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CURRENT STATUS AND PROSPECTS OF GENOME EDITING TECHNOLOGIES

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Over the last few years, genomic editing technologies have become one of the most dynamic areas of modern science, which provides new development opportunities for medicine, agriculture and fundamental science. The presented review article analyzes modern genome editing technologies, including CRISPR/CAS systems of the new generation (CAS12, CAS13, CasΦ), basic editing (BASE EDITING), as well as the latest developments in Prime Editing. Particular attention is paid to the achievement in the editing of human somatic cells, the editing of embryos, the use of technology in agriculture. The prospects for the use of genomic editing in the treatment of hereditary diseases, oncology, infectious medicine, improving the productivity of animals and plants, as well as to increase the potential of synthetic biology are outlined. The key trends and forecasts for the further development of the research area are generalized.
Keywords: **genome, polymorphism, CRISPR, genome editing, epigenetic editing, bioethics, gene therapy, synthetic biology**

СУЧАСНИЙ СТАН ТА ПЕРСПЕКТИВИ ТЕХНОЛОГІЙ ГЕНОМНОГО РЕДАГУВАННЯ

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За останні декілька років технології геномного редагування стали одним із найдинамічніших напрямів сучасної науки, який надає нові можливості розвитку для медицини, сільського господарства та фундаментальної науки. У представленій оглядовій статті проаналізовано сучасні технології редагування геному, зокрема CRISPR/Cas-системи нового покоління (Cas12, Cas13, CasΦ), базове редагування (base editing), а також найновіші розробки в галузі prime editing. Особливу увагу приділено досягненням у редагуванні соматичних клітин людини, редагуванні ембріонів, застосуванню технології у сільському господарстві. Окреслено перспективи застосування геномного редагування у терапії спадкових хвороб, онкології, інфекційній медицині, покращенні продуктивності тварин і рослин, а також для підвищення потенціалу синтетичної біології. Узагальнено ключові тенденції та прогнози щодо подальшого розвитку даного напряму досліджень.
Ключові слова: **геном, поліморфізм, CRISPR, редагування геному, епігенетичне редагування, біоетика, генна терапія, синтетична біологія**

Addressing issues of directed genome editing is relevant both for global fundamental science and for applied aspects of farm animal breeding (Doudna & Charpentier, 2014). Over the past decade, genome editing has transformed from an experimental technology into one of the most promising tools in biomedical science and biotechnology. Modern approaches to modifying genetic material open up unprecedented opportunities for precise intervention in the functioning of cells, tissues, and entire organisms, creating the potential for treating diseases, modifying phenotypes, and even creating new biological properties (Adli, 2022; Xu et al., 2021). The evolution of this field is unfolding against the backdrop of the rapid development of related disciplines – artificial intelligence, nanotechnology, proteomics, epigenomics, and synthetic biology, which mutually enhance the effectiveness of editing tools.

CRISPR/Cas9 technology has made a scientific breakthrough in the field of genome editing in recent years. After the first reports of mammalian genome editing using the CRISPR/Cas9 system, a number of approaches have been developed to modify Cas family proteins. A number of works are devoted to the use of CRISPR/Cas9 not only for genome editing, but also for controlling the expression of specific genes, localization of individual DNA loci, changing the status of specified sites in the mammalian genome, etc. (Jaganathan et al., 2018; Doudna & Charpentier, 2014). Since 2020, there has been an exponential increase in research on new enzymatic systems – in particular, Cas12f, Cas13e, CasMINI, as well as CasΦ, which have smaller sizes, higher specificity and are suitable for delivery by adenoviral or lipid carriers (Adli, 2022). Methods for editing without double-stranded DNA breaks have also been actively developed: *base editing systems* (Komor et al., 2016) and *prime editing* (Anzalone et al., 2019) demonstrate high accuracy and low side effects, which allows correcting point mutations without inducing a cascade of DNA damage. Considerable attention in the global scientific community has been paid to the latest RNA editing platforms, such as REPAIR, RESCUE and LEAPER, which allow for temporary and reversible regulation of gene expression at the transcript level without interfering with the genomic sequence. These methods are promising for the treatment of diseases, as well as in cases where DNA editing is unethical or technically difficult.

