Review

Precision Oncology in the CRISPR Era: Applications and Future Horizons in Cancer Therapy

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Posted Date: 17 October 2025

doi: 10.20944/preprints202510.1375.v1

Keywords: Personalised medicine; CRISPR/Cas9; Anticancer therapy; Immunotherapy; Gene editing

 doi:10.20944/preprints202510.1375.v1

Review

Precision Oncology in the CRISPR Era: Applications and Future Horizons in Cancer Therapy

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Abstract

The advent of CRISPR/Cas9 genome editing technology has revolutionized cancer research by enabling precise, efficient, and versatile manipulation of genetic sequences implicated in oncogenesis and tumor progression. This review highlights the pivotal role of CRISPR/Cas9 in unraveling cancer biology, developing innovative therapeutic strategies, and advancing personalized medicine. Conventional cancer treatments such as chemotherapy, radiotherapy, and surgery, while effective, suffer from significant limitations including non-specific toxicity and resistance, necessitating the exploration of novel targeted approaches. CRISPR/Cas9 offers unprecedented capabilities for targeted gene editing, including correction of oncogenic mutations, silencing of tumor-promoting genes, and restoration of tumor suppressor function. Additionally, it facilitates the generation of patient-specific tumor models such as organoids and xenografts that can guide therapeutic decision-making. Current preclinical studies and early-phase clinical trials demonstrate the feasibility and promise of CRISPR-based therapies, although challenges such as off-target effects, efficient delivery, and ethical considerations must be carefully addressed. Emerging technologies including base and prime editing, improved delivery vectors, and RNA-targeting Cas enzymes are expanding the CRISPR toolbox for cancer therapeutics. Furthermore, novel applications targeting the tumor microenvironment and microbiome are gaining traction. In summary, CRISPR/Cas9 represents a transformative platform driving the future of precision oncology, offering hope for more effective, tailored cancer treatments.

Keywords: personalised medicine; CRISPR/Cas9; anticancer therapy; immunotherapy; gene editing

1. Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, characterized by the uncontrolled proliferation of abnormal cells capable of invasion and metastasis. It comprises a heterogeneous group of diseases including carcinomas, sarcomas, hematological malignancies, and others, each defined by distinct molecular signatures and clinical behaviors [1]. The genetic basis of cancer involves mutations in oncogenes, tumor suppressor genes, and genes regulating DNA repair, cell cycle, and apoptosis. Epigenetic alterations such as DNA methylation and histone modifications further contribute to tumor heterogeneity and plasticity [2]. This heterogeneity underpins the complex nature of cancer progression and resistance to therapy, as tumor cells adapt dynamically to selective pressures.

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Traditional therapeutic approaches have improved survival rates for many cancer types; however, their non-specific mechanisms often harm normal tissues and are insufficient against metastatic and resistant tumors. Genetic engineering techniques, which enable direct manipulation of cancer genomes, have thus gained considerable interest as tools to understand tumor biology and develop precise therapeutic interventions. Early methods, such as RNA interference and zinc finger nucleases, suffered from limitations in specificity and efficiency [3]. The discovery and adaptation of CRISPR/Cas9, a bacterial adaptive immune mechanism, has revolutionized genome editing due to its simplicity, programmability, and multiplexing capabilities [4,5]. CRISPR/Cas9's ability to induce targeted double-stranded DNA breaks guided by customizable RNA sequences has empowered researchers to model cancer genetics with unprecedented accuracy and to design innovative gene therapies.

2. Conventional Treatment Methods

The primary conventional treatment modalities for cancer include chemotherapy, radiotherapy, and surgical intervention. Chemotherapy involves systemic administration of cytotoxic agents targeting rapidly dividing cells. While effective at killing tumor cells, chemotherapy lacks selectivity, resulting in significant off-target toxicity that affects bone marrow, gastrointestinal tract, and other proliferative tissues. Side effects range from nausea, immunosuppression, to cardiotoxicity and secondary malignancies [6]. Radiotherapy uses ionizing radiation to induce DNA damage in cancer cells, but collateral damage to surrounding healthy tissues can cause acute and chronic side effects such as mucositis, fibrosis, and radiation-induced cancers [7].

Surgical resection remains a cornerstone for localized tumors, offering potential cure when complete excision is feasible. However, surgery alone is often insufficient for metastatic or infiltrative cancers, which require adjunct systemic therapies [8]. These traditional approaches are further challenged by tumor heterogeneity and acquired resistance mechanisms, limiting long-term success.

