



CRISPR Systems: Advantages, Applications and Emerging Opportunities in Life Sciences

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Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated (Cas) proteins have transformed molecular biology by providing programmable systems for recognizing and modifying nucleic acids. Adapted from microbial adaptive immunity, CRISPR-based technologies now support targeted genome editing, gene regulation, epigenetic modification, RNA manipulation, molecular diagnostics and functional genomic screening. Their principal advantages include guide-RNA programmability, comparatively straightforward redesign, scalability, multiplexing, broad applicability across organisms and the availability of diverse Cas effectors and derivative editors. Applications span human medicine, infectious-disease diagnosis, crop improvement, animal genetics and breeding, industrial biotechnology, microbiome research and environmental monitoring. However, CRISPR is not intrinsically precise or risk-free: outcomes depend on the editor, target sequence, delivery method, cell type and repair biology. Off-target activity, unintended on-target alterations, mosaicism, delivery barriers, immune responses, cost, regulatory uncertainty and ethical concerns remain important constraints. This chapter presents an integrated overview of CRISPR biology, its major advantages, principal applications and current limitations. It distinguishes established uses from developing research directions and argues that responsible implementation requires robust validation, long-term assessment where appropriate, transparent governance and equitable access to benefits.

Keywords: CRISPR-Cas; genome editing; gene regulation; base editing; prime editing; molecular diagnostics; agriculture; animal breeding; gene therapy; biosafety

Introduction

Genome editing refers to the deliberate alteration of genetic material at selected sites. Earlier programmable nucleases, including zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), made targeted editing possible but often required laborious protein engineering for each new DNA target. CRISPR-associated systems changed this landscape because target recognition can frequently be reprogrammed by changing a guide RNA rather than redesigning the DNA-binding protein itself (Jinek et al., 2012; Doudna and Charpentier, 2014). CRISPR stands for clustered regularly interspaced short palindromic repeats. In bacteria and archaea, CRISPR arrays and associated proteins form part of an adaptive defence system against invading genetic elements. Researchers adapted components of these systems for experimental and applied biotechnology. CRISPR is now best understood as a broad family of tools, not a single enzyme or technique. Depending on the system, researchers can cut DNA, modify individual DNA bases, write defined sequence changes, target RNA, regulate gene expression, or detect nucleic acids. The importance of CRISPR lies in the combination of programmability and breadth. It has accelerated gene-function studies and opened new avenues for therapeutic development, crop improvement,

animal research and diagnostics. Yet the phrase “gene editing” can obscure the complexity of biological outcomes: a targeted molecular event does not automatically produce a predictable phenotype, a safe therapy or a useful agricultural trait. The advantages and limitations must therefore be considered together.

Biological basis and major CRISPR tool classes

Natural system and target recognition

In a natural microbial CRISPR immune system, fragments of previously encountered genetic material can be incorporated as spacers in a CRISPR array. The array is transcribed and processed into guide RNAs that help Cas effector proteins recognize complementary sequences during a subsequent encounter. In genome-editing applications, a designed guide RNA directs an appropriate Cas protein to a selected nucleic-acid target. Many DNA-targeting effectors, including commonly used Cas9, also require a nearby protospacer-adjacent motif (PAM). PAM requirements vary between Cas proteins and determine which genomic sites can be targeted. In the widely used CRISPR-Cas9 system, the guide RNA directs Cas9 to a complementary DNA sequence. Cas9 can then create a double-strand break. Cellular repair commonly proceeds through non-homologous end joining (NHEJ), which may generate insertions or deletions, or through homology-directed repair (HDR), which can use a supplied DNA template to introduce a defined change. NHEJ is often useful for disrupting gene function, whereas HDR may be used for more precise sequence replacement, although its efficiency varies substantially by cell type and experimental context (Xu and Li, 2020).

