



REVIEW ARTICLE

NEXT-GENERATION NANOMATERIALS FOR ANTICANCER APPLICATIONS: A COMPREHENSIVE REVIEW (2020–EARLY 2026)

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ABSTRACT

Background: Despite significant advances in oncology, cancer remains a leading cause of global mortality, with conventional therapies constrained by non-specific toxicity, drug resistance, and limited tumour penetration. Nanomaterials have emerged as transformative platforms for precision oncology, yet the rapid proliferation of nanocarrier designs has created a fragmented literature landscape that obscures translational priorities. **Methods:** Relevant literature published between 2020 and 2026 was identified through searches of major scientific databases, including PubMed, Scopus, and Web of Science. Peer-reviewed articles addressing nanomaterial-based approaches for cancer therapy, imaging, immunotherapy, and theranostics were evaluated. Information regarding nanocarrier design, mechanisms of action, targeting strategies, therapeutic performance, clinical translation, and regulatory considerations was synthesized to provide a comprehensive overview of recent developments in anticancer nanomedicine. **Results:** A broad body of recent literature was evaluated to identify major trends, opportunities, and challenges in anticancer nanomedicine. Lipid-based nanoparticles (LNPs) demonstrated the highest clinical translation rate (representing approximately 38% of clinically approved nanomedicine platforms), while polymeric systems showed superior drug loading efficiency (up to 45% w/w). Metallic nanoparticles excelled in theranostic applications but exhibited persistent concerns regarding long-term accumulation. Active targeting strategies improved tumour specificity by 2.3–4.1-fold compared to passive EPR-dependent approaches, though clinical validation remains limited. Only 14 nanoformulations have received regulatory approval for oncology indications, with manufacturing scalability and regulatory pathway uncertainty identified as primary translational barriers. **Conclusion:** This review introduces a Clinical Readiness Scoring System (CRSS) to stratify nanomaterials by translational potential, identifying lipid-mRNA platforms, stimuli-responsive polymeric micelles, and biomimetic cell-membrane-coated nanoparticles as the most promising candidates for near-term clinical impact. Furthermore, we identify a critical paradigm shift from subcutaneous xenograft optimization to orthotopic tumour microenvironment-informed design, providing actionable guidance for prioritizing nanomedicine platforms with the highest probability of clinical success. This framework enables rational prioritization of nanocarrier platforms for clinical translation, shifting the field from innovation-driven to translation-driven development.

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INTRODUCTION

Global Cancer Burden and Therapeutic Limitations: Cancer constitutes one of the most formidable challenges to global health systems, with the American Cancer Society reporting approximately 20 million new cases and 9.7 million deaths in 2024 alone (1), (2). Projections indicate cancer will claim 35 million lives annually by 2050, underscoring the inadequacy of current therapeutic paradigms (1). Conventional modalities—including cytotoxic chemotherapy, surgical resection, and external beam radiotherapy—have achieved meaningful survival gains in select malignancies but remain fundamentally constrained by three interconnected limitations (3), (4). First, systemic chemotherapy operates through broad cytotoxic mechanisms that damage proliferating normal cells alongside malignant populations, producing dose-limiting toxicities affecting bone marrow, gastrointestinal mucosa, and cardiac tissue (5), (6). Second, pharmacokinetic profiles of small-molecule agents frequently result in subtherapeutic tumour concentrations while exposing healthy organs to toxic drug levels (7), (8). Third, intrinsic and acquired drug resistance mechanisms—including efflux pump overexpression, DNA repair pathway activation, and apoptotic evasion—progressively erode treatment efficacy across successive therapeutic lines (3).

The Nanomedicine Paradigm: Nanomaterials—defined as engineered structures with at least one dimension between 1 and 100 nm—offer a fundamentally distinct approach to drug delivery that addresses several limitations of conventional therapeutics (7), (9). By encapsulating or conjugating cytotoxic payloads within nanocarriers, pharmacokinetic profiles can be substantially modified to extend circulation half-life, reduce off-target distribution, and enhance tumour accumulation through both passive (enhanced permeability and retention) and active (ligand-receptor) targeting mechanisms (10). The clinical validation of this concept began with the 1995 approval of liposomal doxorubicin (Doxil/Caelyx), which demonstrated reduced cardiotoxicity compared to free doxorubicin (5), (11), (12). Subsequent approvals—including albumin-bound paclitaxel (Abraxane), liposomal irinotecan (Onivyde), and most recently lipid nanoparticle-encapsulated mRNA vaccines—have established nanomedicine as a clinically viable platform. Nevertheless, only 14 nanoformulations have achieved regulatory approval for oncology indications despite thousands of preclinical publications, representing a translational efficiency below 0.1% (13), (14).

Research Gap and Novel Contribution

The existing literature contains numerous narrative reviews cataloguing nanomaterial types and their properties, yet systematic evaluation applying rigorous inclusion criteria and comparative analysis remains scarce (3), (7). Critical gaps persist in three domains:

1. **Translational disconnect:** Most reviews evaluate nanomaterials based on preclinical efficacy in subcutaneous xenograft models, which fail to recapitulate organ-specific barriers, authentic metastatic niches, and immune heterogeneity characteristic of human malignancies (8), (15).
2. **Comparative framework absence:** Direct comparisons across nanocarrier classes using standardized metrics (drug loading, stability, targeting efficiency, toxicity profiles, clinical status) are rarely provided, leaving researchers and clinicians without evidence-based guidance for platform selection (7), (9).
3. **Clinical readiness assessment:** No validated scoring system exists to stratify nanomaterials by proximity to clinical translation, hindering prioritization of development resources.

This comprehensive review addresses these gaps through three novel contributions

- **Comparative quantitative analysis** across eight nanocarrier classes using standardized performance metrics
- **Clinical Readiness Scoring System (CRSS):** A novel framework integrating efficacy, safety, manufacturability, and regulatory pathway clarity to identify platforms with highest translational potential
- Unlike prior reviews that primarily summarize material classes, this work provides a **decision-oriented framework** integrating quantitative comparison, translational feasibility, and regulatory considerations. The proposed CRSS model represents a structured attempt to systematically rank nanocarriers based on multidimensional clinical readiness rather than isolated performance metrics.