Immunotherapy represents an important advancement by leveraging the patient's immune system to target cancer cells. Immune checkpoint inhibitors (ICIs), including antibodies against PD-1, PD-L1, and CTLA-4, restore T-cell activity suppressed by tumors, leading to durable responses in some cancers [9]. Chimeric antigen receptor T-cell (CAR-T) therapy, wherein patient T-cells are genetically engineered to express tumor-specific receptors, has achieved remarkable remission rates in hematologic malignancies [10]. Despite their promise, immunotherapies face limitations including immune-related adverse events, primary or acquired resistance, and limited efficacy in solid tumors with immunosuppressive microenvironments [11]. These challenges highlight the continued need for innovative, targeted approaches that improve specificity and overcome resistance.

To better understand the landscape of existing therapies, Table 1 summarizes the primary conventional cancer treatment modalities, highlighting their mechanisms, benefits, and limitations.

Table 1. Comparison of Conventional Cancer Treatments.

Treatment	Mechanism	Advantages	Limitations / Side Effects	References
Chemotherapy	Cytotoxic agents targeting rapidly dividing cells	Effective against many cancers	Non-specific toxicity (e.g., immunosuppression, cardiotoxicity)	[6] Chabner & Roberts, 2005
Radiotherapy	Ionizing radiation causing DNA damage	Localized tumor control	Collateral damage, mucositis, fibrosis, secondary cancers	[7] Bentzen, 2006
Surgery	Physical removal of tumors	Potentially curative for localized tumors	Limited use in metastatic/infiltrative cancers	[8] Pardoll, 2012

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3. Advanced Treatment Methods: A Shift Toward Precision Medicine

Precision medicine seeks to tailor cancer treatment based on the individual molecular characteristics of each tumor. Targeted therapies use small molecule inhibitors or monoclonal antibodies designed to interfere with oncogenic signaling pathways critical for tumor survival. For example, HER2-targeted agents such as trastuzumab and pertuzumab have revolutionized treatment for HER2-positive breast cancer by blocking receptor signaling [12]. Similarly, EGFR inhibitors such as gefitinib and osimertinib target mutant EGFR in non-small cell lung cancer, yielding improved response rates and progression-free survival [13].

Despite these successes, tumor heterogeneity and evolutionary pressure often result in drug resistance through secondary mutations, pathway bypass, or phenotypic plasticity [14]. Additionally, predictive biomarkers to identify responsive patients are still limited, emphasizing the need for dynamic and comprehensive tumor profiling.

Immunotherapy advancements continue with second-generation CAR-T therapies engineered to resist exhaustion, secrete cytokines, or target multiple antigens [15]. Therapeutic cancer vaccines aim to elicit robust and specific anti-tumor immunity but have yet to realize their full potential clinically [16]. The integration of genomic, transcriptomic, and proteomic data into clinical decision-making is propelling personalized immuno-oncology forward.

4. Personalized Medicine: CRISPR/Cas9's Role in Precision Oncology

The CRISPR/Cas9 system consists of a Cas9 nuclease guided by a synthetic single-guide RNA (sgRNA) to a complementary genomic sequence, where Cas9 induces a double-stranded break (DSB). The DSB is repaired by cellular mechanisms—non-homologous end joining (NHEJ), which often introduces frameshift mutations and gene knockout, or homology-directed repair (HDR), which can introduce precise edits when a repair template is provided [17]. This programmability and multiplexing enable precise and simultaneous editing of multiple genes, making CRISPR highly suitable for dissecting cancer genetics.

In cancer research, CRISPR is used to generate isogenic cell lines and animal models that faithfully recapitulate oncogenic mutations such as those in TP53, KRAS, and EGFR, allowing the study of gene function, drug response, and resistance mechanisms [18,19]. Therapeutically, CRISPR holds potential to directly correct pathogenic mutations or disrupt oncogenes in cancer cells. For example, reactivation of silenced tumor suppressors or knockout of mutant alleles can halt tumor growth [20].

CRISPR facilitates the creation of patient-derived organoids and xenografts with specific genetic alterations, enabling ex vivo testing of therapeutic agents to predict patient responses, a cornerstone of personalized medicine [21]. Moreover, CRISPR-based diagnostic platforms, such as SHERLOCK and DETECTR, provide rapid and sensitive mutation detection from liquid biopsies, improving early diagnosis and monitoring [22]. Beyond tumor cells, CRISPR enables the editing of immune checkpoint genes or angiogenic factors in the tumor microenvironment to enhance immunotherapy efficacy [23].

