Journal of Cancer Biomoleculars and Therapeutics

ETERNO PRESS

Review

CRISPR-Cas9 in Precision Oncology: Unraveling Resistance Mechanisms and Redefining Molecular Targeted Cancer Therapy

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Article history

Received: 2 January 2026
Revised: 13 February 2026
Accepted: 2 March 2026
Published online: 8 April 2026

Keywords

CRISPR-Cas9 genome editing
Molecular targeted cancer therapy
Drug resistance
Functional genomics
Precision oncology
Gene editing

Abstract

Cancer therapeutics have evolved from standard cytotoxic chemotherapy to specialized molecular targeted therapies, which scientists now develop using purposeful design methods. The treatments function by targeting molecular changes that lead to cancer development through epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), B-Raf proto-oncogene, serine/threonine kinase (BRAF) pathway mutations. Targeted therapies have achieved outstanding results, but drug resistance development creates a major obstacle that restricts their treatment success in medical practice. Scientists now understand genetic networks that control treatment outcomes and drug resistance because of major developments in Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9 (CRISPR-Cas9) genome-editing technology. This review provides a full examination of molecular targeted cancer therapy development and resistance mechanisms, and CRISPR-Cas9 applications for discovering new cancer cell weaknesses. It explains CRISPR-based functional genomic screens, which identify genes and pathways responsible for drug resistance, to develop new treatment approaches and explore the ethical aspects and technical obstacles, and future development possibilities for combining artificial intelligence with omics data and CRISPR precision oncology. The scientific breakthroughs create a new era for personalized cancer treatment, which unites genetic discoveries with medical practice. Beyond identifying oncogenic drivers, CRISPR-based functional genomics expands the therapeutic paradigm toward systematic interrogation of resistance circuits and synthetic lethal interactions. This shift redefines molecular targeted therapy from static inhibition of single driver mutations to dynamic targeting of adaptive survival networks that sustain tumor progression under therapeutic pressure. The medical field is experiencing a new period of individualized cancer treatment through these technological developments, which connect genetic discoveries to their clinical applications.

1. Introduction to CRISPR/Cas9: A Long Journey in a Short Time

Through years of rigorous research, scientists transformed the early aspiration of combating genetic and hereditary diseases into tangible scientific advancements. Genetic engineering exists because scientists stayed curious while they kept working until, they discovered new things. The scientific discovery of deoxyribonucleic acid (DNA) structure started in the 1950s when Rosalind Franklin used X-ray diffraction to reveal DNA complexity, which led James Watson and Francis Crick to develop their double-helix model in 1953 [1]. The discovery changed our understanding of genetic information because scientists established that DNA functions as the hereditary material that carries biological information through multiple generations. The discovery of DNA established the basis for molecular biology, which scientists used to start developing genetic material manipulation techniques [2].

The field of modern biotechnology emerged from multiple scientific discoveries that occurred throughout the following decades. Scientists discovered DNA ligases in 1967 and restriction endonucleases in 1968, which became fundamental tools for DNA sequence manipulation that established the foundation of recombinant DNA technology. Scientists gained the ability to perform artificial gene manipulation through this innovation which involved combining DNA segments from various organisms to produce initial genetic modifications [3]. The scientific community witnessed a new biological research era through Paul Berg's Nobel Prize-winning work on recombinant DNA which enabled gene editing and foreign genetic material transfer and expression [4].

The 1970s brought a major shift with Köhler and Milstein developing hybridoma technology in 1975. The method allowed scientists to create monoclonal antibodies which are identical antibodies produced from a single immune cell clone, to develop diagnostic and therapeutic applications. The development of monoclonal antibodies enabled scientists to create targeted treatments for cancer and autoimmune diseases and infectious diseases, which demonstrated the direct impact of molecular biology on medical applications [5]. Scientists working in the field developed aspirations to build instruments that would perform exact DNA modifications at specific genome locations during the field's development. The mid-1980s brought about the development of zinc-finger nucleases (ZFNs) because of this vision. These engineered proteins combined a zinc-finger DNA-binding domain with a FokI endonuclease domain, enabling site-specific double-stranded breaks (DSBs) in DNA. The cell activates its natural repair systems which include non-homologous end joining (NHEJ) and homology-directed repair (HDR) to fix DNA breaks and these processes might create mutations or allow new genetic sequences to be inserted. The genome editing field received a major boost from ZFNs, yet scientists encountered difficulties when creating these tools because each target site required unique zinc-finger domain designs [6].

The system needed to become available for all users while maintaining exactness and operational efficiency and a user-friendly interface. The scientific community solved multiple problems when researchers discovered transcription activator-like effector nucleases (TALENs) during their 2011 breakthrough. TALENs emerged from Xanthomonas genus plant pathogenic bacteria which employed modular repeat domains to detect single nucleotides instead of three-base sequences thus delivering superior flexibility and predictability compared to ZFNs [7]. Their design process was less complicated, and their target recognition more accurate. The large size of TALENs combined with their complex delivery into cells made them unsuitable for routine therapeutic applications [8].

Scientists researching bacterial immune systems discovered a separate system that would shape genetic engineering methods for the future. Yoshizumi Ishino and his research team discovered special DNA patterns within Escherichia coli during their 1980s studies, but they could not explain their biological purpose [9]. Francisco Mojica discovered these repeating DNA sequences in the archaeon Haloferax mediterranei when he found that spacer sequences contained viral and plasmid DNA fragments. Mojica observed these sequences which led him to theorize that prokaryotes possess an adaptive immune system which allows bacteria to store viral genetic material for future defense through genome integration of short viral DNA fragments [10].