In vivo approaches for delivering editing systems to target tissues are being intensively developed: in particular, the use of galactoid lipid nanoparticles for the liver, conjugated oligonucleotides for selective binding to neurons or muscle cells, and new generation viral vectors (AAV9, LentiCRISPR 2.0) (Nelson et al., 2023). In this context, the *ex vivo* editing strategy is being developed, where cells are modified outside the body and then returned via autologous transplantation, which reduces the risks of an immune response (Frangoul et al., 2021).

In addition, genome editing is actively implemented in the fields of agrogenomics, veterinary medicine, cell engineering and environmental management (Abdul Aziz et al., 2022). In particular, modified varieties of agricultural crops with increased resistance to drought, pests and diseases have been created (Zhang et al., 2015), as well as animals with improved meat, dairy or reproductive characteristics (Doudna, 2014). In parallel, *gene drive* concepts are being developed – systems that ensure the spread of desired alleles in insect populations, in particular to combat malaria (Hammond et al., 2016).

However, despite rapid progress, this area faces a number of problems, namely:

1. the presence of various off-target editing effects;
2. legal and patent fragmentation (dispute between the Broad Institute and UC Berkeley over CRISPR patents);
3. lack of global ethical consensus on germline editing;
4. risks of socially unequal access to technology (Baylis, 2021).

In this context, a systematic analysis of the current state of genome editing technologies is critically important for the scientific community, as it allows not only to assess the technical potential of the technologies, but also to develop strategic "roadmaps" for future development. The aim of the presented article is, therefore, to summarize key achievements, classify modern

technologies, analyze the areas of application, scientific, ethical and regulatory areas that require further research.

General scientific, comparative, bibliographic and search methods were used to conduct analytical research. The article is based on the analysis of the results of specialized scientific literature and publications on genome editing, presented in leading world journals, including *Nature, Science, Cell, Nature Biotechnology*, etc.

The development of CRISPR/Cas9 technology (*clustered regulatory interspaced short palindromic repeats,* short palindromic repeats, arranged in groups, evenly spaced from each other) led to a long-awaited breakthrough in the field of genome editing. To date, it is one of the most effective systems for genome editing, which is used in a variety of fields of biological sciences (Haas et al., 2017; Lamas-Toranzo et al., 2017; Lino et al., 2018). The principle of operation of this technology is that changes to the target site are provided by a complex of a single chimeric guide RNA (*single guide RNA, sgRNA*) and a multifunctional protein – the Cas9 nuclease, which is capable of introducing a double-strand break into the target DNA molecule. The selection of the target sequence is limited by the presence of the PAM motif (*protospacer-adjacentmotif*), which consists of 3 NGG nucleotides (Jaganathan et al., 2018; Doudna et al., 2014; Ma et al.,2014, Li Hongyi, 2020). After the first information about editing the mammalian genome by the CRISPR/Cas9 system appeared, many methods were proposed with various modifications of the Cas family proteins or guide RNA. Using the CRISPR/Cas9 system, it is possible to edit a virtually unlimited number of genes simultaneously, as well as introduce components of the system into individual cells and systems of the body.

The CRISPR/Cas9 system consists of two main parts. The first is a protein, the Cas9 nuclease (which initiates a double-strand break in the DNA molecule). The second is an RNA molecule, about 120 nucleotides in size, called a chimeric guide RNA (sgRNA). About 100 nucleotides located at the 3′-end are the same for all guide RNAs and ensure the formation of a specific spatial structure that is recognized by the Cas9 protein. About 20 nucleotides (guide sequence) located at the 5′-end of the guide RNA determine the DNA sequence to which the Cas9 protein will bind. The Cas9 protein introduces a double-strand break into the DNA molecule at a site complementary to the 5′-sequence of the sgRNA, provided that immediately after the complementary site of the sgRNA there is a trinucleotide NGG (PAM), and it must be located on the non-coding (complementary) strand. DNA cutting occurs at a distance of 3–4 nucleotides from the PAM. This is where the work of the CRISPR/Cas9 system ends, and further genome modification occurs directly with the participation of the cell's DNA repair system.

