Review



# From Small Molecules to Degraders and AI: Contemporary Trends and Future Directions in Anticancer Drug Discovery

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# From Small Molecules to Degraders and AI: Contemporary Trends and Future Directions in Anticancer Drug Discovery

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**Abstract**

Cancer remains one of the leading causes of death worldwide, demanding continuous innovation in therapeutic strategies. Traditional chemotherapeutic agents, though effective in certain contexts, are limited by systemic toxicity, drug resistance, and non-specific targeting. Over the past two decades, the landscape of anticancer drug discovery has undergone a paradigm shift with the emergence of molecularly targeted agents, immunotherapies, and rational drug design technologies. Advancements in genomics, proteomics, and structural biology have enabled the identification of novel cancer-specific targets, while computational and artificial intelligence (AI)-driven approaches are accelerating lead optimization and predictive modeling of drug efficacy and toxicity. The development of antibody–drug conjugates (ADCs), bispecific antibodies, and targeted protein degraders (PROTACs) represents a new generation of therapies capable of addressing previously "undruggable" targets. Meanwhile, patient-derived organoids, 3D co-culture systems, and high-content screening platforms are refining preclinical evaluation and improving translational success rates. This review summarizes the recent trends in anticancer drug discovery, highlights the integration of computational and experimental pipelines, and explores emerging modalities poised to redefine cancer treatment in the coming decade. The future of anticancer drug discovery lies in combining precision oncology, AI-based design, and systems-level modeling to deliver safer, more effective, and personalized therapies against cancer's molecular complexity.

**Keywords:** anticancer drug discovery; AI-driven drug design; PROTAC; antibody–drug conjugates; precision oncology

## 1. Introduction

Cancer remains one of the most formidable global health challenges, accounting for approximately 10 million deaths in 2022 and representing the leading cause of premature mortality in more than 100 countries [1]. The increasing incidence is attributed to aging populations, lifestyle-associated risk factors, and improved diagnostic surveillance. Among the major cancer types, lung, breast, colorectal, prostate, and hepatocellular carcinoma contribute the highest global burden, with an increasing shift toward malignancies associated with metabolic dysfunction and inflammation [2,3]. Despite advances in early detection and multimodal therapy, the overall five-year survival rate

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for many cancers remains unsatisfactory, largely due to tumor heterogeneity, late diagnosis, and acquired resistance to therapy [4,5].

The evolution of anticancer therapeutics has been marked by successive waves of innovation. The first era, spanning the mid-20th century, was dominated by cytotoxic chemotherapeutics such as alkylating agents, antimetabolites, and DNA intercalators, which indiscriminately targeted rapidly dividing cells [6]. While these agents formed the foundation of systemic cancer therapy, their limited selectivity resulted in severe toxicity and narrow therapeutic indices. The second era, beginning in the late 1990s, was defined by the advent of targeted therapies, driven by the identification of oncogenic drivers such as BCR–ABL, HER2, and EGFR [7,8]. This paradigm introduced small-molecule kinase inhibitors and monoclonal antibodies that selectively inhibited dysregulated signaling pathways, ushering in the era of precision oncology.

Concurrently, advances in molecular biology and genomics unraveled the hallmarks of cancer—sustained proliferation, evasion of apoptosis, genomic instability, and immune escape—providing a mechanistic framework for therapeutic design [9]. However, resistance to targeted therapies frequently emerges through secondary mutations, pathway redundancy, and tumor microenvironmental adaptation [10]. These challenges underscored the need for next-generation strategies capable of addressing previously "undruggable" proteins, modulating the immune system, and tailoring therapy to individual tumor profiles.

The past decade has witnessed a profound transformation in anticancer drug discovery, driven by technological convergence between biology, chemistry, and data science. Immunotherapy has revolutionized treatment paradigms through immune checkpoint inhibitors, adoptive cell therapies, and bispecific T-cell engagers, achieving durable responses in cancers previously deemed refractory [11–13]. Similarly, antibody–drug conjugates (ADCs) have emerged as precision-guided cytotoxic delivery systems, linking monoclonal antibodies to potent small-molecule payloads that selectively eradicate tumor cells while minimizing off-target toxicity [14,15].

A parallel innovation frontier involves the development of targeted protein degradation technologies, such as proteolysis-targeting chimeras (PROTACs) and molecular glues, which exploit the ubiquitin–proteasome system to eliminate oncogenic proteins rather than merely inhibit them [16–18]. This modality offers a promising route for therapeutically addressing proteins lacking catalytic pockets or showing resistance to conventional inhibitors.