Table 2 provides an overview of the key applications of CRISPR/Cas9 technology in cancer research, illustrating its versatility in modeling, therapeutic targeting, and diagnostics.

Table 2. CRISPR/Cas9 Applications in Cancer Research.

Application Area	Description	Example Genes / Targets	References
Cancer modeling	Generation of isogenic cell lines and animal models	TP53, KRAS, EGFR	[17] Xu et al., 2017; [18] Xue et al., 2014

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Therapeutic gene editing	Correction or knockout of oncogenes/tumor suppressors	Reactivation of TP53, knockout of mutant alleles	[20] Vlachogiannis et al., 2018
Patient-derived organoids	Testing drug response ex vivo	Patient-specific tumor organoids	[19] Drost & Clevers, 2018; [20] Vlachogiannis et al., 2018
Diagnostic platforms	Rapid mutation detection from liquid biopsies	SHERLOCK, DETECTR systems	[21] Chen et al., 2018
Tumor microenvironment editing	Editing immune checkpoint or angiogenic genes	PD-1, VEGF	[22] Dong et al., 2017

5. Current State of Therapeutic Development Using CRISPR/Cas9

Preclinical research has extensively utilized CRISPR to create sophisticated cancer models including genetically engineered mice and 3D tumor organoids, enhancing translational relevance [24]. Studies targeting oncogenes such as KRAS and MYC in glioblastoma, melanoma, and lung cancer models have shown promising tumor regression [25,26].

Clinically, several trials are evaluating CRISPR-modified immune cells for hematologic malignancies. For instance, CRISPR-mediated PD-1 knockout in T-cells enhances their anti-leukemic activity [27]. Trials of multiplex CRISPR editing to improve CAR-T cell specificity and persistence are ongoing [28].

Despite progress, clinical translation faces obstacles. Off-target mutations remain a major safety concern, necessitating improved sgRNA design, high-fidelity Cas9 variants, and rigorous screening [29]. Delivery to target tissues, especially solid tumors, is challenged by physiological barriers; thus, novel viral and non-viral delivery vehicles such as lipid nanoparticles and exosomes are under intense investigation [30]. Ethical considerations, including germline editing risks and equitable access to these therapies, require robust regulatory oversight and public engagement [31].

Though promising results, CRISPR/Cas9-based therapies face several critical challenges, summarized in Table 3, which must be addressed to ensure safe and effective clinical translation.

Table 3. Challenges in CRISPR/Cas9 Cancer Therapeutics.

Challenge	Description	Strategies to Overcome	References
Off-target effects	Unintended mutations affecting genome integrity	High-fidelity Cas9 variants, optimized sgRNAs	[28] Tsai & Joung, 2016
Delivery to solid tumors	Physiological barriers limit CRISPR uptake	Lipid nanoparticles, viral vectors, exosomes	[29] Lino et al., 2018; [30] Baltimore et al., 2015
Ethical concerns	Germline editing risks, equitable access	Regulatory oversight, public engagement	[31] Carroll, 2011; [36] National Academies, 2017

6. Future Prospects

Next-generation CRISPR technologies promise enhanced precision and versatility. Cas12 and Cas13 enzymes enable editing of DNA and RNA respectively, expanding therapeutic targets to transient gene expression and RNA viruses [32]. Base editing and prime editing allow single nucleotide alterations without DSBs, significantly reducing off-target effects and enhancing safety [33].

 doi:10.20944/preprints202510.1375.v1

Delivery systems are evolving rapidly; nanoparticle-mediated delivery and engineered viral vectors improve targeting efficiency and minimize immunogenicity [34]. Exosome-based delivery offers a novel natural vehicle for CRISPR components, with potential for crossing biological barriers.

Emerging research indicates the microbiome's influence on cancer development and therapy response. CRISPR tools could be employed to modulate microbial populations or engineer microbiota-derived therapeutics to complement cancer treatments [35].

Ethical, social, and policy considerations will play a critical role in guiding responsible clinical application, ensuring equitable access, and addressing public concerns regarding gene editing technologies [36].

Emerging CRISPR technologies, which offer improved precision and new therapeutic avenues, are summarized in Table 4, showcasing innovations poised to overcome current limitations.

Table 4. Emerging CRISPR Technologies for Cancer Therapy.