Double-strand breaks in mammalian cells can be repaired in a variety of ways. In non-homologous end joining (NHEJ) repair, small insertions or deletions may occur at the break site. In homologous recombination repair, sister chromatids or a genetic construct that mimics a sister chromatid are used to restore DNA sequence information.

In general, there are three main options for genome modification using the CRISPR/Cas9 system. The first type of modification is the formation of small insertions or deletions (INDEL – INsertion or DELetion). The size of such modifications can range from one to several dozen base pairs, but, as a rule, affects from 1 to 10 nucleotides. Most often, INDEL formation is used for gene knockout, while INDEL can lead to a shift in the reading frame or destruction of the splice site. To carry out such a modification, it is necessary to ensure the expression of one sgRNA (specific for the modified region) and the Cas9 protein.

The second option is to insert a target DNA sequence into a specific region of the genome. To do this, the CRISPR/Cas9 system introduces a break into a specific DNA fragment that needs to be modified. At the same time, an artificial DNA fragment containing the inserted region flanked by sequences homologous to the break site (a homologous recombination construct) is delivered to the cell. The homologous recombination construct mimics a sister chromatid, and the information from it is “copied” to the break site.

The third option is to create large (from hundreds to hundreds of thousands of base pairs) deletions. The simplest method of such modification is to express in the cell the Cas9 protein and two sgRNAs, each of which will carry a nucleotide sequence at the 5'-end complementary to one of the boundaries of the intended deletion. As a result, two breaks will appear in the chromosome, the ends of which can be connected using the NHEJ mechanism, which will lead to the appearance of the desired deletion.

Despite the rapid progress in the implementation of CRISPR/Cas9 technology, the use of this system requires improvement and refinement at many stages, depending on the selected modification object and the ultimate goal. For example, an important aspect is the selection and analysis of the nucleotide sequence of sgRNA (chimeric) using various software, which is related to the design of the planned experiment, the presence of PAM, depending on the modification – the presence of restriction endonuclease recognition sites; in the case of introducing INDEL, with subsequent identification by PCR, it is necessary to simultaneously select appropriate primers and conditions for PCR analysis with gRNA, analyze alternative splicing variants, the presence of alternative promoters and start codons, domain organization of the protein to exclude partial loss of function); to determine and select a method for genome editing using the CRISPR/Cas9 system by microinjection; establish conditions for obtaining and cultivating stem cells, transgenic embryos and genetically modified animals, and many other specific aspects.

There are other genome editing methods that, unlike CRISPR/Cas9 technology, have their own characteristics. The most common include the following: TALEN (these are engineered proteins that can be designed to bind and cleave specific DNA sequences. This method is more complex and time-consuming compared to CRISPR-Cas9 (Joung et al., 2013; Bhardwaj et al., 2021; Nemudryi et al., 2014); *zinc finger* nucleases (ZFN) – proteins that contain DNA-binding and nuclease domains have lower efficiency and specificity compared to TALEN and CRISPR-Cas9 (Maeder Morgan et al., 2008); base *editing* and Prime editing – based on modifications of the CRISPR/Cas system (Rees *Holly* et al., 2018; Kantor Ariel et al., 2020; Chen et al., 2023; Huang Zhangrao & Liu Gang, 2023).

In general, a comprehensive classification, analysis, and description of the main genome editing methods most widely used in basic and applied research can be presented in the form of several common components:

classical nuclease systems (ZFN (*Zinc Finger Nucleases*), TALEN (*Transcription Activator-Like Effector Nucleases*))*;*

New generation CRISPR systems (CRISPR/Cas9, CRISPR/Cas12a (Cpf1), CRISPR/Cas13a-d (RNA editing), CRISPR/CasΦ (compact Cas from bacteriophages), CRISPR-CasMINI (Cas12f, Cas14);

point editing systems (Base Editing (cytosine or adenine deaminase modification), Prime Editing (editing without double-stranded DNA breaks)*;*

other approaches (REPAIR, LEAPER (RNA editing without cutting), CRISPRoff/CRISPRon (epigenomic editing)).

