Current Pharmaceutical Letters and Reviews (CPLR)
Website: https://cplr.in/
ISSN: 3049-222X
Vol. 2, Issue 3, July-Sept, 2025
Page No.: 08-15

Review

CRISPR-CAS9 IN Oncology: Applications and Ethical Implications in Cancer Gene Editing

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DOI: *10.62896/cplr.2.3.02*

Conflict of interest: *NIL*

Article History
Received: 12/07/2025
Accepted: 28/08/2025
Published: 10/09/2025

Abstract:
CRISPR-Cas9, a revolutionary gene-editing technology, holds immense promise in the field of oncology, offering potential breakthroughs in cancer treatment. By enabling precise modifications of the genome, CRISPR-Cas9 offers new avenues for targeting and correcting genetic mutations that drive cancer progression. This paper explores the applications of CRISPR-Cas9 in cancer research and therapy, including tumor suppression, gene therapy, and immune cell enhancement. Additionally, it delves into the ethical concerns surrounding the technology, such as off-target effects, the possibility of germline editing, and the equitable distribution of gene therapies. As cancer remains one of the leading causes of death worldwide, CRISPR-Cas9 provides hope for more personalized and effective treatment options. However, these advancements are accompanied by significant ethical challenges that must be addressed to ensure safe and fair use of gene-editing technologies in clinical settings.

Keywords: CRISPR-Cas9, oncology, cancer gene editing, gene therapy, tumor suppression, ethical implications, off-target effects, immune cells, cancer treatment, genetic mutations.

1.1 Introduction:

The advent of CRISPR-Cas9 technology has ushered in a new era in genetics and molecular biology, offering unprecedented precision in gene editing. This innovative tool, derived from a natural defense mechanism in bacteria, enables scientists to make targeted alterations to DNA sequences, paving the way for advancements in treating genetic diseases, including cancer. In oncology, CRISPR-Cas9 presents opportunities for groundbreaking therapeutic strategies, such as the correction of mutations that drive cancer cell proliferation, targeted gene silencing, and enhancing immune system responses against tumors. As the technology progresses, it has the potential to revolutionize cancer treatment, moving beyond conventional methods like chemotherapy and radiation to more personalized and effective approaches.(1)

Despite its promise, the application of CRISPR-Cas9 in cancer treatment raises several ethical concerns that need to be addressed. The precision of the technology, though remarkable, does not guarantee complete accuracy, and unintended genetic changes—off-target effects—pose significant risks, including the potential for new mutations. Moreover, the use of CRISPR in human germline editing could have far-reaching implications, affecting future generations. Questions of access, affordability, and the possible creation of genetic disparities further complicate the integration of this technology into clinical practice. This paper explores both the immense potential of CRISPR-Cas9 in oncology and the ethical challenges it presents, aiming to offer a balanced perspective on its future role in cancer treatment.(2)

1.2 Introduction to CRISPR-Cas9 and its Mechanism of Action

CRISPR-Cas9 is a revolutionary gene-editing tool that enables precise modifications to the DNA of living organisms. The technology is based on a natural defense mechanism found in bacteria, where CRISPR (Clustered Regularly Interspaced Short

Palindromic Repeats) sequences and the associated Cas9 (CRISPR-associated protein 9) enzyme work together to recognize and cut viral DNA.(3)Scientists have harnessed this system to target specific sequences within the genome of any organism, making it possible to add, delete, or alter genetic material with unparalleled accuracy. In CRISPR-Cas9, a small RNA molecule guides the Cas9 enzyme to the exact location of the target DNA sequence. Once located, Cas9 acts like molecular scissors, cutting the DNA, which can then be repaired by the cell's own repair mechanisms. This cutting-edge technology has broad applications in research, medicine, and agriculture, with particular promise in the field of oncology for editing cancer-related genes.(4)

