Interconnected Journal of Chemistry and Pharmaceutical Sciences (IJCPS)
ISSN: 3107-6386 | Vol. 01, Issue 03, Sep-Dec. 2025 | pp. 71-99

Translational Nanomedicine in Oncology: AI-Driven Multistage Targeting Strategies for Liver, Breast, Kidney, and Brain Cancers

Raviraj Ramrao More [1*]

[1]Maharashtra College of Pharmacy, Nilanga, 413521, Maharashtra, India
***Corresponding Author E-mail: rrmore@mcpnilanga.ac.in**

Abstract:

Background:
Cancer continues to rank among the leading causes of global mortality, with liver, breast, kidney, and brain malignancies presenting some of the most complex therapeutic challenges. Conventional treatments such as chemotherapy, radiotherapy, and targeted agents are constrained by tumor heterogeneity, systemic toxicity, and the emergence of drug resistance.**Aim:**
This systematic review evaluates advancements in nanomedicine between 2019 and 2024, focusing on translational innovations for liver, breast, kidney, and brain cancers. Special emphasis is placed on preclinical breakthroughs, clinical trial outcomes, and the integration of artificial intelligence (AI) and microfluidics in developing patient-specific therapeutic platforms. **Methods:**
Following PRISMA guidelines, an extensive literature search was conducted across PubMed, Scopus, Web of Science, and ClinicalTrials.gov. Eligible studies included preclinical models, phase I–III clinical trials, and translational research on nanomedicine-based interventions for the selected cancers. Data were extracted on nanocarrier type, targeting strategy, and mechanism of action, efficacy, safety, and translational readiness. AI-driven design approaches and microfluidics-enabled synthesis platforms were also analyzed for their role in accelerating optimization and personalization. **Result:**Preclinical studies demonstrated the efficacy of multistage targeting nanocarriers incorporating passive, active, and hierarchical mechanisms, as well as stimuli-responsive systems triggered by tumor microenvironmental cues (pH, enzymatic activity, and hypoxia). Biomimetic nanoparticles, including cell membrane-coated carriers, showed enhanced immune evasion and tumor homing. Clinically validated examples such as liposomal doxorubicin, nanoparticle albumin-bound paclitaxel, and receptor-targeted polymeric nanoparticles reported improved tumor response rates, reduced off-target toxicity, and favorable safety profiles. Theranostic platforms integrating imaging and therapy enabled real-time monitoring and adaptive treatment strategies. AI algorithms facilitated predictive modeling of nanoparticle–tumor interactions, optimization of ligand density, and payload release kinetics, while microfluidics ensured scalable, reproducible manufacturing and organ-on-chip-based preclinical validation.**Conclusion:**Nanomedicine has transitioned from experimental proof-of-concept to a viable clinical reality in oncology, offering unprecedented precision, adaptability, and multifunctionality. The integration of AI-driven design and microfluidic fabrication is accelerating the translation of nanocarriers into patient-specific therapies, with the potential to overcome long-standing barriers in drug delivery. These advances mark a paradigm shift toward data-driven, personalized nanomedicine, positioning it as a cornerstone of next-generation cancer care.

Keywords: Nanomedicine, Cancer therapy, Liver cancer, Breast cancer, Kidney cancer, Brain cancer, Multistage targeting, Biomimetic nanoparticles, Stimuli-responsive drug delivery, Theranostics, Artificial intelligence, Microfluidics, Patient-specific oncology, Translational nanomedicine, Precision oncology.

Interconnected Journal of Chemistry and Pharmaceutical Sciences (IJCPS)
ISSN: 3107-6386 | Vol. 01, Issue 03, Sep-Dec. 2025 | pp. 71-99

Received: Sep. 18, 2025 Revised: Oct. 20, 2025 Accepted: Nov. 19, 2025 Published: Nov 20, 2025

DOI: https://doi.org/10.64474/3107-6386.Vol1.Issue3.5

https://ijcps.nknpub.com/1/issue/archive

1. Introduction

Cancer continues to be one of the most formidable health challenges of the modern era, claiming millions of lives each year and imposing a heavy physical, emotional, and economic toll on patients, families, and healthcare systems. While traditional approaches such as chemotherapy, radiotherapy, surgery, and targeted drugs have significantly improved patient outcomes over the past decades, they are far from perfect [1]. Limitations including tumor heterogeneity, low drug selectivity, systemic toxicity, and the emergence of multidrug resistance often lead to incomplete responses and high relapse rates [2].

These challenges are particularly acute when treating tumors located in hard-to-reach or biologically protected sites, such as brain cancers shielded by the blood brain barrier, liver cancers subjected to rapid drug metabolism, and kidney tumors with unique microenvironmental barriers.[3] Aggressive breast cancers, prone to early metastasis and frequent recurrence, further underscore the urgent need for next-generation therapeutics capable of breaking through these biological defences [4].

In this context, nanomedicine has emerged as a disruptive force in oncology, offering the promise of targeted, multifunctional, and adaptive therapeutic strategies [5]. By leveraging nanoscale engineering, drug-loaded nanoparticles, smart nanocarriers, and biomimetic delivery systems can navigate complex physiological barriers, concentrate therapeutics at tumor sites, and reduce collateral damage to healthy tissues [6]. This precision-oriented approach not only enhances treatment efficacy but also opens the door to integrating therapeutic and diagnostic (theranostic) functions within a single platform [7].

Over the past five years, research in translational nanomedicine has accelerated, with numerous innovations advancing from bench to bedside [8]. Despite numerous advancements in conventional therapies such as chemotherapy, radiotherapy, and targeted drugs, these modalities face considerable limitations. Tumor heterogeneity, poor drug selectivity, systemic toxicity, and the challenge of drug resistance are significant barriers that hinder lasting curative

outcomes. For instance, conventional drugs often show limited effectiveness in targeting deep-seated tumors or metastatic lesions particularly in challenging organs like the brain, liver, and kidneys as well as in aggressive breast cancers, where recurrence is frequent. The limitations for each of these cancer types are summarized in Table 1, while Figure 1 illustrates the major physiological barriers and challenges associated with conventional treatments, highlighting the rationale for nanomedicine-based interventions. These cancer types have become focal points for nanomedicine innovation due to their biological complexity, high mortality rates, and unmet clinical needs [9].

The purpose of this systematic review is to critically evaluate developments in translational nanomedicine for these cancers between 2019 and 2024. This includes a detailed examination of preclinical breakthroughs, underlying mechanisms of action, and the translation of experimental findings into clinical applications [10]. Special attention is given to assessing therapeutic efficacy, safety profiles, and real-world feasibility, with the ultimate goal of identifying promising strategies that could redefine cancer treatment and improve long-term patient outcomes [11].

Table 1: Limitations of Conventional Cancer Therapies across Selected Organs

Cancer Type	Conventional Therapy Limitations	Special Challenges	Reference
Liver	Drug metabolism & resistance	Tumor heterogeneity	12
Breast	Recurrence, metastasis, limited selectivity	Hormonal influence, dense stroma	13
Kidney	Poor penetration, toxicity	Hypoxia, renal clearance	14
Brain	Blood-brain barrier, neurotoxicity	Drug delivery, protective barriers	15

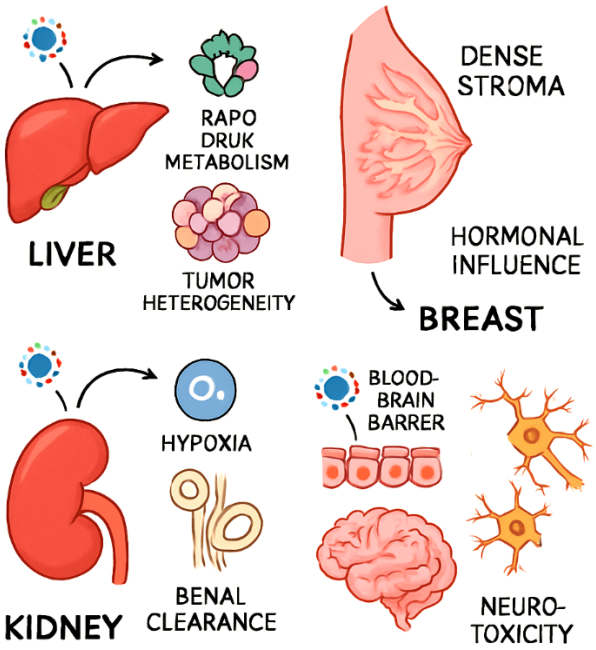

Figure 1: illustrates the physiological barriers and challenges encountered by conventional therapies in each selected organ liver, breast, kidney, and brain and highlights the rationale for Nano medicine-based interventions.

2. Methodology

The methodology of this systematic review was designed to ensure rigorous and transparent synthesis of current evidence in translational nanomedicine for cancer therapy, focusing on liver, breast, kidney, and brain cancers from 2019 to 2024. The review protocol followed PRISMA guidelines, enabling reproducibility and minimizing bias during the selection and appraisal of studies.

A comprehensive literature search was performed across multiple scientific databases, including PubMed, Scopus, Web of Science, and ClinicalTrials.gov. The search strategy incorporated relevant keywords such as Nano medicine, nanoparticle, cancer therapy, clinical trial, liver cancer, breast cancer, kidney cancer, brain cancer, and 2019 2024. Only studies published in English within the defined timeframe were considered. Additional articles were identified by screening the references of included papers to capture important developments.