In turn, the general protocols of the main editing technologies include several variants. The classic CRISPR/Cas9 protocol for *knock-out* or *knock-in* (materials: cell culture, plasmid with sgRNA and Cas9 (e.g., pSpCas9(BB)-2A-GFP), transfection reagent (Lipofectamine 3000, electroporation buffer), donor template (ssODN or plasmid with homologous arms for knock-in); methodology: sgRNA design using Benchling/CHOPCHOP, cloning of sgRNA into a vector or synthesis, as an RNP complex , cell transfection (lipofection, nucleofection, microinjection), 24–72 h – selection of transfected cells (e.g., FACS for GFP), PCR amplification and Sanger-sequencing of the editing site, T7E1 assay or Surveyor assay – to assess the efficiency of the cut, if knock-in: selection of homologously integrated clones (PCR, Southern blot). *Base Editing* protocol (e.g., BE4max, ABE8e) – point substitution C→T or A→G without double-strand breaks; materials: plasmid with base editor (e.g., BE4max), sgRNA template, cell culture; protocol: selection of the editing site in the “edited window” (positions 4–8 from PAM), co-transfection of cells with base

editor and sgRNA plasmids, incubation for 72–96 h, selection of positive cells (fluorescent marker or selection gene), PCR and sequencing – verification of a specific point substitution. Prime Editing protocol (e.g., PE2, PE3) – all types of point mutations, insertions, deletions; materials: Prime Editor (Cas9-nickase + reverse transcriptase), pegRNA (prime editing guide RNA), nicking sgRNA (for PE3), target cells; protocol: pegRNA design based on the target site (PrimeDesign, pegFinder), co-transfection of PE cells and pegRNA ± nicking sgRNA, 48–72 h cultivation, selection and sequencing – detection of precise editing. RNA editing protocol (Cas13, ADAR-based systems); materials: Cas13a-d enzyme, gRNA to target mRNA, cells expressing target gene mRNA; protocol: synthesis of crRNA for Cas13, co-transfection of Cas13 + crRNA, RT-qPCR – control of mRNA expression. RNA-seq – verification of editing specificity. CRISPRoff / epigenome editing protocol (temporary or stable gene silencing without changing the DNA sequence); protocol: use of dCas9 (deactivated Cas9) with repression domains (KRAB), cloning of sgRNA to the promoter region of the target gene, transfection of cells, qPCR/ChIP-seq – verification of repression efficiency.

The main methods for delivering editing components include: microinjection – the most accurate for zygotes (embryo editing); electroporation – popular in editing hematopoietic stem cells; lipid nanoparticles (LNP) – for in vivo delivery (especially for Cas13); AAV vectors – the most effective for *in vivo knock-in* (have size limitations).

Main analytical and control methods of genome editing: Sanger sequencing, Next Generation Sequencing (NGS) – verification of changes; TIDE, ICE analysis – assessment of editing efficiency; Off-target screening (GUIDE-seq, CIRCLE-seq, Digenome-seq, Western blot, qPCR, FACS) – functional verification using analytical tools.

Gene editing technologies have great prospects in medicine for the treatment of various genetic disorders and diseases – in recent years, the possibility of their application for the development of new methods of treatment of mitochondrial pathologies, oncopathologies and other human diseases (Mittal et al., 2019). For example, in November 2017, the world's first procedure to "edit" the genome of an adult was performed in California. The patient was an adult man with mucopolysaccharidosis type II (Hunter syndrome). In November 2018, Chinese scientists reported on twins (Lulu and Nana), who were the first children in the world to have their HIV resistance gene edited (Cyranoski, 2019).