1.3 Overview of Cancer Genetics and the Role of Gene Mutations

Cancer is fundamentally a genetic disease caused by mutations that disrupt the normal regulatory mechanisms controlling cell growth and division. These mutations can be inherited or acquired during a person's lifetime due to environmental factors, lifestyle, or random errors in DNA replication.(5) The mutations can affect proto-oncogenes, which promote cell growth, or tumor suppressor genes, which prevent uncontrolled cell division. When these genes become mutated, they can either cause excessive cell proliferation (oncogenes) or fail to halt growth when necessary (inactivated tumor suppressor genes), leading to cancer. Additionally, mutations can affect DNA repair genes, making the cancer cells more prone to accumulating further mutations. Understanding the specific genetic alterations driving different types of cancers is crucial for developing targeted therapies. By identifying the mutations that drive tumor growth, scientists can use gene-editing technologies like CRISPR-Cas9 to correct these mutations and potentially stop the cancer's progression at a molecular level.(6)

1.4 CRISPR-Cas9 Applications in Cancer Research

CRISPR-Cas9 has opened new doors in cancer research by allowing scientists to study and manipulate genes that are directly involved in cancer initiation, progression, and metastasis. Researchers can use CRISPR to create more accurate cancer models in laboratory settings by editing specific genes known to be involved in various cancers. For example, by knocking out or introducing mutations into key cancer-related genes, scientists can observe the effects on cell growth, survival, and drug response.(7) Additionally, CRISPR has enabled the identification of new cancer targets by systematically screening large sets of genes for their roles in tumorigenesis. In therapeutic applications, CRISPR is being explored for directly editing cancer cells to correct mutations or deactivate genes that contribute to tumor growth. Moreover, CRISPR-based technologies have the potential to enhance immunotherapy by modifying immune cells like T-cells to better recognize and destroy cancer cells. These applications show the potential of CRISPR-Cas9 not only to further our understanding of cancer but also to develop personalized and more effective treatments.(8)

1.5 Targeting Cancer Genes: CRISPR for Tumor Suppression

CRISPR-Cas9 offers powerful potential for targeting the genes responsible for cancer development and progression. Tumors often arise due to mutations in tumor suppressor genes that control cell cycle checkpoints and apoptosis, as well as oncogenes that promote uncontrolled cell division.(9) By precisely editing these genes, CRISPR can be used to restore the normal function of tumor suppressor genes or inhibit the activity of oncogenes, thereby preventing the development and growth of tumors. For example, CRISPR can be utilized to introduce a functional copy of a mutated tumor suppressor gene, such as p53, or to knock down the expression of an overactive oncogene like MYC. This precise gene-editing capability provides a direct way to target the molecular drivers of cancer, allowing for highly tailored treatments that may prevent the onset of cancer or slow down its progression.(10)

1.6 Gene Therapy for Cancer: Potential and Challenges

Gene therapy represents one of the most promising therapeutic strategies for cancer treatment, and CRISPR-Cas9 has significantly advanced the field by enabling precise genetic modifications. The concept behind cancer gene therapy is to either replace defective genes, correct mutations, or introduce new genes into cancer cells to enhance their ability to fight the disease. CRISPR offers the ability to modify cancer-related genes in a highly targeted manner, potentially repairing or replacing damaged genetic material within tumor cells.(11) However, while gene therapy holds immense promise, it faces several challenges. One major concern is the efficient delivery of the CRISPR system to the right cells in the body, as well as ensuring that the editing process only occurs in the targeted cells, avoiding unwanted off-target effects. Additionally, the immune response to CRISPR components or delivery vectors could pose another hurdle. Despite these challenges, ongoing advancements in delivery methods and precision technology are making cancer gene therapy increasingly feasible, bringing it closer to becoming a routine treatment option.(12)