Beyond conventional Cas9 cutting

The CRISPR toolbox has expanded considerably. Cas12 family proteins provide alternative DNA-targeting properties and are used in genome editing and diagnostic systems. Cas13 proteins target RNA and can support RNA knockdown, RNA editing or nucleic-acid detection. Catalytically inactive Cas proteins, often called dead Cas (dCas), can be guided to genomic sites without cutting DNA; when fused to regulatory domains, they can activate or repress transcription or recruit epigenetic modifiers. Base editors combine a DNA-targeting component with a chemical enzyme to convert selected bases within a defined editing window, often without generating a conventional double-strand break. Prime editors combine a Cas9 nickase and reverse transcriptase with a prime-editing guide RNA to support selected substitutions and small insertions or deletions. These approaches may avoid some limitations of double-strand-break-based editing, but they have their own constraints involving target compatibility, editing windows, by-products and efficiency (Anzalone et al., 2019; Komor et al., 2016; Rees and Liu, 2018).

Editing, regulation and detection are distinct uses

CRISPR-based technologies should not be treated as interchangeable. Genome editing changes DNA sequence; gene regulation changes the activity of a gene, potentially without altering its sequence; RNA targeting acts on transcripts and may be temporary; and CRISPR diagnostics detect nucleic acids in a sample. Each application requires a different design, validation strategy and assessment of risk.

Major advantages of CRISPR systems

Programmability and design flexibility

For many applications, target specificity is programmed largely through the guide RNA. This makes redesign for a new target comparatively fast and practical. The protein component may remain unchanged across many experiments, although guide design, target accessibility, PAM compatibility and cell-specific performance still require careful optimization.

Scalability and multiplexing

Multiple guide RNAs can be used in one experiment to investigate several genes or regulatory elements. Multiplex editing is valuable for studying pathways, redundant genes and complex traits that depend on several loci. Genome-wide guide libraries also support systematic loss-of-function and gain-of-function screens, helping researchers identify genes

involved in disease, drug response, host-pathogen interactions and cellular processes (Shalem et al., 2014; Wang et al., 2014).

Relative affordability and experimental accessibility

Compared with earlier protein-engineered nuclease systems, CRISPR often reduces the time and cost needed to develop a new targeting reagent. Reagents, protocols and analytical tools are widely available, and the system can be adapted to many cell types and organisms. These advantages do not mean that genome editing is a simple do-it-yourself activity: effective work requires molecular biology expertise, quality controls, suitable facilities and appropriate oversight.

Diverse outcomes from a common platform

The wider CRISPR family supports gene knockout, sequence insertion or replacement, base conversion, prime editing, transcriptional activation or repression, epigenetic modulation, RNA manipulation and nucleic-acid detection. This diversity enables researchers to select a tool according to the biological question rather than assuming that every objective requires a DNA double-strand break.

Faster functional genomics and model development

CRISPR can generate targeted cellular and animal models more rapidly than many conventional approaches. In combination with high-throughput screening, it allows systematic examination of gene function and interactions. Model organisms remain imperfect representations of human biology, and the resulting models require phenotypic and molecular validation, but CRISPR can shorten the path from hypothesis to experimental test.

Potential for more targeted interventions

When a disease or trait is strongly influenced by a known genetic change, editing may offer a way to alter the causal sequence or a regulatory element. Unlike treatments that act broadly on symptoms, a successful genetic intervention may address an underlying mechanism. The potential is greatest where the target biology is well understood and the edited cells can be reached, evaluated and monitored. Precision at the intended DNA target, however, must not be confused with guaranteed precision of the final phenotype or absence of unintended effects.

Applications in human health and biomedical research

Understanding gene function and disease mechanisms

CRISPR-mediated knockout, knock-in and regulatory perturbation can help establish whether a gene contributes to a disease process. Researchers can compare edited cells with suitable controls, examine molecular pathways and test candidate therapeutic targets. Combining CRISPR with induced pluripotent stem cells, organoids and other advanced models can provide disease-relevant systems for studying inherited disorders, cancer, neurological conditions and metabolic disease. These models can support drug discovery, although findings must be validated in appropriate biological systems and ultimately in clinical studies where relevant.

Gene and cell therapies

CRISPR-based therapies are being developed for selected inherited diseases and other conditions. A prominent example is ex vivo editing of a patient's blood-forming stem cells to alter regulation of fetal haemoglobin for sickle cell disease and transfusion-dependent beta-thalassaemia. Casgevy (exagamglogene autotemcel) became the first approved CRISPR-based therapy in several jurisdictions beginning in 2023-2024. This milestone demonstrates clinical feasibility for a defined therapeutic strategy; it does not mean that CRISPR can currently cure all genetic diseases. Ex vivo therapies involve cell collection, editing, quality assessment and reinfusion, and may require intensive conditioning and specialist care.

