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Omics-enhanced nanomedicine: integrating multi-omics for precision cancer diagnosis and therapy

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Abstract

Cancer nanomedicine has emerged as a transformative approach in oncology, providing targeted therapeutic strategies with enhanced efficacy and reduced systemic toxicity. The integration of multi-omics technologies has further revolutionized this field.This review was conducted based on a systematic literature search using PubMed, Web of Science, and Scopus databases. Keywords included "cancer nanomedicine," "multi-omics," "precision oncology," "nanoparticle," and related terms. The search was limited to articles published between 2000 and 2024. Only English-language full-text articles reporting original research or clinical studies relevant to omics-enhanced nanomedicine were included. This review uniquely synthesizes recent advances in omics-enhanced nanomedicine, highlighting the integration of multi-omics data for precision cancer therapy. Key innovations include omics-driven nanoparticle design, patient stratification via biomarker panels, and synergy with immunotherapy. Future directions focus on AI-aided data integration and clinical translation.

Keywords Cancer nanomedicine, Omics technologies, Tumor heterogeneity, Personalized medicine, Therapeutic strategies

1 Introduction

Cancer continues to be a predominant factor contributing to global mortality, as evidenced by the approximately 19.3 million newly diagnosed cases and around 10.0 million fatalities attributed to the disease in the year 2020 [1]. The global cancer burden, projected to reach 28.4 million cases in the next two decades, is attributed to demographic shifts, unhealthy lifestyles, and various risk factors. Conventional cancer therapies, including surgery, chemotherapy, and radiation, often face significant limitations such as low specificity, adverse side effects, and limited efficacy against metastatic or advanced-stage tumors [2]. These difficulties highlight the pressing requirement for novel treatment approaches. Nanomedicine, leveraging the unique properties of nanomaterials, has rapidly advanced over the past three decades as a promising solution to overcome the limitations of traditional cancer therapies [3]. The improved permeability

and retention (EPR) phenomenon, which promotes the passive gathering of nanoparticles (NPs) in tumor locations, has been fundamental in the advancement of nanomedicine for cancer treatment [4]. The FDA's approval of Doxil® in 1995 marked a significant milestone, heralding the era of nanotherapy. Since then, over 15 FDA-approved anticancer nanomedicines have become commercially available, with approximately 75 new nanomedicines currently undergoing clinical trials [5]. These advancements have established cancer nanomedicine as a vital branch of oncology, offering capabilities such as targeted drug delivery, improved pharmacokinetics, and reduced systemic toxicity [6]. Despite these advancements, tumor heterogeneity—variations between different tumors and within individual tumors—poses a significant challenge to the efficacy of nanomedicine [7]. This heterogeneity is not merely genetic but extends to the transcriptomic, proteomic, and metabolic levels, creating a dynamic and adaptive tumor ecosystem that can evade uniform therapeutic interventions. This complexity necessitates the integration of high-throughput analytical techniques to tailor nanomedicine strategies to specific tumor profiles. Omics technologies, encompassing genomics, epigenomics, transcriptomics, proteomics, metabolomics, and beyond. By dissecting tumor heterogeneity at multiple biological levels, omics technologies support the development of personalized and precise nanomedicine strategies [8]. This review aims to summarize the state-of-the-art omics approaches utilized in cancer nanomedicine, elucidate their integration for enhanced diagnosis and treatment, and discuss the current challenges and future prospects in this rapidly evolving field. Figure 1 showed the Nanomedicine-Driven Cancer Immunotherapy.

2 Omics technologies

The emergence of omics technologies has transformed our comprehension of cancer biology by offering extensive, high-throughput data regarding diverse biological molecules and their interactions. The term "omics" originated with genomics, following the Human Genome Project, and has since expanded to include a wide array of disciplines, each focusing on a specific class of biomolecules [9]. Omics technologies have become fundamental to systems biology and molecular research, offering unprecedented insights into the complexity of cancer [10]. Figure 2 showed the Multi-Omics Integration Framework in Precision Nanomedicine. And Table 1showed Multi-Omics Technologies in Cancer Nanomedicine.

2.1 Genomics

Genomics refers to the extensive examination of the complete genome, which includes its architecture, functionality, evolutionary aspects, and the process of mapping. Within the realm of cancer research, genomics has played a crucial role in uncovering genetic mutations and modifications that contribute to tumor development and the advancement of cancer [11]. Traditional genomic sequencing methods, such as Sanger sequencing, have been largely supplanted by next-generation sequencing (NGS) technologies [12]. NGS has greatly advanced the detection of single nucleotide variants (SNVs), copy number variations (CNVs), and structural alterations within cancer genomes, which has in turn paved the way for the identification of new therapeutic targets [13]. In the field of cancer nanomedicine, genomics is essential for the identification of molecular targets that are pivotal for nanoparticle (NP)-based therapeutic approaches. For instance,

