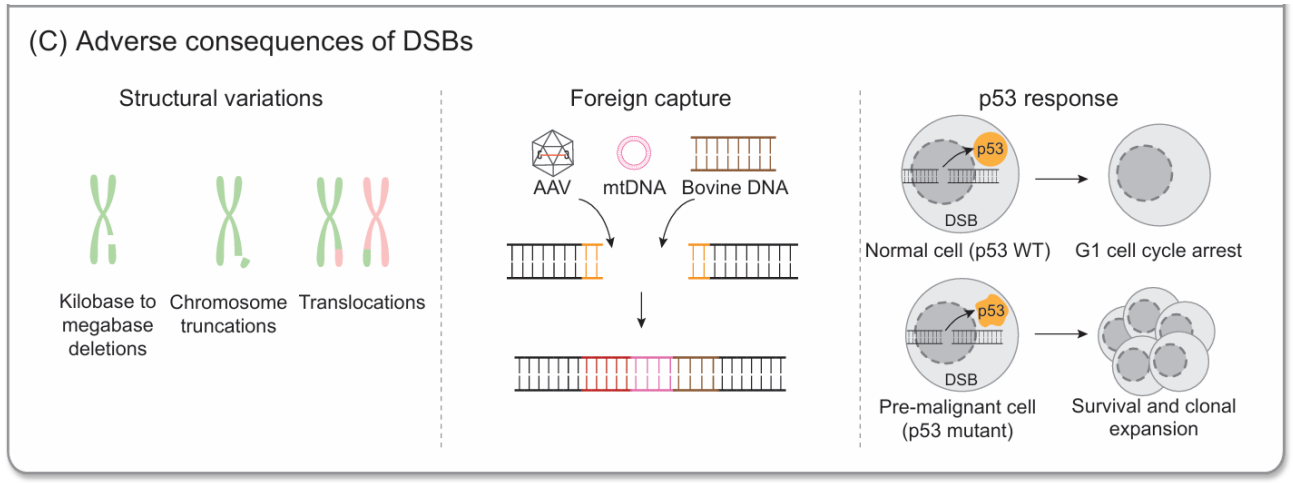
Generative AI models for de novo synthesis.

Future editors

FIGURE 1. Evolutionary Trajectory of Genomic Manipulation

2. Mechanisms of CRISPR-Associated Nucleases, DNA Repair Pathway Competition, and Associated Genotoxicities





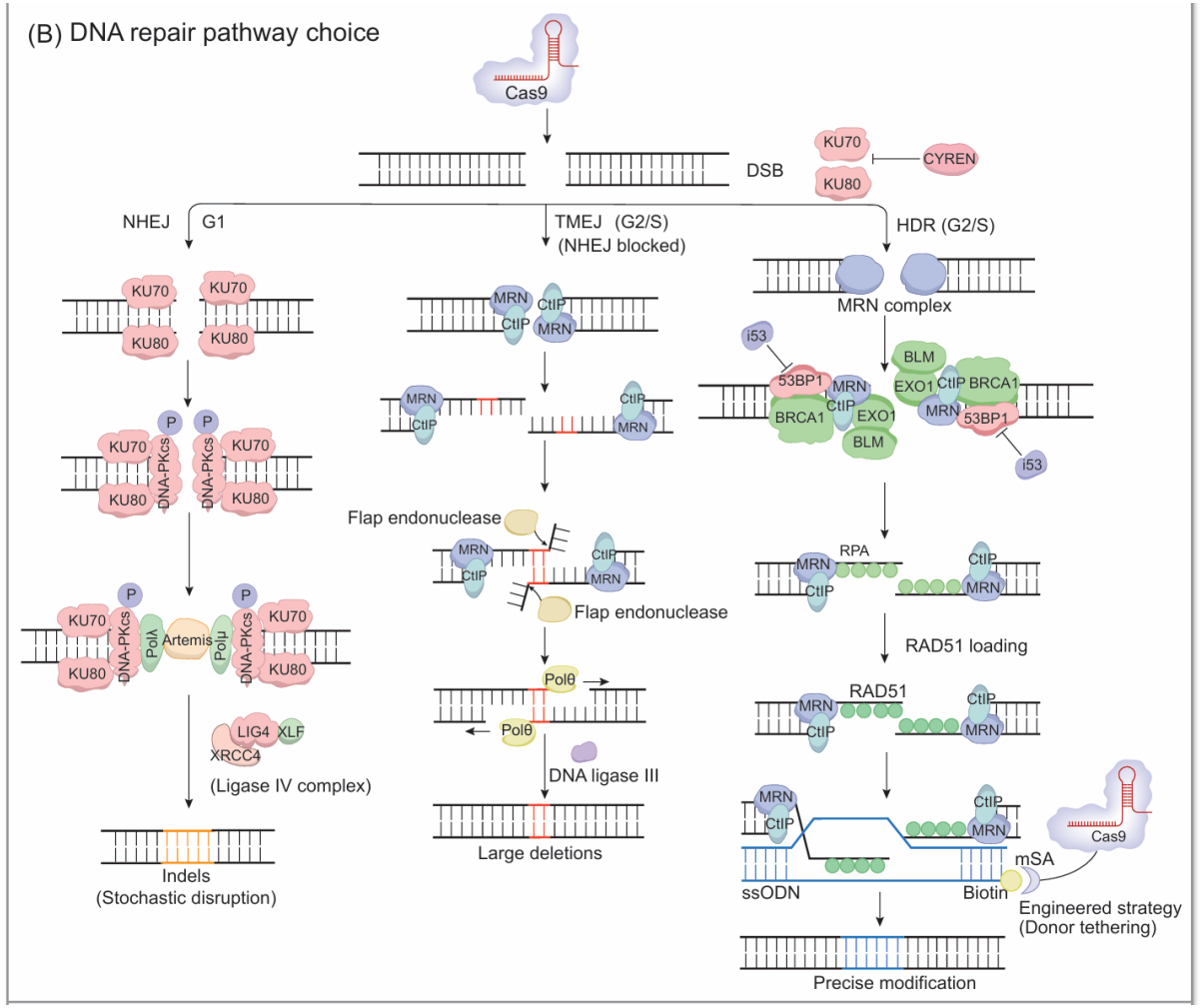


FIGURE 2. Mechanisms of clustered regularly interspaced short palindromic repeats (CRISPR)-associated nucleases, DNA repair pathway competition, and associated genotoxicities