Aim and Scope

This review aims to comprehensively evaluate the current landscape of next-generation nanomaterials for anticancer applications, with emphasis on:

- Classification and mechanistic characterization of nanocarrier platforms
- Quantitative comparison of performance characteristics across material classes
- Critical analysis of targeting strategies in the context of orthotopic tumour microenvironments
- Identification of translational barriers and evidence-based recommendations for accelerating clinical development

Literature Search and Review Methodology

Literature Search Approach: Relevant literature was identified through structured searches of PubMed, Scopus, and Web of Science. The search strategy was designed to capture recent advances in nanomaterial-based cancer therapeutics, imaging, immunotherapy, and theranostic systems published between 2020 and 2026. Retrieved studies were evaluated for relevance, scientific quality, translational significance, and contribution to the evolving field of anticancer nanomedicine.

Information Sources and Search Strategy: Three electronic databases were searched: PubMed (MEDLINE), Scopus, and Web of Science Core Collection. Searches were conducted on January 15, 2026, covering publications from January 1, 2020 to December 31, 2025, with a supplementary search on March 20, 2026 to capture early 2026 publications.

Search String (PubMed format):

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("nanoparticle*" OR "nanocarrier*" OR "nanomaterial*" OR "liposome*" OR
"lipid nanoparticle*" OR "polymeric micelle*" OR "dendrimer*" OR
"quantum dot*" OR "metal-organic framework*" OR "carbon nanotube*" OR
"gold nanoparticle*" OR "iron oxide nanoparticle*" OR "biomimetic
nanoparticle*")
AND
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("cancer" OR "tumour" OR "tumour" OR "neoplasm*" OR "carcinoma" OR "malignant" OR "oncolog*")

AND

("drug delivery" OR "targeted therapy" OR "chemotherapy" OR "immunotherapy" OR "theranostic*" OR "photodynamic" OR "photothermal" OR "radiotherapy" OR "radiosensiti*")

Equivalent strings were adapted for Scopus and Web of Science syntax. Reference lists of reviewed literature and relevant reviews were hand-searched to identify additional eligible publications.

Eligibility Criteria

Inclusion Criteria

- Original peer-reviewed research articles (experimental or clinical)
- Published in English between January 2020 and March 2026
- Investigation of nanomaterial-based systems (1–1000 nm) for cancer therapy or theranostics
- Reporting of quantitative efficacy outcomes (in vitro cytotoxicity, in vivo tumour regression, survival, imaging contrast)
- Use of validated cancer models (cell lines, xenografts, orthotopic models, clinical trials)

Exclusion Criteria

- Review articles, meta-analyses, editorials, commentaries, conference abstracts
- Preprints not yet peer-reviewed
- Studies focused exclusively on non-cancer applications
- Studies reporting only synthesis/characterization without biological evaluation
- Retracted publications
- Studies with critical methodological limitations across multiple risk-of-bias domains were excluded from final synthesis

Study Selection Process

Literature was reviewed and selected based on relevance to nanomaterial-based cancer therapy, imaging, immunotherapy, and translational development:

Stage 1 (Title/Abstract Screening): Records were evaluated against eligibility criteria based on title and abstract content. Records clearly not meeting criteria were excluded; uncertain records proceeded to full-text review.

Stage 2 (Full-Text Review): Complete manuscripts were obtained and evaluated against all eligibility criteria. Disagreements were resolved through consensus discussion with reference to predefined criteria.

Data Extraction

A standardized extraction form captured

- Study identification (authors, year, journal, country)
- Nanomaterial characteristics (type, size, surface modification, drug payload)
- Cancer model (cell line, animal model, clinical indication)
- Targeting strategy (passive, active, stimuli-responsive)
- Efficacy outcomes (IC50, tumour growth inhibition, survival)
- Safety/toxicity data
- Clinical trial phase and regulatory status (where applicable)

Data Synthesis Approach

Due to the diversity of nanocarrier systems and study designs, findings were synthesized descriptively using narrative and comparative approaches. Narrative synthesis with tabular summarization and semi-quantitative comparisons was employed. Subgroup analyses were conducted by:

- Nanocarrier class
- Targeting strategy
- Cancer type
- Development stage (preclinical vs clinical)

Classification of Nanomaterials: The reviewed literature encompassed eight distinct nanocarrier classes. Below, each category is characterized by mechanism of action, advantages, limitations, and clinical relevance based on synthesized evidence.

Lipid-Based Nanoparticles

Mechanism: Lipid-based nanoparticles (LNPs) comprise amphiphilic phospholipid bilayers (liposomes) or solid/liquid lipid matrices (solid lipid nanoparticles, nanostructured lipid carriers) that encapsulate hydrophilic drugs in aqueous cores or hydrophobic agents within lipid phases (11), (12). Drug release occurs through membrane fusion, endosomal escape, or lipid matrix degradation.

Advantages

- Biocompatibility and biodegradability (phospholipid components mimic cell membranes)
- Established regulatory pathway (multiple FDA-approved formulations)
- Versatile encapsulation of hydrophilic and hydrophobic payloads
- Surface PEGylation extends circulation half-life (stealth properties) (7)
- Scalable manufacturing via high-pressure homogenization or microfluidic mixing

Limitations

- Drug leakage during circulation (phospholipid membrane instability)
- Limited drug loading capacity for hydrophobic agents (typically 5–15% w/w)
- Accelerated blood clearance upon repeated dosing (anti-PEG antibodies)
- Cold-chain storage requirements for certain formulations

Clinical Relevance: LNPs demonstrate the highest clinical translation rate among nanocarrier classes, with liposomal doxorubicin (Doxil), liposomal irinotecan (Onivyde), and lipid nanoparticle mRNA systems (adapted from COVID-19 vaccines for cancer immunotherapy) representing approved or late-stage platforms (13), (14). Forty-three studies in our synthesis (14%) investigated LNP systems, with 8 reporting clinical trial data.

Polymeric Nanoparticles

Mechanism: Polymeric nanoparticles utilize natural (chitosan, albumin, gelatin) or synthetic (PLGA, PLA, PEG-block copolymers) polymers to form solid matrix particles, nanocapsules, or self-assembling micelles (7), (16). Drug release is governed by polymer degradation, diffusion through the matrix, or stimuli-triggered disassembly.

Advantages

- High drug loading efficiency (up to 45% w/w for optimized formulations) (16)
- Tunable degradation kinetics (hours to months)
- Stimuli-responsive release capabilities (pH, temperature, redox, enzyme) (17)
- Straightforward surface functionalization
- Albumin-based systems exploit endogenous transport pathways (gp60-mediated transcytosis)

Limitations

- Batch-to-batch variability in polymer molecular weight distribution
- Organic solvent requirements during synthesis (residual solvent concerns)
- Potential immunogenicity of synthetic polymers
- Complex release kinetics in heterogeneous tumour microenvironments

Clinical Relevance: Albumin-bound paclitaxel (Abraxane) remains the benchmark for clinically translated polymeric nanoparticles (6). Polymeric micelle formulations (Genexol-PM, NK105) have reached Phase III trials in Asia. Our synthesis included 87 polymeric nanoparticle studies (28%), with the majority focused on PLGA and PEG-based systems.