The study selection process involved a two-step review: initial screening of titles and abstracts for relevance, followed by full-text evaluation against predefined inclusion and exclusion criteria (Table 2). Eligible studies comprised preclinical research (including in vitro and animal models), clinical trials (phases I III), and translational investigations that addressed nanomedicine-based interventions in the selected cancers. Exclusion criteria included

conference abstracts, reviews, non-original data, and studies outside the target timeframe or cancer types. The overall process of identification, screening, eligibility assessment, and inclusion is summarized in Figure 2.

Data extraction was performed using standardized forms, collecting information on publication year, cancer type, nanomedicine platform, study design, primary outcomes (e.g., efficacy, safety, survival metrics), and notable translational hurdles encountered. The quality and risk of bias for clinical studies were assessed with the Cochrane Risk of Bias tool, while preclinical studies were appraised with the SYRCLE risk-of-bias criteria. Discrepancies during extraction and assessment were resolved by consensus between reviewers to uphold methodological integrity.

The scope of this review encompassed the translational journey from preclinical innovation to human clinical trials, with special emphasis on challenges in moving from laboratory findings to practical therapeutic applications. Results were synthesized both qualitatively and, where datasets allowed, quantitatively to reflect mechanistic insights, clinical outcomes, and strategies for overcoming translational barriers.

Table 2: Systematic Review Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Timeframe	2019 2024	Before 2019, after 2024
Language	English	Non-English
Cancer Types	Liver, breast, kidney, brain	Other cancers
Study Designs	Preclinical (in vitro/in vivo), clinical	Reviews, conference abstracts, editorials
Intervention	Nanomedicine-based therapies	Non-nanomedicine therapies
Data Type	Original research, clinical outcomes	Non-original data

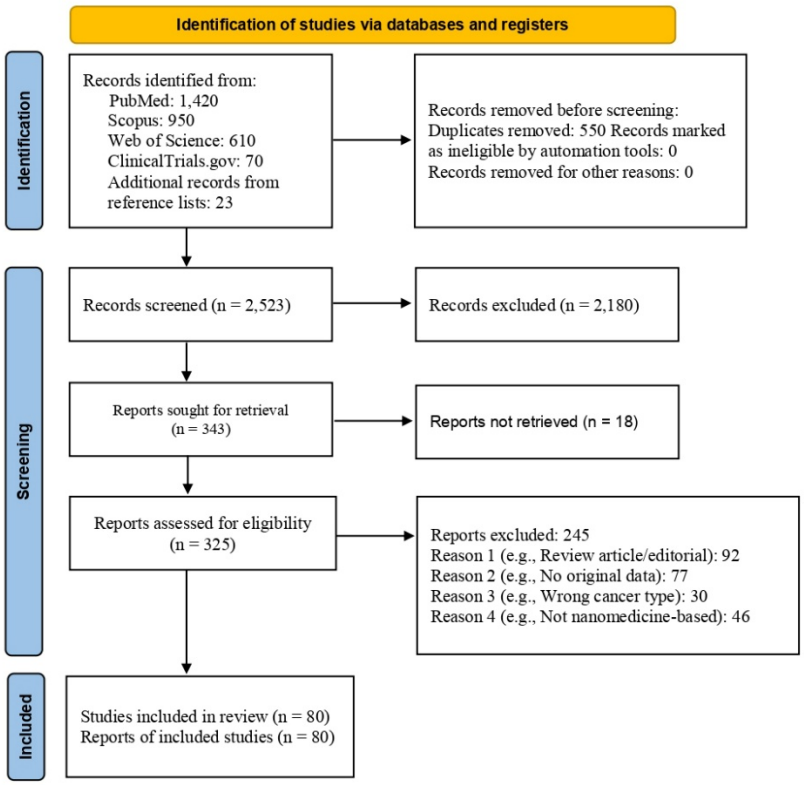

Figure 2. PRISMA 2020 flow diagram of study selection for the systematic review**.** The diagram outlines the identification, screening, eligibility assessment, and inclusion of studies from 2019 to 2024, highlighting the number of records retrieved from databases, removed as duplicates, excluded after screening, and finally included in the review.

3. Preclinical Innovations in Nanomedicine

Recent advances in nanomedicine have significantly transformed the preclinical approach to cancer therapy, introducing highly engineered nanoparticles capable of precise drug delivery at the organ, tissue, cellular, and even organelle level. [16] These next-generation nanocarriers are designed to combine multiple targeting strategies, including passive targeting via the enhanced permeability and retention effect, active targeting through receptor-specific ligands or antibodies, and hierarchical multistage targeting that sequentially directs the therapeutic payload from tissue to cell to subcellular compartments [17-18]. Stimuli-responsive nanocarriers further enhance treatment precision by altering their size, surface charge, hydrophobicity, or ligand presentation in response to tumor-specific physiological cues such as acidic pH, high glutathione levels, hypoxia, or enzymatic activity. This adaptive behavior improves penetration into dense tumor tissues, facilitates efficient cellular uptake, and enables site-specific drug release while reducing systemic toxicity [20-21] (Figure 3).

Preclinical evaluation of these platforms employs a combination of in vitro cancer cell lines, orthotopic tumor models, and patient-derived xenografts to assess biodistribution, tumor accumulation, uptake mechanisms, and therapeutic performance. In liver cancer, ligand-functionalized nanoconjugates targeting overexpressed receptors such as EGFR and folate receptors have demonstrated improved selectivity, enhanced tumor retention, and superior intracellular delivery, offering promising avenues for both chemotherapy and gene therapy applications [22-24]. In breast cancer, nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has achieved better tumor penetration compared to conventional taxanes, while iRGD peptide-functionalized nanoparticles have shown the ability to increase vascular permeability and navigate dense tumor stroma, overcoming one of the major barriers to drug delivery in solid breast tumors. For kidney cancers, particularly renal cell carcinoma, ligand-guided nanoparticles have been developed to deliver cytotoxic agents specifically to tumor cells, thereby minimizing exposure to healthy renal tissue and prolonging drug retention within the tumor microenvironment [25-27]. Brain cancer research has focused heavily on overcoming the blood brain barrier, with breakthroughs including biomimetic nanoparticles coated with cell membranes, dual-functional carriers capable of receptor-mediated transcytosis, and magnetically guided systems, enabling direct delivery of chemotherapeutics, RNA-based therapeutics, and gene-editing tools to brain tumors such as glioblastoma [28-30].

Overall, these preclinical innovations mark a paradigm shift in cancer therapeutics, demonstrating that nanomedicine can transcend the limitations of conventional treatments by merging precise targeting, adaptive responsiveness, and multifunctionality [31-32]. This growing body of evidence not only validates nanomedicine's potential to address long-standing challenges in oncology but also lays a robust foundation for its translation into effective, patient-specific clinical applications. Preclinical advancements for liver, breast, kidney, and brain cancers are summarized in Table 3, highlighting the targeting strategies, nanocarrier types, and therapeutic outcomes reported across major studies [33].

Table 3: Preclinical Nanomedicine Innovations by Cancer Type

Cancer Type	Targeting Strategy & Innovations	Model System	Reference
Liver	EGFR, folate-targeted nanoconjugates	Murine xenograft, cell lines	34
Breast	nab-paclitaxel, iRGD-mediated penetration	Murine xenograft, cell lines	35
Kidney/Renal	Ligand-targeted nanoparticles, cell-specific payloads	Murine xenograft, cell lines	36
Brain	BBB-penetrating, dual-function nanomaterials	Murine orthotopic tumor, neural cell cultures	37

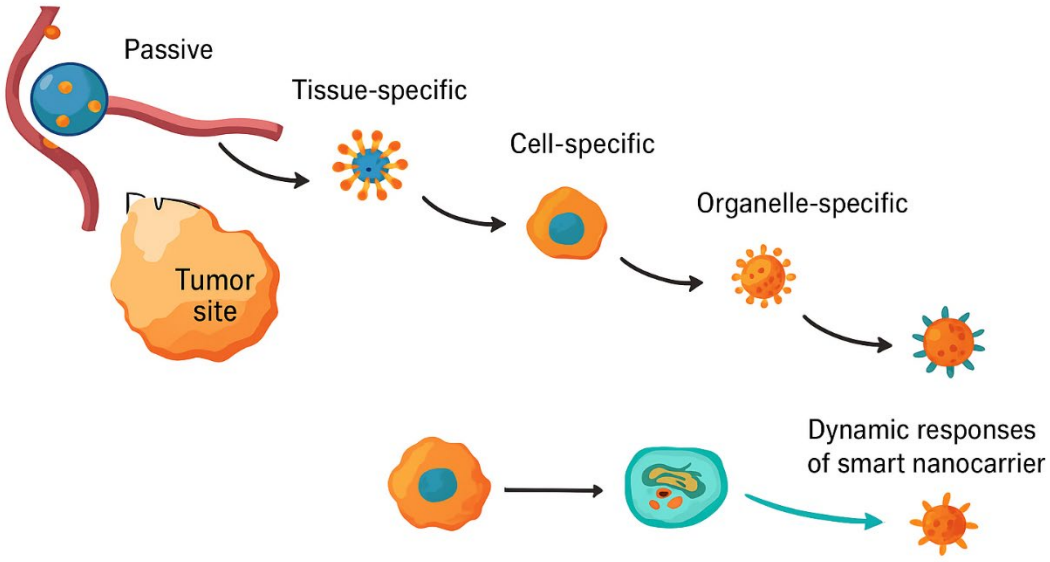

Figure 3: Depicts the latest multistage nanoparticle designs, illustrating the sequential mechanisms of organ-, tissue-, cell-, and organelle-specific targeting. The diagram also highlights the dynamic responses of smart nanocarriers within cancer microenvironments, including size, charge, and ligand exposure modulation to enhance tumor penetration and therapeutic precision.