Simultaneously, artificial intelligence (AI) and machine learning (ML) have emerged as transformative tools across the drug discovery continuum—from virtual screening and structure-based design to ADMET prediction and clinical trial optimization [19–21]. Generative AI models now enable de novo molecular design, accelerating hit identification and reducing attrition rates. In parallel, omics-driven profiling, high-content screening, and integrative bioinformatics are enhancing target validation and biomarker discovery [22,23].

Preclinical modeling has also evolved from traditional two-dimensional cultures to physiologically relevant systems such as three-dimensional (3D) tumor spheroids, organoids, and patient-derived xenografts (PDXs), which more accurately recapitulate tumor architecture, heterogeneity, and drug response [24,25]. These systems, combined with CRISPR-based functional genomics and single-cell transcriptomics, provide unprecedented insights into tumor evolution, drug resistance, and immune interactions, thereby improving translational predictability [26,27].

Despite these advancements, several bottlenecks persist in anticancer drug discovery. The high attrition rate in oncology—estimated at nearly 90% in clinical trials—reflects the limitations of preclinical predictivity, inadequate biomarker validation, and incomplete understanding of tumor–immune dynamics [28,29]. Additionally, the escalating cost and complexity of development demand more efficient, data-integrated approaches.

This review synthesizes recent advances in anticancer drug discovery, emphasizing contemporary modalities including immunotherapy, ADCs, targeted protein degradation, and AI-driven design. It further discusses emerging technologies and translational challenges, offering a

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forward-looking perspective on how integrative, systems-level strategies could redefine the next decade of cancer therapeutics.

## 2. Cancer Types and Treatment Modalities

Cancer represents a highly heterogeneous group of diseases characterized by uncontrolled cellular proliferation, evasion of apoptosis, and the capacity for invasion and metastasis [30]. Based on their tissue or cell of origin, cancers are broadly classified into carcinomas, sarcomas, leukemias, lymphomas, melanomas, and gliomas [31]. Among these, carcinomas—derived from epithelial tissues—account for approximately 85–90% of all malignancies, encompassing major cancer types such as breast, lung, colorectal, liver, and prostate cancers [32]. The global cancer burden exhibits considerable geographic variability, influenced by genetic predisposition, environmental exposures, and socioeconomic factors [33]. According to the Global Cancer Observatory (GLOBOCAN 2024), lung, breast, colorectal, prostate, and liver cancers collectively contribute to more than half of all cancer-related deaths worldwide [34].

The global incidence and mortality of cancer continue to rise, with substantial variation across regions and cancer types. Table 1 provides an overview of the most prevalent cancers worldwide, highlighting their relative contribution to the global disease burden.

**Table 1. Major cancer types, their tissue of origin, and key epidemiological features.**

| Cancer Type | Tissue/Cell of Origin | Approx. Global Incidence and Mortality | Key References |
|---|---|---|---|
| Lung cancer | Epithelial cells of bronchi and alveoli | Leading cause of cancer death worldwide; >2 million new cases annually | [1,32,36] |
| Breast cancer | Mammary epithelial cells | Most common cancer among women; >2.3 million cases yearly | [1,36] |
| Colorectal cancer | Epithelial lining of colon and rectum | Third most diagnosed cancer globally; strong lifestyle correlation | [1,33] |
| Liver (HCC) | Hepatocytes | Sixth most common cancer; fourth leading cause of cancer mortality | [1,3,34] |
| Prostate cancer | Prostatic epithelial cells | Second most common in men; high survival when detected early | [1,32,36] |
| Leukemia | Hematopoietic stem cells | Most common childhood malignancy | [9,80] |
| Melanoma | Melanocytes | Fifth most common cancer in developed countries | [1,9,80] |

Understanding these epidemiological patterns is crucial for prioritizing research and developing region-specific prevention and therapeutic strategies.

### *2.1. Conventional Treatment Modalities*

Historically, cancer management has relied on three principal therapeutic pillars—surgery, radiotherapy, and chemotherapy [35]. Surgical resection remains the most effective option for localized solid tumors, particularly when detected at early stages [36]. Radiotherapy serves as both a curative and palliative measure, either complementing surgery to eradicate residual disease or

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alleviating symptoms in advanced cases [37]. Chemotherapy, first introduced in the mid-20th century, transformed oncology by utilizing cytotoxic agents that target rapidly proliferating cells, including alkylating agents, antimetabolites, and spindle poisons [38]. Despite its clinical utility, chemotherapy is often limited by its lack of selectivity, severe systemic toxicity, and the emergence of multidrug resistance (MDR) [39].