3. Mechanisms and Engineering of Deaminase-Mediated Base Editors

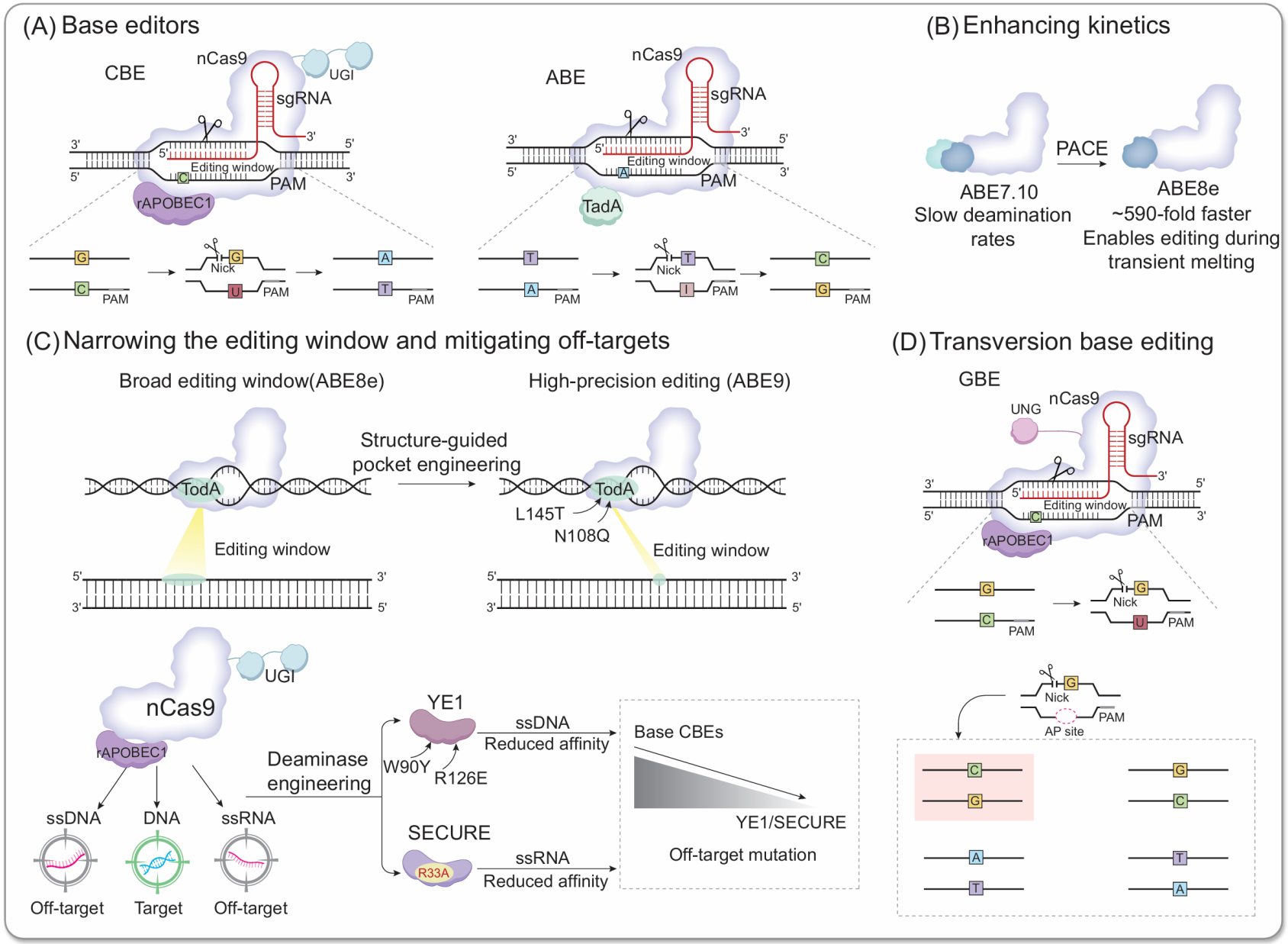


FIGURE 3. Mechanisms and engineering of deaminase-mediated base editors

4. Mechanisms and Optimization of Prime Editing

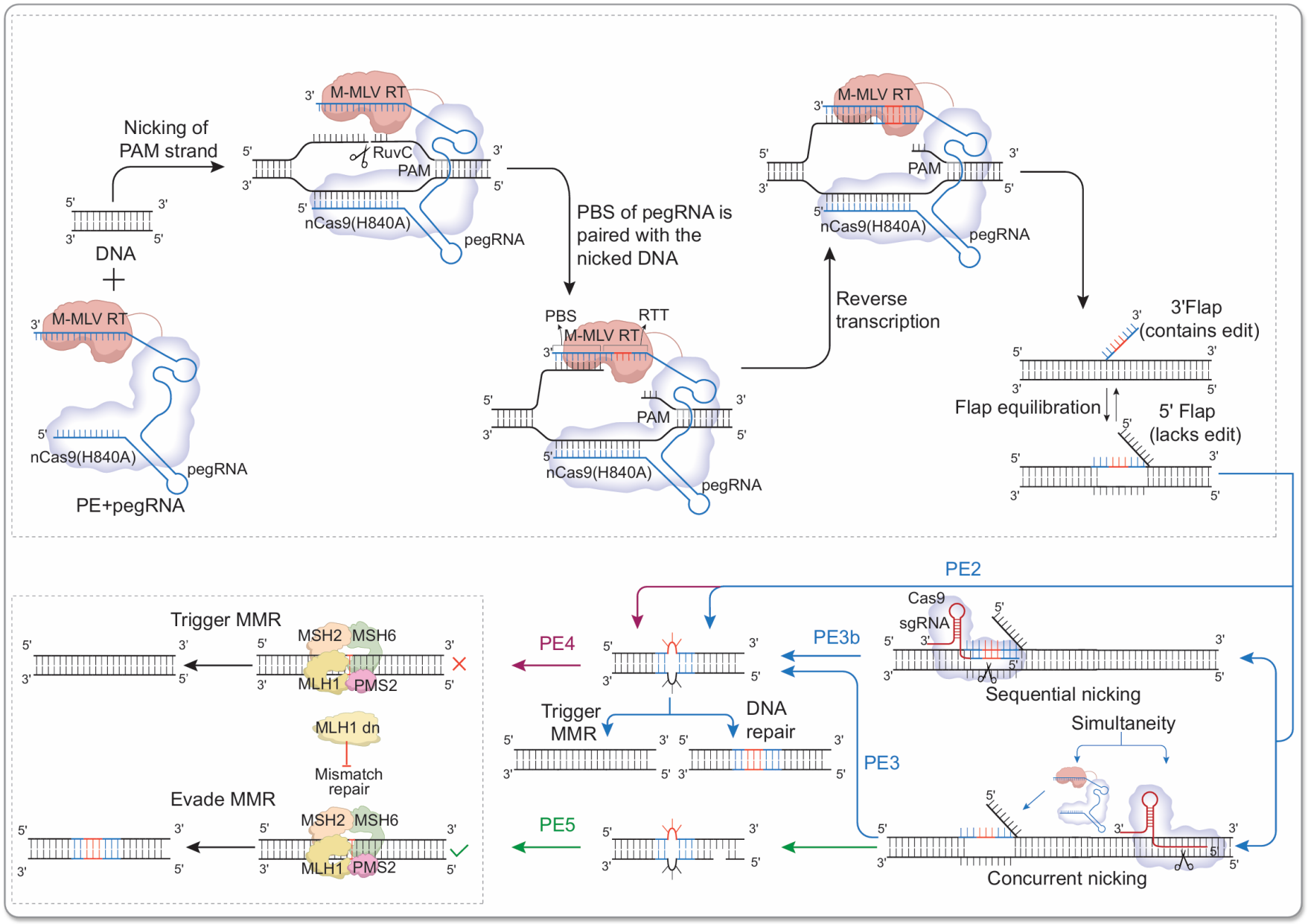