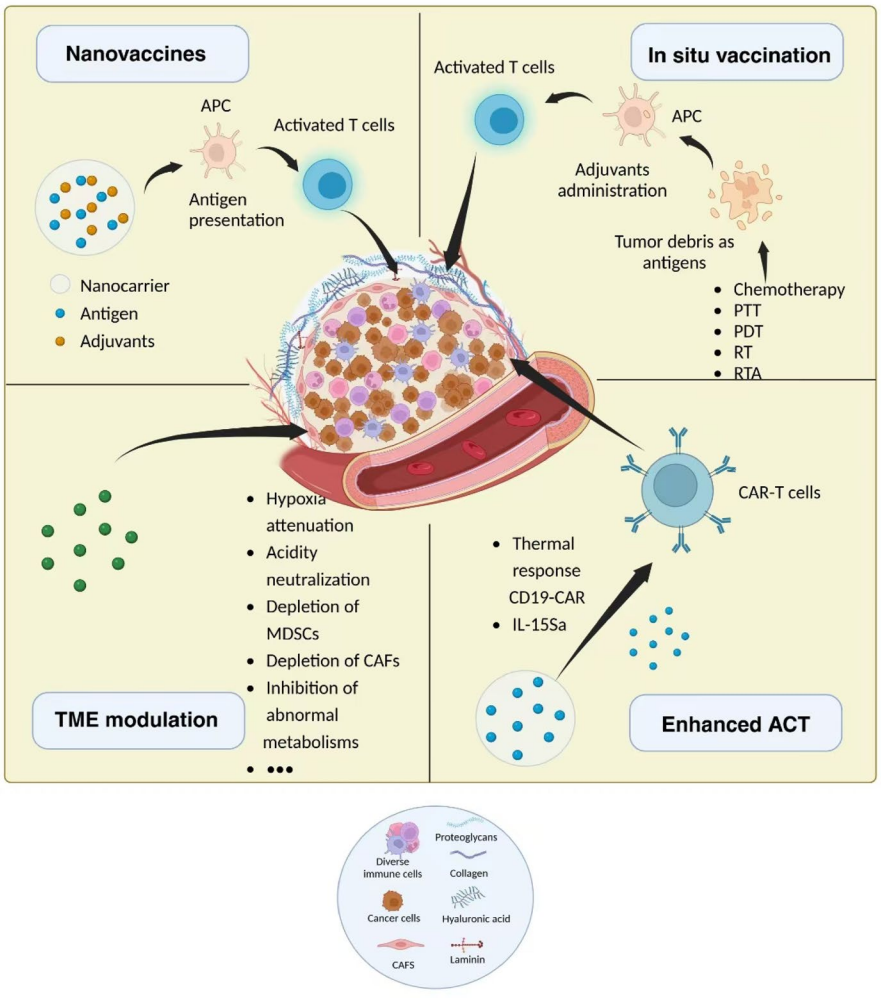

Fig. 1 Nanomedicine Driven Cancer Immunotherapy

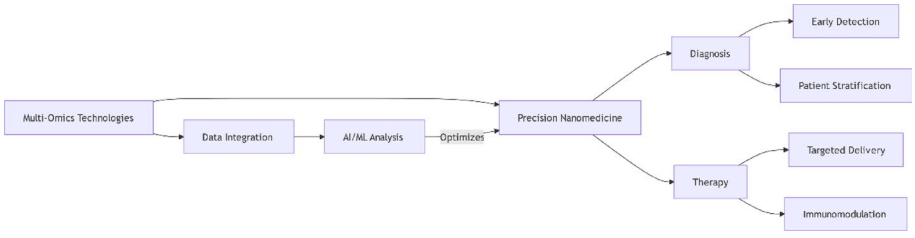

Fig. 2 Multi-Omics Integration Framework in Precision Nanomedicine

whole-exome sequencing (WES) has been used to uncover frequently mutated genes in diffuse large B-cell lymphoma, identifying potential targets for nanotherapy [14]. Additionally, third-generation sequencing (TGS), characterized by single-molecule sequencing, has enhanced the ability to analyze tumor heterogeneity at a finer resolution, supporting the development of personalized nanomedicine approaches [15].

Table 1 Multi-omics technologies in cancer nanomedicine

Omics type	Key analytical platforms	Nanomedicine applications	Clinical impact
Genomics	NGS, TGS, WES	Identify SNVs/CNVs for NP target design	Personalized siRNA nanodelivery (e.g., POLR2A in TNBC)
Epigenomics	Bisulfite-seq, ChIP-seq, MeRIP-seq	Develop NPs modulating DNA/RNA methylation	Early diagnosis via NP-enabled methylation beads
Transcriptomics	scRNA-seq, Spatial Transcriptomics	Design NPs targeting specific gene expression profiles	Stratify high-risk medulloblastoma patients
Proteomics	LC-MS/MS, Tandem Mass Tags	Analyze NP-protein corona interactions	Diagnostic biomarker discovery (e.g., hydrogel NPs)
Metabolomics	NMR, GC-MS, LC-MS	Identify metabolic vulnerabilities for NP targeting	Plasma metabolic fingerprints for gastric cancer
Lipidomics	Shotgun Lipidomics, LC-MS	Optimize lipid-based NP membranes	Assess ferroptosis in TNBC after Fe_3O_4 NP therapy
Glycomics	Lectin arrays, Ion Mobility MS	Develop glycan-targeted NPs	NSCLC diagnosis via silica NP-enriched fibrinogen
Microbiomics	16 S rRNA-seq, Metagenomic sequencing	Engineer microbiome-modulating NPs (e.g., SCXN for CRC)	Reverse chemoresistance via lung microbiota targeting

2.2 Epigenomics

Epigenomics investigates the inheritable modifications in gene expression that occur without any changes to the DNA sequence itself [16]. Such modifications encompass DNA methylation, histone alterations, and mechanisms linked to non-coding RNAs. These epigenetic changes are pivotal in the context of cancer, as they govern the expression of genes that are crucial for processes such as cell proliferation, programmed cell death (apoptosis), and the spread of cancer cells (metastasis) [17]. Advanced epigenomic profiling techniques, such as bisulfite sequencing and chromatin immunoprecipitation sequencing (ChIP-seq), have enabled the comprehensive mapping of epigenetic alterations in cancer genomes [18]. In the context of nanomedicine, epigenomic insights facilitate the design of NPs that can modulate epigenetic states to inhibit tumor growth. For example, NP-enabled methylation on beads technology has enhanced the sensitivity and specificity of DNA methylation analysis in pancreatic cancer, aiding in early diagnosis [19]. Moreover, methylated RNA immunoprecipitation sequencing (MeRIP-seq) has identified therapeutic targets that mediate m6A RNA modifications, leading to the development of mRNA-loaded folic acid-modified exosome–liposome hybrid NPs for targeted cancer therapy [20].

2.3 Transcriptomics

Transcriptomics pertains to the comprehensive examination of the entirety of RNA transcripts generated by the genome in particular conditions or within specific cellular environments [21]. This domain encompasses the investigation of messenger RNA (mRNA), non-coding RNAs, and the phenomena of alternative splicing. Employing transcriptomic methodologies yields critical insights into gene expression dynamics and regulatory frameworks associated with cancer, thereby aiding in the identification of biomarkers and the formulation of targeted therapeutic strategies [22]. Cutting-edge transcriptomic technologies, including single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST), have fundamentally transformed cancer research by facilitating the evaluation of gene expression at the resolution of individual cells and within the anatomical context of tissues [23]. scRNA-seq enables the profiling of transcriptomes in individual cells by isolating single cells, reverse-transcribing their RNA into cDNA,

and performing high-throughput sequencing to quantify gene expression levels, thereby uncovering cellular heterogeneity and rare cell populations within tumors. In cancer nanomedicine, transcriptomic data can guide the design of NPs that target specific gene expression profiles or pathways. For instance, scRNA-seq has been employed to identify high-risk patient cohorts in medulloblastoma and to assess the synergistic effects of NP-based combination therapies in lung cancer [24].