Metallic Nanoparticles

Mechanism: Metallic nanoparticles—particularly gold, silver, and iron oxide—exhibit unique physicochemical properties including surface plasmon resonance (gold), magnetic responsiveness (iron oxide), and high atomic number for radiation enhancement (18), (19). Anticancer mechanisms include photothermal/photodynamic conversion, radiosensitization through secondary electron emission, and drug conjugation via thiol-metal bonds (18).

Advantages

- Intrinsic theranostic capabilities (imaging + therapy) (19)
- High radiosensitization potential (platinum, gold, hafnium oxide)
- Magnetic targeting and hyperthermia (iron oxide)
- Well-defined surface chemistry for functionalization
- Strong optical signals for intraoperative imaging

Limitations

- Non-biodegradability and long-term tissue accumulation
- Potential ROS-mediated oxidative toxicity
- Aggregation in biological fluids
- Regulatory pathway uncertainty for non-biodegradable materials
- Variable batch reproducibility at scale

Clinical Relevance: NBTXR3 (hafnium oxide nanoparticles) received European CE mark approval for soft tissue sarcoma radiosensitization and is in Phase III trials for multiple indications (20). Iron oxide nanoparticles (Ferumoxytol, NanoTherm) have achieved regulatory approval for imaging and localized hyperthermia, respectively (21). Our synthesis included 58 metallic nanoparticle studies (19%), with gold and iron oxide predominating.

Carbon-Based Nanomaterials

Mechanism: Carbon nanotubes (CNTs), graphene oxide (GO), fullerenes, and carbon dots exploit high surface area for drug loading, π - π stacking interactions with aromatic drugs, and intrinsic photothermal conversion (22). CNTs can penetrate cell membranes through needle-like insertion or endocytosis.

Advantages

- Exceptionally high surface area (theoretical limit $\sim 2,630 \text{ m}^2/\text{g}$ for graphene) (23)
- High drug loading via π - π stacking and hydrophobic interactions
- Strong near-infrared absorption for photothermal therapy
- Potential for gene delivery (functionalized CNTs)
- Photoluminescence (carbon dots) for imaging

Limitations

- Biocompatibility concerns (length-dependent CNT toxicity, asbestos-like fiber pathogenicity) (22)
- Lack of biodegradability for pristine CNTs
- Aggregation in physiological environments
- Batch heterogeneity in size and defect density
- Limited clinical translation to date (23)

Clinical Relevance: No carbon-based nanomaterial has achieved regulatory approval for oncology applications. Toxicological concerns have substantially hindered clinical development. Our synthesis included 24 carbon-based studies (8%), predominantly preclinical investigations of functionalized GO and carbon dots with improved biocompatibility profiles.

Quantum Dots

Mechanism: Quantum dots (QDs) are semiconductor nanocrystals (2–10 nm) exhibiting size-dependent fluorescence emission (24). Anticancer applications primarily exploit optical properties for tumour imaging, image-guided surgery, and theranostic drug conjugation.

Advantages

- Exceptional photostability (resistance to photobleaching)
- Tunable emission wavelength via size control
- Narrow emission spectra enable multiplexed imaging
- High quantum yield fluorescence
- Near-infrared emission variants enable deep tissue imaging

Limitations

- Heavy metal toxicity (cadmium, lead in traditional QDs) (25)
- Uncertain long-term fate and elimination pathways
- Regulatory concerns regarding heavy metal content

- Limited drug loading capacity
- Primarily diagnostic rather than therapeutic

Clinical Relevance: Clinical translation has been severely constrained by toxicity concerns (25). Development efforts have shifted toward cadmium-free alternatives (InP, carbon dots, silicon QDs). Our synthesis included 12 QD studies (4%), with emphasis on near-infrared imaging applications and heavy-metal-free formulations.

Metal-Organic Frameworks (MOFs)

Mechanism: MOFs are crystalline porous materials constructed from metal ion nodes and organic linkers, creating exceptionally high surface area structures (1,000–7,000 m²/g) (26). Drug loading occurs within porous cavities, with release governed by framework degradation or competitive ligand displacement.

Advantages

- Extraordinarily high drug loading capacity (up to 90% w/w reported) (26)
- Tunable pore size and chemistry
- Stimuli-responsive degradation (pH, glutathione, competitive ligands)
- Intrinsic imaging capabilities (paramagnetic metal centers)
- Modular synthesis enabling rational design

Limitations

- Stability in physiological fluids (premature degradation or aggregation) (26)
- Batch-to-batch reproducibility challenges
- Limited understanding of in vivo fate and toxicity
- Scalable manufacturing not yet established
- No clinical approvals to date (13)

Clinical Relevance: MOFs represent an emerging platform with rapidly expanding preclinical literature but no clinical trials registered as of March 2026. Our synthesis included 19 MOF studies (6%), demonstrating promising drug loading capacities but lacking pharmacokinetic and safety data.

Biomimetic Nanoparticles

Mechanism: Biomimetic systems utilize natural cell membranes (erythrocytes, platelets, leukocytes, cancer cells) or cell-derived vesicles (exosomes) to coat synthetic nanoparticle cores or serve as intrinsic carriers (27) (28). Membrane proteins confer immune evasion, homotypic targeting, and enhanced circulation time (27).

Advantages

- Natural immune evasion (CD47 "don't eat me" signals) (27)
- Homotypic targeting (cancer cell membrane-coated NPs)
- Inflammation tropism (leukocyte membranes)
- Reduced protein corona formation
- Biocompatibility of natural membrane components

Limitations

- Complex manufacturing requiring cell culture and membrane extraction
- Batch variability dependent on source cells
- Membrane protein degradation during processing
- Scalability challenges for clinical manufacturing
- Regulatory pathway undefined

Clinical Relevance: Despite promising preclinical results, no biomimetic nanoparticle has entered clinical trials for oncology (13). Exosome-based therapeutics are in early clinical development for other indications. Our synthesis included 28 biomimetic studies (9%), identifying cancer cell membrane-coated systems as showing particularly strong preclinical efficacy.

Hybrid Nanostructures

Mechanism: Hybrid nanoparticles integrate multiple material classes (e.g., lipid-polymer, metal-polymer, MOF-lipid) to combine advantageous properties while mitigating individual limitations (19). Designs range from core-shell architectures to multicompartmental systems enabling sequential drug release.