FIGURE 4. Mechanism and optimization of prime editing

5. Mechanisms of Precision Epigenome and Transcriptome Engineering

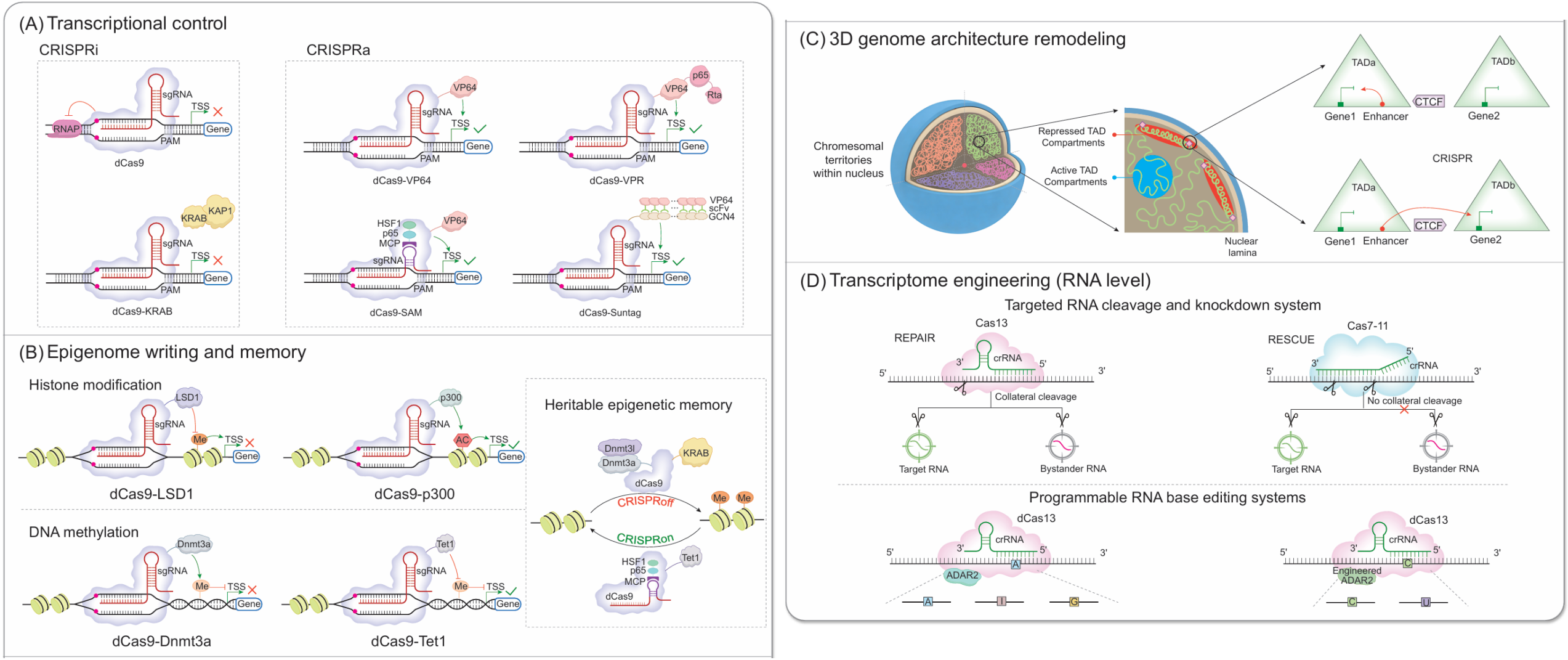


FIGURE 5. Mechanisms of precision epigenome and transcriptome engineering

6. Mechanisms of Large-Scale Genome Writing and Synthetic Design