2.4 Proteomics

Proteomics refers to the extensive examination of proteins, encompassing aspects such as their structures, functions, interactions, and modifications [25]. Proteins are fundamental to virtually all biological processes, and their dysregulation is a hallmark of cancer [26]. Mass spectrometry (MS)-based proteomics has become the cornerstone of protein analysis, offering high-throughput, precise, and scalable methods for protein identification and quantification. In cancer nanomedicine, proteomic analyses of NP-induced protein coronas provide critical insights into NP interactions with biological systems [27]. For example, hydrogel NPs coupled with LC-MS/MS have been used to identify proteins associated with invasive ductal carcinoma, aiding in the development of diagnostic biomarkers. Additionally, quantitative tandem mass-tag mass spectrometry combined with CRISPR-Cas9 techniques has elucidated the protein expression profiles of cancer-derived extracellular vesicles, uncovering mechanisms of metastasis and potential therapeutic targets [28, 29].

2.5 Metabolomics

Metabolomics refers to the analysis of low-molecular-weight metabolites found in cells, tissues, or entire organisms. These metabolites act as direct markers of biochemical processes and provide insight into the physiological condition of the system. Metabolomic profiling offers a snapshot of the metabolic alterations in cancer, revealing vulnerabilities that can be targeted therapeutically [30]. Nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-mass spectrometry (LC-MS) represent the principal methodologies employed in metabolomic investigations. Each of these techniques provides unique benefits in terms of sensitivity and specificity [31]. In cancer nanomedicine, metabolomics aids in the identification of metabolic biomarkers for early diagnosis and in understanding the metabolic impact of NP-based therapies. For instance, NP-enhanced MS techniques have been employed to analyze plasma metabolic fingerprints in gastric cancer, facilitating the identification of diagnostic markers [32]. Furthermore, mass spectrometry imaging (MSI) allows for the spatial visualization of metabolite distributions in tissues treated with NPs, providing insights into the metabolic perturbations induced by nanotherapies.

2.6 Lipidomics

Lipidomics, which is a branch of metabolomics, is dedicated to the thorough examination of lipids present in biological systems [33]. Lipids play critical roles in cellular membrane structure, energy storage, and signaling pathways, all of which are pertinent to cancer biology [34]. The lipidome is highly complex, comprising over 200,000 distinct molecular species, necessitating advanced analytical techniques for thorough characterization [35]. Mass spectrometry (MS)-based lipidomics, including shotgun lipidomics

and LC-MS platforms, has become the dominant approach for lipid analysis due to its high sensitivity and specificity [36]. In cancer nanomedicine, lipidomic profiling informs the design of lipid-based NPs and elucidates the interactions between NPs and cellular lipid membranes. For example, lipidomic analysis has been utilized to map the lipid composition of exosome-like NPs derived from tea leaves, providing a structural foundation for their antitumor effects [37]. Additionally, LC-MS has facilitated the assessment of treatment responses to Fe_3O_4 magnetic NPs in triple-negative breast cancer, revealing alterations in polyunsaturated fatty acids that underpin ferroptosis mechanisms [38].

2.7 Glycomics

Glycomics involves the comprehensive study of glycans, which are complex carbohydrates attached to proteins and lipids, forming glycoproteins and glycolipids [39]. Glycans are essential for various biological processes, including cell-cell communication, signaling, and immune recognition. In cancer, aberrant glycosylation patterns are associated with tumor progression, metastasis, and immune evasion [40]. Analyzing glycan structures and glycoprotein profiles requires sophisticated analytical techniques such as lectin arrays, capillary electrophoresis, chromatography, ion mobility spectrometry, and MS [41]. Glycomics provides critical insights into tumor biology and supports the development of glycan-targeted nanomedicines. For instance, silica NPs have been employed to enrich plasma fibrinogen, enabling N-glycosylation profiling for lung cancer diagnosis [42]. Additionally, lectin-coated magnetic NPs combined with glycosylation profiling have revealed distinct glycoproteome landscapes [43].

2.8 Microbiomics

Microbiomics encompasses the comprehensive study of microbial communities and their interactions within various environments, including the human body. The human microbiome, comprising trillions of microorganisms, plays a pivotal role in maintaining health and modulating disease processes, including cancer [44]. Recent studies have identified diverse microbial populations within tumors, influencing the tumor microenvironment (TME) and therapeutic responses. Next-generation sequencing (NGS)-based techniques, such as 16 S rRNA gene sequencing and shotgun metagenomic sequencing, have revolutionized microbiomics by enabling the identification and characterization of microbial species without the need for culturing [45]. These insights are increasingly leveraged to design microbiome-modulating nanomedicines that enhance therapeutic efficacy. For instance, capecitabine-loaded prebiotic nanoparticles (SCXN) have been engineered to restore beneficial gut microbes and boost antitumor immunity in colorectal cancer, while inhalable nanoparticles targeting lung microbiota have shown promise in reversing chemoresistance. By performing deep sequencing on local or systemic microbial communities, researchers can identify signature taxa and functional genes that influence immunotherapy or chemotherapy responsiveness. Preliminary pilot studies in colorectal cancer detected imbalances in beneficial gut microbes via NGS-based profiling and then developed nanoparticles capable of releasing short-chain fatty acids or prebiotics to bolster drug sensitivity. Moreover, translational research projects are now integrating metagenomic data with tumor immune microenvironment analyses to create nanoparticle formulations that specifically modulate the lung microbiome in murine models, demonstrating encouraging efficacy in reducing chemoresistance. These

early successes underscore the clinical potential of microbiome-driven nanoparticle strategies and indicate that microbiome modulation may become a cornerstone of next-generation precision nanomedicine. Inter-patient microbiome variability indeed poses challenges for the broad application of microbiome-targeted nanomedicine [46, 47]. To address this, personalized microbiome profiling via metagenomic sequencing is essential for patient stratification. For instance, studies have used machine learning to correlate microbial signatures with drug response, enabling the design of adaptive nanoparticles that can be tailored to individual microbiome landscapes.