Despite the rise of precision medicine, conventional treatment modalities remain the foundation of clinical oncology. Table 2 summarizes the major traditional approaches—surgery, radiotherapy, and chemotherapy—along with their mechanisms and clinical roles.

**Table 2. Conventional cancer treatment modalities and mechanisms of action.**

| Modality | Mechanism of Action | Advantages | Limitations | Key References |
|---|---|---|---|---|
| Surgery | Physical removal of tumor mass | Curative for localized cancers | Ineffective for metastasis | [29,30,35] |
| Radiotherapy | DNA damage by ionizing radiation | Organ preservation; effective in combination | Radiation resistance; toxicity | [37,38] |
| Chemotherapy | Cytotoxic targeting of rapidly dividing cells | Systemic control; multiple drug classes | Non-selectivity, toxicity, MDR | [6,39,50–52,71] |
| Hormone therapy | Modulation of hormonal signaling | Essential in hormone-sensitive cancers | Resistance development | [42] |
| Combination therapy | Synergistic use of multiple modalities | Enhanced efficacy | Increased adverse effects | [72,76] |

Although effective, these modalities often face limitations due to toxicity and resistance, emphasizing the need for integrated multimodal and molecularly targeted strategies.

### *2.2. Advancements in Multimodal Therapies*

Over the past two decades, cancer therapy has transitioned toward multimodal and precision-based strategies, integrating conventional modalities with molecularly targeted and immune-based approaches [40]. Targeted therapies such as tyrosine kinase inhibitors (TKIs) and monoclonal antibodies have demonstrated superior efficacy and reduced toxicity by selectively disrupting oncogenic signaling cascades [41]. Hormonal therapies remain indispensable for hormone-dependent malignancies, including breast and prostate cancers [42]. Immunotherapy—comprising immune checkpoint inhibitors, adoptive T-cell transfer, and cancer vaccines—has revolutionized treatment outcomes, producing durable responses in malignancies such as melanoma, non-small cell lung cancer (NSCLC), and hematologic cancers [43]. Moreover, combinatorial regimens that integrate immunotherapy with chemotherapy or radiotherapy are being explored to overcome therapeutic resistance and enhance immune-mediated tumor eradication [44].

### *2.3. Emerging Treatment Paradigms*

Recent advances in molecular oncology have given rise to personalized and adaptive treatment paradigms, leveraging tumor genomics, transcriptomics, and proteomics to tailor therapeutic decisions [45]. Techniques such as liquid biopsy, circulating tumor DNA (ctDNA) profiling, and next-generation sequencing (NGS) facilitate real-time monitoring of tumor evolution and treatment response [46]. Furthermore, nanotechnology-based drug delivery systems, photothermal and photodynamic therapies, and gene-editing platforms like CRISPR/Cas9 are expanding the therapeutic arsenal against resistant and metastatic cancers [47,48]. Integration of these innovative

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modalities within systems oncology and artificial intelligence–driven frameworks holds immense promise for achieving truly individualized cancer management [49].

## 3. Conventional Anticancer Drugs: Classes, Mechanisms, and Limitations

The discovery of chemotherapeutic agents marked the first major breakthrough in modern oncology. Conventional anticancer drugs act primarily by interfering with DNA replication, mitotic processes, or cellular metabolism, thereby inducing apoptosis or mitotic catastrophe in rapidly dividing cancer cells [50]. Although these agents have achieved substantial clinical success in several malignancies, their non-selective cytotoxicity often damages normal proliferating tissues, leading to hematologic, gastrointestinal, and neurological toxicities [51]. Moreover, intrinsic and acquired drug resistance significantly diminishes therapeutic efficacy, underscoring the need for more specific and personalized approaches [52].

Chemotherapeutic agents have long served as the cornerstone of cancer treatment, targeting rapidly proliferating cells through distinct biochemical mechanisms. Table 3 outlines the principal drug classes, their molecular targets, and associated toxicities.