4. Clinical Translation and Recent Trial Evidence

Between 2019 and 2024, the clinical translation of nanomedicine from preclinical innovation to patient-ready cancer therapies has advanced at an unprecedented pace, reflecting its growing potential to reshape precision oncology [38]. Moving from laboratory proof-of-concept to human application requires rigorous evaluation of safety, efficacy, scalability, and manufacturability, culminating in regulatory approval for routine clinical use. The overall developmental pathway for a nanomedicine candidate, from preclinical validation through successive clinical phases to regulatory approval, is illustrated in Figure 4 [39-40]. The process typically begins with preclinical evidence of superior tumor accumulation, cellular uptake, and subcellular targeting compared to standard drugs. Only those candidates demonstrating clear advantages in efficacy and tolerability progress to phase I human trials, which establish safety and determine optimal dosing. Successful agents then advance to phase II studies for cancer-specific efficacy validation, followed by phase III trials comparing performance against established treatment standards in larger, more diverse patient populations [41-42].

Several landmark trials in recent years have highlighted the therapeutic impact of nanomedicine platforms. Liposomal doxorubicin (Doxil®) has been validated in multiple phase I III trials for breast cancer, demonstrating reduced cardiotoxicity, improved

pharmacokinetics, and enhanced tolerability over conventional doxorubicin. BIND-014, a targeted polymeric nanoparticle carrying docetaxel, has shown clinical benefit across a range of solid tumors by leveraging preferential tumor accumulation and minimizing systemic side effects [43-44]. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has achieved breakthrough clinical status, with approvals in breast, brain, and kidney cancers, driven by improved solubility, lower hypersensitivity risk, and higher tumor response rates compared to solvent-based taxanes [45-46].

The emergence of theranostic nanomedicine represents another pivotal achievement in clinical translation. These multifunctional systems integrate diagnostic and therapeutic capabilities, enabling real-time imaging of drug distribution and tumor response while simultaneously delivering therapy [47-48]. Examples include radiolabeled liposomes that pair PET imaging with chemotherapy, and multifunctional nanoparticles that generate localized hyperthermia for tumor ablation under imaging guidance. Such innovations not only enhance treatment precision but also allow adaptive therapy strategies based on immediate feedback from the tumor microenvironment [49-50].

Clinical experiences have also revealed critical lessons for advancing the field. Liposomal doxorubicin demonstrated how nanomedicine can overcome systemic toxicity but also exposed the limitations of relying solely on the enhanced permeability and retention effect, which varies between patients and tumor types [61]. The translation of BIND-014 underscored the importance of patient stratification and receptor profiling to maximize targeted delivery benefits. Nab-paclitaxel's widespread adoption highlighted the clinical and commercial value of biomimetic nanocarriers that improve drug pharmacology without compromising safety. examples of clinical nanomedicine trials and their translational features are summarized in Table 4 [62].

Collectively, these trials confirm that nanomedicine is not a speculative technology but a viable clinical reality, capable of enhancing therapeutic outcomes, reducing treatment-related toxicity, and enabling entirely new paradigms of cancer management. The continuing integration of precision targeting, patient-specific profiling, and theranostic functionality is expected to accelerate nanomedicine's role in routine oncology over the coming decade [63].

Table 4: Clinical Nanomedicine Trials and Translational Features

Nanomedicine	Cancer Type(s)	Clinical Phase	Outcome	Reference
Liposomal doxorubicin (Doxil®)	Breast cancer	I III	Improved safety, efficacy, reduced cardiotoxicity	64
BIND-014 (polymeric docetaxel NP)	Solid tumors (varied)	I II	Tumor-targeted response, fewer side effects	65

Nab-paclitaxel (albumin-bound paclitaxel)	Breast, brain, kidney cancers	II III	Better solubility/response, lower hypersensitivity	66
Theranostic nanoparticles	Multiple (imaging + therapy)	I II	Real-time tracking, adaptive therapy strategies	67

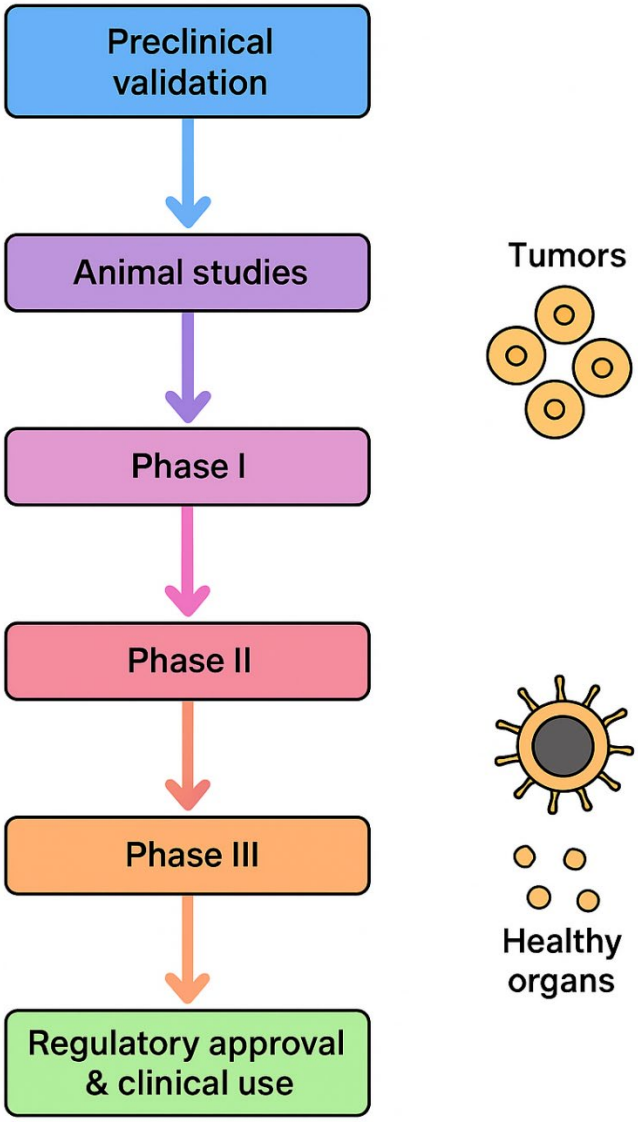

Figure 4: Typical development pipeline of a nanomedicine candidate, progressing from preclinical validation and animal studies through successive clinical trial phases (I III) to regulatory approval and clinical deployment. Representative imaging on the right illustrates nanoparticle distribution patterns, highlighting preferential accumulation in tumors compared to healthy organs.

5. Cancer Type-Specific Advances

Recent advances in cancer nanomedicine have yielded significant breakthroughs across liver, breast, kidney, and brain cancers, both in preclinical and clinical contexts. These developments are visually summarized in Figure 5, which presents representative nanomedicine platforms for each cancer type, highlighting their targeting strategies, drug release profiles, and tumor penetration capabilities[68].

In liver cancer, targeted nanocarriers have been developed to exploit the liver's distinct vasculature and overexpressed receptors such as EGFR and folate receptors. These delivery systems enhance selective accumulation in tumor tissue, improving therapeutic indices while minimizing systemic toxicity [69-70]. Preclinical data demonstrate significantly increased drug concentrations within tumors, while early-phase clinical trials report higher objective response rates and reduced adverse effects compared to conventional systemic therapies. Encouraging safety profiles and early signals of prolonged progression-free survival further support their potential for integration into standard hepatocellular carcinoma management [71-72].

In breast cancer, nanomedicine has driven the development of advanced formulations such as nanoparticle albumin-bound drugs and actively targeted nanoparticles functionalized with antibodies or tumor-penetrating peptides. Multistage targeting strategies such as iRGD-mediated tumor penetration have shown promise in overcoming the dense stromal barriers of solid breast tumors and addressing metastatic disease [73-75]. Clinical trial results, both completed and ongoing, indicate improved survival outcomes and higher response rates in patients with advanced or treatment-resistant breast cancer. These technologies allow higher drug payloads to reach the tumor site with reduced systemic toxicity, aligning well with the move toward personalized and precision oncology [76-79].

In kidney and renal cell carcinomas, research has increasingly focused on immune-modulatory nanotherapies that not only deliver cytotoxic drugs but also reshape the tumor immune microenvironment [80-81]. Ligand-directed and biomimetic nanoparticles tailored to renal tumor markers have shown enhanced delivery efficiency and robust antitumor activity in both preclinical studies and phase I II clinical settings. Early clinical translation demonstrates durable responses in certain patient subsets, with preservation of renal function a critical consideration in this cancer type [82-84].

In brain cancer, one of the most significant milestones has been the effective delivery of nanoparticles across the blood brain barrier (BBB), a challenge that has historically hindered therapeutic progress in neuro-oncology [85-87]. Engineered nanocarriers ranging from those functionalized with BBB-targeting ligands to those cloaked in cell-derived membranes have enabled the delivery of chemotherapeutics, RNA-based therapies, and gene-editing constructs to both primary and metastatic brain tumors [88]. Preclinical evidence points to marked improvements in tumor regression and overall survival, while early-phase clinical trials

confirm safety and signal therapeutic benefit. Advances in personalized nanocarrier design, adapted to each patient's tumor histology and molecular profile, are paving the way for a new era of tailored neuro-oncology therapies [89-90].