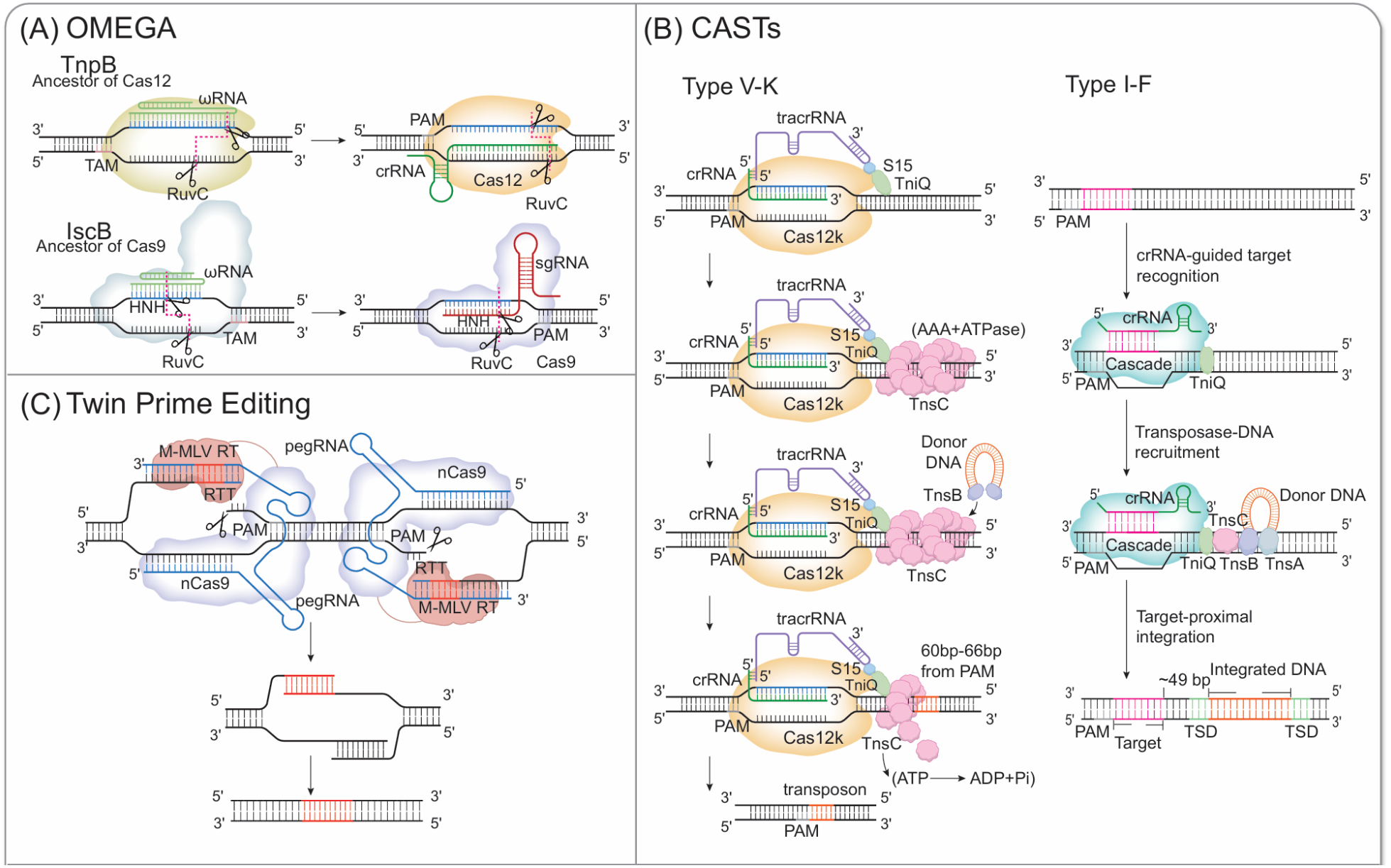


FIGURE 6(A, B, C). Mechanisms of large-scale genome writing and synthetic design.

6. Mechanisms of Large-Scale Genome Writing and Synthetic Design

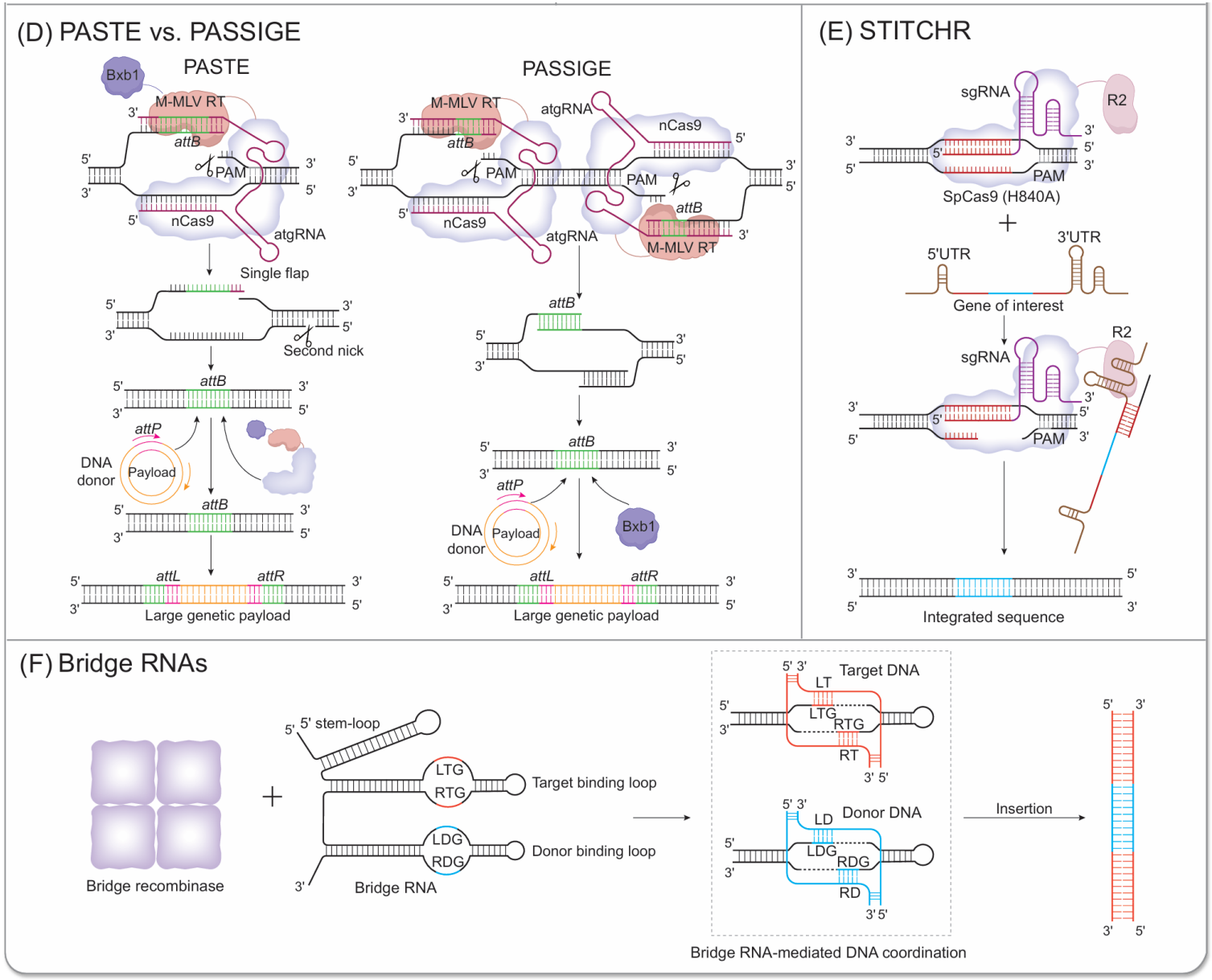


FIGURE 6(D, E, F). Mechanisms of large-scale genome writing and synthetic design.