The system which scientists named Clustered Regularly Interspaced Short Palindromic Repeats CRISPR functions with its Cas (CRISPR-associated) genes to protect bacteria from threats [11]. The defense mechanism operates through CRISPR-derived RNAs (crRNAs), which guide Cas proteins to identify and delete foreign DNA sequences from viruses that the body has encountered before. Scientists implemented this natural defense mechanism into genome engineering techniques in 2012. Jennifer Doudna, together with Emmanuelle Charpentier, revealed that a basic two-part system, which includes single-guide RNA (sgRNA) and Cas9 endonuclease, allows scientists to modify DNA sequences at specific locations. Their breakthrough research showed that scientists could use synthetic RNA molecules to guide CRISPR-Cas9 for precise DNA double-strand breaks at specific genome sites [12].

Human beings demonstrated their creative abilities when they discovered DNA’s structure and then developed CRISPR-Cas9 as a result of their scientific exploration into basic life components [13]. The path to genetic code control has progressed through multiple stages which started with ligases and restriction enzymes and continued with programmable nucleases and RNA-guided editing technologies [14]. Scientists have achieved their highest level of scientific progress through CRISPR-Cas9 which provides exact and adaptable genome editing capabilities to transform medical, agricultural and biotechnological fields. Traditionally, molecular targeted therapy has focused on inhibiting dominant oncogenic drivers. However, clinical experience has revealed that driver suppression alone rarely produces durable responses due to adaptive resistance and clonal evolution. CRISPR-Cas9-based functional screening enables a paradigm shift by allowing systematic identification of resistance mediators, compensatory signaling pathways, and synthetic lethal dependencies. In this context, targeted therapy is redefined not only as inhibition of oncogenic mutations, but as strategic disruption of the broader genetic networks that sustain tumor survival [15].

1.1 Evolution of Molecular Targeted Cancer Therapy

The medical field has undergone a complete transformation through the development of molecular targeted cancer therapy, which stands as a key advancement in contemporary cancer treatment. Cancer treatment methods used conventional chemotherapy drugs, which attacked fast-growing cells throughout the body for many decades [16]. Medical treatments showed some therapeutic results, but patients had to endure multiple harmful effects, which included dangerous side effects and widespread systemic toxicity and harm to their healthy body tissues. The treatments stopped working because they didn't target specific areas, which also led to poor quality of life for patients [17]. Scientists discovered through genomics and molecular biology research that cancer exists as multiple complex diseases that result from specific genetic and molecular changes. Scientists established the basis for personalized treatment through molecular targeted therapy when they understood cancer genetics [18].

Scientists reached a major turning point in their research progress when they identified the Philadelphia chromosome as the cause of chronic myeloid leukemia

(CML) in the 1960s. Scientists discovered that chromosome 9 and 22 translocation produced breakpoint cluster region-Abelson (BCR-ABL) fusion gene which created a continuously active tyrosine kinase enzyme that caused cells to grow uncontrollably [19]. Scientists established the root causes of cancer through their discovery of molecular defects, which replaced the previous belief that cancer resulted from random cellular events. Scientists established a new treatment method that targets a specific abnormal protein through this discovery. The development of imatinib (Gleevec) led to the creation of first successful tyrosine kinase inhibitor (TKI). The selective inhibition of BCR-ABL protein by Imatinib brought a new era to CML treatment and established molecular abnormality targeting as an effective method for achieving superior treatment results with reduced side effects [20].

The scientific community experienced fast expansion of the field after imatinib proved successful because researchers discovered multiple molecular elements that drive different types of cancer. Scientists made a major discovery when they found human epidermal growth factor receptor 2 (HER2) overexpression in certain breast cancer cases [21]. The tumors that contained this amplification showed aggressive characteristics and resulted in poor patient survival rates. Scientists achieved a breakthrough in breast cancer treatment when they developed trastuzumab (Herceptin) which functions as a monoclonal antibody that attaches to the HER2 receptor. The drug trastuzumab functions through HER2 pathway blockage which stops tumor progression while activating immune system responses to eliminate cancer cells. The research reached a major achievement because treatments now focus on individual tumor molecular profiles for personalized therapy [22].

Scientists established driver mutation targeting as an essential treatment approach through their identification of the B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600E mutation in melanoma patients. The introduction of vemurafenib, a selective inhibitor of mutant BRAF, provided another striking example of how understanding molecular mechanisms can translate into life-saving therapies [23]. The treatment of advanced melanoma patients through targeted mutation inhibition brought about substantial tumor shrinkage and extended their survival period [24]. The medical field achieved simultaneous advancements in lung cancer treatment methods. Scientists discovered that epidermal growth factor receptor (EGFR) mutations function as cancer-causing genes which led to the creation of erlotinib and gefitinib as small-molecule inhibitors. The drugs worked by attacking the mutated EGFR tyrosine kinase domain which led to strong treatment results for patients whose tumors contained these specific mutations. The medical field entered a new era through this discovery which established molecular testing as a critical factor for selecting suitable treatments [25].

Cancer cells continue to show exceptional abilities to adapt because they function as biological systems. The development of drug resistance after treatment has turned into an ongoing problem for scientists who study targeted cancer therapy. The reduction of drug effectiveness occurs when target genes develop mutations and tumors develop multiple cell types and alternative signaling pathways become active [26]. For example, secondary mutations in the BCR-ABL gene can render CML cells resistant to imatinib, necessitating the development of second- and third-generation TKIs. The development of resistance to EGFR inhibitors occurs through two primary mechanisms which include the T790M mutation and mesenchymal–epithelial transition factor (MET) amplification [27].