1.7 CRISPR-Cas9 in Immune Cell Enhancement for Cancer Immunotherapy

Cancer immunotherapy has emerged as a revolutionary approach in cancer treatment, harnessing the body's immune system to target and eliminate cancer cells. CRISPR-Cas9 is playing a pivotal role in enhancing immune cell therapies, particularly by genetically modifying immune cells like T-cells to improve their cancer-fighting capabilities. One well-known example is the development of CAR-T (Chimeric Antigen Receptor T-cell) therapy, where T-cells are genetically engineered to express receptors that allow them to recognize and attack cancer cells.(13) CRISPR can streamline this process, offering a more precise way to modify immune cells. For instance, CRISPR can be used to knock out genes that inhibit the immune system's ability to detect tumors or introduce genes that enhance the immune response. This has the potential to create more effective and targeted immune therapies, improving patient outcomes and expanding the use of immunotherapies to different cancer types. However, this approach is still in the experimental stages, and challenges such as ensuring safety, preventing immune resistance, and minimizing side effects remain to be fully addressed.(14)

1.8 Precision Medicine in Oncology: The Role of CRISPR-Cas9

Precision medicine in oncology refers to the tailoring of cancer treatment based on the specific genetic makeup of an individual's tumor. The goal is to identify the unique genetic mutations driving a particular cancer and select therapies that specifically target these molecular alterations. CRISPR-Cas9 is a powerful tool in the context of precision medicine, enabling the detailed study of individual cancer genomes and the identification of potential therapeutic targets.(15) By editing specific genes in patient-derived cancer models, CRISPR can help researchers discover novel biomarkers for cancer diagnosis and prognosis. Additionally, CRISPR allows for the development of more personalized therapies, where genetic modifications can be made to the patient's own cells, ensuring a treatment approach that is tailored to their genetic profile. The technology also plays a critical role in identifying new drug targets and testing potential treatments in a more precise and efficient manner. However, the integration of CRISPR into routine clinical practice in precision medicine still faces challenges, such as regulatory hurdles, cost, and ethical considerations related to genetic editing. Nonetheless, CRISPR's ability to provide highly targeted and individualized therapies makes it a promising cornerstone of the future of cancer care.(16)

1.9 Advancements in CRISPR-Cas9 for Targeted Cancer Treatment

Recent advancements in CRISPR-Cas9 technology have significantly improved its precision and effectiveness for targeted cancer treatment. In earlier versions of gene-editing, off-target effects—unintended genetic changes—were a significant concern, but recent modifications to CRISPR technology have addressed these issues. (17)Enhanced versions of the Cas9 enzyme, such as the high-fidelity Cas9, and innovations like base editing, allow for even more accurate and precise DNA modifications, minimizing the risk of altering unintended parts of the genome. Additionally, CRISPR-Cas9 can be coupled with other technologies, like nanoparticle-based delivery systems, to increase its efficiency in reaching tumor cells while minimizing damage to healthy tissues. These advancements have made CRISPR a promising candidate for direct gene therapy in cancer treatment, whether by repairing mutated genes in tumor cells, editing the immune system to recognize and attack cancer more effectively, or even creating cancer-resistant cells. As a result, CRISPR is being explored not only for traditional tumor gene editing but also for developing innovative approaches such as CRISPR-driven vaccines or personalized cancer therapies.(18)

1.10 Off-Target Effects: Risks and Mitigations in Cancer Gene Editing

While CRISPR-Cas9 has revolutionized gene editing, off-target effects remain one of the most significant risks when applying this technology in cancer therapy. Off-target effects occur when the Cas9 enzyme inadvertently cuts DNA at unintended sites, potentially causing harmful mutations. In the context of cancer, such mutations could lead to unanticipated cellular transformations, potentially exacerbating the disease or creating new issues such as tumor resistance or unforeseen genetic disorders. These risks are particularly critical in human clinical applications, where the precision of the gene-editing process directly influences patient safety. (19)To mitigate these risks, researchers have developed several strategies. Improved versions of the Cas9 enzyme, like the high-fidelity Cas9 and other engineered variants, have demonstrated significantly reduced off-target activity. Additionally, more advanced computational tools and genome-wide screening techniques are now available to predict and identify potential off-target sites before CRISPR is applied, providing a safeguard against unintended genetic alterations. Another strategy involves using CRISPR in a controlled, localized manner, such as targeting specific cancer cells while leaving healthy tissues unaffected. Although these advancements have helped reduce the risks of off-target effects, ongoing research and technological refinement are necessary to further improve the safety and accuracy of CRISPR-based cancer therapies.(20)