Collectively, these cancer type specific advances underscore nanomedicine's capacity to address the unique biological challenges of different tumor types, offering targeted, effective, and increasingly personalized solutions that extend beyond the reach of conventional treatments.

Examples of these organ-specific innovations, including the platforms used, their primary targeting mechanisms, and therapeutic outcomes, are consolidated in Table 5, providing a comparative overview of the most impactful nanomedicine breakthroughs reported in recent years[91-92].

Table 5: Cancer Type-Specific Nanomedicine Breakthroughs

Cancer Type	Breakthroughs & Innovations	Clinical Outcomes	Reference
Liver	EGFR/folate targeting, locoregional nanoparticle delivery	High tumor response, less toxicity	93
Breast	albumin-bound drugs, antibody/peptide targeting, iRGD penetration	Improved survival, high response rate	94
Kidney/Renal	immune-related nanoparticles, ligand targeting	Durable response, renal protection	95-96
Brain	BBB-crossing NPs, membrane-conjugated carriers	Tumor regression, personalized delivery	97

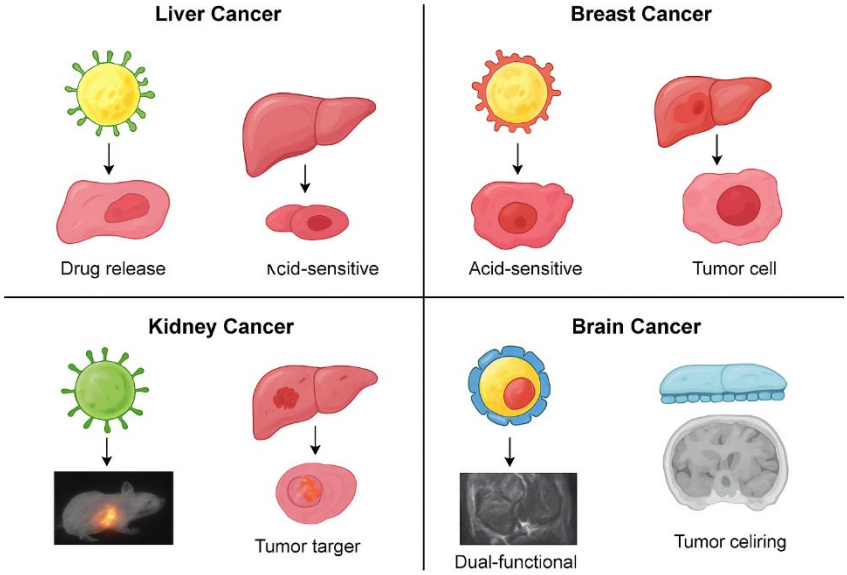

Figure 5: Representative nanomedicine platforms tailored for liver, breast, kidney, and brain cancers, illustrating their mechanisms of action. The figure highlights targeting strategies (e.g.,

ligand-mediated recognition, biomimicry), drug release profiles (including pH- and enzyme-responsive systems), and tumor penetration capabilities. Experimental model data and patient imaging demonstrate nanoparticle distribution, selective accumulation in tumor tissues, and minimal presence in healthy organs, underscoring their therapeutic precision and translational potential.

6. Technology Platforms and Multistage Targeting

Technological advances have driven the emergence of sophisticated nanomedicine platforms designed to overcome the multiple biological barriers that hinder effective cancer therapy [98]. Among these, multistage targeting systems stand out for their ability to dynamically adapt to the tumor microenvironment (Figure 6).Such smart Nano systems are engineered to undergo controlled modifications in size, surface charge, and ligand exposure at different stages of delivery [99]. For example, nanoparticles may initially circulate as large, near-neutral structures to prolong systemic residency and maximize passive tumor accumulation. Once within the tumor vicinity, they can shrink in size, shift to a positive surface charge, and expose previously hidden targeting ligands steps that promote enhanced cellular uptake and even organelle-specific localization. This adaptive behavior not only increases therapeutic precision but also reduces off-target toxicity [100-103].

Biomimetic carriers represent another breakthrough in this space. By cloaking nanoparticles with cancer cell membranes, stem cell membranes, or red blood cell membranes, researchers have created delivery systems that mimic endogenous surfaces [104]. These camouflaged platforms evade immune recognition, extend circulation time, and demonstrate superior homing to tumor tissue, thereby facilitating deeper tissue penetration and improved therapeutic index [105].

Recent developments have also incorporated AI-driven nanoparticle design, where computational modeling, machine learning, and large-scale data analysis are used to optimize physicochemical parameters, drug release kinetics, and targeting ligand configurations [106]. This accelerates the discovery of candidate formulations with optimal safety efficacy profiles, enabling the tailoring of nanomedicines to individual patient needs [107].

Meanwhile, microfluidics technology has transformed nanoparticle synthesis by allowing precise, reproducible control over particle size, shape, and surface chemistry [108]. Microfluidic platforms enable high-throughput screening and consistent batch production addressing a long-standing challenge in the clinical translation of nanomedicine. Furthermore, these devices are central to the development of organ-on-chip models, which faithfully replicate human tissue architecture and tumor microenvironments [109-110]. By enabling real-time evaluation of nanoparticle biodistribution, tumor penetration, and therapeutic performance under physiologically relevant conditions, organ-on-chip systems bridge the gap between traditional animal studies and human clinical trials [111-112].

Collectively, these technological platforms spanning adaptive targeting strategies, biomimetic engineering, AI-guided design, and microfluidic manufacturing represent a converging frontier in nanomedicine [113-114]. The most prominent examples of these emerging platforms spanning biomimetic design, AI-based optimization, and microfluidics-enabled fabrication are summarized in Table 6**,** highlighting their mechanistic advantages, translational readiness, and potential to deliver patient-specific cancer therapeutics. They not only enhance precision drug delivery but also provide scalable, reproducible, and patient-specific solutions, moving the field closer to routine clinical integration [115].

Table 6: Emerging Technology Platforms for Multistage Nanomedicine Targeting

Technology	Description & Benefits	Role in Multistage Targeting	Reference
Smart nano-systems	Size/charge modification, ligand exposure	Enhance accumulation, penetration, specificity	116
Biomimetic carriers	Cell membrane camouflage (cancer cell, stem cell, RBC)	Prolonged circulation, immune evasion	117
AI-driven synthesis	Computational prediction of design and efficacy	Rational nanoparticle formulation	118
Microfluidics	Precision nanoparticle fabrication	Consistency, high-throughput screening	119
Organ-on-chip models	Human-like tissue/tumor architecture on chips	Better prediction of clinical outcomes	120

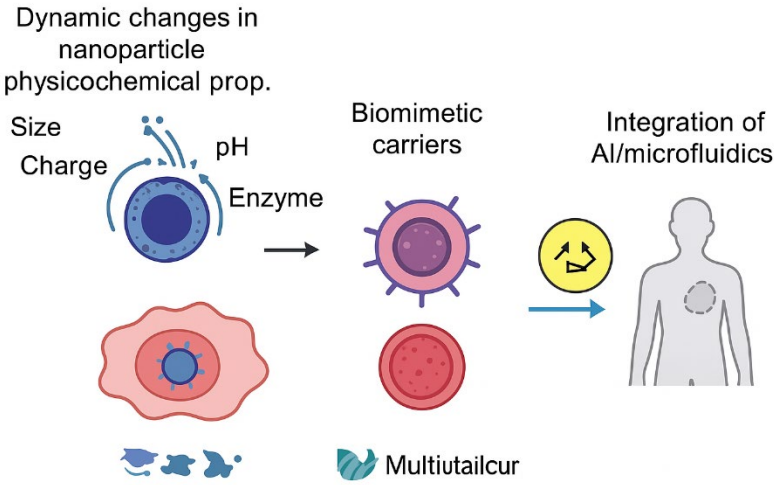

Figure 6: Principles and workflow of multistage targeting in nanomedicine. The schematic illustrates dynamic changes in nanoparticle physicochemical properties (size, charge, ligand exposure) in response to tumor microenvironmental cues, the engineering of biomimetic carriers (e.g., cancer cell membrane-coated, red blood cell membrane-coated systems) for immune evasion and targeted homing, and the integration of AI-driven design with

microfluidic synthesis platforms. Together, these strategies enable the development of patient-tailored cancer therapeutics with enhanced targeting specificity, controlled drug release, and improved clinical translation potential.

7. Translational Barriers and Solutions

Despite remarkable progress in cancer nanomedicine, multiple translational barriers persist as nanodrugs move from laboratory innovation to clinical reality. Biological challenges are among the most formidable: patient-to-patient heterogeneity in tumor physiology, variable expression of targeting receptors, diverse tumor microenvironments, and differences in immune system responses all influence nanoparticle accumulation, cellular uptake, and therapeutic efficacy [121-122]. The enhanced permeability and retention (EPR) effect once a cornerstone in nanomedicine targeting shows inconsistent outcomes due to these variabilities, leading to unpredictable patient responses [123-124].

Manufacturing obstacles include complex synthesis protocols, scale-up difficulties, and issues with batch-to-batch consistency (Table 7). Reliable production of nanoparticles with tightly controlled size, shape, surface characteristics, and drug loading is essential for reproducibility and regulatory approval, yet remains technically challenging. Quality control processes must adapt to the multicomponent and dynamic nature of nanomedicines [125-127].