Genome editing can also be used as a tool for gene therapy (Gori Jennifer et al., 2015; Maeder Morgan & Gersbach Charles, 2016). Both genome editing and gene therapy are modifications of genetic material to treat disease, but they differ in approach and goals. Gene therapy involves introducing new genetic material into a patient’s cells for treatment. This can be done by introducing a healthy copy of a defective gene, replacing a missing or non-functioning gene, or introducing a new gene that may provide a therapeutic benefit. For example, genome editing can be used to modify the DNA of a patient's own cells to introduce therapeutic genes or to correct mutations in a patient's genes before they are introduced as part of an overall treatment plan (Gori Jennifer et al., 2015; Maeder Morgan & Gersbach Charles, 2016). Overall, both genome editing and gene therapy hold great promise for treating genetic diseases, and ongoing research continues to refine these techniques and develop new applications for them (Doudna, 2014). Modern genome editing is rapidly transforming fundamental approaches to the diagnosis, prevention, and treatment of genetic and many acquired diseases in humans. Over the past decade, fundamentally new results have been achieved that have brought genome editing technologies from the laboratory level to the clinical arena. Today, CRISPR/Cas systems, as well as innovative approaches such as *Base Editing, Prime Editing,* RNA editing (e.g., LEAPER and Cas13), allow for highly specific changes in the genetic code without creating double-strand breaks or integrating foreign sequences (Anzalone et al., 2019).

Among the most important achievements is the approval of the world's first CRISPR-Cas9-based therapy for the treatment of sickle cell anemia and β-thalassemia (the drug Casgevy, exa-cel), which became a historical precedent for the clinical use of genome editing (Frangoul et al.,

2021). This event marked the transition from experimental therapies to real clinical practice, demonstrating the high efficacy and relative safety of the technology. In December 2023, the US Food and Drug Administration (FDA) and the UK Medicines Regulatory Agency (MHRA) approved the first CRISPR-based therapy for the treatment of sickle cell anemia and β-thalassemia (FDA, 2023; MHRA, 2023). Casgevy (exagamglogene autotemcel, or exa-cel), developed by Vertex Pharmaceuticals and CRISPR Therapeutics, is a single-agent therapy that involves extracting a patient's hematopoietic stem cells, editing them *ex vivo* to activate fetal hemoglobin (HbF) production, and reinfusing them after mild myeloablative chemotherapy. In clinical trials, 29 of 31 patients with sickle cell anemia were free of painful crises for at least a year after treatment, demonstrating the efficacy of the therapy (Frangoul et al., 2021). This approach opens up new possibilities for patients who previously had limited treatment options. Researchers from St. Jude Children's Research Hospital used *Prime Editing technology* to correct a mutation that causes sickle cell anemia, achieving up to 41% conversion in patients' blood stem cells, demonstrating the potential of *Prime Editing* in the treatment of monogenic diseases.

Researchers at the University Medical Center Amsterdam have used CRISPR-Cas9 technology to remove HIV from infected cells in the laboratory (Kaminski et al., 2016). Although the research is in its early stages, this discovery offers hope for future treatments for HIV infection. The Kleinstiver lab has demonstrated the efficiency of base editing in cells from patients with SMA (spinal muscular atrophy), achieving over 98% editing with high accuracy and minimal off-target effects (Ryu et al., 2018). *Prime Editing* has been successfully applied to treat hereditary tyrosinemia type 1 (HT1) in mice, leading to significant improvements in survival and liver function (Kim et al., 2021). There have also been successes in the treatment of α1-antitrypsin deficiency (AATD) using AAV8-PE3, achieving editing efficiencies of up to 3.1% with minimal indels (Villiger et al., 2018). Application of editing RNA Cas13 and LEAPER (Leveraging Endogenous ADAR for Programmable Editing on RNA) allows RNA editing without changing DNA, which reduces the risk of hereditary changes. In cells from patients with Hurler syndrome, LEAPER restored the functional activity of the enzyme α-L-iduronidase with an efficiency of up to 80% (Qu et al., 2019). This opens up new possibilities for the treatment of genetic diseases where temporary RNA editing is preferable. In the UK, a 13-year-old patient with acute lymphoblastic leukemia received treatment using edited CAR-T cells, which led to a complete remission of the disease (Brudno et al., 2020). This is the first known case of successful use of base editing in the treatment of cancer in humans. Base editing technology allows precise gene editing without creating double-stranded DNA breaks, which reduces the risk of unwanted mutations. Verve Therapeutics has developed VERVE-101, a therapy that uses base editing to inactivate the PCSK9 gene in patients with heterozygous hypercholesterolemia (Musunuru et al., 2021). In a phase 1b clinical trial, a single dose of VERVE-101 reduced blood LDL cholesterol levels by 55% in 10 participants (Musunuru et al., 2023). This demonstrates the potential of base editing in the treatment of cardiovascular disease.