The field of oncology experienced a permanent transformation through molecular targeted therapy despite facing multiple challenges. Scientists have shifted medical treatment methods by leaving behind standard procedures through the use of genetic and molecular cancer analysis which leads to personalized therapies that target specific weaknesses in each patient's cancer [28]. Scientists can study cancer biology through the combination of genomic sequencing with bioinformatics and CRISPR-based functional screens, which leads to the discovery of new drug targets [29]. The emergence of molecularly targeted therapies exemplifies how precision medicine has successfully overcome longstanding challenges in clinical treatment. The study demonstrates how molecular-level knowledge enables scientists to create medical treatments that extend human life. The ongoing development of molecular diagnostics together with combination therapy approaches, will solve the current medical difficulties which include drug resistance and tumor progression [30]. Science advances through this ongoing journey while people become more hopeful about managing cancer which used to be viewed as untreatable because of improved precision and compassionate care [31]. Figure 1 illustrates the fundamental principles and key molecular pathways involved in targeted cancer therapy, highlighting how specific cellular targets are selectively modulated to inhibit tumor growth and progression.

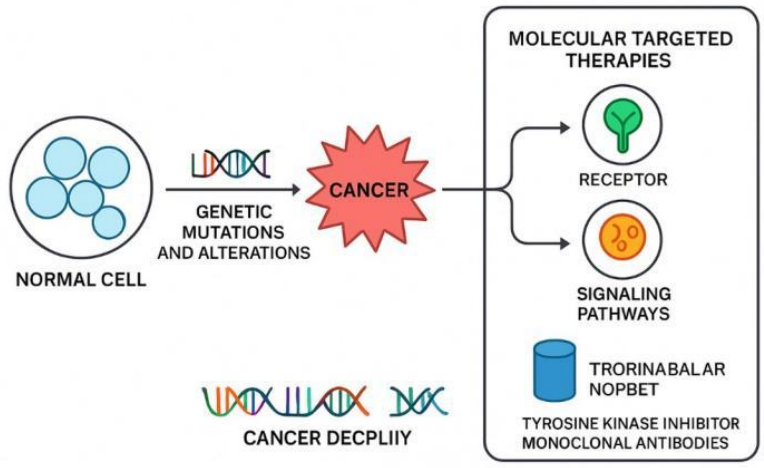

Figure 1. Overview of molecular targeted cancer therapy

1.2 Mechanisms of Drug Resistance

The phenomenon of drug resistance continues to serve as a major obstacle that prevents doctors from achieving successful cancer treatment results. The first-line treatments for many cancers today include molecularly targeted therapies and precision medicine but patients often show resistance to these treatments during the initial stages or develop resistance after some time [32]. Drug resistance exists in two main categories which include primary (intrinsic) resistance that occurs when tumors show natural treatment resistance at the beginning and acquired resistance that develops after patients respond to treatment at first. The biological systems that create this resistance patterns need thorough analysis to generate new treatment approaches that will either prevent or slow down therapeutic resistance. Although genetic mutations often initiate resistance by directly altering drug targets or signaling pathways, they rarely act in isolation. Early molecular alterations frequently trigger downstream epigenetic remodeling, metabolic adaptation, and microenvironmental reprogramming that collectively reinforce tumor survival. Over time, selective pressure from therapy promotes expansion of resistant clones, enrichment of cancer stem–like populations, and engagement of tumor–stroma signaling networks that sustain adaptive escape. Thus, drug resistance evolves through a dynamic and layered process in which primary genetic events establish resistance potential, while epigenetic plasticity, metabolic shifts, and tumor microenvironment (TME) interactions consolidate and stabilize the resistant phenotype. Understanding this hierarchy provides a mechanistic rationale for employing CRISPR-based functional screens to systematically dissect both initiating drivers and adaptive survival pathways [33].

1.3 Genetic Mutations and Bypass Signalling

The research extensively studies genetic mutations that occur in cancer-driving genes and their related signaling pathways as a primary mechanism. Under the selective pressure of therapy cancer cells which have genetic instability, develop mutations that restore or change oncogenic pathway signaling [34]. The T790M mutation in the EGFR gene represents a well-known example that develops in lung cancer patients who receive first-generation EGFR inhibitors. The mutation causes EGFR to bind adenosine triphosphate (ATP) more strongly which makes the drug less effective at blocking its target. The C797S mutation, which develops in patients receiving osimertinib treatment blocks drug binding to the target site and results in drug resistance. The cancer cells maintain their proliferation through bypass signaling mechanisms which function independently from any genetic mutations. The targeted pathway inhibition in cancer cells triggers the activation of compensatory pathways through alternative kinases including MET and HER3 and insulin-like growth factor 1 receptor (IGF1R) which restore essential downstream signals for cell survival and growth [35].

1.4 Epigenetic Modification

Epigenetic changes result in drug resistance through two main pathways which produce heritable DNA sequence variations that do not involve genetic mutations and can reverse their effects. The three main epigenetic mechanisms which affect gene expression are DNA methylation and histone modifications and non-coding RNA regulation. Tumor suppressor genes undergo hypermethylation which turns off their expression thus enabling cancer cells to avoid therapy-induced apoptosis. The process of histone deacetylation leads to chromatin compaction which blocks the transcription of genes that determine drug sensitivity. Cancer cells develop epigenetic plasticity which enables them to modify their behavior under treatment stress to become drug-resistant without changing their genetic makeup. The reversible nature of these changes makes epigenetic modulators suitable for combination therapies to bring back drug sensitivity [20,31].