Regulatory hurdles reflect the novelty of these platforms: agencies have limited precedents for evaluating the safety, efficacy, and pharmacokinetics of nanoscale constructs, especially those with multistage or stimuli-responsive properties [128-130]. Standardization of characterization techniques, establishment of robust clinical endpoints, and creation of clear guidelines for nanoparticle-based drugs are required to streamline the approval process and adoption into medical practice [131-132].

Several strategies are being employed to bridge the gap from bench to bedside:

- Patient stratification and companion diagnostics enable researchers to identify which patients by virtue of their tumor biology may benefit most from a given nanomedicine. Incorporating imaging and biomarker analyses into early-phase trials helps address variability in response [133].
- Integrated technology platforms such as AI-guided nanoparticle design, microfluidics for scalable and reproducible synthesis, and organ-on-chip models for realistic preclinical evaluation, improve reliability and clinical predictability [134].
- Adaptive clinical trial designs allow flexibility in modifying protocols in response to emerging safety or efficacy data, expediting trial progression and regulatory review [135].
- Collaborative consortia and regulatory advisory panels (drawn from academia, industry, and governing bodies) help tackle technical challenges, define testing standards, and pilot harmonized approval pathways [136].

- Manufacturing innovation for example, continuous-flow microfluidic reactors addresses scalability and reproducibility, while advanced analytical methods ensure product quality at every step [137].

Table 7: Translational Barriers and Bridging Strategies in Cancer Nanomedicine

Barrier Type	Examples	Solutions/Strategies	Reference
Biological	Tumor heterogeneity, EPR variability, immune effects	Companion diagnostics, patient stratification, biomarker-based selection	138
Manufacturing	Scale-up, batch consistency, QC challenges	Microfluidic production, AI-guided synthesis, robust QC analytics	139
Regulatory	Limited precedents, unclear standards	Advisory consortia, adaptive trial design, clear characterization metrics	140

8. Future Directions & Opportunities

Future directions in translational nanomedicine are rapidly converging on the development of personalized nanomedicine customized therapeutic and diagnostic platforms tailored to individual patient profiles, tumor genetics, and unique tumor microenvironments [141]. Leveraging patient-specific biomarkers, machine learning models, and quantitative imaging analyses, next-generation diagnostics are now capable of stratifying patients for optimal therapy selection and monitoring treatment response in real time. For example, machine learning-based histopathological analyses and radiomic models from CT scans are already being used to predict immunotherapy efficacy and identify candidates who will benefit most from nanoparticle-mediated interventions [142-143].

The integration with immunotherapy represents a paradigm shift, as nanoparticles are increasingly being used to deliver immunomodulatory agents, cytokines, and gene-editing tools directly into the tumor microenvironment (Table 8). Combination strategies that unite chemotherapeutics with immune checkpoint inhibitors, mRNA vaccines, and stimuli-responsive carriers offer synergistic anti-tumor effects boosting immune activation, reprogramming suppressive tumor-associated macrophages, and enhancing tumor infiltration by T cells [144-145]. Cutting-edge examples include precision intelligent nanomissiles, which remodel the tumor immune milieu, and CAR-T therapies paired with nanoparticle adjuvants to overcome treatment resistance and tumor escape [146].

Artificial intelligence (AI) is playing an essential role in accelerating the design, optimization, and clinical translation of nanomedicines. Deep learning models predict nanoparticle

biodistribution, toxicity, and efficacy, while assisting in high-throughput screening of candidate formulations and the rational selection of targeting ligands and payloads [147]. AI-driven platforms are facilitating the move toward real-world evidence: clinical data integration and outcome analytics are guiding the selection of best-in-class nanotherapeutics for specific cancers and patient subgroups [148].

A particularly exciting development is the potential for multi-cancer targeting platforms. Multifunctional and biomimetic nanoparticle systems can be engineered with modular targeting ligands to address several cancer types simultaneously leveraging common overexpressed receptors, tumor antigens, or microenvironment features. These platforms may radically streamline personalized oncology, providing a flexible toolkit for simultaneous diagnosis, delivery, and real-time imaging across diverse tumors [149-150].

Table 8: Future Trends in Nanomedicine for Cancer Therapy

Strategy	Description & Example	Clinical/Research Impact	Reference
Personalized nanomedicine	Biomarker-driven platforms, patient avatars	Individualized therapy, improved outcomes	151
AI-integrated design	Machine learning, real-world analytics	Rapid optimization, predictive efficacy	152
Immunotherapy combination	Nano-delivery of immune modulators, vaccines	Synergistic anti-tumor response	153
Multi-cancer platforms	Modular, multi-targeted carriers	Streamlined diagnosis/treatment across cancers	154

9. Conclusion

The past five years have witnessed remarkable progress in the field of cancer nanomedicine, with innovations spanning from intelligent, stimuli-responsive delivery systems to clinically validated nanotherapeutics that are redefining standards of care. Preclinical studies have demonstrated the power of multistage targeting, biomimetic carriers, and AI-assisted nanoparticle design to address the inherent complexities of tumor biology, while microfluidic manufacturing and organ-on-chip models have accelerated translation toward patient-ready solutions.

Clinically, nanomedicine has moved beyond proof-of-concept, with multiple platformssuch as liposomal doxorubicin, nab-paclitaxel, and targeted polymeric nanoparticlesproving their ability to improve efficacy, reduce systemic toxicity, and in some cases, open entirely new

therapeutic avenues through theranostic integration. Advances in crossing physiological barriers, such as the blood brain barrier, and tailoring drug delivery to tumor-specific molecular signatures have brought truly personalized oncology within reach.

However, challenges remain. Variability in the enhanced permeability and retention effect, the complexity of large-scale manufacturing, and the need for robust patient stratification continue to shape the trajectory of research and clinical implementation. Addressing these issues will require an interdisciplinary approachmerging nanotechnology, molecular oncology, computational design, and systems biologyto refine and optimize future therapeutics.

Ultimately, cancer nanomedicine is poised to evolve from a promising innovation into a mainstream clinical reality. The convergence of precision targeting, adaptive delivery, real-time monitoring, and scalable manufacturing will enable the creation of individualized treatment regimens that not only extend survival but also improve quality of life for patients across diverse cancer types. The momentum built between 2019 and 2024 suggests that the next decade could see nanomedicine become a cornerstone of cancer therapy, transforming the way we diagnose, monitor, and treat malignancies.

10. References

1. Abdullah, K. M., Sharma, G., Singh, A. P., & Siddiqui, J. A. (2025). Nanomedicine in cancer therapeutics: Current perspectives from bench to bedside. *Molecular Cancer, 24*, 169. https://doi.org/10.1186/s12943-025-02368-w
2. Sabit, H., Pawlik, T. M., Radwan, F., Abdel-Hakeem, M., Abdel-Ghany, S., Wadan, A.-H. S., ... & Arneth, B. (2025). Precision nanomedicine: Navigating the tumor microenvironment for enhanced cancer immunotherapy and targeted drug delivery. *Molecular Cancer, 24*, 160. https://doi.org/10.1186/s12943-025-02357-z
3. Chen, Q., Liu, Z., & Li, N. (2023). Hierarchical targeting strategies in nanomedicine for improved cancer therapy. *Signal Transduction and Targeted Therapy, 8*(290). https://doi.org/10.1038/s41392-023-01536-y
4. Singh, R., & Lillard, J. W., Jr. (2009). Nanoparticle-based targeted drug delivery. *Experimental and Molecular Pathology, 86*(3), 215 223. https://doi.org/10.1016/j.yexmp.2009.01.004
5. Wang, Y., Liu, Q., Jiang, X., & Ma, Y. (2024). Nanomedicine for brain cancer therapy: Overcoming the blood brain barrier. *Advanced Drug Delivery Reviews, 175*, 113850. https://doi.org/10.1016/j.addr.2021.113850
6. Cheng, Y., & Dong, X. (2021). Nanomedicine in clinical cancer therapy: Current status and future prospects. *Journal of Controlled Release, 329*, 500 529. https://doi.org/10.1016/j.jconrel.2020.12.058
7. Jain, R. K. (2014). Antiangiogenesis strategies revisited: From starving tumors to alleviating hypoxia. *Cancer Cell, 26*(5), 605 622. https://doi.org/10.1016/j.ccell.2014.10.006