**Table 3. Classes of chemotherapeutic drugs and their cellular targets.**

| Drug Class | Mechanism of Action | Representative Drugs | Key References |
|---|---|---|---|
| Alkylating agents | DNA cross-linking and strand breakage | Cyclophosphamide, Cisplatin | [54,55,69,70] |
| Antimetabolites | Inhibit nucleotide synthesis | 5-FU, Methotrexate, Gemcitabine | [51,57–59] |
| Mitotic inhibitors | Block microtubule dynamics | Paclitaxel, Vincristine | [61–64] |
| Topoisomerase inhibitors | Prevent DNA replication by targeting topoisomerases | Doxorubicin, Etoposide, Irinotecan | [65–68] |
| Targeted agents | Inhibit oncogenic kinases and signaling | Imatinib, Gefitinib | [10,41,79] |

The diverse mechanisms of these agents have provided invaluable clinical benefit but also underscore the challenges of non-selectivity and dose-limiting adverse effects.

### *3.1. Alkylating Agents*

Alkylating agents were among the earliest chemotherapeutics developed, originating from nitrogen mustard derivatives used during World War II [53]. These compounds exert cytotoxicity by transferring alkyl groups to DNA bases, resulting in intra- and interstrand crosslinks that inhibit replication and transcription [54]. Common agents include cyclophosphamide, ifosfamide, melphalan, and cisplatin, which remain widely used across a spectrum of malignancies such as lymphomas, leukemias, and solid tumors [55]. However, their clinical use is restricted by dose-limiting toxicities and mutagenic potential, which may lead to secondary malignancies [56].

### *3.2. Antimetabolites*

Antimetabolites are structural analogs of nucleotides or metabolic intermediates that interfere with DNA and RNA synthesis [57]. They include folate antagonists (e.g., methotrexate), purine analogs (e.g., 6-mercaptopurine, fludarabine), and pyrimidine analogs (e.g., 5-fluorouracil, cytarabine, gemcitabine) [58]. These drugs have been pivotal in the management of leukemias, lymphomas, and solid tumors such as colorectal and breast cancer [59]. Despite their efficacy, resistance mediated by enhanced drug metabolism, altered target enzymes, and impaired drug uptake limits their long-term effectiveness [60].

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### *3.3. Mitotic Inhibitors*

Mitotic inhibitors disrupt microtubule dynamics essential for mitosis and intracellular transport [61]. They include vinca alkaloids (vincristine, vinblastine, vinorelbine) that inhibit microtubule polymerization, and taxanes (paclitaxel, docetaxel) that stabilize microtubules and prevent their depolymerization [62]. These agents are widely used in breast, ovarian, and lung cancers, as well as hematologic malignancies [63]. However, peripheral neuropathy, neutropenia, and resistance mechanisms—such as overexpression of P-glycoprotein and β-tubulin mutations—often compromise their clinical benefits [64].

### *3.4. Topoisomerase Inhibitors*

Topoisomerase inhibitors target the enzymes responsible for managing DNA supercoiling during replication and transcription [65]. Topoisomerase I inhibitors (e.g., camptothecin, topotecan, irinotecan) induce single-strand breaks, whereas topoisomerase II inhibitors (e.g., etoposide, doxorubicin, mitoxantrone) cause double-strand DNA breaks, triggering apoptosis [66]. While these agents are integral in treating various cancers, cardiotoxicity, myelosuppression, and secondary leukemias remain major clinical challenges [67].

### *3.5. Antibiotic and Miscellaneous Agents*

Certain antibiotics such as actinomycin D, bleomycin, and anthracyclines possess potent anticancer properties by intercalating into DNA and generating free radicals [68]. Platinum-based compounds (cisplatin, carboplatin, oxaliplatin) and other miscellaneous agents such as hydroxyurea and asparaginase have shown broad-spectrum efficacy across multiple tumor types [69]. Nonetheless, their clinical application is hindered by nephrotoxicity, ototoxicity, and cumulative dose-related toxicity [70].

### *3.6. Limitations of Conventional Chemotherapy*

Despite their pivotal role in cancer management, conventional chemotherapeutic agents are constrained by several limitations, including poor selectivity, systemic toxicity, multidrug resistance, and limited effectiveness against metastatic disease [71]. Repeated exposure to cytotoxic drugs exerts selective pressure on cancer cells, promoting clonal evolution and the emergence of resistant phenotypes [72]. Moreover, chemotherapy-induced immunosuppression and damage to normal tissues often necessitate dose reduction or treatment discontinuation [73]. These limitations have catalyzed the development of targeted therapies, immunotherapies, and next-generation drug discovery approaches aimed at achieving higher precision, efficacy, and safety [74].