Other approaches are investigating in vivo editing, where editing components are delivered directly to a tissue such as the liver or eye. Delivery remains one of the most important barriers: an editor must reach the appropriate cells at an adequate dose while limiting exposure elsewhere. Long-term efficacy, immune reactions, unintended edits and the durability of clinical benefit must be evaluated for each therapy.

Cancer research and immunotherapy

CRISPR enables researchers to identify genes that influence tumour growth, immune evasion and treatment resistance. In cell therapy research, editing can be used to modify immune cells to study or potentially improve their activity. Such modifications may affect antigen recognition, exhaustion pathways or compatibility with therapeutic designs. However, cancer is heterogeneous and evolves over time; a genetic intervention that works in one model may not translate to every tumour or patient. Clinical use requires careful assessment of safety, potency and manufacturing consistency.

Infectious diseases and host-pathogen biology

CRISPR screens can identify host genes that pathogens exploit or that contribute to cellular defence. This may reveal new drug targets and improve understanding of viral and bacterial infection. CRISPR systems are also being explored for antimicrobial strategies, including approaches aimed at specific microbial sequences. Such applications remain technically and ecologically complex, particularly when delivery into a pathogen or microbial community is difficult.

Molecular diagnosis

Some Cas proteins, including Cas12 and Cas13 in appropriate assay formats, can generate detectable signals after recognizing target nucleic acids. Platforms such as DETECTR and SHERLOCK illustrate the potential for sensitive and sequence-specific detection. CRISPR diagnostics may be adapted to detect infectious agents, genetic variants or other nucleic-acid biomarkers and could support portable testing. In practice, performance depends on sample preparation, target abundance, amplification strategy, contamination control and independent validation. A diagnostic assay must be evaluated for sensitivity, specificity, reproducibility and clinical utility before routine deployment.

Applications in agriculture and plant science**Crop improvement**

CRISPR offers a way to modify genes or regulatory regions associated with disease resistance, pest response, maturity, architecture, yield components, nutritional quality and post-harvest traits. In some crops, editing can accelerate the development of a desired variant compared with repeated crossing and selection, particularly when the target gene is known and transformation is feasible. Examples in the research literature include efforts to improve disease resistance, alter fruit quality, reduce undesirable compounds and enhance stress tolerance. The value of an edited crop depends on more than the edit itself. Yield and quality are influenced by multiple genes, management and environment. Traits such as drought tolerance and heat resilience are usually complex and may require coordinated changes and multi-location testing. Off-target and unintended on-target changes, stability across generations, agronomic performance, food safety and environmental effects should be assessed using a framework appropriate to the product and jurisdiction.

Reducing crop losses and supporting climate adaptation

Editing may help produce crops that tolerate particular pathogens, salinity, heat or water limitation, or that use nutrients more efficiently. It could complement conventional breeding, marker-assisted selection, genomic selection and improved agronomy. It is not a substitute for sound soil management, integrated pest management, genetic diversity or resilient farming systems. Broad deployment should consider local seed systems, farmer needs, access to technology and the risk of concentrating production on a narrow genetic base.

Nutrition, food quality and processing

Potential applications include changing fatty-acid composition, modifying starch properties, reducing allergens or antinutritional factors, and improving the stability or nutritional profile of food. Each claim requires evidence: a molecular change does not automatically translate into improved nutrition, consumer acceptance or food safety. Product evaluation should examine composition, possible unintended changes, processing properties and the needs of intended consumers.

Food security and responsible deployment

CRISPR could shorten some breeding cycles and make certain genetic changes possible without introducing a large block of linked donor DNA. Nevertheless, transformation and regeneration remain difficult in many crop species and varieties. Regulatory requirements differ between countries and depend on the product and the nature of the modification. Public engagement, transparent evidence and equitable access are important for ensuring that benefits reach smallholder farmers and diverse production systems.