3 Omics-enhanced nanomedicine in cancer diagnosis

The prompt and precise diagnosis of cancer is crucial for effective treatment strategies and enhancing patient outcomes. Although conventional diagnostic approaches are vital, they frequently fall short in terms of the sensitivity and specificity necessary for the early identification and accurate categorization of tumors [48]. The integration of omics technologies with nanomedicine offers innovative diagnostic platforms that leverage the unique properties of NPs and the comprehensive molecular insights provided by omics data.

3.1 Early detection

Early detection of cancer significantly improves prognosis by enabling timely interventions. Omics-enhanced nanomedicine facilitates the identification of low-abundance biomarkers with high sensitivity and specificity, crucial for distinguishing cancer patients from healthy individuals NP-based biomolecular coronas, formed by the adsorption of biomolecules from biofluids onto NP surfaces, serve as a rich source of diagnostic biomarkers [49–53]. For example, Wang et al. developed a nanospectral library, ProteoFish, using SiO_2 NPs to enrich proteins from serum samples of non-small cell lung cancer (NSCLC) patients [54]. ProteoFish demonstrated superior capability in enriching low-molecular-weight and low-abundance proteins compared to commercial kits, identifying 1,915 proteins versus 1,607. Machine learning algorithms were employed to identify a panel of 15 differential proteins effective in diagnosing early-stage NSCLC and distinguishing between benign and malignant nodules. Similarly, PEGylated liposomes were utilized to capture circulating cell-free DNA (cfDNA) in ovarian cancer patients, with proteomic analysis revealing core histone proteins in the biomolecular corona, highlighting the diagnostic potential of NP-based detection platforms. Glycomic profiling using silica NPs to enrich plasma fibrinogen has enabled the identification of specific N-glycan peaks, aiding in the diagnosis of lung cancer. Additionally, superparamagnetic iron oxide NPs (SPIONs) have been engineered for high-throughput proteomic analysis, enhancing the identification of over 2,000 proteins and achieving an area under the curve (AUC) of 0.91 for early-stage NSCLC diagnosis [55]. Hydrogel NPs (HNs) selectively capturing biomolecules via high-affinity dye interactions have identified tumor-specific proteins with 100% sensitivity and 85.37% specificity for early-stage breast cancer diagnosis [56].

3.2 Patient stratification and prognosis prediction in nanomedicine

Patient stratification involves categorizing individuals into distinct subgroups based on criteria such as tumor subtype, grade, stage, and treatment response, with omics-assisted biomarker identification enhancing the accuracy of this process for more

personalized treatment strategies. For instance, NP-enhanced laser desorption ionization-mass spectrometry (LDI-MS) has been used for metabolic fingerprinting in retinoblastoma (RB) staging, identifying 16 molecular features that differentiate early and advanced stages [57]. Similarly, corona-coated AuNPs from serum have been employed to detect differentially expressed proteins among breast cancer subtypes, aiding in the classification of patients for targeted therapies. In prognosis prediction, the integration of omics-enhanced nanomedicine enables better quantification of tumor aggressiveness and prediction of patient outcomes. Ferric nanoparticles (NPs) have been utilized to establish a metabolic prognosis scoring system (MP-score) based on four metabolites, demonstrating superior performance over traditional TNM staging in predicting patient prognoses [58]. Furthermore, multi-omics analyses, including RNA-seq and methylation profiling, have advanced prognostic models by identifying key molecular alterations associated with treatment responses and survival outcomes. For instance, the metabolic prognosis scoring system (MP-score) based on nanoparticle-enriched metabolites has been validated in cohorts of patients, showing superior prognostic accuracy compared to TNM staging [59, 60]. However, further multi-center studies are needed to standardize these approaches.

3.3 Real-world case studies

In current clinical and advanced preclinical research, there are emerging examples of multi-omics approaches guiding nanomedicine development and patient stratification. For instance, an ongoing Phase II clinical trial for recurrent ovarian cancer employs combined transcriptomic and proteomic analyses to identify subgroups that overexpress certain tumor-promoting pathways. These patients then receive inhibitor-loaded nano-liposomes targeting those pathways, and preliminary data indicate a marked improvement in overall response rates and progression-free survival. Meanwhile, in an advanced-stage preclinical study, investigators used integrated transcriptomic and metabolomic datasets to reveal highly activated immune pathways in triple-negative breast cancer, leading to the development of a "nanoliposome–checkpoint inhibitor" combination therapy that significantly reduced chemoresistance in murine models. Similarly, another preclinical project utilized single-cell RNA sequencing (scRNA-seq) to characterize the tumor immune microenvironment, enabling researchers to select siRNA or mRNA nanodelivery systems optimally suited for specific immune-cell populations. This personalized nanomedicine approach yielded superior tumor suppression compared to standard chemotherapy regimens in a heterogeneous soft tissue sarcoma model. Collectively, these examples demonstrate how multi-omics data can inform nanocarrier design, refine drug selection, and stratify patients, thereby advancing the realization of truly individualized cancer therapies. Table 2 showed the Omics-Enhanced Nanodiagnostics Performance. Despite promising preclinical data, several omics-guided nanomedicine trials have faced challenges [61]. For example, a phase II trial of genomics-stratified lipid nanoparticles in metastatic colorectal cancer was terminated early due to insufficient patient response heterogeneity. Conversely, a successful phase I/II trial using proteomics-guided albumin-bound nanoparticles (nab-paclitaxel) in pancreatic cancer demonstrated improved overall survival in biomarker-selected subgroups [62]. These cases underscore the importance of robust biomarker validation and patient selection in omics-driven nanomedicine.