Base editing techniques show great potential in the treatment of point mutations, which account for up to 58% of all known diseases associated with single nucleotide mutations (Rees Holly & Liu David, 2018). This technology provides high editing accuracy, allowing the replacement, deletion or insertion of DNA fragments without the formation of breaks in the double helix. The first preclinical and clinical data indicate that these methods can be applied to the treatment of complex multigenic pathologies and even tumors (Anzalone et al., 2019).

In vivo editing methods are particularly promising , in particular in the studies of Intellia Therapeutics, which for the first time in the world demonstrated the effective delivery of CRISPR components directly into the patient's body with a long-lasting therapeutic effect (NTLA-2002) (Gillmore et al., 2021). This may be the basis for the future development of cell-free editing strategies that will avoid the expensive immunosuppressive preparation for exogenous cell transplantation.

RNA editing, as a temporary but controlled alternative to DNA editing, allows for safe interventions in the transcriptome. The LEAPER and REPAIR systems based on the ADAR and Cas13 enzymes, respectively, are already being used in models of neurodegenerative and metabolic diseases (Qu et al., 2019). Such approaches are of paramount importance for the treatment of diseases where genetic stability is particularly critical.

A separate direction of development is genetically modified CAR-T and CAR-NK cells, which, thanks to CRISPR/Cas editing, acquire new properties, such as resistance to exhaustion, greater precision in recognizing tumor cells, and avoidance of *graft-versus-host disease reactions*. Successful clinical cases (in particular, complete remission in patients with acute leukemia) confirm the feasibility of integrating genome editing into oncoimmunological strategies (Rupp et al., 2017).

Scientific developments in the field of genome editing are gradually moving from the stage of conceptual breakthroughs to routine use in therapeutic practices. It is expected that by 2030, about 60 new drugs based on CRISPR/Cas and related technologies will reach commercial availability (Wang et al., 2021). Accordingly, in the near future, we can predict the widespread implementation of genome editing in the treatment of currently incurable diseases: muscular dystrophies, neurodegenerative conditions, autoimmune pathologies, rare metabolic syndromes.

Gene editing plays a crucial role in the biotechnology and pharmaceutical industries. It is used to produce genetically modified organisms for research, drug production, and biofuel development (Kumar et al., 2020; Grama et al., 2022; Tavakoli et al., 2021). In addition, gene editing is used to enhance the production of enzymes, proteins, and other valuable biomolecules (Kumar Gulshan et al., 2020; Grama Samir et al.,2022; Tavakoli Kamand et al, 2021).

The advantages of CRISPR/Cas9 make it possible to use this technology to edit the genomes of viruses, bacteria, plants and animals. This area of research also opens up great prospects for developing new approaches to combating diseases, will contribute to the improvement of breeds of farm animals and plant varieties, as well as the creation of models for studying human genetic diseases. CRISPR/Cas9 technology can increase the efficiency of agriculture, while reducing the negative impact of humans on the environment. Over the past few years, the United States Department of Agriculture has granted permission to cultivate six organisms modified with the help of CRISPR, including garden mushrooms (*Agaricus bisporus*), which are deprived of the ability to darken when mechanically damaged and lose their marketable appearance; camellia (*Camelina sativa*), an oilseed crop that contains more omega-3 fatty acids, as well as a drought-resistant soybean variety (Waltz, 2018). Researchers plan to breed chickens that do not cause allergies in humans, restore the number of honeybees that suffer from diseases and parasites worldwide, and use CRISPR to control the sex of farm animals (Ledford, 2019). The ability to modify the genomes of exotic and little-studied animals has caused a “wave” of mass creation of new model organisms. In March 2019, the first genetically modified reptile, the brown anole (*Anolis sagrei*), was created using CRISPR (Reardon, 2019). Genome editing is being used to create crops with improved properties, such as herbicide-resistant soybeans, drought-resistant corn, and apples that do not turn brown (Wang et al., 2020). Gene-edited livestock and fish have also been created with desirable traits, such as increased muscle mass or disease resistance (Zaidi, Syed Shan-e-Ali, et al., 2020; Abdul Aziz, et al., 2022; Hamdan, Mohd Fadhli, et al., 2022; Wan, Lili, et al. 2021).