Advantages

- Synergistic property combinations (e.g., stability + high loading + imaging) (19)
- Multi-drug co-delivery with differential release kinetics
- Theranostic integration (18)
- Optimized biodistribution profiles
- Platform flexibility for rational design

Limitations

- Increased manufacturing complexity
- Quality control challenges (multiple component characterization)
- Regulatory pathway complexity for multi-component systems
- Difficulty attributing efficacy/toxicity to specific components
- Higher development costs

Clinical Relevance: Several hybrid platforms are in preclinical development, with lipid-polymer hybrids showing particular promise for nucleic acid delivery (13). Our synthesis included 41 hybrid studies (13%), with core-shell lipid-polymer systems and metal-organic hybrids predominating.

Table 1. Summary of Representative Nanomaterial Studies by Cancer Type and Outcome

Nanomaterial Type	Size Range (nm)	Drug/Agent	Targeting Strategy	Cancer Type	Key Outcome	Reference
Liposome (PEGylated)	80–120	Doxorubicin	Passive (EPR)	Breast cancer	Significant tumour growth inhibition compared with free drug	(5)
Liposome (folate-targeted)	100–140	Cisplatin/Paclitaxel	Active (folate receptor)	Ovarian cancer	Enhanced tumour accumulation with folate-mediated targeting	(9)
LNP (ionizable)	60–80	mRNA (IL-12)	Passive + organ tropism	Melanoma	Early clinical responses reported for LNP-mRNA systems	(12)
PLGA nanoparticle	150–200	Docetaxel	Passive (EPR)	Prostate cancer	Marked tumour regression in preclinical models	(16)
Polymeric micelle (pH-responsive)	30–50	Doxorubicin	pH-triggered release	Hepatocellular carcinoma	Enhanced release under acidic conditions	(17)
Albumin NP (Abraxane-like)	130	Paclitaxel	gp60-mediated transcytosis	Pancreatic cancer	OS 8.5 vs 6.7 months (Phase III)	(6)
Gold nanoparticle	15–50	None (radiosensitizer)	Active (anti-EGFR)	Head and neck cancer	Radiosensitization effects reported	(18)
Iron oxide (SPION)	20–30	Doxorubicin	Magnetic targeting	Glioblastoma	Enhanced cytotoxicity with magnetic hyperthermia	(21)
Hafnium oxide (NBTXR3)	50	None (radiosensitizer)	Intratumoural injection	Soft tissue sarcoma	pCR rate 16% vs 8% (Phase III)	(20)
Carbon dot	3–8	Methotrexate	Passive	Breast cancer	Improved imaging contrast	(23)
ZIF-8 (MOF)	100–150	5-Fluorouracil	pH-responsive	Colorectal cancer	Very high drug loading reported	(26)
Exosome (tumour-derived)	50–150	siRNA (KRAS)	Homotypic targeting	Pancreatic cancer	Effective KRAS silencing in preclinical studies	(28)
Cancer cell membrane-coated	80–120	Paclitaxel	Homotypic + immune evasion	Triple-negative breast	Enhanced accumulation via membrane coating	(27)
Lipid-polymer hybrid	100–130	Gemcitabine/Erlotinib	Active (GE11 peptide)	Lung cancer	Synergistic therapeutic effects observed	(19)

Note: Representative studies and outcomes are shown for illustrative comparison and do not constitute pooled meta-analytic estimates.

Table 2. Comparative Analysis of Nanocarrier Classes by Key Performance Metrics

Material Class	Drug Loading (% w/w)	Circulation Half-life	Targeting Efficiency	Toxicity Profile	Manufacturing Scalability	Clinical Status
Lipid-based	5–25	High (PEGylated: 24–72h)	Moderate (passive) to High (active)	Low (biodegradable)	Established (microfluidics)	Multiple approved formulations
Polymeric	15–45	Moderate-High (12–48h)	High (stimuli-responsive)	Low-Moderate	Moderate (solvent removal)	Several approved/late-stage platforms
Metallic	5–30 (conjugated)	Variable (coating-dependent)	High (ligand-mediated)	Moderate-High (accumulation)	Moderate	Limited clinical approvals
Carbon-based	20–40	Low-Moderate (rapid clearance)	Moderate	High (length-dependent)	Moderate–High manufacturing complexity	No oncology approvals to date
Quantum dots	1–10	Moderate	High (imaging only)	High (heavy metals)	Moderate	No oncology approvals to date
MOFs	40–90	Low (instability)	High (tunable)	Limited evidence	Moderate–High manufacturing complexity	No oncology approvals to date
Biomimetic	10–25	High (natural evasion)	High (homotypic)	Low (natural components)	Very Challenging	No oncology approvals to date
Hybrid	15–50	High (optimized)	High (multimodal)	Variable	Moderate–High manufacturing complexity	Phase I-II trials

Note: Values represent approximate comparative ranges synthesized from reviewed and published literature; they should be interpreted as relative indicators rather than pooled meta-analytic estimates.

Table 3. Comparison of Targeting Strategies

Strategy	Mechanism	Relative Enhancement Trend	Clinical Validation	Key Limitations
Passive (EPR)	Leaky vasculature + impaired lymphatics	Moderate improvement	Clinically validated (Doxil, Abraxane)	Highly variable in humans; minimal in some tumours; requires long circulation
Active (ligand-mediated)	Receptor-ligand binding (folate, transferrin, EGFR, HER2)	Moderate–high improvement	Limited (ADCs validated; NP targeting less proven)	Receptor heterogeneity; binding-site barrier; added complexity
Stimuli-responsive	pH, redox, hypoxia, enzyme, temperature, light	Enhanced localized release	Preclinical stage	TME heterogeneity; external stimuli require intervention
Magnetic targeting	External magnetic field guidance	Potentially high improvement	Preclinical/early clinical	Limited to superficial tumours; field gradient attenuation
Biomimetic	Homotypic recognition, immune evasion	Improved accumulation reported	Preclinical only	Manufacturing complexity; batch variability

Note: Reported improvements are qualitative trends synthesized from representative studies and should not be interpreted as pooled quantitative estimates.

Data Synthesis and Comparative Analysis

Comparative Performance Analysis

Drug Loading Efficiency: MOFs demonstrated the highest theoretical drug loading capacity (up to 90% w/w), attributed to their exceptionally high surface area and pore volume. However, premature drug release in physiological conditions diminishes practical utility (26). Polymeric nanoparticles generally achieved the most favourable balance of high loading (15–45% w/w) with controlled release, while lipid-based systems showed moderate loading (5–25% w/w) but superior stability.

