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CRISPR-Cas as a Chemically Programmable System: Advances in Modulation and Delivery

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INTRODUCTION & AIM

CRISPR, first discovered in the 1980s, functions as an adaptive immune system in bacteria and archaea, protecting against viruses and foreign DNA. CRISPR systems are classified into Class 1 (multi-protein effectors) and Class 2 (single-protein effectors like Cas9, Cas12, and Cas13), with Class 2 type II Cas9 being the most widely used for genome editing. CRISPR/Cas9 enables precise gene modifications via single-guide RNA (sgRNA) directing Cas9 to target sequences, inducing double-strand breaks for gene removal or insertion. Compared to previous genome editing tools like ZFNs and TALENs, CRISPR is simpler, efficient, and highly adaptable.

A chemistry-driven understanding of CRISPR–Cas9—covering DNA cleavage, off-target effects, and functional enhancements through chemical modifications—supports rational design and delivery strategies, improving stability, specificity, and therapeutic potential. Integrating structural biology, synthetic chemistry, and computation is key to advancing CRISPR from a molecular tool to precise, safe, and adaptable clinical applications.

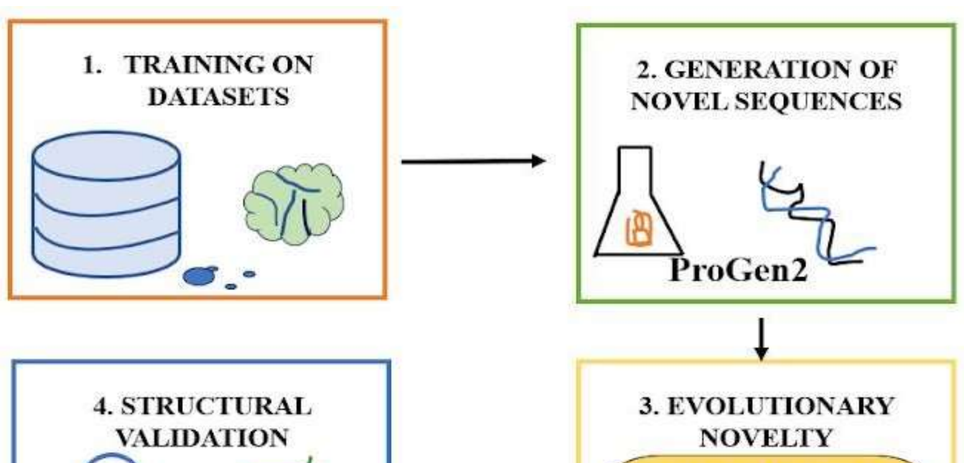
METHOD

Training on Datasets: Large-scale datasets of known Cas protein sequences and structures are used to train machine learning models, enabling the system to learn sequence–structure relationships and functional features of Cas9, Cas12, and Cas13 proteins.

Generation of Novel Sequences: Using models like ProGen2, new protein sequences are computationally generated, designed to maintain key functional motifs while exploring sequence diversity for improved or novel properties.

Evolutionary Novelty Assessment: The generated sequences are compared with natural Cas variants to evaluate evolutionary novelty, ensuring that the new sequences retain functional similarity but expand the sequence space for potential engineering.

Structural Validation: The predicted structures of the generated sequences are modeled and validated using tools like AlphaFold2 to ensure proper folding, structural integrity, and potential activity, providing a reliable framework for downstream experimental or computational applications



RESULTS & DISCUSSION

Recent advances demonstrate that CRISPR–Cas systems can be chemically programmed for precise, tunable, and safe genome editing. Structural analyses of Cas9, Cas12, and Cas13 revealed domain-specific functions—REC, HNH/RuvC nuclease, and PAM-interacting domains—highlighting the importance of metal ion–dependent catalysis and conformational dynamics in target recognition and cleavage. Synthetic modulators, including anti-CRISPR proteins, small molecules, and optogenetic switches, allow reversible and spatiotemporal control of CRISPR activity, expanding therapeutic applications.

Bioorganic delivery platforms such as lipid nanoparticles (LNPs), cell-penetrating peptides (CPPs), and biodegradable polymers have improved in vivo administration. Notably, the first-in-human trial using LNP-encapsulated CRISPR/Cas9 (NTLA-2001) achieved >90% reduction of transthyretin in patients with minimal adverse effects, demonstrating clinical feasibility. Computational approaches, including molecular docking, molecular dynamics simulations, and AI-based generative models, facilitated identification of high-affinity ligands (e.g., BRD0539) and novel Cas protein variants, enhancing both specificity and efficiency.Overall, integrating structural, chemical, delivery, and computational strategies positions CRISPR–Cas as a flexible, chemically tunable system, with the potential for safe and precise therapeutic, diagnostic, and biotechnological applications.

Table 3. Free Energies of BRD0539 Binding to SpCas9 Evaluated by Various Methods.

COMPOUND	BINDING-SITE	GBSA	TI	MBAR
BRD0539	REC1-REC2	–50.1	–9.8	–10.0
	RuvC3	–41.0	–6.2	–6.7
	RuvC-CTD	–41.9	–6.0	–6.1
	CTD	–58.5	–21.2	–21.1

CONCLUSION

CRISPR–Cas systems have transformed from bacterial defense tools into highly programmable genome-editing platforms. Advances in structural understanding, synthetic modulators, and bioorganic delivery systems enable precise, controllable, and safe gene editing. Combined with computational and AI-based approaches, these developments make CRISPR a chemically tunable system with immense potential for therapeutic, diagnostic, and biotechnological applications.

FUTURE WORK / REFERENCES

The integration of CRISPR with electrochemical biosensors (E-CRISPR) offers rapid, affordable, and portable diagnostics, with potential to expand beyond nucleic acids to proteins and metabolites. Polymer–lipid hybrid nanoparticles provide stable, biocompatible, and targeted delivery platforms for CRISPR, even across barriers like the blood–brain barrier. Exosome-based CRISPR delivery shows promise for precise epigenetic modulation with low immunogenicity, and advancements in cargo loading and imaging could enable combined therapeutic and diagnostic (theranostic) applications.