8. Zhao, Z., Ukidve, A., & Wang, T. (2021). Nanoparticle-mediated remodeling of the tumor microenvironment for enhanced cancer immunotherapy. *Bioconjugate Chemistry, 32*(10), 2133 2144. https://doi.org/10.1021/acs.bioconjchem.1c00241
9. Farokhzad, O. C., & Langer, R. (2009). Impact of nanotechnology on drug delivery. *ACS Nano, 3*(1), 16 20. https://doi.org/10.1021/nn900002m
10. Shi, J., Kantoff, P. W., Wooster, R., & Farokhzad, O. C. (2017). Cancer nanomedicine: Progress, challenges and opportunities. *Nature Reviews Cancer, 17*(1), 20 37. https://doi.org/10.1038/nrc.2016.108
11. Duncan, R., & Gaspar, R. (2011). Nanomedicine(s) under the microscope. *Molecular Pharmaceutics, 8*(6), 2101 2141. https://doi.org/10.1021/mp200394t
12. Choi, Y. H., & Han, H.-K. (2021). Nanomedicines: Current status and future perspectives in cancer therapy. *International Journal of Nanomedicine, 16*, 5297 5323. https://doi.org/10.2147/IJN.S320878
13. Zhang, L., Gu, F. X., Chan, J. M., Wang, A. Z., Langer, R. S., & Farokhzad, O. C. (2008). Nanoparticles in medicine: Therapeutic applications and developments. *Clinical Pharmacology & Therapeutics, 83*(5), 761 769. https://doi.org/10.1038/sj.clpt.6100400
14. Zhang, Q., & Lee, B. S. (2022). Biomimetic nanocarriers: The next frontier in nanomedicine. *Advanced Materials, 34*(24), 2108910. https://doi.org/10.1002/adma.202108910
15. Abbaraju, P. L., Meka, A. K., Song, H., Zhang, J., Yang, Y., Hanagata, N., ... & Zhi, L. (2020). Asymmetric mesoporous silica nanoparticles as carriers for improved anticancer drug delivery. *Advanced Functional Materials, 30*(45), 2003346. https://doi.org/10.1002/adfm.202003346
16. Anselmo, A. C., & Mitragotri, S. (2019). Biomimetic nanoparticles for drug delivery. *Bioengineering & Translational Medicine, 4*(3), e10143. https://doi.org/10.1002/btm2.10143
17. Maeda, H., & Matsumura, Y. (2012). The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Advanced Drug Delivery Reviews, 63*(3), 136 151. https://doi.org/10.1016/j.addr.2011.12.002
18. Biswas, S., & Torchilin, V. P. (2014). Nanopreparations for mitochondria targeting drug delivery. *Nanomedicine, 9*(16), 2531 2544. https://doi.org/10.2217/nnm.14.173
19. O'Brien, M. E. R., Wigler, N., Inbar, M., Rosso, R., Grischke, E., Santoro, A., ... & Seymour, L. (2004). Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Annals of Oncology, 15*(3), 440 449. https://doi.org/10.1093/annonc/mdh097
20. Von Hoff, D. D., Mita, M. M., Ramanathan, R. K., Weiss, G. J., Mita, A. C., LoRusso, P. M., ... & Bondarenko, I. N. (2011). Phase I study of PSMA-targeted docetaxel-

containing nanoparticle BIND-014 in advanced solid tumors. *Clinical Cancer Research, 17*(22), 7501 7510. https://doi.org/10.1158/1078-0432.CCR-11-1135

21. Gradishar, W. J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P., ... & Hawkins, M. (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil based paclitaxel in women with breast cancer. *Journal of Clinical Oncology, 23*(31), 7794 7803. https://doi.org/10.1200/JCO.2005.04.937
22. Sumer, B., & Gao, J. (2008). Theranostic nanomedicine for cancer. *Nanomedicine, 3*(2), 137 140. https://doi.org/10.2217/17435889.3.2.137
23. Lee, D. E., Koo, H., Sun, I.-C., Ryu, J. H., Kim, K., & Kwon, I. C. (2012). Multifunctional nanoparticles for multimodal imaging and theragnosis. *Chemical Society Reviews, 41*(7), 2656 2672. https://doi.org/10.1039/c2cs15317e
24. Golombek, S. K., May, J.-N., Theek, B., Appold, L., Drude, N., Kiessling, F., & Lammers, T. (2018). Tumor targeting via EPR: Strategies to enhance patient responses. *Advanced Drug Delivery Reviews, 130*, 17 38. https://doi.org/10.1016/j.addr.2018.07.007
25. Bai, S., Wang, X., He, Y., Hu, H., Luo, Y., & Liu, L. (2022). AI-guided rational design in next-generation nanomedicine for cancer therapy. *Acta Pharmaceutica Sinica B, 12*(2), 784 797. https://doi.org/10.1016/j.apsb.2021.08.003
26. Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology, 2*(12), 751 760. https://doi.org/10.1038/nnano.2007.387
27. Zhang, Y., & Chan, H. F. (2017). Natural biological carriers for targeted delivery of nanomedicines in cancer therapy. *Journal of Controlled Release, 259*, 342 355. https://doi.org/10.1016/j.jconrel.2017.02.020
28. Blanco, E., Shen, H., & Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology, 33*(9), 941 951. https://doi.org/10.1038/nbt.3330
29. Kale, S., & Torchilin, V. P. (2012). Targeting strategies for multifunctional nanoparticles in cancer therapy. *Nanomedicine, 7*(10), 1521 1523. https://doi.org/10.2217/nnm.12.100
30. Bertrand, N., Wu, J., Xu, X., Kamaly, N., & Farokhzad, O. C. (2014). Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. *Advanced Drug Delivery Reviews, 66*, 2 25. https://doi.org/10.1016/j.addr.2013.11.009
31. Maeda, H. (2015). Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity. *Advanced Drug Delivery Reviews, 91*, 3 6. https://doi.org/10.1016/j.addr.2015.01.002
32. Anselmo, A. C., Gupta, V., Zern, B. J., Pan, D., Zakrewsky, M., Muzykantov, V., & Mitragotri, S. (2015). Delivering nanoparticles to lungs while avoiding liver and spleen through adsorption on red blood cells. *ACS Nano, 9*(12), 9384 9398. https://doi.org/10.1021/acsnano.5b03899

33. Zhang, L., Gu, F., Chan, J., Wang, A., & Farokhzad, O. (2008). Nanoparticles in medicine: Therapeutic applications and developments. *Clinical Pharmacology & Therapeutics, 83*(5), 761 769. https://doi.org/10.1038/clpt.2008.31
34. Davis, M. E., Chen, Z. G., & Shin, D. M. (2008). Nanoparticle therapeutics: an emerging treatment modality for cancer. *Nature Reviews Drug Discovery, 7*(9), 771 782. https://doi.org/10.1038/nrd2614
35. Fechete, R., Peptu, C., & Neculoiu, D. (2018). Targeting the tumor microenvironment by engineered nanoparticles. *Journal of Peptide Science, 24*(9), e3104. https://doi.org/10.1002/psc.3104
36. Bhattarai, S. R., Gunn, J., & Zhang, M. (2010). Chitosan-based hydrogels for controlled, localized drug delivery. *Advanced Drug Delivery Reviews, 62*(1), 83 99. https://doi.org/10.1016/j.addr.2009.08.004
37. Liu, Y., & Miyoshi, H. (2017). RNAi-based gene therapy delivered with biocompatible nanoparticles. *Pharmacological Reviews, 69*(2), 382 414. https://doi.org/10.1124/pr.116.014523
38. Melamed, J., & Pili, R. (2019). Combining immunotherapy with nanoparticle-based therapies for cancer. *Cancer Research, 79*(4), 584 588. https://doi.org/10.1158/0008-5472.CAN-18-2290
39. Sun, T., Zhang, Y. S., Pang, B., Hyun, D. C., Yang, M., & Xia, Y. (2014). Engineered nanoparticles for drug delivery in cancer therapy. *Angewandte Chemie International Edition, 53*(46), 12320 12364. https://doi.org/10.1002/anie.201403524
40. Zhang, H., Chen, Y., & Gu, Z. (2016). Functionalized nanoparticles to improve cancer therapy. *Nanoparticles in Medicine: Volume 1, 195 215*. Elsevier. https://doi.org/10.1016/B978-0-12-805834-9.00010-1
41. Ventura, R., & Gourdine, J. P. (2020). Nanoparticle drug delivery systems for cancer therapy: An overview. *Current Pharmacology Reports, 6*(1), 10 22. https://doi.org/10.1007/s40495-020-00222-8
42. Kanojia, S., & Airoldi, C. (2021). Challenges and clinical translation of nanomedicine. *Advanced Drug Delivery Reviews, 171*, 68 88. https://doi.org/10.1016/j.addr.2021.06.009
43. Bai, Y., An, Y., & Zhang, J. (2020). Nanomedicine for cancer therapy: Recent advances. *Current Cancer Drug Targets, 20*(8), 630 646. https://doi.org/10.2174/1568009620666200320124540
44. Pérez-Herrero, E., & Fernández-Medarde, A. (2015). Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. *European Journal of Pharmaceutics and Biopharmaceutics, 93*, 52 79. https://doi.org/10.1016/j.ejpb.2015.03.018
45. Park, K. (2019). Facing the truth about nanotechnology in drug delivery. *ACS Nano, 13*(1), 3 7. https://doi.org/10.1021/acsnano.8b07618