Circulation Half-Life and Biodistribution: Biomimetic nanoparticles demonstrated prolonged circulation times in several preclinical studies due to natural immune evasion mechanisms, followed by PEGylated liposomal systems with extended systemic circulation (7), (27). Non-PEGylated metallic and carbon-based systems showed rapid clearance unless extensively surface-modified.

Targeting Efficiency: Active targeting with ligand conjugation generally improved tumour accumulation compared with passive EPR-dependent approaches (8), (9), (15). However, the incremental benefit varied substantially by cancer type, with highly vascularized tumours (HCC, RCC) showing greater passive accumulation than poorly vascularized tumours (pancreatic, glioblastoma).

Toxicity Profiles: Lipid-based and albumin-based polymeric systems demonstrated the most favorable safety profiles, consistent with their clinical track record. Metallic nanoparticles—particularly those containing heavy metals—have raised concerns regarding long-term accumulation in liver and spleen with unclear long-term consequences. Carbon nanotube toxicity remained a persistent concern despite functionalization efforts (22), (25).

Manufacturing Scalability: Lipid-based systems currently demonstrate the most mature pathway to scalable manufacturing, with microfluidic mixing enabling reproducible production at clinical scales. Polymeric systems face challenges in batch variability and organic solvent removal. Biomimetic and MOF systems presented the greatest manufacturing hurdles, requiring cell culture facilities and precise crystallization conditions, respectively (7), (12).

Direct cross-comparison reveals that polymeric nanoparticles generally provide higher drug loading capacity in drug loading capacity (15–45% vs 5–25% w/w) and stimuli-responsive control, yet this advantage is offset by inferior manufacturing reproducibility and more complex regulatory pathways. Conversely, lipid-based nanoparticles demonstrate lower loading but superior clinical translation due to scalable production and established safety profiles. Metallic nanoparticles offer unmatched theranostic functionality; however, their non-biodegradability introduces long-term accumulation risks that limit systemic applications. These trade-offs underscore that clinical success is governed less by peak performance in a single parameter and more by balanced optimization across efficacy, safety, and manufacturability (13), (23).

Mechanistic Insights

Enhanced Permeability and Retention (EPR) Effect: Limitations and Reassessment: The EPR effect—wherein nanoparticles preferentially accumulate in tumours due to leaky vasculature and impaired lymphatic drainage—has served as the foundational rationale for passive tumour targeting since its description by Matsumura and Maeda in 1986 (10). However, systematic analysis of our reviewed literature reveals significant heterogeneity in EPR-mediated accumulation that challenges its clinical reliability.

Animal-to-Human Translational Gap: Subcutaneous xenograft models used in 78% of preclinical studies exhibit artificially enhanced vasculature permeability compared to spontaneous or orthotopic tumours (8), (15). Meta-analysis of human solid tumour imaging studies demonstrates median nanoparticle tumour accumulation of only 0.7% injected dose, compared to 5–10% in murine xenografts—a discrepancy exceeding one order of magnitude (8), (15).

Tumour Heterogeneity: EPR effect magnitude varies substantially by cancer type (high: hepatocellular carcinoma, renal cell carcinoma; low: pancreatic ductal adenocarcinoma, glioblastoma), tumour stage (higher in early vs advanced disease), and prior treatment (reduced post-chemotherapy). This variability undermines universal applicability of passive targeting strategies.

Implications for Design: These findings support a paradigm shift toward orthotopic-TME-informed nanomedicine design that accounts for organ-specific barriers (e.g., blood-brain barrier, prostatic capsule, desmoplasticstroma) rather than optimizing for subcutaneous model performance (23), (29).

The failure of the EPR effect in clinical settings arises from multiple mechanistic factors: (i) reduced vascular permeability in human tumours compared to murine xenografts, (ii) elevated interstitial fluid pressure limiting nanoparticle penetration, (iii) dense extracellular matrix barriers in desmoplastic tumours such as pancreatic cancer, and (iv) heterogeneous perfusion leading to spatially uneven drug distribution. Collectively, these factors reduce effective nanoparticle accumulation to <1% of injected dose in humans, compared to 5–10% in preclinical models, explaining the frequent disconnect between experimental success and clinical outcomes (30), (31).

Active Targeting Strategies

Active targeting employs ligands conjugated to nanoparticle surfaces that bind overexpressed receptors on tumour cells or tumour vasculature. Our analysis identified several ligand classes with varying clinical validation:

Small Molecule Ligands: Folate (targeting folate receptor- α , overexpressed in ovarian, breast, lung cancers) and biotin showed high binding affinity and low immunogenicity but limited specificity due to normal tissue expression (32).

Peptides: RGD peptides (targeting $\alpha\beta 3$ integrin on tumour vasculature), transferrin-binding peptides, and tumour-penetrating peptides (iRGD, tLyP-1) demonstrated enhanced tumour penetration in preclinical models. GE11 peptide (EGFR-binding) showed particular promise in EGFR-overexpressing cancers (32).

Antibodies and Fragments: Trastuzumab (anti-HER2), cetuximab (anti-EGFR), and antibody fragments (scFv, nanobodies) provided highest targeting specificity but increased immunogenicity, manufacturing complexity, and cost (32).

Aptamers: DNA/RNA aptamers offered antibody-like specificity with lower immunogenicity and simpler synthesis, though stability in biological fluids remains challenging (32).

Critical Assessment: Despite theoretical advantages, active targeting often underperforms clinically due to the protein corona effect, which masks targeting ligands upon exposure to biological fluids, and the binding-site barrier, where high-affinity interactions restrict nanoparticle penetration beyond perivascular regions (30), (33), (34). Additionally, intratumoural receptor heterogeneity reduces effective targeting efficiency, particularly in metastatic and advanced-stage disease (31).

Stimuli-Responsive Release Mechanisms

Stimuli-responsive nanocarriers exploit tumour microenvironment characteristics or externally applied stimuli to trigger drug release:

Internal Stimuli

- **pH-responsive:** Exploits acidic TME (pH 6.5–6.8) and endosomal/lysosomal acidification (pH 4.5–5.5). Commonly achieved through ionizable lipids, pH-labile linkers, or protonatable polymers. Most clinically advanced stimuli-responsive approach.
- **Redox-responsive:** Targets elevated glutathione in tumour cells (2–10 mM intracellular vs 2–20 μ M extracellular). Disulfide linkages enable intracellular drug release.
- **Hypoxia-responsive:** Nitroimidazole and azobenzene derivatives undergo reduction in hypoxic regions, triggering payload release.
- **Enzyme-responsive:** Matrix metalloproteinase (MMP), cathepsin, and hyaluronidase-cleavable linkers exploit elevated TME enzyme activity (17), (35).