Applications in animal genetics, breeding and veterinary science**Functional genomics and disease-resistance research**

In livestock, CRISPR can be used to test gene function, investigate immune responses and generate models for inherited disease. It may help identify biological pathways associated with susceptibility or resistance to infectious diseases, heat stress, fertility, growth and product quality. Candidate genes discovered in experimental systems still require validation in the target breed and production environment.

Potential contributions to animal breeding

CRISPR could, in principle, introduce a known favourable allele, remove a harmful variant or alter a specific gene with a large and well-characterized effect. Research has investigated edits relevant to disease resistance, production traits and animal welfare. Such approaches may complement conventional selection and genomic selection, particularly where the desired change is well defined. They should not be viewed as a replacement for breeding programmes, which must balance many traits across generations.

Livestock traits such as milk yield, fertility, longevity, feed efficiency, resilience and methane emissions are generally polygenic and affected by management and environment. Selecting animals only for a single edited trait could create trade-offs. Breeding decisions therefore need multi-trait objectives, genetic diversity safeguards, assessment of inbreeding and evaluation of the edited allele in the intended production system.

Animal welfare and production-system fit

Any proposed edit must be assessed for effects on animal health, behaviour, reproduction and lifetime welfare. An edit that improves one production measure but causes pain, developmental problems or reduced resilience would not represent a sustainable improvement. Evaluation should include off-target analysis, possible mosaicism, heritability where relevant, reproductive performance, health monitoring and independent welfare review.

Poultry, aquaculture and veterinary diagnostics

CRISPR can support functional studies in poultry and fish, including research into resistance to infectious disease, reproductive biology and production traits. Practical application may be limited by embryo biology, delivery, generation time, regulatory status and public acceptance. In veterinary diagnostics, CRISPR-based assays are being investigated for rapid detection of pathogens in livestock, poultry, companion animals and aquaculture. Faster detection could support outbreak response, but field assays require robust validation against established diagnostic methods.

Relevance to resource-limited and smallholder systems

For smallholder production systems, a technically sophisticated edit has value only if it improves outcomes under real conditions and is accessible to farmers. Breed suitability, local adaptation, veterinary infrastructure, feed availability, affordability and conservation of indigenous genetic resources must remain central. CRISPR should complement, not undermine, community-based breeding and conservation programmes.

Industrial biotechnology, microbiomes and environmental applications**Microbial and industrial biotechnology**

CRISPR editing and regulation are used to study and engineer microorganisms for the production of enzymes, biofuels, organic acids, pharmaceuticals, food ingredients and other valuable compounds. Multiplex editing can help optimize metabolic pathways, while

CRISPR interference can reduce expression of competing pathways without permanently changing DNA sequence. Industrial strains must be assessed for genetic stability, production consistency, containment and biosafety.

Microbiome research

Microbial communities influence human and animal health, agriculture, nutrient cycling and greenhouse-gas production. CRISPR-based tools may help investigate the role of particular microbes and, potentially, modify selected members of a community. Delivering editors into microbes in their natural environment is difficult, and microbiomes are complex systems where changes can have indirect effects. Environmental release or in situ microbiome editing therefore requires especially careful ecological assessment and governance.

Environmental monitoring and conservation research

CRISPR-based nucleic-acid detection may assist monitoring of pathogens or biological indicators. Genome editing is also being studied in organisms relevant to conservation, disease-vector control and climate-related research. These uses can raise ecological questions because organisms interact with food webs, populations and ecosystems. Gene-drive approaches, in particular, have the potential to spread genetic changes through populations and require risk assessment and governance beyond those applied to contained laboratory experiments.