1.11 Ethical Implications of CRISPR-Cas9 in Cancer Therapy

The use of CRISPR-Cas9 in cancer therapy raises several ethical concerns that need to be carefully addressed before widespread clinical application. One major issue is the potential for germline editing, where changes to the genetic material in reproductive cells could be passed on to future generations. While this is more of a concern in hereditary genetic modifications than in somatic gene editing for cancer treatment, the implications for future generations cannot be ignored, particularly if off-target effects cause unintended, heritable changes.(21) Another key ethical consideration is the accessibility and equity of CRISPR-based cancer therapies. As these treatments may require sophisticated technology and highly personalized approaches, there is a risk that only wealthier patients or developed nations will benefit from these breakthroughs, exacerbating health disparities. Additionally, the long-term consequences of gene editing, especially in the context of complex diseases like cancer, are still not fully understood. Ethical dilemmas arise regarding how far we should go in modifying the human genome, especially when considering the potential for "designer" therapies or unforeseen biological consequences. To ensure the responsible use of CRISPR in cancer treatment, rigorous ethical guidelines and regulations must be established, along with transparent public discourse regarding the social, moral, and economic implications of these powerful technologies.(22)

1.12 Germline Editing: Ethical and Social Considerations in Cancer Research

Germline editing refers to modifications made to the DNA of human embryos, sperm, or eggs, which can be inherited by future generations. While germline editing is not yet common in cancer research, it raises significant ethical and social concerns, particularly regarding its potential use in oncology. The ability to modify genes in the germline could theoretically prevent inherited cancers, such as those caused by mutations in the BRCA1 or BRCA2 genes, thereby reducing the risk of cancer in future generations.(23) However, this prospect raises concerns about the long-term implications of genetic alterations that could be passed down indefinitely. One of the key ethical issues is the potential for unintended consequences or "designer babies," where genetic modifications are made not just for therapeutic reasons, but for non-medical purposes, such as enhancing physical traits or intelligence. Furthermore, germline editing could exacerbate social inequality if access to such technology is limited to certain socioeconomic groups. The ethical debate also includes concerns about consent, as future generations would be unable to consent to genetic modifications made before their birth. These complex ethical dilemmas make germline editing a controversial area of cancer research, necessitating careful consideration and regulation to ensure that it is used responsibly.(24)

1.13 Regulatory Frameworks for CRISPR-Cas9 in Oncology

As CRISPR-Cas9 technology continues to advance, there is an urgent need for clear and comprehensive regulatory frameworks to guide its application in oncology. These frameworks are essential to ensure the safety, efficacy, and ethical use of CRISPR-based treatments for cancer. In many countries, regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are responsible for overseeing the approval of gene-editing therapies. (25)However, the rapid pace of CRISPR development has outpaced the creation of regulations, leading to uncertainty in clinical trials and potential treatments. Key concerns in regulatory frameworks include the standards for preclinical testing, guidelines for assessing off-target effects, and protocols for gene delivery methods. Additionally, regulatory agencies must address the unique challenges posed by gene therapies that are individualized to a patient's specific cancer. As gene editing in oncology evolves, international cooperation on setting global standards will be essential to ensure consistent and ethical practices. The creation of these frameworks should also include public engagement and transparency to balance innovation with patient safety and societal values.(26)

1.14 Equity and Accessibility of CRISPR-Based Cancer Therapies

One of the major concerns surrounding CRISPR-based cancer therapies is the issue of equity and accessibility. While CRISPR has the potential to revolutionize cancer treatment, its advanced nature, high costs, and individualized nature may make it inaccessible to many patients, particularly in low- and middle-income countries. The development of CRISPR-based therapies typically requires specialized expertise, high-end technology, and significant financial investment, which can create barriers to access for the broader population. (27)Furthermore, the need for personalized treatments means that these therapies may only be available to those who can afford the costs associated with advanced genetic testing and treatment customization. This disparity could exacerbate existing healthcare inequalities, as wealthier individuals and developed countries may be able to benefit from these breakthroughs, while others remain excluded. To address these concerns, it is critical to establish frameworks that promote equitable access to CRISPR-based therapies, including efforts to reduce treatment costs, improve accessibility to necessary technology, and provide global access to cutting-edge cancer treatments. This includes increasing international collaborations, promoting public-private partnerships, and ensuring that these life-saving innovations are distributed fairly to all populations, regardless of socioeconomic status.(28)