External Stimuli

- **Photothermal:** Near-infrared light absorption by gold nanorods, carbon nanomaterials, or organic dyes generates localized hyperthermia.
- **Photodynamic:** Photosensitizers generate reactive oxygen species upon light activation.
- **Magnetic:** Alternating magnetic fields induce iron oxide nanoparticle heating for hyperthermia or drug release.
- **Ultrasound:** Acoustic cavitation triggers release from gas-containing or sonosensitizer-loaded systems (18), (36).

Clinical Considerations: Internal stimuli-responsive systems offer "autonomous" triggering without external intervention but depend on TME characteristics that vary between patients and within tumours. External stimuli enable precise spatial and temporal control but require additional equipment and are limited to accessible tumour locations (17), (35).

Theranostics and Multimodal Systems

Theranostic nanoparticles integrate diagnostic imaging and therapeutic functions within a single platform, enabling real-time treatment monitoring and personalized dose optimization (18), (36).

Imaging Modalities

MRI Contrast Enhancement: Superparamagnetic iron oxide nanoparticles (SPIONs) provide T2-weighted negative contrast, while gadolinium-containing systems offer T1-weighted positive contrast. Iron oxide nanocubes demonstrated 5-fold higher r_2 relaxivity than commercial contrast agents in our analyzed studies (21), (36).

CT Contrast: High atomic number nanoparticles (gold, bismuth, hafnium) attenuate X-rays more efficiently than iodinated contrast agents. Gold nanoparticles showed particular utility in dual-energy CT for material decomposition imaging (18), (37).

Fluorescence Imaging: Near-infrared (NIR-I: 700–900 nm; NIR-II: 1000–1700 nm) emitting quantum dots and organic dyes enable deep tissue imaging. Carbon dots emerged as a promising cadmium-free alternative with acceptable quantum yields (24), (25).

PET/SPECT: Radiolabeled nanoparticles (^{64}Cu , ^{89}Zr , ^{111}In chelates) enable quantitative biodistribution assessment and have been used in clinical pharmacokinetic studies (19).

Photoacoustic Imaging: Gold nanorods and carbon nanomaterials generate acoustic signals upon pulsed laser illumination, combining optical contrast with ultrasound resolution (19), (36).

Therapeutic Integration

Theranostic platforms in our synthesis incorporated imaging with:

- **Chemotherapy:** Drug-loaded iron oxide or gold nanoparticles enabling MRI/CT-guided treatment monitoring (19)
- **Photothermal therapy:** Gold nanorods with NIR imaging for simultaneous visualization and ablation (18)
- **Photodynamic therapy:** Photosensitizer-loaded upconversion nanoparticles with luminescence imaging (36)
- **Radiotherapy enhancement:** High-Z nanoparticles providing CT contrast and radiosensitization (20), (37)

Real-Time Monitoring

Emerging closed-loop systems aim to adjust therapy based on real-time imaging feedback. Examples include:

- MRI-guided focused ultrasound with temperature mapping (19)
- Photoacoustic monitoring of nanoparticle accumulation to optimize photothermal dosing (36)
- Fluorescence lifetime imaging to assess drug release kinetics (18)

Clinical translation remains limited, with only iron oxide agents (ferumoxytol for MRI; NanoTherm for hyperthermia) achieving regulatory approval (13), (14).

Immunotherapy and Nanovaccines

The intersection of nanomedicine and cancer immunotherapy represents one of the most dynamic areas identified in our systematic analysis.

mRNA Delivery Systems: Lipid nanoparticle-mRNA platforms developed for COVID-19 vaccines have been rapidly adapted for cancer applications (12), (13):

Tumour Antigen Encoding: Personalized mRNA vaccines encoding patient-specific neoantigens demonstrated durable responses in Phase I melanoma trials when combined with checkpoint inhibitors (38), (39).

Immunomodulatory Cytokines: LNP-encapsulated mRNA encoding IL-12, IL-15, or type I interferons enables localized cytokine expression while avoiding systemic toxicity of recombinant protein administration (40).

Chimeric Antigen Receptor Delivery: In situ CAR-T generation through LNP-mRNA delivery offers potential to circumvent ex vivo cell manufacturing (41).

Optimization Strategies: Ionizable lipid chemistry (pKa optimization), lipid composition, and tissue tropism modification enable targeting of dendritic cells, T cells, or tumour cells depending on formulation (12), (42).

Immune Modulation

Nanoparticle-mediated immune modulation strategies include

Adjuvant Delivery: Co-delivery of antigens with immunostimulatory adjuvants (CpG ODN, STING agonists, TLR ligands) within the same particle enhances dendritic cell activation and cross-presentation (42), (43).

Tumour Microenvironment Reprogramming: Nanoparticles targeting tumour-associated macrophages (TAMs) for M2-to-M1 polarization, myeloid-derived suppressor cell (MDSC) depletion, or regulatory T cell inhibition (43).

Immunogenic Cell Death Induction: Certain chemotherapeutic agents (doxorubicin, oxaliplatin) and physical modalities (photothermal, photodynamic) trigger immunogenic cell death when delivered via nanoparticles, converting "cold" tumours to "hot" phenotypes (40), (41).

Checkpoint Inhibition Strategies

Nanocarrier-mediated checkpoint inhibitor delivery offers several potential advantages:

- **Reduced systemic immune-related adverse events** through tumour-targeted delivery
- **Combination with chemotherapy or radiotherapy** in single formulations
- **TME-localized release** avoiding systemic immunosuppression (32), (42)

However, clinical validation remains limited, with most studies at preclinical stages.

Challenges and Critical Discussion

Toxicity and Long-Term Safety: Despite the theoretical safety advantages of targeted delivery, nanoparticle toxicity remains a critical translational barrier:

Acute Toxicity: Infusion reactions (complement activation-related pseudoallergy) occur with some liposomal formulations, manageable through premedication and slow infusion rates (44).

Chronic Accumulation: Non-biodegradable materials (gold, silica, carbon nanotubes) accumulate in liver and spleen with unclear long-term consequences. Studies in our synthesis rarely exceeded 30-day follow-up, leaving chronic toxicity inadequately characterized (45), (46).

Immunotoxicity: Repeated administration of PEGylated nanoparticles induces anti-PEG antibody formation in 40–70% of patients, accelerating clearance upon subsequent dosing (accelerated blood clearance phenomenon) (44), (46).

Secondary Effects: Nanoparticle-mediated alterations in gut microbiome, endocrine disruption, and developmental toxicity represent emerging concerns inadequately addressed in current literature (47).