Table 2 Omics-enhanced nanodiagnostics performance

Nanoplatform	Cancer type	Omics approach	Biomarkers identified	Performance metrics
SiO_2 NPs (ProteoFish)	NSCLC	Proteomics + ML	15 differential proteins	Early-stage AUC: 0.91
PEGylated Liposomes	Ovarian Cancer	Proteomics of cfDNA corona	Core histone proteins	Improved malignant nodule discrimination
Silica NPs	Lung Cancer	Glycomics	Specific N-glycan peaks	Subtype classification accuracy > 85%
SPIONs	NSCLC	High-throughput Proteomics	> 2,000 proteins	Early-stage AUC: 0.91
Hydrogel NPs	Breast Cancer	Proteomics	Tumor-specific proteins	Sensitivity: 100%, Specificity: 85.37%
AuNPs (Corona-coated)	Breast Cancer	Proteomics	Subtype-specific proteins	Accurate molecular subtyping
Ferric NPs	Multi-Cancer	Metabolomics	MP-score (4 metabolites)	Superior to TNM staging ($p < 0.01$)

4 Omics-enhanced nanomedicine in cancer treatment

The primary objective of cancer treatment is to eradicate tumors while minimizing systemic toxicity [63]. Nanomedicine, with its ability to deliver therapeutic agents specifically to tumor sites, has significantly enhanced the precision and efficacy of cancer therapies. Omics technologies contribute to this enhancement by unraveling the molecular complexities of tumors.

4.1 Therapeutic target identification

Identifying therapeutic targets is fundamental to the design of effective nanomedicine strategies. Omics approaches enable the comprehensive analysis of genetic, epigenetic, and metabolic alterations in tumors, revealing vulnerabilities that can be exploited therapeutically [64, 65]. For example, RNA-seq analyses in colorectal cancer (CRC) have identified the Erbin gene as a critical regulator of metastasis, leading to the development of RGD-modified nanovesicles delivering siRNA against Erbin, effectively suppressing lung metastasis in mouse models [66]. Similarly, POLR2A has been identified as a collateral vulnerability target in triple-negative breast cancer (TNBC) through genomic data analysis, leading to the design of low-pH-activated "nanobomb" NPs for targeted siRNA delivery [67]. Proteomic and metabolomic profiling further supports target identification. Elevated expression of CNPY2 across various cancer types identified through pancancer transcriptomic data has been targeted using lipid-like NPs for Cas9 mRNA and sgRNA delivery, demonstrating significant therapeutic effects. Metabolomic analysis of CRC plasma identified reduced matairesinol levels, leading to the development of matairesinol-encapsulated liposomes that synergize with chemotherapy regimens to enhance treatment efficacy.

4.2 Drug delivery system (DDS) design

The design of drug delivery systems (DDS) is crucial for the effective delivery of therapeutic agents to tumor sites. Omics technologies inform the architectural design of nanocarriers, ensuring precise targeting and controlled release [68–76]. Nanocarriers are designed to protect therapeutic agents and facilitate their controlled release at target sites, with omics data playing a crucial role in optimizing carrier design. For example, microbiomic insights into lung tumor microbiota have guided the development of GaTa-CP nanoparticles, which mimic host-tissue molecules to evade immune

clearance and improve efficacy against chemoresistant tumors [77]. Additionally, lipid nanoparticle (LNP) libraries screened for organ-specific delivery have shown that certain formulations preferentially accumulate in the lungs, informed by proteomic analysis of protein coronas. Understanding the kinetics of nanocarrier interactions with biological systems is key to enhancing therapeutic outcomes and safety. Techniques like capillary electrophoresis-MS (CE-MS) and liquid chromatography-MS (LC-MS) are used to analyze protein coronas and their evolution in cellular environments. For instance, gold nanoparticles (GNPs) have helped study protein corona dynamics across intracellular compartments, providing insights into stable protein interactions crucial for nanoparticle transport and action [78]. Tumor-targeting strategies further refine nanocarrier specificity by incorporating ligands for cancer-specific markers, guided by omics analyses of cell membranes and lipid profiles. For example, NK cell membrane-coated nanoparticles enriched with tumor-targeting proteins identified through shotgun proteomics showed superior tumor-homing abilities, while lipidomic studies have optimized membrane fluidity, enhancing uniform coverage and targeting efficacy [79]. Figure 3 showed the Nanoparticle Targeting and Drug Release Mechanisms.

4.3 Treatment strategy determination

Tailoring treatment strategies to the complex and heterogeneous tumor microenvironment (TME) is essential for maximizing therapeutic outcomes. Omics-enhanced approaches enable the optimization of administration routes, identification of effective combination therapies, and personalization of treatment regimens [80, 81]. The selection of optimal administration routes for nanomedicines is guided by the molecular landscape of tumors and the properties of therapeutic agents, with omics data, particularly from single-cell and spatial transcriptomic analyses, playing a pivotal role in identifying the most effective routes. For example, intravenous (IV) administration of self-assembling nanoparticle vaccines induced a stem-like gene signature in $CD8^{+}$T cells, promoting more durable immune responses compared to subcutaneous (SC) injections [82]. Combining nanomedicine with other therapeutic modalities further enhances