7. Mechanisms of Precision Genome Recording and Temporal Recording

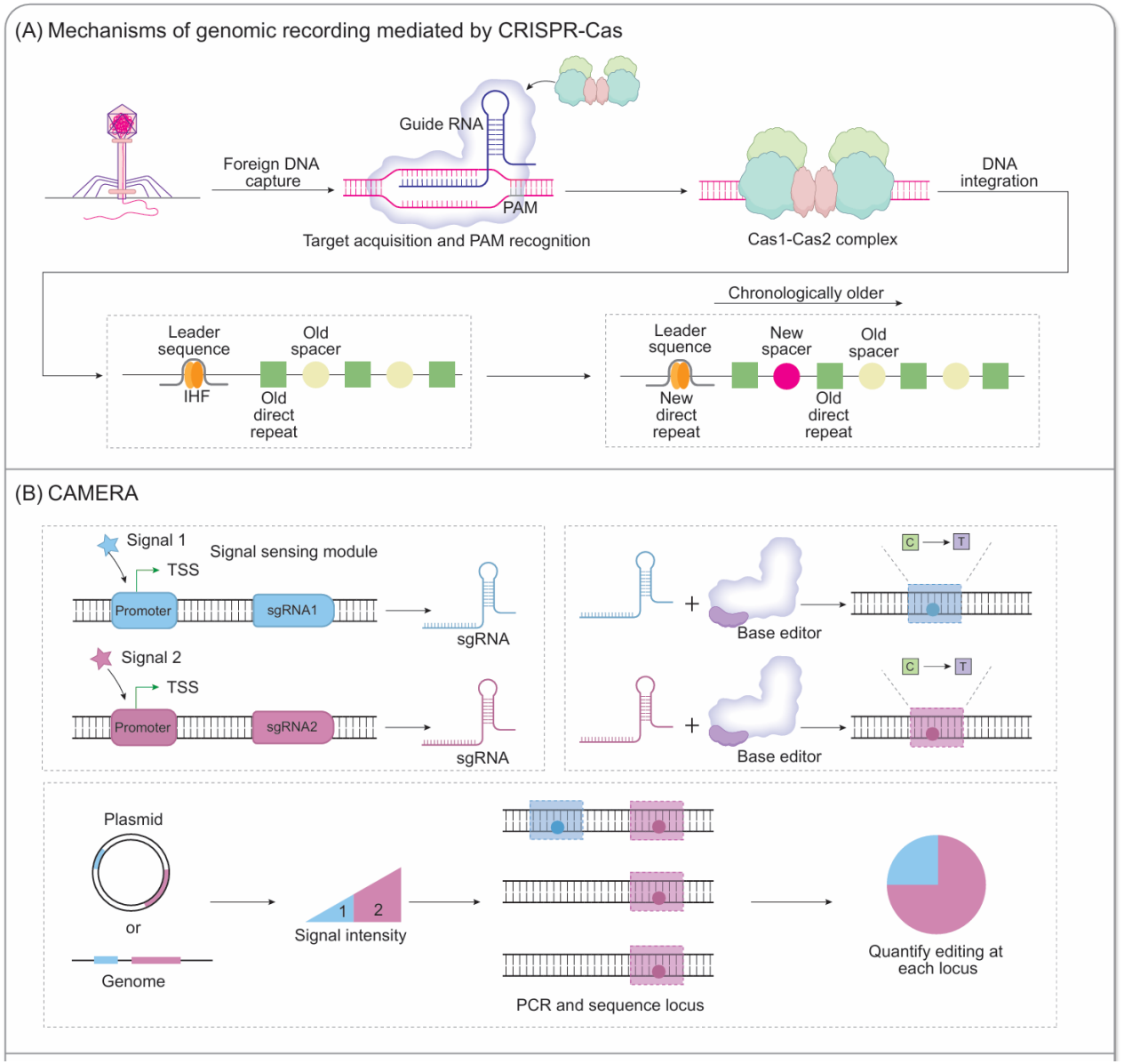


FIGURE 7(A, B). Mechanisms of precision genomic recording and temporal logging.