1.15 Future Prospects: The Next Frontier in Cancer Treatment with CRISPR-Cas9

The future of cancer treatment with CRISPR-Cas9 holds exciting potential as the technology continues to evolve and mature. In the coming years, CRISPR-based therapies could move beyond simply repairing single gene mutations to offer more complex solutions, such as editing multiple genes simultaneously to create personalized, multi-faceted treatment regimens. The development of "CRISPR libraries" could allow researchers to target a wider range of genetic mutations simultaneously, improving the efficiency and scope of cancer treatments.(29) Additionally, combining CRISPR with other emerging technologies, such as artificial intelligence for drug discovery or nanoparticle-based delivery systems for gene-editing tools, could vastly improve the precision and effectiveness of therapies. Another promising area is the use of CRISPR to enhance the immune system, particularly in cancer immunotherapies like CAR-T cell therapy, which could become more widely applicable to different types of cancer. While the clinical use of CRISPR in oncology is still in its early stages, future research could lead to therapies that are less invasive, more effective, and more personalized than current options. As challenges related to delivery mechanisms, off-target effects, and ethical concerns are addressed, CRISPR-Cas9 could play a central role in the next frontier of cancer treatment, offering hope for more effective, individualized care for patients worldwide.(30)

Category	Applications	Challenges/Implications
Gene Editing for Tumor Suppression	Targeting tumor suppressor genes (e.g., p53, BRCA1) to halt cancer cell proliferation.	Ensuring precision in gene edits without disrupting other genes.
Gene Therapy	Gene replacement or repair in cancer cells to correct mutations.	Efficient and safe delivery of CRISPR components to target cells.
Immune Cell Enhancement	Genetic modification of immune cells (e.g., T-cells) for enhanced cancer immunotherapy.	Risk of immune responses to genetically modified immune cells, safety concerns.

Precision Medicine	Personalized cancer treatment based on genetic mutations driving tumor growth.	Complexity in identifying specific genetic drivers for individual tumors.
Off-Target Effects	Unintended genetic changes in non-target regions that may lead to new mutations or tumor resistance.	Potential for off-target effects leading to safety risks and unforeseen genetic consequences.
Ethical Concerns	Concerns about germline editing, accessibility, and equity of CRISPR-based therapies.	Regulatory, social, and ethical considerations, including issues of consent and long-term consequences.

Conclusion

CRISPR-Cas9 technology represents a transformative advancement in the field of cancer research and treatment, offering unprecedented opportunities to modify the genetic basis of cancer at the molecular level. The ability to precisely target and edit cancer-related genes holds the potential to not only halt cancer progression but also revolutionize how we approach personalized medicine. From gene therapy to immune cell enhancement and tumor suppression, CRISPR opens doors to more effective, targeted, and individualized cancer treatments, offering hope for patients with limited options. However, these breakthroughs come with significant challenges, including off-target effects, ethical concerns regarding germline editing, and the accessibility of these therapies across different socioeconomic groups. As CRISPR technology continues to evolve, it is crucial to establish robust regulatory frameworks, ensure equitable access to treatments, and address ethical dilemmas to guide its safe and responsible application in oncology.

The future of CRISPR-based cancer therapies is promising, with ongoing research pushing the boundaries of what is possible. While there are still hurdles to overcome, particularly regarding safety, delivery mechanisms, and ethical considerations, the potential to significantly improve cancer care is immense. As scientists continue to refine CRISPR technology and its applications in oncology, we move closer to a future where precision gene-editing therapies become a routine part of cancer treatment, ultimately improving patient outcomes and offering new hope in the fight against cancer.

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