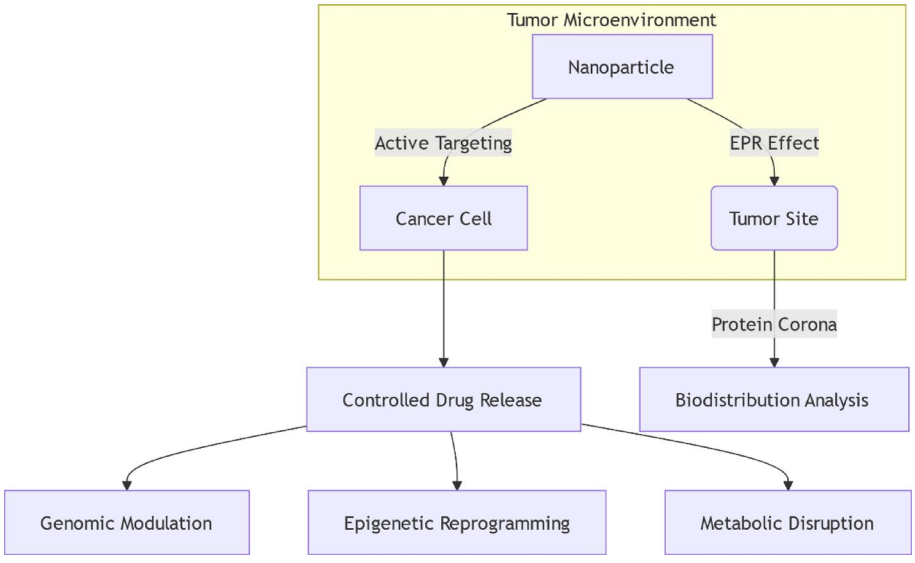

Fig. 3 Nanoparticle Targeting and Drug Release Mechanisms

antitumor efficacy by targeting multiple pathways simultaneously. Omics analyses help identify synergistic combinations that exploit metabolic vulnerabilities or modulate immune responses. For instance, combining liposomal doxorubicin with antibiotics to deplete gut microbiota significantly increased nanoparticle accumulation in tumors, improving therapeutic outcomes in triple-negative breast cancer (TNBC) models [83]. Similarly, combining radiotherapy with immunostimulatory nanocarriers modulated the tumor microenvironment (TME), reducing immunosuppressive monocytes and enhancing T cell activation. Personalized therapy, informed by patient-specific omics data, tailors nanomedicine interventions to individual tumor profiles. Multiomics analyses of patient-derived xenografts (PDX) and organoid models enable the testing and optimization of personalized nanotherapeutics. For example, organoid models of intrahepatic cholangiocarcinoma (iCC) guided the combination of ALDH1A1 inhibitors with albumin-bound paclitaxel, demonstrating synergistic effects in stem-like tumor subtypes [84]. Patient-specific omics data are prioritized using integrated algorithms, such as random forest or neural networks, which analyze multi-omics profiles to recommend optimal nanomedicine combinations. For example, in TNBC, transcriptomic and metabolomic data are combined to score patients for likelihood of response to immunotherapy-based nanoparticles [85, 86].

4.4 Synergy between nanomedicine and immuno-oncology

Omics technologies provide crucial insights not only into tumor genetics and metabolism but also into the immuno-oncological landscape. By integrating transcriptomics, proteomics, and single-cell analyses, researchers can characterize tumor-infiltrating lymphocytes (TILs) and identify key immune checkpoints and pathways, thereby informing the rational design of nanomedicines [87–92]. For instance, in triple-negative breast cancer (TNBC) models, a combination of RNA sequencing and spatial transcriptomics revealed that PD-L1 is significantly upregulated in highly invasive tumor subpopulations. Consequently, a targeted PD-L1 nanoliposome delivery system was developed to transport antibodies or siRNA specifically to areas with elevated PD-L1 expression and immunosuppressive microenvironments. This approach not only increased T-cell infiltration but also reversed local immunosuppression, resulting in markedly improved tumor inhibition rates. Another successful example involves single-cell sequencing and proteomic data to pinpoint tumor-associated macrophage (TAM) immune checkpoints—such as B7-H4—or chemokine pathways. Researchers designed functionalized nucleic acid nanoparticles to silence relevant genes, promoting a shift of TAMs toward a pro-inflammatory phenotype. In vivo studies showed that compared to stand-alone checkpoint inhibitors, these nanoparticles offered enhanced specificity in reprogramming the tumor immune microenvironment and exhibited synergistic effects with anti-PD-1/PD-L1 therapies. Such multiomics-driven nanomedicine strategies may be extended to other solid tumors or immune-refractory cancers, paving the way for personalized immuno-oncology applications. Figure 4 showed the Synergistic Immunomodulation Mechanism with Checkpoint Inhibitors. And Table 3 showed the Therapeutic Nanomedicine Strategies Guided by Omics. For instance, in a preclinical TNBC model, scRNA-seq revealed PD-L1 upregulation in invasive subpopulations. This led to the development of PD-L1-targeted nanoliposomes that delivered siRNA, resulting in a 60% increase in T-cell infiltration and tumor regression compared to controls [93, 94].

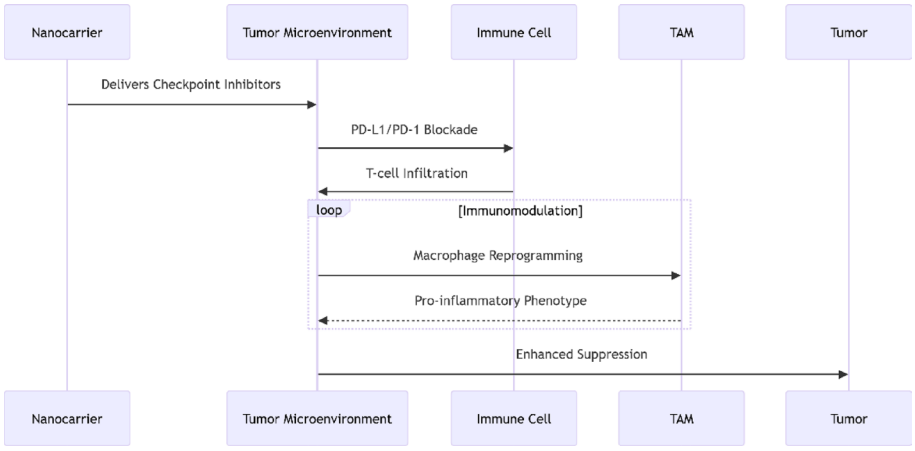

Fig. 4 .Synergistic Immunomodulation Mechanism with Checkpoint Inhibitors

Table 3 Therapeutic nanomedicine strategies guided by omics

Strategy	Omics input	Nanoplatform	Key outcomes
Target Identification	RNA-seq (Erbin in CRC)	RGD-modified nanovesicles with siRNA	Suppressed lung metastasis in vivo
	Genomics (POLR2A in TNBC)	pH-activated "nanobombs" with siRNA	Selective tumor targeting
DDS Optimization	Microbiomics (Lung microbiota)	GaTa-CP NPs mimicking host tissue	3.2× higher accumulation in chemoresistant tumors
	Lipidomics + Proteomics	NK membrane-coated NPs	Tumor-homing efficiency ↑ 78% vs. conventional NPs
Combination Therapy	Transcriptomics + Metabolomics	Nanoliposome + Checkpoint inhibitor (TNBC)	Chemoresistance ↓ 60% in murine models
	Multi-omics (PDX/organoids)	Albumin-paclitaxel + ALDH1A1 inhibitor (iCC)	Synergistic effect in stem-like subtypes (IC_{50} ↓ 4.7-fold)
Immuno-Oncology Synergy	Spatial Transcriptomics (PD-L1)	PD-L1-targeted nanoliposomes	T-cell infiltration ↑ 300%, tumor inhibition ↑ 45%
	scRNA-seq + Proteomics (TAMs)	Nucleic acid NPs silencing B7-H4	Macrophage reprogramming + anti-PD-1 synergy