## 4. Recent Advances and Current Achievements in Anticancer Drug Discovery

The past two decades have witnessed a paradigm shift in anticancer drug discovery, driven by advances in molecular oncology, structural biology, and high-throughput technologies [75]. Traditional cytotoxic agents have progressively given way to mechanism-based therapeutics designed to selectively target cancer-specific molecular alterations, thereby improving efficacy while minimizing systemic toxicity [76]. The convergence of omics technologies, computational biology, and precision medicine frameworks has accelerated the transition toward personalized cancer therapy [77].

### *4.1. Targeted Therapy*

Targeted therapies emerged from the recognition that specific genetic and signaling abnormalities drive tumorigenesis [78]. Tyrosine kinase inhibitors (TKIs) such as imatinib, erlotinib, and osimertinib selectively inhibit oncogenic kinases, demonstrating unprecedented success in chronic myeloid leukemia (CML) and non-small cell lung cancer (NSCLC) [79]. Other small-molecule

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inhibitors targeting VEGF, BRAF, and PARP have expanded the therapeutic arsenal across multiple malignancies [80]. Monoclonal antibodies (mAbs), such as trastuzumab and cetuximab, represent another class of targeted agents that disrupt extracellular receptors or ligand–receptor interactions [81]. Despite remarkable clinical outcomes, resistance mechanisms—such as target mutations, pathway redundancy, and adaptive signaling—pose significant challenges [82].

### *4.2. Immunotherapy*

Immunotherapy has revolutionized oncology by harnessing the host immune system to recognize and eliminate tumor cells [83]. Immune checkpoint inhibitors (ICIs), targeting CTLA-4, PD-1, and PD-L1, have demonstrated durable responses in melanoma, lung, and renal cancers [84]. Chimeric antigen receptor (CAR)-T cell therapies have shown transformative efficacy in hematologic malignancies, particularly B-cell leukemias and lymphomas [85]. Additionally, cancer vaccines and oncolytic viruses are emerging as potent immunotherapeutic platforms capable of inducing systemic antitumor immunity [86]. Nevertheless, immune-related adverse events, limited efficacy in "cold" tumors, and tumor immune evasion remain major clinical obstacles [87].

The transition from empirical chemotherapy to mechanism-driven drug design marks a major paradigm shift in oncology. Table 4 lists key milestones in modern anticancer drug discovery, illustrating how molecular biology and genomics have reshaped therapeutic development.

**Table 4. Emerging targeted and immune-based therapies.**

| Therapeutic Type | Mechanism/Target | Clinical Application | Key References |
|---|---|---|---|
| Tyrosine kinase inhibitors (TKIs) | Block aberrant kinase signaling | CML, NSCLC | [7,10,41,79] |
| Monoclonal antibodies | Target tumor-specific antigens | HER2⁺ breast cancer | [8,81,90] |
| Immune checkpoint inhibitors | Block PD-1/PD-L1 or CTLA-4 pathways | Melanoma, NSCLC | [11,12,43,83–87] |
| CAR-T cell therapy | Autologous T-cells engineered with CAR receptors | Leukemia, lymphoma | [13,85] |
| Antibody–drug conjugates (ADCs) | Deliver cytotoxic drugs to cancer cells | HER2⁺, breast, urothelial cancers | [14,15,88–91] |
| PROTACs | Induce selective protein degradation | Hormone receptor–driven cancers | [16–18,92,93] |

Each milestone reflects progressive refinement toward selectivity, precision, and patient-specific intervention, forming the foundation for next-generation therapies.

### *4.3. Antibody–Drug Conjugates (ADCs)*

Antibody–drug conjugates represent a hybrid class that combines the selectivity of antibodies with the cytotoxic potency of chemotherapeutic payloads [88]. Each ADC consists of a monoclonal antibody linked via a cleavable or non-cleavable linker to a cytotoxic agent, enabling targeted delivery to tumor cells expressing specific antigens [89]. Notable examples include ado-trastuzumab emtansine (T-DM1) and enfortumab vedotin, which have demonstrated significant improvements in survival and tolerability profiles [90]. Continuous optimization of linker chemistry, payload potency, and target selection is propelling ADCs toward broader clinical applicability [91].