7. Mechanisms of Precision Genome Recording and Temporal Recording

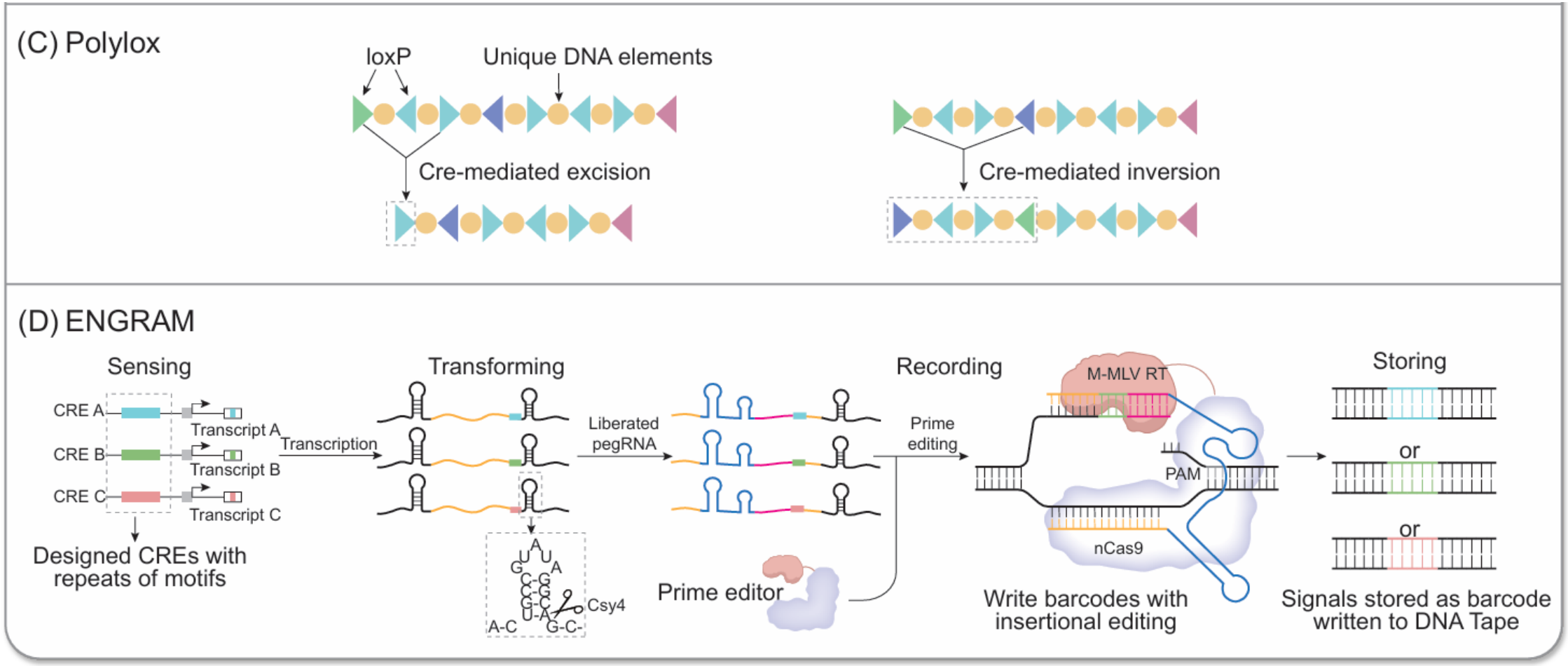


FIGURE 7(C, D). Mechanisms of precision genomic recording and temporal logging.

8. Enabling Technologies for Precision Genome Engineering

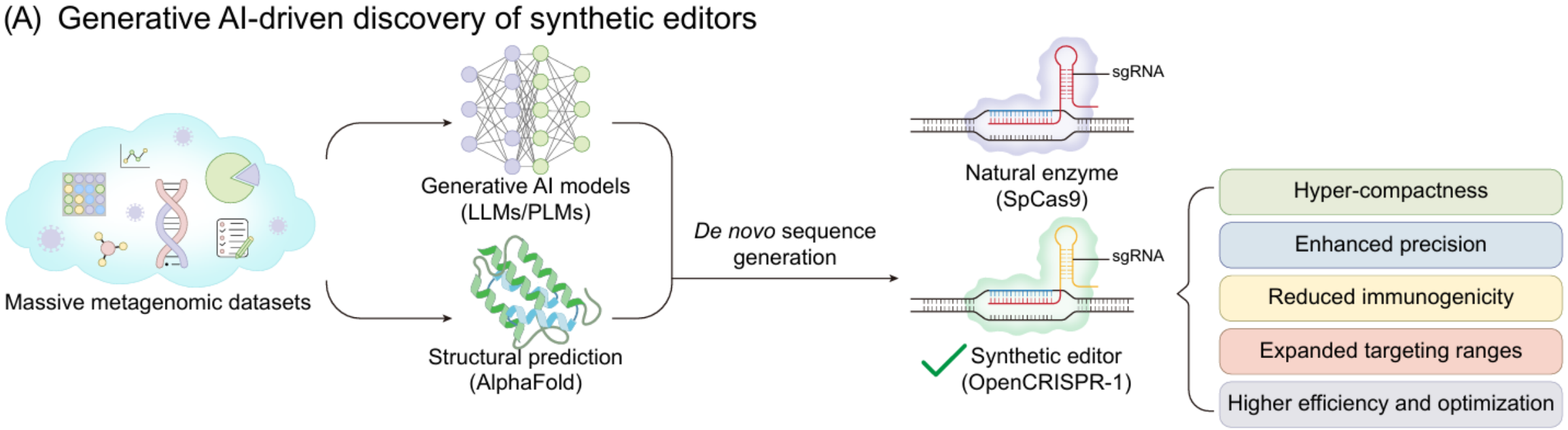


FIGURE 8(A). Enabling technologies for precision genome engineering.