1.5 Tumor Microenvironment

The TME plays a dual role in cancer progression, acting both as a barrier and as a facilitator of drug resistance. It is composed of tumor-associated stromal cells, including fibroblasts, immune cells, and extracellular matrix (ECM) components, which together form a protective niche for cancer cells. Hypoxic conditions, commonly observed in solid tumors, stabilize hypoxia-inducible factors (HIFs), triggering angiogenesis, metabolic adaptation, and

activation of survival pathways that collectively contribute to reduced drug sensitivity. The TME also secretes immunosuppressive molecules, such as transforming growth factor beta (TGF-β) and interleukin 10 (IL-10), and recruits regulatory T cells, which together diminish the effectiveness of immune-based and cytotoxic therapies. Structural features of the TME, including dense ECM and abnormal vasculature, further restrict drug delivery, preventing therapeutic agents from reaching effective concentrations within tumor tissues. Moreover, the TME supports the survival and expansion of cancer stem cells (CSCs), a subpopulation of tumor cells with self-renewal capacity and intrinsic resistance to standard therapies. CSCs evade treatment through mechanisms such as enhanced DNA repair, quiescence, and the overexpression of drug efflux transporters. Signaling interactions between CSCs and stromal cells, mediated by pathways such as IL-6, Wnt, and Notch, reinforce drug resistance and contribute to tumor recurrence. From an ethical standpoint, therapies targeting TME and CSCs, particularly those involving CRISPR-based approaches, hold immense potential but raise concerns about equitable access. High costs, the need for specialized infrastructure, and regulatory hurdles may limit availability in resource-constrained regions, emphasizing the importance of global strategies to ensure fair distribution of advanced cancer treatments [36].

1.6 Drug Efflux and Metabolic Reprogramming

Cancer cells use biochemical defense systems to disable or remove therapeutic drugs from their cells. The overexpression of ATP-binding cassette (ABC) transporters including P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP1), leads to active drug expulsion from cells which results in lower drug concentrations inside cells and reduced treatment effectiveness. The development of resistance to multiple drugs creates a significant obstacle that impacts various types of cancer. Cancer cells undergo metabolic changes through the Warburg effect, which leads them to choose glycolysis for energy production during oxygen-rich conditions. The metabolic transition enables cells to multiply rapidly while it also affects redox equilibrium and drug processing, which results in improved survival when facing therapeutic treatment [19,36].

1.7 Cancer Stem Cells

A small subpopulation of tumor cells, known as cancer stem cells (CSCs), plays a central role in drug resistance, recurrence, and metastasis. The cells show characteristics of stem cells because they can self-renew while remaining inactive and they possess improved DNA repair mechanisms. Their inherently slow proliferation makes them less susceptible to drugs targeting dividing cells. CSCs demonstrate elevated levels of efflux transporters and anti-apoptotic proteins which enable them to resist treatment and then regrow the tumor. The ability of cancer cells to transform through epithelial-to-mesenchymal transition (EMT) and their plastic nature allows them to resist treatment while spreading to new areas of the body [35]. Figure 2 outlines the principal molecular and cellular pathways underlying cancer drug resistance, emphasizing mechanisms such as altered drug targets, enhanced efflux activity, DNA repair modulation, and survival signaling activation.

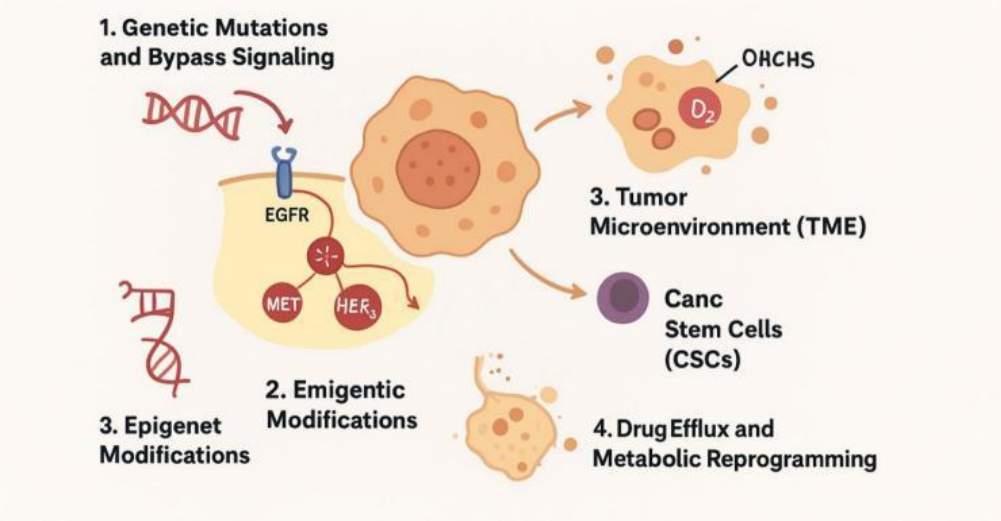

Figure 2. Mechanism of cancer drug resistance

2. CRISPR-Cas9 in Identifying Resistance Pathways

CRISPR-Cas9 technology enables scientists to study cancer resistance through genetic and molecular analysis which has transformed scientific research [37]. CRISPR-Cas9 offers permanent genome editing through targeted DNA double-strand breaks which distinguishes it from RNA interference (RNAi) and other gene-silencing tools [17,20]. This method enables scientists to create systematic gene alterations, including disruption and activation, across the entire genome for studying the effects of genes on treatment outcomes. CRISPR technology enables scientists to identify resistance mechanisms and discover new drug targets through its high precision and scalability, leading to combination therapies that combat treatment failure [38].