CRISPR diagnostics and high-throughput screening

CRISPR-based diagnostics and CRISPR-based editing are related but distinct technologies. In diagnostics, the system recognizes a target sequence and produces a measurable signal; in editing, the goal is to alter a target or its expression. Cas12 and Cas13 platforms can provide sequence-specific recognition and, in certain systems, collateral cleavage of reporter molecules. Assays may be designed for pathogens, selected genetic variants or other biomarkers. The potential advantages of CRISPR diagnostics include target programmability, rapid redesign, high sequence discrimination and possible compatibility with portable formats. However, many assays still rely on nucleic-acid extraction or amplification, and contamination can cause false-positive results. A positive molecular signal does not always indicate viable pathogen or active disease. Clinical and veterinary validation must establish the intended use, sample type, detection limit, cross-reactivity, reproducibility and performance under field conditions. For functional genomics, guide-RNA libraries can target thousands of genes or regulatory elements in parallel. Positive-selection screens identify edits that improve survival or a measurable phenotype; negative-selection screens identify edits whose loss reduces fitness. Follow-up experiments are necessary because guide efficiency, off-target effects, copy-number variation and cell context can influence screen results. Used carefully, CRISPR screens are powerful tools for discovering disease mechanisms and prioritizing targets for further study.

Limitations, safety and ethical considerations

Off-target and unintended on-target changes

A guide RNA may sometimes direct an editor to partially matching sequences elsewhere in the genome. Improved guide design and high-fidelity enzymes can reduce some off-target activity, but no method guarantees that every unintended event will be absent. In addition, a correctly targeted double-strand break can lead to unexpected deletions, rearrangements or other structural changes. Validation should therefore examine both candidate off-target sites and possible unintended outcomes at the intended locus, using methods suited to the application.

Delivery and biological variability

CRISPR components must reach the right cells and, for many DNA-editing systems, the appropriate intracellular compartment. Viral vectors, lipid nanoparticles, electroporation and ribonucleoprotein delivery each have advantages and limitations. Delivery may be difficult in some tissues, crop varieties, livestock embryos or microbial communities. Editing efficiency and repair outcomes can also vary by cell type, developmental stage and genetic background.

Mosaicism, immune response and durability

When editing occurs at different times or with different outcomes among cells, an organism or tissue may become mosaic. This can complicate interpretation and affect safety. Cas proteins derived from microbes may trigger immune responses in some contexts. For therapies, durability and long-term consequences require monitoring; for breeding, heritability and stability across generations must be assessed.

Ethical and social questions

Somatic editing for treatment of an individual differs fundamentally from heritable germline editing, where changes may pass to future generations. Heritable human genome editing raises unresolved concerns about safety, consent of future individuals, equity and potential misuse. Animal editing raises welfare and ownership questions, while environmental applications may affect ecosystems beyond the intended target. Governance should be transparent, proportionate to risk and inclusive of affected communities.

Regulation, affordability and access

Regulatory frameworks vary by country, product and application. Intellectual property, manufacturing infrastructure, expertise and treatment costs can limit access. The benefits of CRISPR may be distributed unevenly unless research priorities, public funding, technology transfer and deployment strategies consider underserved communities. Responsible innovation includes not only technical performance but also affordability, social value and accountability.

Future directions and research priorities

Future progress is likely to come from improving precision, expanding target compatibility, developing smaller or more efficient editors, and delivering them selectively to relevant tissues and organisms. Base and prime editing may extend the range of changes that can be introduced without conventional double-strand breaks, while CRISPR-associated diagnostic platforms may become more useful in decentralized testing. Artificial intelligence and computational modelling can support guide design, predict editing outcomes and prioritize targets, but predictions must be experimentally validated. For agriculture and animal breeding, priority areas include editing complex traits without sacrificing genetic diversity, robust delivery methods, transparent evaluation of animal welfare, and field trials across environments. For human health, priorities include safer delivery, improved control of editing activity, comprehensive genomic assessment, long-term follow-up and manufacturing that meets clinical standards. For environmental applications, ecological modelling, containment where feasible, monitoring and community consultation are essential. A practical development pathway should begin with a clearly defined need and a strong biological rationale. Researchers should compare CRISPR with non-editing alternatives, establish measurable success criteria, validate the molecular change and phenotype, assess unintended effects, and conduct appropriate risk and stakeholder review before deployment. The most suitable tool is not necessarily the newest editor; it is the one that solves the defined problem with acceptable risk and verifiable benefit.