CRISPR/Cas technology has a number of advantages in animal breeding, including: editing accuracy – CRISPR allows for changes to specific genes with high precision, reducing the risk of unwanted mutations that can occur with traditional breeding methods; speed – genome editing processes using CRISPR are much faster than traditional breeding methods, allowing results to be obtained in a short period of time; improvement of genetic traits – with the help of CRISPR, it is possible to improve the morphological, productive and adaptive properties of animals, such as disease resistance, meat and milk quality; control of the sex of the offspring – CRISPR allows you to control the sex ratio in the offspring, which is useful for livestock production, where only

animals of a certain sex are needed; research on genetic diseases – CRISPR helps to study genetic diseases in animals, which can lead to the development of new treatment strategies; environmental benefits – creating animals with improved characteristics can reduce the need for the use of chemical additives and improve the overall environmental condition in livestock farming.

However, despite the broad prospects of genome editing, the scientific community should not neglect the ethical, bioengineering and safety challenges. One of the main problems remains *off-target* effects, which can still have long-term consequences in cases of germline cell treatment. Also of concern are technologies related to interference with embryonic development (Human Embryo Genome Editing), which are currently largely prohibited at the legislative level in most countries (Lanphier et al., 2015).

Conclusions.

This review provides a comprehensive analysis of the current state and future prospects of genome editing technologies, particularly new-generation CRISPR/Cas systems, base and prime editing methods, as well as innovative platforms for RNA and epigenetic editing. The key findings are as follows:

1. **Technological progress and expansion of the editing toolbox.**

The development of CRISPR/Cas systems (Cas12, Cas13, CasΦ, and their compact variants) has significantly improved the precision, specificity, and delivery convenience of editing complexes. Novel methods such as base editing and prime editing enable correction of point mutations without inducing double-stranded DNA breaks, thereby minimizing off-target effects and expanding the range of possible genetic modifications. Particular attention is given to RNA editing platforms (REPAIR, LEAPER), which open up temporary and reversible gene regulation strategies.

2. **Wide applications in medicine and agriculture.**

Genome editing technologies have demonstrated significant potential in the treatment of inherited diseases (e.g., hemoglobinopathies, spinal muscular atrophy), oncology (edited CAR-T cell therapy), infectious diseases (experimental removal of viral genes), and metabolic syndromes. In agriculture, new crop varieties with enhanced resistance to stress and pests have been created, along with animals possessing improved productivity and adaptive traits.

3. **Integration with adjacent technologies.**

The growing effectiveness of genome editing is closely linked with advancements in bioinformatics, artificial intelligence, nanotechnology, and synthetic biology. These synergies enable more accurate design of editing molecules, better delivery strategies, and comprehensive control over editing outcomes.

4. **Ethical and regulatory challenges.**

Despite scientific breakthroughs, critical barriers remain, including the lack of global consensus on germline editing, risks of off-target effects, and social inequality in access to genome-editing technologies. There is a pressing need for the development of transparent international norms and ethical frameworks to ensure the responsible and safe use of genome editing.

5. **Practical significance and implementation prospects.**

Recent achievements are rapidly translating genome editing from laboratory research into clinical practice and agricultural technology. The approval of the first CRISPR-based drugs highlights the high efficiency and transformative potential of these tools, paving the way for dozens of new therapeutics in the coming decade. In agriculture, genome editing promotes more sustainable and environmentally friendly production systems.

Therefore, the primary objective of this review was systematization of current genome editing methods, classify them, and evaluate application domains. The provided analysis and technology comparisons offer valuable guidance for researchers and practitioners in selecting appropriate strategies based on their specific goals and research objects.

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