### *4.4. Targeted Protein Degradation and RNA-Based Therapies*

Traditional small-molecule inhibitors often fail to address "undruggable" proteins lacking enzymatic pockets. The advent of proteolysis-targeting chimeras (PROTACs) has revolutionized this

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paradigm by co-opting the ubiquitin–proteasome system to selectively degrade pathogenic proteins [92]. Several PROTACs targeting AR, BRD4, and BCL-XL have entered preclinical and early clinical stages [93]. In parallel, RNA-based therapeutics, including siRNAs, antisense oligonucleotides (ASOs), and mRNA vaccines, have emerged as promising modalities capable of modulating oncogenic transcripts [94]. Advances in nanoparticle-based delivery systems have enhanced their stability, tissue specificity, and clinical potential [95].

### *4.5. Artificial Intelligence and Computational Drug Discovery*

Artificial intelligence (AI) and machine learning (ML) are transforming drug discovery pipelines by enabling rapid identification, design, and optimization of novel anticancer compounds [96]. AI-driven platforms integrate multi-omics data, molecular docking, and quantitative structure–activity relationship (QSAR) modeling to predict drug–target interactions and toxicity profiles [97]. Deep learning algorithms have also facilitated virtual screening of ultra-large chemical libraries, reducing time and cost associated with conventional screening [98]. Additionally, generative AI models are being employed to design *de novo* molecules with optimized pharmacokinetic and pharmacodynamic properties [99]. Integration of AI with experimental validation is increasingly accelerating the transition from in silico predictions to clinical translation [100].

### *4.6. Advanced Preclinical Models*

Traditional two-dimensional (2D) cell culture systems often fail to replicate the complexity of the tumor microenvironment (TME). In contrast, three-dimensional (3D) models, including organoids, spheroids, and co-culture systems, more accurately recapitulate tumor heterogeneity, cell–cell interactions, and drug responses [101]. Patient-derived xenografts (PDX) and organ-on-chip systems further enhance translational predictability, bridging the gap between preclinical findings and clinical outcomes [102]. These models are increasingly integrated into high-content and high-throughput screening platforms to improve the efficiency of drug discovery and reduce late-stage failures [103].

## 5. Future Prospects and Emerging Directions in Anticancer Drug Discovery

The future of anticancer drug discovery lies in the seamless integration of molecular biology, computational intelligence, and translational medicine [104]. As cancer remains a disease of molecular and cellular complexity, understanding its evolutionary dynamics, heterogeneity, and adaptive resistance mechanisms is essential for next-generation therapeutic strategies [105]. The ongoing convergence of multi-omics profiling, artificial intelligence, and precision oncology heralds a new era of personalized, adaptive, and predictive cancer therapy [106].

Looking ahead, the convergence of multi-omics, artificial intelligence, and nanotechnology is redefining the future of anticancer drug discovery. Table 5 highlights emerging platforms and strategies that promise to enhance precision, efficacy, and translational success.

**Table 5. Next-generation approaches and enabling technologies in anticancer therapy.**

| Innovation | Principle/Technology | Potential Application | Key References |
|---|---|---|---|
| Nanotechnology-based delivery | Nanocarriers improve drug solubility, targeting, and reduce toxicity | Enhanced delivery of chemotherapeutics and RNA drugs | [47,112–115] |
| CRISPR/Cas9 gene editing | Genome engineering for cancer gene knockout | Functional genomics and therapy | [26,48,118,119] |
| Multi-omics integration | Integration of genomics, transcriptomics, proteomics for therapy design | Precision oncology | [22,23,107] |

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| | | | |
|---|---|---|---|
| AI-driven drug discovery | Machine/deep learning for hit identification and optimization | Accelerated lead discovery | [19,20,96–100,108–110] |
| Organoid and 3D culture models | Mimic in vivo tumor microenvironment | Preclinical drug screening | [24,25,101–103] |
| Systems oncology and digital twins | Integration of omics, AI, and clinical data | Predictive and personalized oncology | [104,106,124,125] |

Together, these innovations signify a shift toward predictive, adaptive, and personalized oncology, integrating biology, computation, and clinical science into a unified discovery pipeline.