8. Enabling Technologies for Precision Genome Engineering

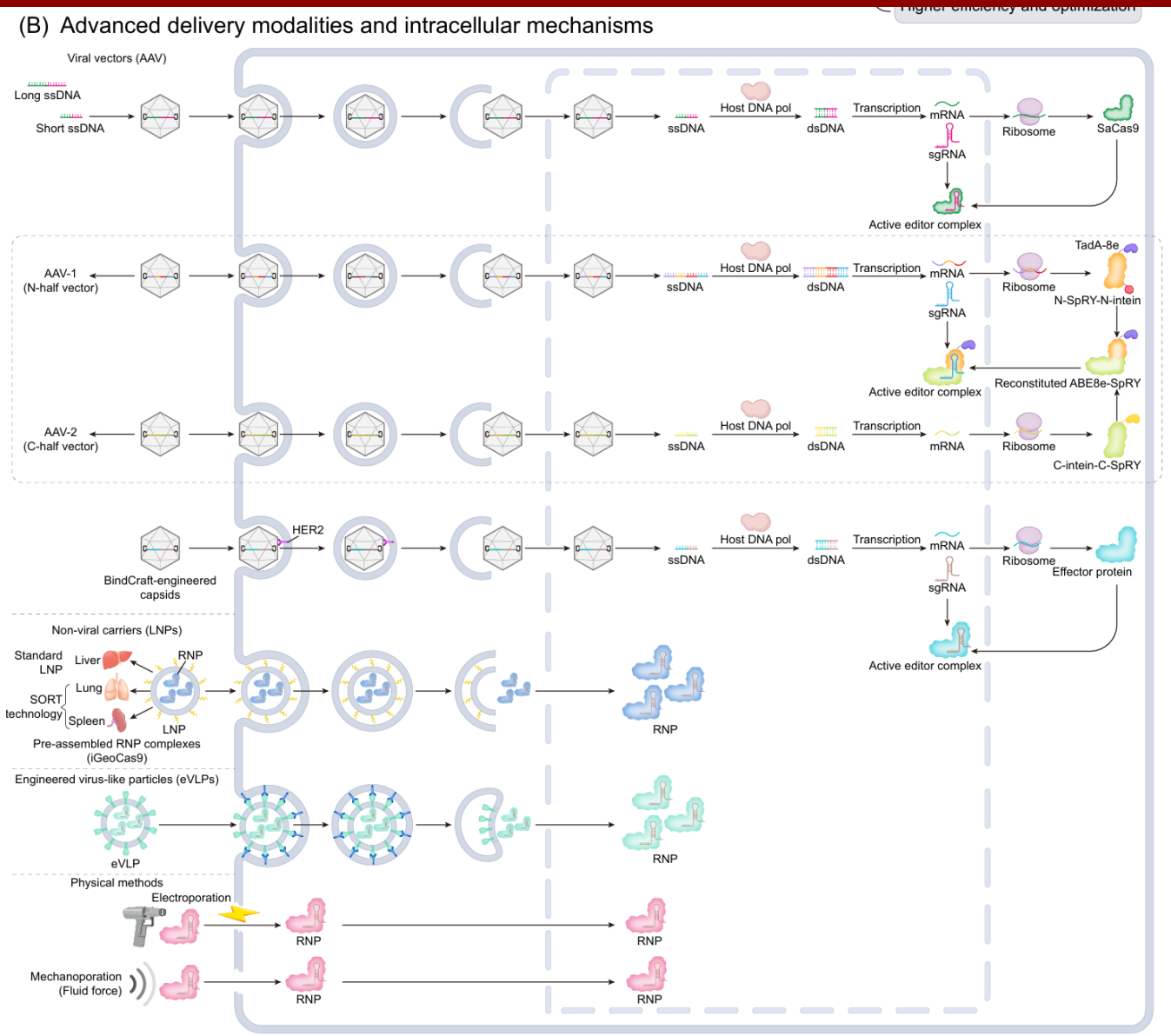


FIGURE 8(B). Enabling technologies for precision genome engineering.

9. Precision Validation Strategies for Genome Engineering

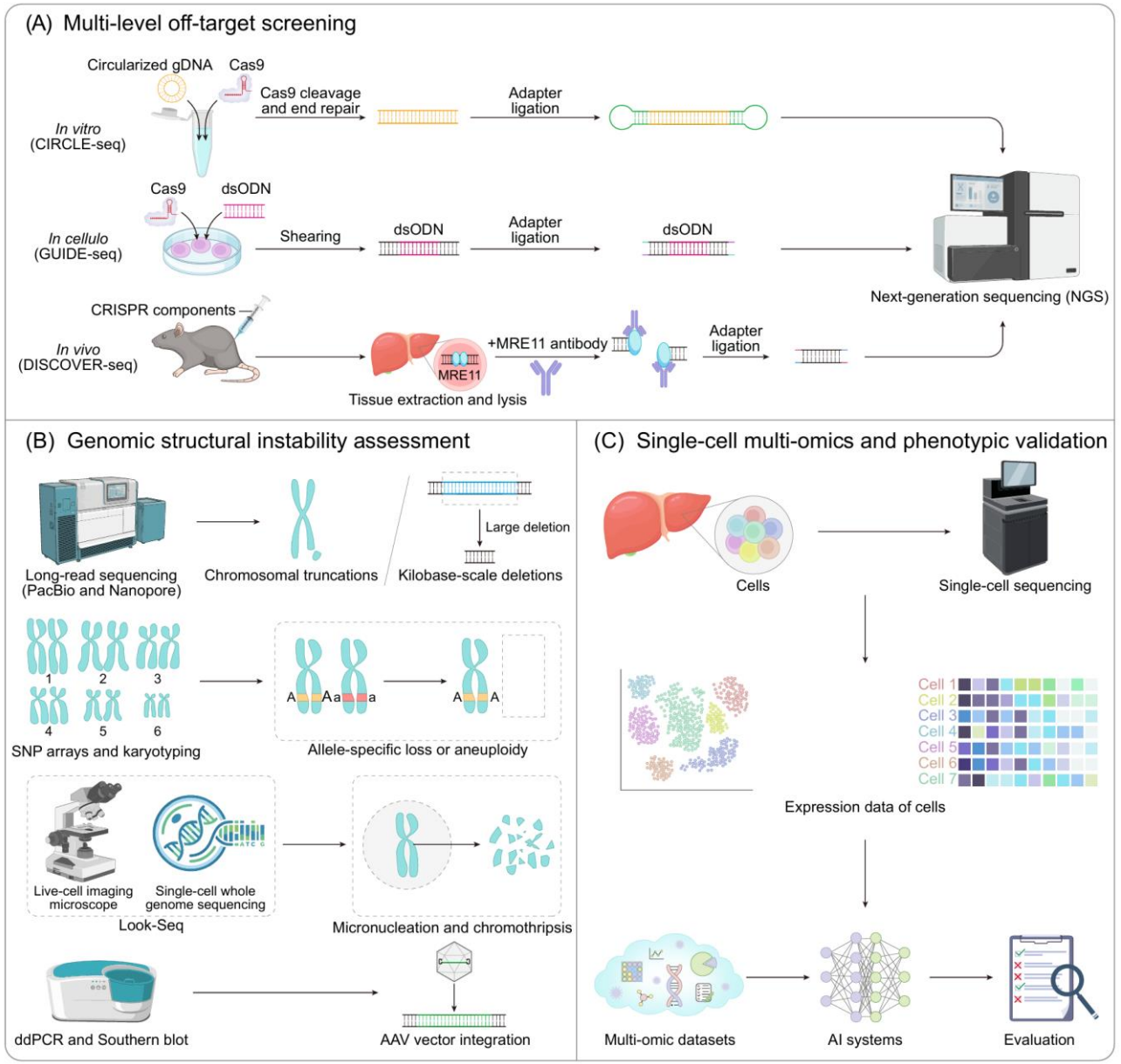


FIGURE 9 Precision validation strategies for genome engineering.