Reproducibility and Quality Control

Batch-to-Batch Variability: Critical quality attributes (size distribution, surface charge, drug loading, ligand density) often show >20% inter-batch variability in academic studies, exceeding pharmaceutical acceptability thresholds (48).

Characterization Standardization: Absence of consensus characterization protocols (dynamic light scattering conditions, zeta potential measurement parameters) limits inter-study comparisons (49).

In Vivo-In Vitro Correlation: Poor correlation between in vitro release profiles and in vivo performance undermines predictive capability of screening assays (4), (23).

Scale-Up and Manufacturing

Process Translation: Laboratory synthesis methods (thin-film hydration, solvent evaporation, batch reactions) often fail to translate to scalable manufacturing without significant reformulation (7).

Microfluidic Manufacturing: Continuous flow microfluidic systems enable reproducible LNP production but require substantial capital investment and process development (7), (12).

Sterilization Challenges: Terminal sterilization (autoclaving, gamma irradiation) damages many nanoformulations, necessitating aseptic manufacturing with associated complexity and cost (13).

Supply Chain: Specialized excipients (ionizable lipids, PEG-lipids, functionalized polymers) have limited suppliers, creating supply chain vulnerabilities (14).

Regulatory Pathway Uncertainty

Classification Ambiguity: Nanoformulations may be classified as drugs, biologics, devices, or combination products depending on composition and mechanism, creating regulatory pathway uncertainty.

Characterization Requirements: FDA and EMA guidance documents for nanomedicines remain evolving, with limited precedent for novel platforms.

Generic/Biosimilar Pathways: Lack of established bioequivalence criteria for nanomedicines complicates generic development, affecting market dynamics and pricing (13), (14).

Clinical Trial Failures

Analysis of discontinued nanomedicine clinical programs reveals common failure modes:

- Insufficient efficacy improvement over standard of care despite promising preclinical results
- Manufacturing challenges preventing adequate supply for Phase III trials
- Unexpected toxicities at efficacious doses
- Inability to identify biomarkers for patient selection

The translational success rate from first-in-human to regulatory approval (approximately 6–8% for oncology nanomedicines) is comparable to conventional small molecules, suggesting that nanomedicine alone does not overcome fundamental drug development attrition (4), (8), (23).

Why Most Nanomedicine Fails: Despite decades of research, the majority of nanomedicine platforms fail during clinical translation due to three fundamental issues. First, over-reliance on subcutaneous mouse models leads to overestimation of therapeutic efficacy, as these models do not replicate the vascular, stromal, and immune complexity of human tumours (8), (15). Second, insufficient tumour penetration limits therapeutic distribution, particularly in hypovascular and fibrotic cancers, resulting in perivascular drug localization without deep tissue diffusion (30), (31). Third, the absence of patient stratification strategies prevents identification of individuals most likely to benefit from nanotherapy, leading to diluted efficacy signals in clinical trials (9). Addressing these systemic limitations is essential for improving translational success rates.

Future Perspectives

Artificial Intelligence in Nanomedicine Design: Machine learning and artificial intelligence approaches are increasingly being integrated into nanomedicine design workflows for formulation optimization, predictive modelling, and personalized therapeutic strategies:

Formulation Optimization: Predictive models correlating composition variables (lipid ratios, polymer molecular weight, drug:carrier ratios) with critical quality attributes and biological performance (50), (51).

In Silico Screening: Molecular dynamics simulations predicting protein corona formation, cell membrane interactions, and intracellular trafficking (52), (53), (54).

Closed-Loop Synthesis: Autonomous synthesis platforms integrating real-time characterization with machine learning-guided parameter adjustment (51).

Patient Selection: AI-driven analysis of tumour imaging and molecular profiles to predict nanoparticle accumulation and treatment response (50), (55).

Personalized Nanotherapy

The convergence of nanomedicine with precision oncology offers several personalized approaches

Patient-Derived Tumour Models: Patient-derived orthotopic xenografts (PDOX) and tumour organoids enable individualized nanoparticle screening before treatment selection (55), (56).

Companion Diagnostics: Imaging biomarkers (tumour perfusion, vascular permeability) to predict EPR effect magnitude and guide formulation selection (9), (57).

Adaptive Dosing: Real-time imaging of nanoparticle accumulation to adjust dosing schedules for individual patients (18), (58).

Biomimetic and Cell-Mediated Delivery

Natural carrier systems offer solutions to persistent delivery challenges:

Exosome Engineering: Genetic modification of producer cells to generate exosomes with defined targeting ligands and therapeutic payloads (28), (59).

Cell-Mediated Delivery: Live cell carriers (neutrophils, macrophages, stem cells) that actively traffic to inflammatory or tumour sites and release payloads (27), (60).

Membrane Camouflage: Next-generation membrane coatings incorporating multiple cell-type membranes or artificial membrane proteins (27), (60).

Multi-Omics Integration

Integration of genomic, transcriptomic, proteomic, and metabolomic data with nanoparticle design offers several opportunities

Target Identification: Systematic identification of tumour-specific surface markers for active targeting (57), (58).

Resistance Prediction: Molecular signatures predicting nanoparticle sensitivity or resistance (50).

Combination Rationale: Multi-omics guided selection of drug combinations and delivery strategies (55), (61).

Novel Contribution: Clinical Readiness Scoring System (CRSS): To address the critical need for objective prioritization of nanomaterial platforms for clinical development, we introduce a Clinical Readiness Scoring System (CRSS) integrating efficacy, safety, manufacturability, regulatory feasibility, and clinical validation domains informed by existing translational nanomedicine and regulatory evaluation frameworks (47), (49), (62), (63).

Domain	Weight	Scoring Criteria (0–10)
Efficacy (E)	25%	Preclinical tumour growth inhibition, survival extension, comparison to standard of care
Safety (S)	25%	Acute toxicity profile, chronic accumulation, immunotoxicity, organ pathology
Manufacturability (M)	20%	Scalability, batch consistency, characterization feasibility, stability
Regulatory Pathway (R)	15%	Precedent approvals, guidance document applicability, classification clarity
Clinical Validation (C)	15%	Clinical trial data, human pharmacokinetics, biomarker development

CRSS = 0.25E + 0.25S + 0.20M + 0.15R + 0.15C (maximum score: 10)

Weighting prioritizes efficacy and safety because these remain the primary determinants of oncology drug approval, while manufacturability and regulatory feasibility were included to reflect major translational bottlenecks repeatedly identified in nanomedicine development literature (14), (47), (62).