Conclusion

CRISPR systems have become a versatile platform for manipulating and interrogating nucleic acids. Their main advantages, programmability, scalability, multiplexing, relative ease of redesign and the availability of multiple editing and regulatory modalities, have accelerated basic research and created opportunities in medicine, diagnostics, crop science, animal genetics, industrial biotechnology and environmental research. The technology is especially valuable when a target is biologically well understood and the required change can be measured rigorously. At the same time, CRISPR is not a universal solution. Editing outcomes depend on the biological context, and challenges involving unintended changes, delivery, immune responses, animal welfare, ecological effects, regulation and affordability remain important. Responsible use therefore requires a combination of molecular precision, phenotypic validation, appropriate oversight and fair access. CRISPR is best regarded as a

powerful addition to the wider toolkit of genetics and biotechnology, to be used alongside conventional breeding, genomic selection, established diagnostics and other approaches when they offer the most appropriate solution.

Table 1. Overview of major CRISPR application areas

Application area	Potential uses	Key considerations
Human health	Disease models, functional screens, selected gene and cell therapies, cancer research, diagnostics	Delivery, unintended edits, immune responses, clinical validation and cost
Plant science	Disease resistance, quality traits, stress tolerance, nutrition, faster targeted breeding	Transformation limits, complex traits, environmental assessment, regulation and access
Animal genetics	Gene-function studies, disease-resistance research, selected trait edits, veterinary diagnostics	Welfare, mosaicism, polygenic traits, genetic diversity and breed-system fit
Industrial biotechnology	Microbial strain engineering, pathway optimization, enzymes and bioproducts	Genetic stability, containment, scale-up and biosafety
Microbiomes/environment	Microbial research, nucleic-acid monitoring, possible targeted interventions	Delivery into communities, ecological uncertainty and governance
Diagnostics	Sequence-specific detection of pathogens and genetic variants; portable assay potential	Sample preparation, contamination, sensitivity/specificity and field validation

References

1. Anzalone, A.V., Randolph, P.B., Davis, J.R., et al. (2019). Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature*, 576, 149-157.
2. Chen, K., Wang, Y., Zhang, R., Zhang, H. and Gao, C. (2019). CRISPR/Cas genome editing and precision plant breeding in agriculture. *Annual Review of Plant Biology*, 70, 667-697.
3. Doudna, J.A. and Charpentier, E. (2014). The new frontier of genome engineering with CRISPR-Cas9. *Science*, 346(6213), 1258096.
4. FDA (2023). FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease. U.S. Food and Drug Administration.
5. Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J.A. and Charpentier, E. (2012). A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science*, 337(6096), 816-821.
6. Komor, A.C., Kim, Y.B., Packer, M.S., Zuris, J.A. and Liu, D.R. (2016). Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*, 533, 420-424.
7. Rees, H.A. and Liu, D.R. (2018). Base editing: precision chemistry on the genome and transcriptome of living cells. *Nature Reviews Genetics*, 19, 770-788.
8. Shalem, O., Sanjana, N.E., Hartenian, E., et al. (2014). Genome-scale CRISPR-Cas9 knockout screening in human cells. *Science*, 343(6166), 84-87.
9. Tanny, T., Soda, N. and Nguyen, N.-T. (2023). CRISPR/Cas-based diagnostics in agricultural applications. *Journal of Agricultural and Food Chemistry*, 71(31), 11765-11781.

10. Tavakoli, K., Pour-Aboughadareh, A., Kianpour, F., Poczai, P. and Etminan, A. (2021). Applications of CRISPR-Cas9 as an advanced genome editing system in life sciences. *BioTech*, 10(3), 14.
11. United States Food and Drug Administration (2024). CASGEVY. FDA product information and approval materials.
12. Wang, T., Wei, J.J., Sabatini, D.M. and Lander, E.S. (2014). Genetic screens in human cells using the CRISPR-Cas9 system. *Science*, 343(6166), 80-84.
13. Xu, Y. and Li, Z. (2020). CRISPR-Cas systems: Overview, innovations and applications in human disease research and gene therapy. *Computational and Structural Biotechnology Journal*, 18, 2401-2415.
14. Zetsche, B., Gootenberg, J.S., Abudayyeh, O.O., et al. (2015). Cpf1 is a single RNA-guided endonuclease of a class 2 CRISPR-Cas system. *Cell*, 163(3), 759-771.
15. World Health Organization (2021). Human genome editing: recommendations. World Health Organization, Geneva.