2.1 Genome-Wide CRISPR Screens

CRISPR technology is one of the most effective applications in cancer is the genome-wide CRISPR

screening approach. Researchers employ sgRNA libraries to conduct fast functional studies by targeting specific genes in cancer cells through drug exposure. Scientists use this method to detect genes that produce drug resistance or increased sensitivity when they become nonfunctional or change their structure. Genome-scale CRISPR knockout screens have identified key EGFR inhibitor resistance regulators in lung and colorectal cancers through Gee et al. [35] who discovered neurofibromin 1 (NF1) and phosphatase and tensin homolog (PTEN) and kelch-like ECH-associated protein 1 (KEAP1) as essential genes that control therapy response. The screening process for kirsten rat sarcoma viral oncogene homolog (KRAS)-mutant cancers revealed genes which function as synthetic lethal partners through their involvement in metabolic and signaling networks since blocking both genes together causes targeted death of cancer cells. These results highlight the ability of CRISPR to identify hidden defects in cancer genomes that may be used therapeutically. CRISPR screens function as a dual-purpose tool because they pinpoint resistance genes while revealing how cells adjust their survival pathways during drug treatment [38]. When a particular signaling route is inhibited, cancer cells often activate alternate pathways to restore growth and evade apoptosis. CRISPR-based functional genomics enables scientists to identify these bypass mechanisms which produce data to develop combination therapies that block multiple escape routes at the same time [39].

2.2 Synthetic Lethality and Target Discovery

Synthetic lethality exists as a genetic relationship which causes cell death when two genes become inactive at the same time. The loss of either one by itself does not cause death but scientists have started to study this phenomenon extensively for its potential medical applications. Scientists use CRISPR-Cas9 technology to find synthetic lethal relationships which serve as targets for cancer treatment development. Scientists working with BRCA1/2-deficient tumors use CRISPR technology to discover synthetic lethal partners that increase Poly (ADP-ribose) polymerase (PARP) inhibitor drug effectiveness through the DNA repair pathway [36]. Scientists achieve this by deleting partner genes to determine how specific genes work together to cause cell death, which leads to new cancer treatments based on individual tumor genetics. CRISPR technology enables scientists to find druggable interactions within cancers that scientists previously labeled as undruggable. Scientists use genome-scale CRISPR analysis to investigate RAS-driven malignancies, which reveals genes that work together to control autophagy and metabolic processes and oxidative stress responses. The combination of auxiliary pathway targeting with major oncogenic driver inhibition proves to be an effective strategy for blocking treatment resistance and improving medical results [40].

2.3 Functional Genomics and Immune Resistance

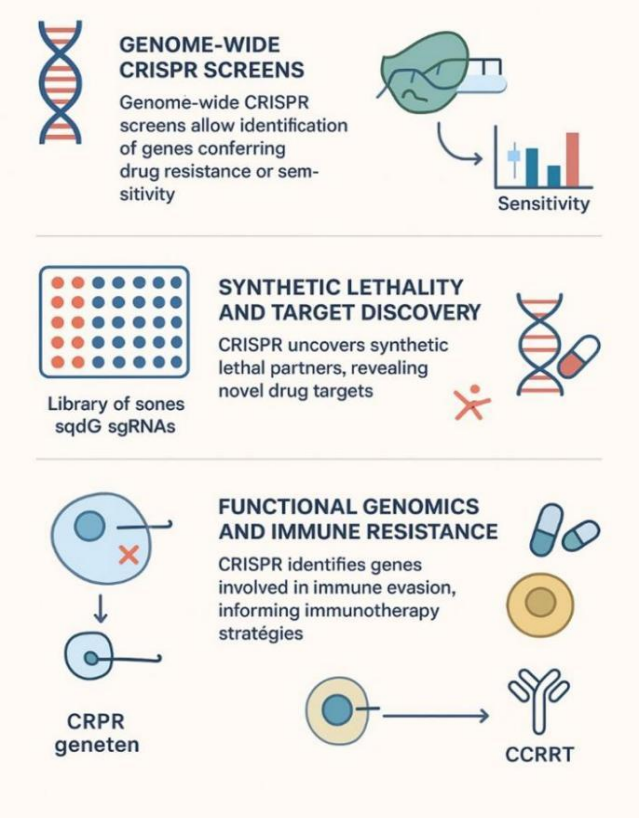

Figure 3. CRISPR-Cas9 in identifying resistance pathways

Beyond chemotherapy and targeted drugs, CRISPR-Cas9 has played a pivotal role in deciphering immune resistance mechanisms that limit the success of immunotherapies such as immune checkpoint inhibitors. Cancer cells employ two main methods to protect themselves from immune system attacks through genetic changes that affect their antigen presentation capabilities and their interferon signaling pathways and their T-cell

recognition processes. Scientists have discovered vital genes that control immune system avoidance through genome-wide CRISPR knockout studies, which revealed janus kinase 1 (JAK1) and B2M (β2-microglobulin) and programmed death-ligand 1 (PD-L1) [37]. For instance, loss of JAK1 or janus kinase 2 (JAK2) disrupts interferon-γ signaling, rendering tumor cells invisible to cytotoxic T-cells. The ability of cancer cells to avoid immune detection results from B2M gene mutations, which prevent antigen presentation through major histocompatibility complex class I (MHC-I) molecules. The research results provided important information about tumor resistance to checkpoint blockade therapies which allowed scientists to develop new treatment methods that restore immune system detection and make resistant tumors vulnerable to treatment [32]. Scientists have developed chimeric antigen receptor T cells (CAR-T) cells through CRISPR technology which enables the production of engineered immune cells that demonstrate superior tumor-fighting capabilities. The CRISPR editing technology uses gene knockout methods and synthetic receptor insertion to improve immune cell performance which leads to better therapeutic results [41]. Figure 3 illustrates the application of CRISPR-Cas9-based screening approaches in identifying and validating molecular pathways associated with therapeutic resistance.