Material Class	E Score	S Score	M Score	R Score	C Score	CRSS Total
Lipid-based (LNP-mRNA)	8	8	9	9	8	8.35
Stimuli-responsive polymeric	8	7	7	6	4	6.65
Biomimetic (membrane-coated)	9	9	4	3	2	5.90
Albumin-based	7	9	9	9	9	8.45
Gold/Platinum (radiosensitizer)	7	5	7	7	6	6.40
Iron oxide (theranostic)	6	7	8	8	7	7.05
MOFs	8	5	3	2	1	4.30
Carbon-based	7	4	4	2	1	4.00

The scoring outcomes highlight a recurring trend across nanomedicine development: platforms with superior theoretical performance do not necessarily achieve higher translational readiness if manufacturing reproducibility, safety characterization, and regulatory pathways remain uncertain (47), (49), (63).

Top Three Most Promising Nanoplatforms

Based on CRSS analysis and qualitative assessment, we identify the following platforms as having highest near-term clinical translation potential:

- Lipid Nanoparticle-mRNA Systems (CRSS: 8.35):** Established manufacturing infrastructure from vaccine production, clear regulatory pathway, expanding oncology applications in immunotherapy. Near-term opportunities include personalized neoantigen vaccines and intratumoural cytokine expression.
- Albumin-Based Nanoparticles (CRSS: 8.45):** Proven clinical track record (Abraxane), excellent safety profile, natural transport mechanisms. Pipeline opportunities include combination formulations and new drug payloads exploiting albumin's intrinsic targeting capabilities.
- Stimuli-Responsive Polymeric Micelles (CRSS: 6.65):** High drug loading, controlled release, and pH-responsive mechanisms well-matched to TME characteristics. Manufacturing challenges represent the primary translational barrier, with microfluidic production offering potential solutions.

Importantly, the CRSS framework is intended as a dynamic translational assessment model rather than a fixed ranking system, and scores may evolve as additional clinical data, regulatory guidance, and scalable manufacturing technologies emerge. The CRSS framework enables a decision-making shift from performance-centric to translation-centric evaluation, allowing researchers to prioritize nanocarrier systems not only based on efficacy but also on manufacturability and regulatory feasibility. This approach

may significantly reduce resource allocation to platforms with low clinical viability. Although CRSS provides a structured framework for comparative translational assessment, several limitations should be acknowledged. Scoring weights were derived from literature-informed expert interpretation rather than formal Delphi consensus or machine-learning optimization. Additionally, rapid advances in nanomedicine manufacturing, regulatory science, and personalized oncology may alter translational priorities over time. Future validation using prospective clinical datasets and inter-reviewer scoring reproducibility studies will strengthen the framework's predictive utility.

CONCLUSIONS

This review of studies published between 2020 and 2026 provides a comprehensive evaluation of next-generation nanomaterials for anticancer applications. Several key conclusions emerge from our synthesis:

The translational gap persists: Despite exponential growth in preclinical nanomedicine publications, clinical translation efficiency remains extremely low despite the large volume of preclinical research. Only 14 nanoformulations have achieved regulatory approval for oncology indications, with the majority representing incremental improvements on established liposomal or albumin-based platforms rather than fundamentally novel material classes.

Platform selection should be evidence-based: Comparative analysis reveals that no single nanocarrier class excels across all performance metrics. Lipid-based systems offer the clearest regulatory pathway and manufacturing scalability; polymeric systems provide superior drug loading and stimuli-responsive capabilities; metallic systems enable unique theranostic applications; and biomimetic systems achieve exceptional tumour targeting but face manufacturing hurdles.

EPR limitations demand paradigm shift: The substantial animal-to-human translational gap in passive tumour accumulation underscores the need for orthotopic-TME-informed nanomaterial design. Optimization for subcutaneous xenograft models—which remain dominant in preclinical research—likely contributes to clinical failure.

Active targeting requires validation: While ligand-mediated active targeting improves tumour accumulation 2–4-fold in preclinical models, clinical evidence for this benefit in nanoparticle delivery (as opposed to antibody-drug conjugates) remains limited.

Immunotherapy integration is accelerating: The successful clinical deployment of LNP-mRNA vaccines has catalyzed rapid translation of similar platforms for cancer immunotherapy, representing the most dynamic area of nanomedicine development.

Standardization is essential: Reproducibility challenges arising from batch variability, inconsistent characterization methods, and inadequate reporting standards undermine systematic evaluation and comparison of nanocarrier platforms. The Clinical Readiness Scoring System introduced in this review provides an objective framework for prioritizing nanomaterial platforms based on translational potential. Our analysis identifies lipid nanoparticle-mRNA systems, albumin-based nanoparticles, and stimuli-responsive polymeric micelles as the three platforms best positioned for near-term clinical impact. In conclusion, the future of nanomedicine lies not in the development of increasingly complex nanostructures, but in the strategic alignment of design with clinical and biological realities. Based on our analysis, three immediate research priorities emerge: (1) transition from subcutaneous to orthotopic and patient-derived models, (2) integration of predictive biomarkers for patient stratification, and (3) development of scalable and regulatory-compliant manufacturing processes. By adopting these principles and leveraging frameworks such as CRSS, the field can move beyond incremental innovation toward meaningful clinical impact. Continued progress in clinically relevant model systems, manufacturing technologies, and regulatory science will be essential for realizing the full potential of nanomedicine. By aligning nanomaterial design with the authentic constraints of human tumour microenvironments rather than convenient animal models, the next generation of nanomedicines may finally realize the transformative potential that has long been promised.

Limitations of This Review: This review has several limitations. First, the rapidly evolving nature of nanomedicine research means that newly published studies may not be fully represented. Second, the reviewed literature includes diverse nanocarrier platforms, cancer types, and experimental models, which limits direct comparison across studies. Third, publication bias toward positive findings may lead to overestimation of therapeutic performance. Finally, variability in nanoparticle characterization methods, biological models, and reporting standards continues to complicate cross-study interpretation and highlights the need for greater standardization within the field.

Implications for Clinicians and Industry: From a clinical perspective, lipid-based and albumin-bound nanoparticles represent immediately deployable platforms, supported by established regulatory pathways and manufacturing infrastructure. In contrast, biomimetic and MOF-based systems remain long-term innovations, requiring advances in scalability and safety validation. For industry stakeholders, cost and manufacturability considerations strongly favor platforms compatible with continuous manufacturing technologies such as microfluidics, while complex multi-component systems may face prohibitive production costs. Strategic alignment between platform selection and clinical indication will be essential to maximize return on development investment. The CRSS framework proposed in this review may assist researchers, clinicians, regulatory agencies, and industry stakeholders in prioritizing nanopatforms with the greatest likelihood of successful clinical translation.

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