10. Reflections and Future Directions in Precision Genome Engineering

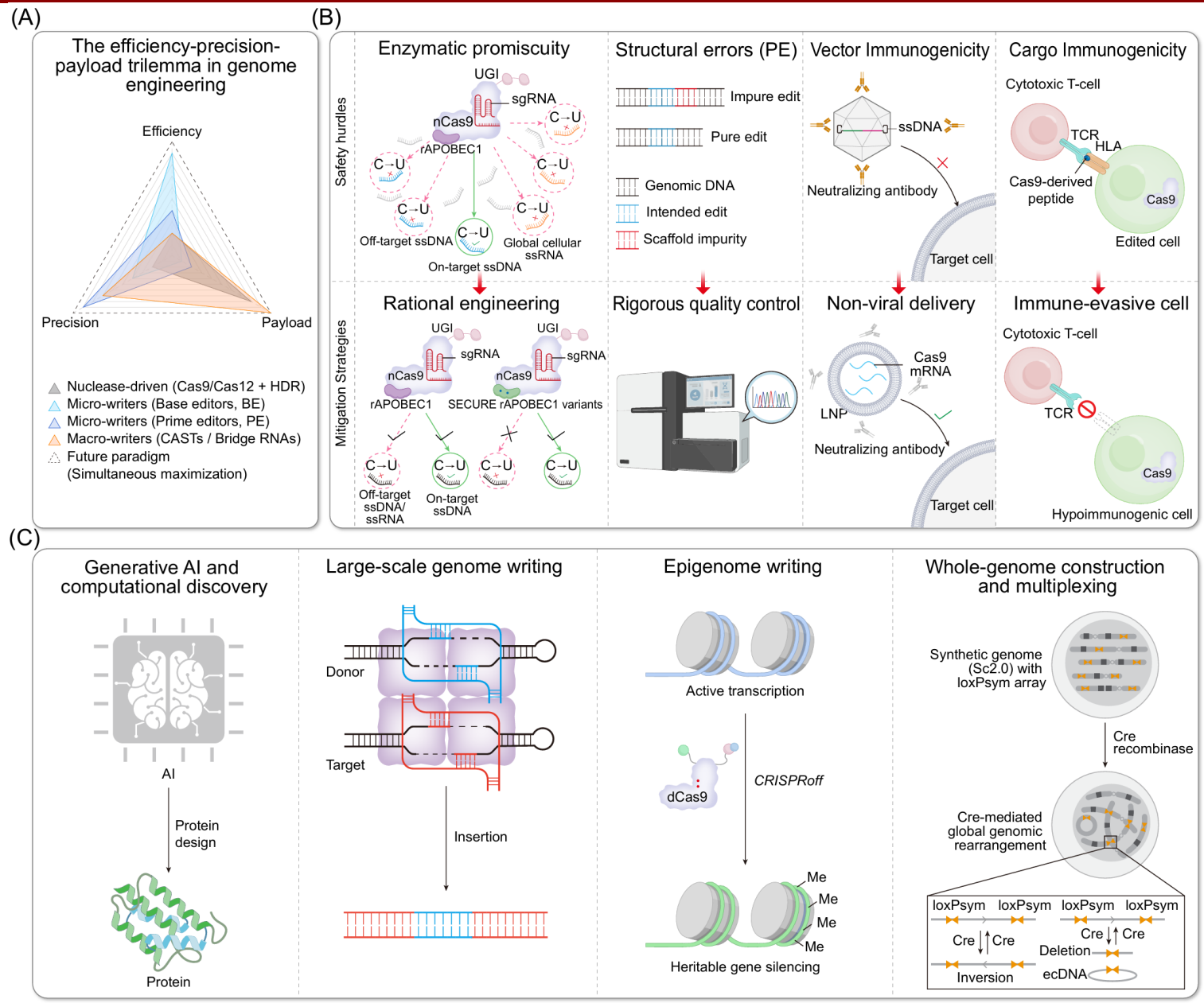


FIGURE 10. Reflections and future directions in precision genome engineering.

Summary

- Genome engineering is transitioning from stochastic perturbation reliant on double-strand breaks and endogenous DNA repair toward precise and predictable genome writing.
- Base and prime editing enable single-nucleotide substitutions and small-scale sequence rewriting.
- Technologies such as CASTs, PASTE, and bridge RNAs further support the site-specific integration of multi-kilobase functional modules.
- Efficiency, precision, and payload capacity remain difficult to optimize simultaneously, while off-target effects, structural variants, immunogenicity, and in vivo delivery remain major barriers to clinical translation.
- The convergence of generative AI, structural biology, high-throughput screening, and advanced delivery platforms may enable more compact, safe, and efficient editors, transforming the genome into a biological information platform that can be designed, rewritten, and dynamically regulated.

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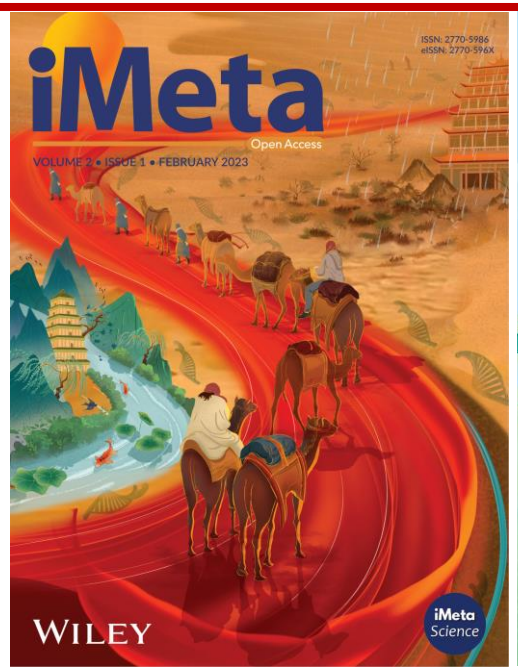

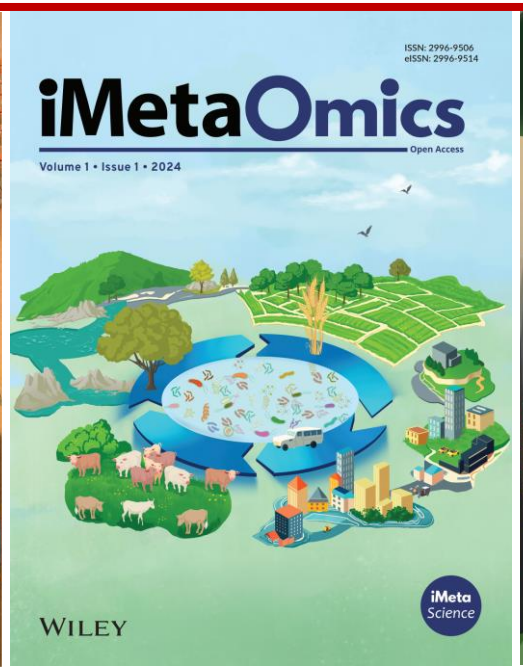

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