3. Novel Opportunities Identified by CRISPR Screening

The incorporation of CRISPR-Cas9 technology into cancer biology has opened up hitherto unexplored avenues for uncovering novel therapeutic targets, understanding resistance mechanisms, and developing rational combination therapies. CRISPR technology provides scientists with an advanced method to study functional gene networks across entire genomes which surpasses the capabilities of traditional genetic tools [29]. High-throughput knockout and activation screens enable scientists to identify the genetic elements which determine how tumors survive and how they respond to drugs and develop resistance. Scientists have made significant advances in cancer therapy development because they now understand molecular mechanisms beyond what genomic and transcriptomic data can reveal. CRISPR research has led to multiple promising treatment possibilities through its investigation of cell death processes and DNA repair mechanisms and metabolic changes and epigenetic modifications [42].

3.1 Apoptosis Regulators

Apoptosis functions as a programmed cell death process which helps maintain cellular balance while protecting against tumor formation. Cancer cells develop resistance to apoptosis through their ability to increase pro-survival gene expression and their capacity to block death signaling pathways. The identification of apoptosis regulators through CRISPR knockout screens enables scientists to understand the mechanisms cancer cells use to survive during therapeutic treatments [28]. The proteins encoded by B-cell lymphoma 2 (BCL2) and myeloid cell leukemia 1 (MCL1) and B-cell lymphoma-extra large (BCL-XL) genes function as anti-apoptotic agents which lead to chemoresistance and targeted therapy failure. CRISPR-based studies that remove specific genes show tumors become more responsive to chemotherapy and kinase inhibitors [31]. The development of BH3 mimetics arose from this need to create drugs which block BCL2 family proteins so cancer cells that resist treatment can undergo apoptotic cell death. The discovered pro-survival dependencies provide a therapeutic path because they show how combining apoptosis modulators with targeted agents can stop resistance development and improve treatment longevity [43].

3.2 DNA Damage Response Pathways

CRISPR screening technology enables scientists to identify weak points which exist in the DNA damage response (DDR) system. Cancer cells depend on alternate DNA repair systems to maintain their survival when exposed to genotoxic damage from radiation treatments and chemotherapy drugs. Scientists use genome-wide CRISPR studies to disable DDR-related genes which helps them identify specific weaknesses in tumors that already have DNA repair deficiencies [30]. The loss of backup repair mechanisms in tumors with mismatch repair (MMR) and homologous recombination (HR) deficiencies leads to increased vulnerability which synthetic lethality-based therapies use for treatment. CRISPR technology enables scientists to study DDR interactions which helps them improve PARP inhibitors and discover new candidates for radiation therapy combinations [33]. Scientists achieve selective tumor cell death by targeting DNA repair pathways including ataxia telangiectasia and Rad3-related protein (ATR) and checkpoint kinase 1 (CHK1) and DNA polymerase theta (POLQ) which leads to DNA damage that exceeds cellular repair mechanisms [44].

3.3 Metabolic Reprogramming

The ability of cancer cells to adjust their metabolism according to changing nutrient and oxygen availability characterizes metabolic plasticity as a fundamental cancer characteristic. Scientists have used CRISPR-Cas9 screening to create a complete metabolic dependency map which shows how tumors grow and develop drug resistance. Research shows that specific cancer types depend on isocitrate dehydrogenase 1 (IDH1) together with glutaminase 1 (GLS1) and pyruvate kinase M2 (PKM2) enzymes to fuel their energy needs and keep their redox balance stable. The disruption of glutamine metabolism through GLS1 inhibition affects two vital cellular processes which include nucleotide synthesis and antioxidant defense mechanisms thus creating a potential treatment approach for tumors that depend on glutamine [34]. Scientists have made IDH1-mutant cancers treatable through CRISPR-identified synthetic lethal interactions which block the epigenetic changes caused by their oncometabolite production. The studies demonstrate that tumor metabolism serves as a possible treatment approach when combined with standard cancer

therapies because metabolic changes create resistance to chemotherapy and targeted treatments [45].

3.4 Epigenetic Modifiers

The scientific community now studies epigenetic regulation as a major influence on drug resistance because CRISPR technology has proved essential for discovering genes that control chromatin remodeling and DNA methylation and histone modification which affect therapeutic resistance [26]. Genome-wide CRISPR screening for loss-of-function genes revealed that removing histone methyltransferase genes including enhancer of zeste homolog 2 (*EZH2)* and SET domain containing 2 (*SETD2)* together with demethylase genes such as lysine demethylase 5A (*KDM5A)* and lysine demethylase 6B (*KDM6B)* affects the regulation of survival and proliferation and drug resistance genes. The research results indicate that epigenetic reprogramming stands as an effective approach to defeat resistance mechanisms. The dual administration of epigenetic medications which include histone deacetylase inhibitors (HDACi) and DNA methyltransferase inhibitors (DNMTi) with targeted therapies or immune-based treatments produces a combined approach to combat tumor resistance and diversity in cancer cells [46]. Figure 4 highlights the novel therapeutic targets and actionable pathways uncovered through CRISPR-Cas9 screening strategies, underscoring their potential to guide precision oncology interventions.