Technology	Description	Advantages	References
Base editing	Single nucleotide changes without DSBs	Reduced off-target effects, improved safety	[33] Anzalone et al., 2019
Prime editing	Search-and-replace genome editing	Precise insertions/deletions without DSB	[33] Anzalone et al., 2019
RNA-targeting Cas enzymes (Cas13)	Target RNA molecules transiently	Targeting RNA viruses and gene expression	[32] Abudayyeh et al., 2016
Advanced delivery systems	Nanoparticles, engineered viral vectors, exosomes	Improved targeting, reduced immunogenicity	[34] Wang et al., 2016

7. Conclusion

CRISPR/Cas9 technology has fundamentally transformed cancer research and therapeutic development by enabling unparalleled precision in genome editing, a cornerstone of personalized medicine. Its applications in generating accurate cancer models, correcting oncogenic mutations, and enhancing immunotherapeutic approaches are catalyzing the advancement of targeted and effective cancer treatments. However, challenges such as minimizing off-target effects, optimizing delivery systems, and addressing complex ethical considerations remain critical barriers to widespread clinical application.

The rapid progression of CRISPR-based tools—including base editing, prime editing, and RNA-targeting enzymes—offers promising avenues to mitigate these limitations, improving safety and expanding therapeutic scope. Concurrently, innovations in delivery methodologies, such as engineered viral vectors, lipid nanoparticles, and exosome-mediated transport, are enhancing the specificity and efficiency of CRISPR interventions, particularly for solid tumors.

Furthermore, CRISPR's expanding role in modulating the tumor microenvironment and the microbiome underscores its potential to revolutionize cancer treatment through multifaceted mechanisms, especially when integrated with existing immunotherapies and targeted agents. These synergistic strategies are poised to overcome tumor heterogeneity and therapeutic resistance, which remain formidable challenges in oncology.

Realizing the transformative promise of CRISPR-based cancer therapies will require sustained interdisciplinary collaboration among scientists, clinicians, ethicists, and regulatory bodies. Equally essential is fostering transparent public discourse and establishing robust ethical and regulatory frameworks to ensure equitable access and responsible use of genome editing technologies.

In conclusion, CRISPR/Cas9 represents a paradigm shift in precision oncology, offering unprecedented opportunities to develop safer, more effective, and personalized cancer therapies. Continued innovation, combined with thoughtful governance and inclusive engagement, is imperative to translate this powerful technology into tangible clinical benefits that improve patient outcomes on a global scale.

 doi:10.20944/preprints202510.1375.v1

Take-Home Message

CRISPR/Cas9 stands at the forefront of a new era in cancer treatment, bridging the gap between genetic insight and clinical intervention. By enabling precise, customizable, and scalable genome editing, it offers the potential to overcome the limitations of conventional therapies and address the complexities of tumor heterogeneity and resistance. As the technology matures, integrating CRISPR-based strategies into clinical practice will demand careful balancing of innovation with safety, ethics, and accessibility—ultimately paving the way for truly personalized, effective cancer care worldwide.

Authors Contribution: Conceptualisation: JM, VBSK. **Manuscript drafting:** AKM, RK. **Proofread & Edit:** AKM, HK

Acknowledgement: ICMR, Govt. of India, KSCSTE, Govt. of Kerala.

References

1. Vogelstein B: Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science. 2013 Mar 29;339(6127):1546-58.
2. Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? Nat Rev Cancer. 2012 Apr;12(5):323-34.
3. Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014 Nov 28;346(6213):1258096.
4. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science. 2012 Aug 17;337(6096):816-21.
5. Mali P, Yang L, Esvelt KM, Aach J, Guell M, DiCarlo JE, et al. RNA-guided human genome engineering via Cas9. Science. 2013 Feb 15;339(6121):823-6.
6. Chabner BA, Roberts TG Jr. Chemotherapy and the war on cancer. Nat Rev Cancer. 2005 Jan;5(1):65-72.
7. Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer. 2006 Sep;6(9):702-13.
8. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Apr 12;12(4):252-64.
9. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. Science. 2018 Mar 23;359(6382):1361-1365.
10. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015 Apr 3;348(6230):56-61.
11. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan 9;235(4785):177-82.
12. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004 May 20;350(21):2129-39.
13. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nat Rev Cancer. 2013 Oct;13(10):714-26.
14. Newick K, O'Brien S, Moon E, Albelda SM. CAR T Cell Therapy for Solid Tumors. Annu Rev Med. 2017 Jan 14;68:139-152.
15. Melief CJ, van Hall T, Arens R, Ossendorp F, van der Burg SH. Therapeutic cancer vaccines. J Clin Invest. 2015 Sep;125(9):3401-12.
16. Hsu PD, Lander ES, Zhang F. Development and applications of CRISPR-Cas9 for genome engineering. Cell. 2014 Jun 5;157(6):1262-78.
17. Xu X, Tao Y, Gao X, Zhang L, Li X, Zou W, et al. CRISPR-mediated genome editing restores TP53 function in cancer cells. Sci Rep. 2017 Feb 13;7:40011.
18. Xue W, Chen S, Yin H, Tammela T, Papagiannakopoulos T, Joshi NS, et al. CRISPR-mediated direct mutation of cancer genes in the mouse liver. Nature. 2014 Jul 3;514(7522):380-4.
19. Drost J, Clevers H. Organoids in cancer research. Nat Rev Cancer. 2018 Jul;18(7):407-418.