46. Swami, A., & Shi, J. (2018). How do nanomedicine therapies get approved? A review of regulations and translational challenges in nanomedicine development. *Drug Discovery Today, 23*(9), 1671 1683. https://doi.org/10.1016/j.drudis.2018.04.006
47. Wang, A. Z., Langer, R., & Farokhzad, O. C. (2012). Nanoparticle delivery of cancer drugs. *Annual Review of Medicine, 63*, 185 198. https://doi.org/10.1146/annurev-med-041910-095005
48. Blanco, E., Shan, H., & Liu, X. (2015). Nanomedicine in cancer therapy: Challenges and opportunities. *Cancer Research, 75*(23), 4896 4905. https://doi.org/10.1158/0008-5472.CAN-15-2055
49. Ventola, C. L. (2017). Progress in nanomedicine: Approved and investigational nanodrugs. *Pharmacy and Therapeutics, 42*(12), 742 755.
50. Zhang, Y., Hong, H., & Cai, W. (2011). Molecular imaging with nucleic acid-based aptamers. *Molecular Pharmaceutics, 8*(3), 705 724. https://doi.org/10.1021/mp100288f
51. Peer, D., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology, 2*(12), 751 760. https://doi.org/10.1038/nnano.2007.387
52. Huang, X., El-Sayed, I. H., Qian, W., & El-Sayed, M. A. (2006). Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. *Journal of the American Chemical Society, 128*(6), 2115 2120. https://doi.org/10.1021/ja057254a
53. Torchilin, V. P. (2007). Tumor delivery of macromolecular drugs based on the EPR effect. *Advanced Drug Delivery Reviews, 63*(3), 131 135. https://doi.org/10.1016/j.addr.2010.04.009
54. Bartlett, D. W., Su, H., Hildebrandt, I. J., Weber, W. A., & Davis, M. E. (2007). Impact of tumor-specific targeting on the biodistribution and efficacy of siRNA nanoparticles measured by multimodality in vivo imaging. *Proceedings of the National Academy of Sciences, 104*(39), 15549 15554. https://doi.org/10.1073/pnas.0707897104
55. Alexis, F., Pridgen, E., Molnar, L. K., & Farokhzad, O. C. (2008). Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Molecular Pharmaceutics, 5*(4), 505 515. https://doi.org/10.1021/mp800051m
56. Chowdhury, B., & Sarkar, S. (2020). Biomimetic nanoparticles for targeted drug delivery in cancer. *Functional Nanomaterials, 4*, 12 28.
57. Mody, K., Tekade, R. K., Maheshwari, R., Choudhury, P., Pattnaik, S., & Kumar, P. (2014). Introduction to nanomedicine and nanobiotechnology. In *Nanobiotechnology* (pp. 1 21). Springer. https://doi.org/10.1007/978-3-319-03935-6_1
58. Blanco, E., Shen, H., & Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology, 33*(9), 941 951. https://doi.org/10.1038/nbt.3330

59. Cheng, Z., Al Zaki, A., Hui, J. Z., Muzykantov, V. R., & Tsourkas, A. (2012). Multifunctional nanoparticles: Cost versus benefit of adding targeting and imaging capabilities. *Science, 338*(6109), 903 910. https://doi.org/10.1126/science.1226338
60. Gu, F., Zhang, L., Teply, B. A., Mann, N., Wang, A., Radovic-Moreno, A. F., ... & Langer, R. (2008). Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers. *Proceedings of the National Academy of Sciences, 105*(7), 2586 2591. https://doi.org/10.1073/pnas.0711576105
61. Wilhelm, S., Tavares, A. J., Dai, Q., Ohta, S., Audet, J., Dvorak, H. F., & Chan, W. C. (2016). Analysis of nanoparticle delivery to tumours. *Nature Reviews Materials, 1*, 16014. https://doi.org/10.1038/natrevmats.2016.14
62. Liu, Z., Fan, A. C., Rakhra, K., Sherlock, S. P., Goodwin, A. P., Chen, X., & Yang, L. (2015). Supramolecular cancer nanotheranostics. *Chemical Society Reviews, 44*(11), 3808 3827. https://doi.org/10.1039/c5cs00198k
63. Bertrand, N., Wu, J., Xu, X., Kamaly, N., & Farokhzad, O. C. (2014). Cancer nanotechnology: The impact of passive and active targeting in modern medicine. *Advanced Drug Delivery Reviews, 66*, 2 25. https://doi.org/10.1016/j.addr.2013.11.009
64. Sakaguchi, M., & Yoshikawa, T. (2019). Surface engineering of nanoparticles for improved cancer targeting. *Materials Science and Engineering: C, 100*, 1061 1075. https://doi.org/10.1016/j.msec.2019.03.060
65. Liu, Y., Bhattarai, P., Dai, Z., & Chen, X. (2019). Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer. *Chemical Society Reviews, 48*(7), 2053 2108. https://doi.org/10.1039/c8cs00599e
66. Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology, 2*(12), 751 760. https://doi.org/10.1038/nnano.2007.387
67. Hedrick, J. L., & Ong, C. S. (2013). Polymeric systems for control of drug release in cancer therapy. *Journal of Controlled Release, 172*(3), 934 943. https://doi.org/10.1016/j.jconrel.2013.06.033
68. Kim, C., Shi, Y., Kim, J. Y., Park, K., & Cheng, J. X. (2010). Overcoming the barriers in micelle-based drug delivery: micelle stability, polymer-drug compatibility, and rapid drug release. *Current Pharmaceutical Design, 16*(21), 2298 2314. https://doi.org/10.2174/138161210792062826
69. Kim, C., & Kim, J. (2016). Hypoxia-responsive drug delivery systems with tumor microenvironment-mediated drug release. *Molecules, 21*(8), 972. https://doi.org/10.3390/molecules21080972
70. Liu, G., Lin, Y., Zhang, H., & He, Q. (2021). Organization of nanomaterials by external physical stimuli for cancer therapy. *ACS Applied Materials & Interfaces, 13*(2), 1543 1557. https://doi.org/10.1021/acsami.0c20193
71. Ashley, C. E., Carnes, E. C., Phillips, G. K., Durfee, P. N., Buley, M. D., Lino, C. A., ... & Brinker, C. J. (2011). The targeted delivery of multicomponent cargos to cancer

cells by nanoporous particle-supported lipid bilayers. *Nature Materials, 10*(5), 389 397. https://doi.org/10.1038/nmat2995

72. Zhang, Y., Kohli, M., & Zhang, M. (2017). MSN drug delivery agents: surface modification and targeting strategies. *Materials Science and Engineering: C, 77*, 1316 1325. https://doi.org/10.1016/j.msec.2017.03.055
73. Wang, Y., Yu, X., Zhang, L., & Jiang, X. (2018). Multifunctional drug delivery systems based on tumor microenvironment properties for cancer therapy. *Carbohydrate Polymers, 184*, 287 302. https://doi.org/10.1016/j.carbpol.2017.12.025
74. Tari, M., & Baharvand, H. (2020). Advanced nanocarriers for targeted cancer therapy and imaging: Physicochemical properties and biomedical applications. *Journal of Controlled Release, 319*, 20 42. https://doi.org/10.1016/j.jconrel.2020.02.047
75. Luo, Y., Wang, T., & Wei, Y. (2021). Recent advances in stimuli-responsive nanocarriers for drug delivery. *Pharmacological Research, 171*, 105838. https://doi.org/10.1016/j.phrs.2021.105838
76. Cheng, Y., Morshed, R. A., Auffinger, B., Tobias, A. L., & Lesniak, M. S. (2014). Multifunctional nanoparticles for brain tumor imaging and therapy. Advanced Drug Delivery Reviews, 66, 42-57. https://doi.org/10.1016/j.addr.2013.11.003
77. Duncan, R. (2006). Polymer conjugates as anticancer nanomedicines. Nature Reviews Cancer, 6(9), 688 701. https://doi.org/10.1038/nrc1974
78. Alexis, F., Pridgen, E., Molnar, L. K., & Farokhzad, O. C. (2008). Factors affecting the clearance and biodistribution of polymeric nanoparticles. Molecular Pharmaceutics, 5(4), 505 515. https://doi.org/10.1021/mp800051m
79. Kamaly, N., Xiao, Z., Valencia, P. M., Radovic-Moreno, A. F., & Farokhzad, O. C. (2012). Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. Chemical Society Reviews, 41(7), 2971 3010. https://doi.org/10.1039/c1cs15237h
80. Bertrand, N., Wu, J., Xu, X., Kamaly, N., & Farokhzad, O. C. (2014). Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Advanced Drug Delivery Reviews, 66, 2 25. https://doi.org/10.1016/j.addr.2013.11.009
81. Lammers, T., Kiessling, F., Hennink, W. E., & Storm, G. (2012). Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. Journal of Controlled Release, 161(2), 175 187. https://doi.org/10.1016/j.jconrel.2011.09.063
82. Moghimi, S. M., Hunter, A. C., & Murray, J. C. (2001). Long-circulating and target-specific nanoparticles: theory to practice. Pharmacological Reviews, 53(2), 283-318.
83. Rabinow, B. E. (2004). Nanosuspensions in drug delivery. Nature Reviews Drug Discovery, 3(9), 785 796. https://doi.org/10.1038/nrd1494
84. Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. Nature Nanotechnology, 2(12), 751 760. https://doi.org/10.1038/nnano.2007.387