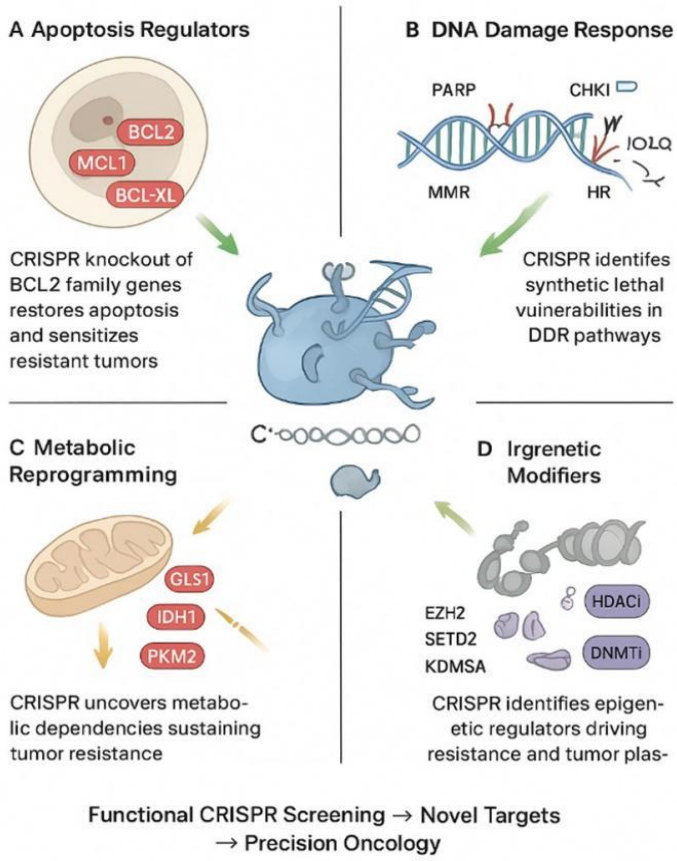

Figure 4. Novel therapeutic opportunities identified through CRISPR-Cas9 screening in cancer

4. Therapeutic Implications and Clinical Advances

CRISPR-based research has established a foundation for creating modern cancer treatment solutions. CRISPR-assisted drug validation enables fast detection of actual therapeutic targets which reduces the number of false leads during preclinical testing [47]. The ex vivo CRISPR modification of immune cells has achieved success in producing better adoptive cell therapies through CAR-T cell development which blocks Programmed cell death protein 1 (PD-1)-based suppression [23]. Clinical tests using CRISPR-edited cells (e.g., NCT03399448, NCT04557436) have shown positive safety outcomes. CRISPR activation (CRISPRa) and CRISPR interference (CRISPRi) systems enable scientists to adjust gene activity levels through precise control which broadens the potential uses for medical treatments [48].

4.1 Ethical and Safety Considerations

The scientific community experienced a major shift through CRISPR-Cas9 technology development which now shows potential to treat cancer and genetic diseases but creates multiple ethical and safety complications and social problems [19]. Scientists must apply rigorous preventive measures to stop accidental genetic alterations when using precise human genome editing methods. The main technical problem emerges from CRISPR tools making unplanned genetic modifications through off-target effects which affect genome areas outside their intended targets [17]. The errors in DNA replication process led to unwanted mutations, which may cause genomic instability and activate oncogenes while

disabling tumor suppressor functions. The unplanned changes create two major issues for drug safety, and they bring up doubts about delayed adverse reactions that might not become visible during initial testing phases [49].

Scientists face a major ethical issue when dealing with germline editing because this method creates genetic changes that families could transmit to their descendants [16]. Scientists support somatic cell editing for medical treatment, but they oppose germline modification because it violates fundamental rights of unconsenting future people (non-heritable genetic modifications for medical intervention seem acceptable but germline modification violates essential ethical standards since it changes the DNA of people who cannot approve these changes) [14]. The clinical use of CRISPR technology faces increased ethical scrutiny because of its potential to create designer genetics and its potential for eugenics-based misuse. The international bioethics organizations back strict human germline editing restrictions until safety proof and effective results and social support reach acceptable levels [50]. The system needs to solve two essential problems which include technical difficulties and fair access to all users. The high costs, together with the technical complexity of CRISPR-based treatments, may limit their accessibility in low-resource regions. As a result, these advanced therapies could widen global disparities in cancer treatment and healthcare outcomes [13]. The ethical frameworks need to focus on justice and transparency and require informed consent to make sure CRISPR advantages reach all people fairly. The system needs public participation and ethical monitoring and regulatory oversight to achieve a proper balance between innovation and responsibility [51].

Clinical trial design in CRISPR-based oncology also presents distinctive ethical tensions. In cases involving advanced or treatment-refractory malignancies, conventional randomized control models may conflict with patient expectations for access to innovative interventions. At the same time, premature therapeutic deployment without rigorous comparative evaluation risks overstating benefit. Ethical balance may be better achieved through adaptive designs, biomarker-stratified enrollment, and carefully justified use of standard-of-care comparators rather than placebo arms. Maintaining scientific integrity while minimizing therapeutic misconception remains essential in trials involving genome-editing technologies [52].