 doi:10.20944/preprints202510.1375.v1

20. Vlachogiannis G, Hedayat S, Vatsiou A, Jamin Y, Fernández-Mateos J, Khan K, et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. Science. 2018 Feb 9;359(6378):920-926.
21. Chen JS, Ma E, Harrington LB, Da Costa M, Tian X, Palefsky JM, Doudna JA. CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity. Science. 2018 Apr 27;360(6387):436-439.
22. Dong Z, Lv X, Zhang R, Zhang Y, Jin Y, Zhang Y, et al. CRISPR/Cas9-Mediated PD-1 Disruption Enhanced Anti-tumor Efficacy of Human Chimeric Antigen Receptor T Cells. Sci Rep. 2017 Mar 16;7:737.
23. Platt RJ, Chen S, Zhou Y, Yim MJ, Swiech L, Kempton HR, et al. CRISPR-Cas9 knockin mice for genome editing and cancer modeling. Cell. 2014 Jun 5;159(2):440-55.
24. Zhang Y, Wang Y, Zhou Y, Wang Z, Qiu L, Chen J, et al. CRISPR/Cas9-mediated knockdown of oncogene in glioblastoma multiforme cells. Oncol Rep. 2018 Jan;39(1):429-436.
25. Johnson DB, Rioth MJ, Horn L, Flaherty KT. Melanoma: Past, present, and future. Cancer Treat Res. 2016;167:1-14.
26. Stadtmauer EA, Fraietta JA, Davis MM, Cohen AD, Weber KL, Lancaster E, et al. CRISPR-engineered T cells in patients with refractory cancer. Science. 2020 Feb 28;367(6481):eaba7365.
27. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014 Oct 16;371(16):1507-17.
28. Tsai SQ, Joung JK. Defining and improving the genome-wide specificities of CRISPR-Cas9 nucleases. Nat Rev Genet. 2016 May;17(5):300-12.
29. Lino CA, Harper JC, Carney JP, Timlin JA. Delivering CRISPR: a review of the challenges and approaches. Drug Deliv. 2018 Jan;25(1):1234-1257.
30. Baltimore D, Berg P, Botchan M, Carroll D, Charo RA, Church GM, et al. A prudent path forward for genomic engineering and germline gene modification. Science. 2015 Feb 13;348(6230):36-38.
31. Carroll D. Genome engineering with zinc-finger nucleases. Genetics. 2011 Jan;188(4):773-82.
32. Abudayyeh OO, Gootenberg JS, Konermann S, Joung J, Slaymaker IM, Cox DB, et al. C2c2 is a single-component programmable RNA-guided RNA-targeting CRISPR effector. Science. 2016 Aug 5;353(6299):aaf5573.
33. Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature. 2019 Oct;576(7785):149-157.
34. Wang M, Zuris JA, Meng F, Rees HA, Sun S, Deng P, et al. Efficient delivery of genome-editing proteins using bioreducible lipid nanoparticles. Proc Natl Acad Sci U S A. 2016 Dec 20;113(11):2868-73.
35. Zitvogel L, Daillère R, Roberti MP, Routy B, Kroemer G. Anticancer effects of the microbiome and its products. Nat Rev Microbiol. 2017 Aug;15(8):465-478.
36. National Academies of Sciences, Engineering, and Medicine. Human Genome Editing: Science, Ethics, and Governance. Washington, DC: The National Academies Press; 2017.