5 Assessment for nanomedicine-mediated biological response

Understanding the biological responses elicited by nanomedicines is critical for evaluating their efficacy and safety. Omics technologies provide comprehensive assessments of cellular and molecular changes induced by NP interactions, offering insights into toxicity, biodistribution, genomic and pathway alterations, protein synthesis differentiation, metabolic impact, and TME regulation. Nevertheless, the high dimensionality of omics data and the profound spatial and temporal heterogeneity of tumors pose significant challenges in data integration, interpretation, and translation to clinically actionable insights. For instance, while powerful, single-cell omics may not fully capture the spatial dynamics of the tumor microenvironment, and the high cost and computational demands of multi-omics profiling currently limit its large-scale clinical adoption. Table 4 showed the Therapeutic Nanomedicine Strategies Guided by Omics.

5.1 Toxicity

Despite their therapeutic potential, NPs may induce toxicological effects in normal cells and organs. Omics approaches, particularly proteomics and metabolomics, enable the identification of molecular pathways affected by NP exposure, elucidating mechanisms

Table 4 Omics-Based assessment of nanomedicine responses

Assessment domain	Omics techniques	Nanoparticle example	Key findings
Toxicity	Proteomics/Metallomics	AgNPs	Inhibited GST activity → hepatotoxicity
	Lipidomics	Iron oxide NPs	Modulated phospholipids → cytoskeletal disruption
Biodistribution	MALDI-MS Imaging	AIE NPs	Metabolic alterations in liver tumors after NP accumulation
	Spatial Transcriptomics + Imaging	Generic NPs	Hypoxic/apoptotic regions show preferential NP uptake
Pathway Alterations	RNA-seq	PNA-loaded NPs (Glioblastoma)	Dysregulated PI3K-Akt/HIF-1 pathways → suppressed angiogenesis
	Quantitative Proteomics	Pt-lipid NPs + Phototherapy	Activated apoptosis/ferroptosis pathways
TME Modulation	scRNA-seq	CDN-delivering NPs	TAMs reprogrammed to proinflammatory state → antitumor immunity ↑
	CyTOF	Albumin NPs (PI3Kγ inhibitor)	TAM repolarization + T/B cell activation

of toxicity [95]. For example, proteomic and metallomic analyses revealed that silver NPs (AgNPs) impair cellular antioxidant defenses by inhibiting glutathione S-transferase (GST) activity in hepatic cells, elucidating the hepatotoxic mechanisms of AgNPs [96]. Similarly, lipidomic studies have shown that iron oxide NPs modulate phospholipid components, affecting cellular cytoskeletal integrity and apoptotic pathways.

5.2 Biodistribution

Assessing the biodistribution of NPs is essential for understanding their therapeutic and off-target effects. Mass spectrometry imaging (MSI) and spatial transcriptomics (ST) are advanced omics techniques that map the spatial distribution of NPs and their impact on endogenous metabolite distributions within tissues. For instance, MALDI-MS has been utilized to map the distribution of aggregation-induced emission (AIE) NPs and endogenous metabolites in liver tumor models, revealing metabolic alterations induced by NP accumulation [97]. Additionally, combined ST and fluorescence imaging have elucidated molecular patterns associated with NP uptake in hypoxic and apoptotic tumor regions, informing the design of more effective nanotherapeutics.

5.3 Genomic and pathway alterations

Nanomedicines can modulate gene expression and disrupt specific cellular pathways essential for tumor survival and proliferation. Omics analyses, particularly RNA-seq and phosphoproteomics, provide insights into the genomic and signaling pathway alterations induced by NP-based therapies [98]. For example, RNA-seq analyses of glioblastoma cells treated with peptide nucleic acid (PNA)-loaded NPs identified significant dysregulation of genes involved in the PI3K-Akt and HIF-1 signaling pathways, highlighting the impact of NPs on tumor growth and angiogenesis [99]. Similarly, quantitative proteomics revealed that platinum-loaded lipid NPs in combination with photothermal therapy modulate apoptosis, ferroptosis, and reactive oxygen species (ROS) synthesis pathways, enhancing therapeutic efficacy. The reported alterations, such as PI3K-Akt pathway dysregulation, have been validated in murine xenograft models, demonstrating consistent in vivo effects. For example, PNA-loaded NPs showed significant tumor growth inhibition in glioblastoma mice, corroborating pathway findings.

5.4 Protein synthesis differentiation

Proteomic analyses elucidate how nanomedicines influence protein synthesis and function, shedding light on the mechanisms of therapeutic action. Combined therapies involving NPs and photosensitizers have been shown to downregulate global protein translation and disrupt energy metabolism pathways, leading to apoptosis in cancer cell. Phosphoproteomic studies of cerium oxide NPs have identified alterations in cell adhesion and RNA splicing pathways, contributing to tumor suppression.

5.5 Metabolic impact

Metabolic reprogramming is a hallmark of cancer, and metabolomic profiling facilitates the identification of metabolic vulnerabilities that can be targeted by nanomedicines. Omics-enhanced nanomedicine approaches have demonstrated significant metabolic alterations in tumors treated with NP-based therapies, such as increased amino acid and fatty acid levels, indicating disrupted glycolysis and tricarboxylic acid (TCA) cycle pathways [100]. These insights guide the development of NPs that target specific metabolic pathways, enhancing therapeutic outcomes.