4.2 Revised Addition (Artificial Intelligence in sgRNA Design & Multi-Omics Integration)

CRISPR-Cas9 technology brings a revolutionary change to cancer research because it allows scientists to perform large-scale genome analysis and editing of cancer cells through precision medicine. Technology continues to improve, which leads to new applications that extend past gene knockout research [11]. The development of artificial intelligence (AI)-based sgRNA design systems will lead to better target specificity and reduced off-target editing in future advancements. AI algorithms function to predict ideal guide sequences and simulate Cas9-sgRNA interactions and combine multi-omics information for creating customized treatments which enable personalized gene editing [9]. The development of delivery technology continues to transform the practical implementation of CRISPR therapeutics. Scientists develop non-viral delivery systems through nanoparticle-based methods and biodegradable carriers which function as safe alternatives to deliver CRISPR components into tumor tissues. These systems improve biocompatibility, reduce immune responses, and enhance tissue penetration key steps toward clinical translation [7]. Scientists can study tumor diversity at high resolution through CRISPR single-cell transcriptomics and spatial genomics integration which reveals how cancer cells develop resistance at their most basic level. Scientists can use high-resolution mapping to create personalized treatment plans which stop resistance from developing in the first place [53]. The future of CRISPR in oncology also lies in its integration with multi-omics platforms, encompassing genomics, proteomics, and metabolomics [1]. The complete method allows scientists to study cellular reactions to genetic changes and their effects on signaling pathways and immune systems at a complete system level [54]. The combination of these technologies with CRISPR-based synthetic lethality screens enables researchers to identify specific cancer subtype weaknesses, which will lead to the creation of advanced targeted treatments [3].

Scientists have developed new CRISPR variants, including base editors and prime editors, and CRISPRi/CRISPRa systems to enable gene modification without double-strand break induction. These tools enable safer and more adaptable genetic editing, which opens new treatment possibilities while decreasing the risk of genotoxic damage Beyond guide design, AI-assisted multi-omics integration platforms combine genomic mutation profiles, transcriptomics, proteomics, and metabolic signatures to prioritize context-specific vulnerabilities identified through CRISPR screens. For instance, machine learning models integrating CRISPR screening data with RNA-seq and proteomic datasets have enabled identification of synthetic lethal interactions in KRAS-driven tumors, improving precision target selection. Such integrative computational frameworks move CRISPR applications from exploratory screening toward clinically actionable target prioritization [55,56].

5. Conclusions

In conclusion, the CRISPR-Cas9 system functions as a dual force that drives scientific advancement and medical treatment transformation. Researchers now understand cancer biology at a deeper level through this method because it identifies the specific resistance patterns and reveals new treatment options that can be used. The combination of advanced computational systems with innovative delivery methods and strict ethical oversight enables CRISPR to create long-lasting cancer treatments which provide personalized care with reduced side effects. The achievement of this goal demands ongoing teamwork between geneticists and oncologists and

bioengineers and ethicists because scientific progress needs to move forward with ethical responsibility. Scientists from different fields will continue to work together to create CRISPR-based cancer treatments, which will transform genetic knowledge into life-saving treatments for future generations.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgement and Funding

This review article did not get any financial support from any agency/institution.

Data Availability

All the data collected is included in the article.

Ethics Statement

No study was conducted on live animals/humans; thus, it did not require any ethical approval.

Autor's Contribution

MO and MJ conceived and designed the project. AG, TF, and MS contributed to the literature search and drafting of the manuscript. KJ, ZB, and B assisted in organizing content and editing. MJ supervised the work and provided critical revisions.

Generative AI Statement

The authors declare that no generative artificial intelligence technologies were used when preparing this manuscript.

Abbreviations

ABC: ATP-binding cassette

AI: Artificial intelligence

ATP: Adenosine triphosphate

ATR: Ataxia telangiectasia and Rad3-related protein

B2M: Beta-2 microglobulin

BCL2: B-cell lymphoma 2

BCL-XL: B-cell lymphoma-extra large

BCR-ABL: Breakpoint cluster region-Abelson

BRAF: B-Raf proto-oncogene, serine/threonine kinase

CAR-T: Chimeric antigen receptor T cells

CHK1: Checkpoint kinase 1

CML: Chronic myeloid leukemia

CRISPR-Cas9: Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9

CRISPRa: CRISPR activation

CRISPRi: CRISPR interference

CSCs: Cancer stem cells

DDR: DNA damage response

DNA: Deoxyribonucleic acid

DNMTi: DNA methyltransferase inhibitors

DSBs: Double-strand breaks

ECM: Extracellular matrix

EGFR: Epidermal growth factor receptor

EMT: Epithelial-to-mesenchymal transition

EZH2: Enhancer of zeste homolog 2

GLS1: Glutaminase 1

HDACi: Histone deacetylase inhibitors

HDR: Homology-directed repair

HER2: Human epidermal growth factor receptor 2

HIF: Hypoxia-inducible factor

HR: Homologous recombination

IDH1: Isocitrate dehydrogenase 1

IGF1R: Insulin-like growth factor 1 receptor

IL-10: Interleukin 10

JAK1: Janus kinase 1

JAK2: Janus kinase 2

KDM5A: Lysine demethylase 5A

KDM6B: Lysine demethylase 6B

KEAP1: Kelch-like ECH-associated protein 1

KRAS: Kirsten rat sarcoma viral oncogene homolog

MCL1: Myeloid cell leukemia 1

MET: Mesenchymal–epithelial transition factor

MHC-I: Major histocompatibility complex class I

MMR: Mismatch repair

MRP1: Multidrug resistance-associated protein 1

NF1: Neurofibromin 1

NHEJ: Non-homologous end joining

PARP: Poly (ADP-ribose) polymerase

PD-1: Programmed cell death protein 1

PD-L1: Programmed death-ligand 1

P-gp: P-glycoprotein

PKM2: Pyruvate kinase M2

POLQ: DNA polymerase theta

PTEN: Phosphatase and tensin homolog

RNA: Ribonucleic acid

RNAi: RNA interference

SETD2: SET domain containing 2

sgRNA: Single-guide RNA

TALENs: Transcription activator-like effector nucleases

TGF-β: Transforming growth factor beta

TKI: Tyrosine kinase inhibitor

TME: Tumor microenvironment

ZFNs: Zinc-finger nucleases

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