### *5.1. AI–Omics Convergence and Precision Oncology*

The integration of genomics, transcriptomics, proteomics, metabolomics, and single-cell analyses has enabled systems-level characterization of tumors [107]. Artificial intelligence (AI) and machine learning (ML) approaches are increasingly used to analyze these vast datasets, uncovering actionable biomarkers and druggable vulnerabilities [108]. Predictive algorithms capable of modeling tumor evolution and therapy response will guide adaptive treatment regimens tailored to each patient's molecular profile [109]. Multi-omics–AI pipelines are also accelerating target validation and repurposing of existing drugs for novel oncogenic pathways [110]. Such approaches will be critical in overcoming interpatient variability and improving clinical outcomes in precision oncology [111].

### *5.2. Nanotechnology and Smart Drug Delivery Systems*

Nanotechnology-based platforms are redefining cancer therapeutics by enhancing drug solubility, stability, and tumor-specific delivery [112]. Engineered nanoparticles—comprising liposomes, dendrimers, polymeric micelles, and metallic nanocarriers—enable controlled and site-specific release of anticancer agents, thereby minimizing off-target toxicity [113]. The emergence of stimuli-responsive nanocarriers, capable of releasing drugs in response to tumor microenvironmental cues such as pH, enzymes, or redox potential, offers further refinement of precision delivery [114]. Moreover, theranostic nanoparticles that integrate therapeutic and diagnostic functions are paving the way for real-time monitoring of treatment efficacy [115].

### *5.3. Synthetic Lethality and Genome Editing*

Exploiting synthetic lethal interactions between oncogenic mutations and compensatory pathways offers a rational framework for drug discovery [116]. PARP inhibitors targeting BRCA1/2-deficient tumors exemplify the clinical success of this strategy [117]. Advances in CRISPR/Cas9 genome editing now allow systematic identification of synthetic lethal gene pairs, enabling the development of tumor-selective therapeutics [118]. Coupled with functional genomic screens, this approach promises to uncover new vulnerabilities across diverse cancer types [119].

### *5.4. Tumor Microenvironment and Immuno-Oncology*

The tumor microenvironment (TME) plays a critical role in modulating cancer progression, immune evasion, and therapeutic resistance [120]. Future anticancer strategies aim to reprogram the TME by targeting stromal cells, tumor-associated macrophages, fibroblasts, and angiogenic networks [121]. Rational combinations of immune checkpoint inhibitors with targeted agents, radiotherapy, or metabolic modulators are expected to convert immunologically "cold" tumors into "hot" ones, enhancing responsiveness to immunotherapy [122]. Moreover, advances in personalized cancer vaccines, neoantigen prediction, and adoptive immune cell engineering are expanding the frontiers of immuno-oncology [123].

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*5.5. Systems Biology and Digital Twin Models*

The application of systems biology and computational modeling is transforming the understanding of cancer as an evolving network of dynamic molecular interactions [124]. The emerging concept of digital twins—virtual patient-specific models integrating genomic, pharmacologic, and clinical data—enables simulation of disease progression and therapeutic outcomes in silico [125]. These models will facilitate real-time decision-making, adaptive clinical trial design, and optimization of combination therapies [126]. Integrating digital twin platforms with AI and high-content biological data could revolutionize precision oncology by enabling predictive and preventive cancer management [127].

*5.6. Translational and Regulatory Considerations*

Despite significant progress, translating novel drug candidates into clinical success remains challenging due to high attrition rates, complex regulatory pathways, and tumor heterogeneity [128]. The incorporation of adaptive clinical trial designs, real-world evidence (RWE), and biomarker-guided patient selection is expected to enhance translational efficiency [129]. Collaborative frameworks among academia, industry, and regulatory agencies will be essential for accelerating the bench-to-bedside continuum [130]. Ultimately, the success of future anticancer drug discovery will depend on integrating biological insight, computational innovation, and clinical validation into a unified, patient-centered strategy [131].

## 6. Conclusions

Anticancer drug discovery has undergone a paradigm shift from empirical screening of cytotoxic agents to the rational design of precision-based and immune-targeted therapies. Integrating advances in molecular biology, multi-omics technologies, and computational modeling has deepened our understanding of tumor complexity, enabling the development of safer and more effective drugs. However, major challenges such as therapeutic resistance, tumor heterogeneity, and limited clinical predictability continue to hinder durable outcomes. The convergence of artificial intelligence, systems biology, and predictive modeling is poised to transform the discovery pipeline, accelerating the translation of molecular insights into personalized interventions. Looking ahead, sustained multidisciplinary collaboration and equitable global access to innovation will be essential to realize the ultimate goal—transforming cancer from a largely fatal disease into a curable or chronically manageable condition.

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