5.6 Tumor microenvironment regulation

The TME plays a critical role in cancer progression and therapeutic resistance. Omics technologies, particularly single-cell RNA sequencing (scRNA-seq) and mass cytometry by time-of-flight (CyTOF), enable the detailed characterization of the TME and its modulation by nanomedicines. For instance, scRNA-seq analyses have revealed that nanoparticle-mediated delivery of cyclic dinucleotides (CDNs) reprograms tumor-associated macrophages (TAMs) from an immunosuppressive to a proinflammatory state, enhancing antitumor immunity [101]. Additionally, CyTOF analyses have shown that albumin NPs delivering PI3Kγ inhibitors and paclitaxel repolarize TAMs and activate T and B cells within the TME, underscoring the potential of omics-enhanced nanomedicine in modulating immune responses.

6 Future directions

As the integration of multi-omics and nanomedicine progresses toward clinical application, scientific and technical challenges intertwine with regulatory and data-management bottlenecks. Despite promising preclinical data, the clinical translation of omics-driven nanomedicine is often hindered by issues of reproducibility, batch effects in omics data, ethical concerns regarding patient data privacy, and the lack of robustly validated biomarkers predictive of therapeutic response.For multi-omics–enhanced nanomedicines to successfully enter the clinical arena, the following considerations are essential.

6.1 Regulatory pathways and approval processes

Current regulatory frameworks for nanotherapeutics generally follow established guidelines for combination products or advanced biologics. However, the integration of multi-omics data for guiding diagnostics and treatment decisions introduces new challenges in risk assessment and efficacy evaluation [102, 103]. Currently, regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have begun to establish guidelines specific to nanomedicine. The FDA has issued

several relevant guidance documents, including "Drug Products, Including Biological Products, that Contain Nanomaterials" and "Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation." These documents emphasize the importance of thorough physicochemical characterization (e.g., size, surface charge, stability) and biodistribution studies. Similarly, the EMA has published a "Reflection Paper on Nanomedicines" which outlines requirements for quality, safety, and efficacy evaluation, highlighting the need for novel characterization methods due to the unique properties of nanomaterials. Despite these advancements, a significant regulatory gap exists for nanomedicines guided by multi-omics data. The current frameworks lack specific provisions for the validation of complex, multi-omics-derived biomarkers used for patient stratification. Furthermore, there is limited guidance on standards for omics-based companion diagnostics that are integral to the deployment of personalized nanotherapies. The dynamic nature of treatment adaptation based on longitudinal omics profiling also presents a challenge for existing clinical trial paradigms and approval processes, which are typically designed for static treatment regimens [104]. Regulatory agencies such as the FDA and EMA may need to establish clear guidelines specifically addressing "multi-omics-driven nanomedicine" to ensure precise classification and effective risk-benefit evaluation. Additionally, multi-omics-based patient stratification often requires more stringent inclusion/exclusion criteria and the use of complex companion diagnostics. As a result, ethics committees and regulatory bodies should adapt their review processes to ensure clinical trials are designed with robust statistical power and comprehensive safety monitoring.

6.2 Data standardization and sharing

Omics data are generated from various platforms such as next-generation sequencing, mass spectrometry, and single-cell analysis, each with its own unique file formats and annotation styles. Adopting community-wide or cross-platform standards, like MIABiome and MIAPE, can significantly improve reproducibility and interoperability. While resources like TCGA and CPTAC provide large-scale omics datasets, few platforms specifically curate data linking nanomedicine interventions with multi-omics profiles. Developing rigorously peer-reviewed repositories focused on omics-nanomedicine research would accelerate knowledge exchange and facilitate cross-laboratory validation.

6.3 Artificial intelligence and machine learning: challenges and best practices

The integration of artificial intelligence (AI) and machine learning (ML) for multi-omics data analysis presents both opportunities and significant challenges. Common pitfalls include overfitting due to high-dimensional omics data with limited sample sizes, lack of external validation cohorts, and limited interpretability of complex models. To address these issues, several best practices should be implemented. Employ rigorous cross-validation strategies, such as nested cross-validation, to reduce overfitting. Utilize independent validation cohorts from multiple institutions to ensure generalizability. Apply regularization techniques (L1/L2 regularization) and feature selection methods to enhance model robustness. Incorporate explainable AI (XAI) approaches, such as SHAP (Shapley Additive Explanations) and LIME (Local Interpretable Model-agnostic Explanations), to improve model interpretability. Implement data augmentation techniques

and transfer learning to address limited dataset sizes. Furthermore, prospective validation in clinical trials is essential before clinical implementation.

6.4 Potential solutions

To address data heterogeneity and limited comparability, multicenter collaborations should establish formal data-sharing agreements, ensuring consistent protocols, quality-control steps, and analysis pipelines. The creation of "gold-standard" datasets, recognized and reused by the community, will promote reproducibility. Additionally, partnerships among pharmaceutical companies, research institutes, and regulatory agencies can form working groups to periodically discuss technical guidelines, data exchange standards, and privacy regulations for multi-omics-based nanomedicine. Such initiatives could be funded through joint grants or consortia to accelerate adoption. With the increasing use of deep learning and cloud-based platforms, developing integrated pipelines for multi-omics–nanomedicine data analysis has become more feasible. These user-friendly, automated solutions reduce the need for specialized personnel, minimize operator errors, and improve reproducibility. Concrete initiatives include the NCI Nanotechnology Characterization Lab, which provides standardized protocols for nanomedicine evaluation. Pilot projects like the EU's Nanomed2020 have demonstrated data-sharing frameworks that integrate omics data from multiple centers, improving reproducibility.

7 Conclusions

The integration of omics technologies with nanomedicine has revolutionized cancer diagnosis and treatment by providing high-throughput molecular insights, enabling precise biomarker identification and targeted drug delivery. Omics-enhanced nanomedicine optimizes drug delivery systems (DDS), minimizes off-target effects, and improves therapeutic efficacy. However, challenges such as tumor heterogeneity, limited sample sizes, complex data analysis, and high costs hinder its widespread adoption. Addressing these barriers requires integrated multiomics approaches, advanced bioinformatics tools, and cost-effective sequencing technologies. Future research should focus on combining single-cell and spatial omics with nanomedicine, leveraging artificial intelligence (AI) and machine learning (ML) for biomarker discovery and treatment optimization. Establishing comprehensive omics-based cancer nanomedicine databases will facilitate data sharing and accelerate clinical translation. In conclusion, omics-driven nanomedicine offers immense potential for personalized cancer therapy, and continued advancements in this field will enhance patient outcomes and reduce therapeutic burdens.

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