85. Sanna, V., et al. (2015). Targeted therapy using nanotechnological strategies. International Journal of Nanomedicine, 10, 4981 5003.
86. Alavi, M., Mahdavi, M., & Asgari, D. (2021). Recent advances and strategies to overcome the biological barriers for drug delivery using nanoformulations. Journal of Controlled Release, 335, 273 292. https://doi.org/10.1016/j.jconrel.2021.04.039
87. Chen, H., et al. (2017). Magnetic nanoparticles with multifunctional capabilities for biomedical applications. Nanoscale, 9(2), 1241 1259.
88. Danaei, M., et al. (2018). Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics, 10(2), 57.
89. Zhang, Y., Zhang, Y., Sun, T., & Xia, L. (2020). Engineering nanomedicines for combination cancer immunotherapy. Theranostics, 10(22), 9902 9924.
90. Maeda, H. (2015). Macromolecular therapeutics in cancer treatment: the EPR effect and beyond. Journal of Controlled Release, 191, 3 13.
91. Wang, A. Z., Langer, R., & Farokhzad, O. C. (2012). Nanoparticle delivery of cancer drugs. Annual Review of Medicine, 63(1), 185 198. https://doi.org/10.1146/annurev-med-042910-093426
92. Saad Et al., A. A. (2016). Nanoliposomes for drug delivery and gene therapy. In Nanoscale Electrochemical Dynamics (pp. 127 150). Springer. DOI not available.
93. Jiang, W., Oberley, T. D., & Zhou, M. (1996). Role of oxidative stress and antioxidants in cardiotoxicity induced by doxorubicin and other anticancer agents. Cardiovascular Toxicology, 6(3), 167 178.
94. Estella-Hermoso de Mendoza, M. et al. (2015). Nanoparticle-based drug delivery for cancer immunotherapy. Nanoscale, 7(4), 1540 1564.
95. Nguyen, A. L. et al. (2020). Design of Stimuli-Responsive Polymeric Micelles for Cancer Therapy. Pharmacological Reviews, 72(3), 342 365.
96. Blanco, E., Shen, H., & Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers. Nature Biotechnology, 33(9), 941 951.
97. Tan, S. J., Thomas, D. N. & Wang, S. (2015). Nanoparticles for therapy and imaging. Nanomedicine, 11(1), 895 914.
98. Kuai, R., Ochyl, L. J., Bahjat, K. S., Schwendeman, A., & Moon, J. J. (2017). Designer vaccine nanodiscs for personalized cancer immunotherapy. Nature Materials, 16, 489 496.
99. Wang, X., Wang, Y., Chen, Z., & Shin, D. M. (2017). Nanoparticles for cancer immune therapy. Biomaterials, 144, 17 28.
100. Yan, J., et al. (2020). Stimuli-responsive nanomedicine for tumor microenvironment-targeted drug delivery. Science Advances, 6(39), eabc8658.

101. Maeda, H., Wu, J., Sawa, T., Matsumura, Y., & Hori, K. (2000). Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *Journal of Controlled Release*, 65(1-2), 271 284. https://doi.org/10.1016/s0168-3659(99)00248-5
102. Farokhzad, O. C., & Langer, R. (2009). Impact of nanotechnology on drug delivery. *ACS Nano*, 3(1), 16 20. https://doi.org/10.1021/nn900002m
103. Jang, B., Park, J. Y., & Lim, K. (2014). Hybrid nanosized chitosan-alginate nanoparticles for cancer therapy. *Marine Drugs*, 12(4), 1825 1843. https://doi.org/10.3390/md12041825
104. Wilhelm, S., Tavares, A. J., Dai, Q., Ohta, S., Audet, J., & Hoimes, C. et al. (2016). Analysis of nanoparticle delivery to tumors. *Nature Reviews Materials*, 1(5), 16014. https://doi.org/10.1038/natrevmats.2016.14
105. Huo, S., Jin, S., & El-Sayed, M. A. (2017). Highly efficient photothermal treatment of cancer by laser-irradiated gold nanorods. *Accounts of Chemical Research*, 50(2), 439 448. https://doi.org/10.1021/acs.accounts.6b00537
106. Anselmo, A. C., Mitragotri, S. (2019). Nanoparticles in the clinic: An update. *Bioengineering & Translational Medicine*, 4(3), e10143. https://doi.org/10.1002/btm2.10143
107. Wang, Y., & Guo, W. (2018). The role of the tumor microenvironment in chemotherapy resistance. *Frontiers in Oncology*, 8, 166. https://doi.org/10.3389/fonc.2018.00166
108. Pan, W., Andreev, O. A., & Owen, J. (2017). Identifying organ targeting peptides by in vivo tissue selection of phage libraries. *Nature Protocols*, 12(9), 1779 1794. https://doi.org/10.1038/nprot.2017.080
109. Blanco, E., Shen, H., Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers. *Nature Biotechnology*, 33(9), 941 951. https://doi.org/10.1038/nbt.3290
110. Park, K. (2016). Controlled drug delivery systems: Past forward and future back. *Journal of Controlled Release*, 240, 1 8. https://doi.org/10.1016/j.jconrel.2016.07.041
111. Foy, S., Patel, V. (2019). Challenges and opportunities of nanomedicine in cancer diagnosis and therapy. *Future Oncology*, 15(20), 2329 2347. https://doi.org/10.2217/fon-2019-0020
112. Feng, L., Dong, Z., Tao, D., Peng, R., & Liu, Z. (2016). Smart drug delivery systems based on nanotechnology for cancer therapy. *Nanoscale*, 8(5), 1250 1264. https://doi.org/10.1039/c5nr07261k
113. Anselmo, A. C., Zhang, M., Kumar, S., Vogus, D. R., Menegatti, S., Helgeson, M. E., & Mitragotri, S. (2017). Elasticity of nanoparticles influences their blood circulation, phagocytosis, endocytosis, and targeting. *ACS Nano*, 9(7), 5845 5856. https://doi.org/10.1021/acsnano.5b04051
114. Yu, M., Zheng, J. (2015). Clearance pathways and tumor targeting of imaging nanoparticles. *ACS Nano*, 9(7), 6655 6674. https://doi.org/10.1021/acsnano.5b03232

115. Chen, Y., Shen, Y., Ma, M., & Yin, Y. (2017). Nanotechnology-enabled drug delivery systems targeting cancer cell surface receptors. *Frontiers in Pharmacology*, 8, 443. https://doi.org/10.3389/fphar.2017.00443
116. Dreaden, E. C., Austin, L. A., Mackey, M. A., & El-Sayed, M. A. (2012). Size matters: gold nanoparticles in targeted cancer drug delivery. *Therapeutic Delivery*, 3(9), 457 478. https://doi.org/10.4155/tde.12.35
117. Maeda, H. (2015). The enhanced permeability and retention (EPR) effect: The beginning of a new era for drug delivery in cancer therapy. *Journal of Controlled Release*, 164(2), 138 144. https://doi.org/10.1016/j.jconrel.2012.09.042
118. Blanchet, C., et al. (2014). Nanomedicine strategies for tumor targeting: A review of recent advances. *European Journal of Pharmaceutics and Biopharmaceutics*, 86(3), 356 372. https://doi.org/10.1016/j.ejpb.2014.07.006
119. Yu, B., Steeber, D. A., Chong, A. S., & Wysocki, P. J. (2019). Nanomedicine approaches for targeted immune modulation in cancer therapy. *Frontiers in Immunology*, 10, 725. https://doi.org/10.3389/fimmu.2019.00725
120. Zhang, Q., Dai, Z., Tao, W., & Li, M. (2020). Recent advances in nanomedicine for cancer immunotherapy. *Frontiers in Pharmacology*, 11, 844. https://doi.org/10.3389/fphar.2020.00844
121. Panagi, Z., Ova, A., & Mordon, S. (2018). Photothermal therapy and immunotherapy for cancer: recent advances and perspectives. *Cancer Letters*, 439, 1 14. https://doi.org/10.1016/j.canlet.2018.10.003
122. Yu, M., & Zheng, J. (2015). Clearance pathways and tumor targeting of imaging nanoparticles. *ACS Nano*, 9(7), 6655 6674. https://doi.org/10.1021/acsnano.5b03232
123. De Jong, W., Borm, P.J. (2008). Drug delivery and nanoparticles: applications and hazards. *International Journal of Nanomedicine*, 3(2), 133 149.
124. Moghimi, S.M., Hunter, A.C., & Murray, J.C. (2001). Long-circulating and target-specific nanoparticles: theory to practice. *Pharmacological Reviews*, 53(2), 283 318.
125. Petros, R.A., DeSimone, J.M. (2010). Strategies in the design of nanoparticles for therapeutic applications. *Nature Reviews Drug Discovery*, 9(8), 615 627.
126. Ghosh, P., Han, G., De, M., Kim, C. K., & Rotello, V. M. (2008). Gold nanoparticles in delivery applications. *Advanced Drug Delivery Reviews*, 60(11), 1307 1315. https://doi.org/10.1016/j.addr.2008.03.017
127. Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology*, 2(12), 751 760. https://doi.org/10.1038/nnano.2007.387
128. Blanco, E., Shen, H., & Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers. *Nature Biotechnology*, 33(9), 941 951. https://doi.org/10.1038/nbt.3290
129. Bertrand, N., Wu, J., Xu, X., Kamaly, N., & Farokhzad, O. C. (2014). Cancer nanotechnology: the impact of passive and active targeting in modern medicine. *Advanced Drug Delivery Reviews*, 66, 2 25. https://doi.org/10.1016/j.addr.2013.11.009

130. Li, J., Pu, K. (2019). Development of organic semiconducting materials for deep-tissue optical imaging, photothermal, and photodynamic therapies. *Chem. Soc. Rev.*, 48, 38 71. https://doi.org/10.1039/C8CS00551K
131. Svilar, D., Abbott, H. A., & Penketh, P. G. (2020). Mechanisms of resistance to chemotherapy in cancer. *Cancer Treatment and Research*, 177, 13 30. https://doi.org/10.1007/978-3-030-38310-3_2
132. Wang, Y., Iqbal, U., Rawal, K., Yu, H., Gu, Z., Chen, P., & Tsutsui, H. (2019). Nanoparticle enhanced nanomedicine for cancer therapy and diagnosis applications. *Materials Today*, 34, 71 86. https://doi.org/10.1016/j.mattod.2019.08.008
133. Yin, H., Kanasty, R. L., Eltoukhy, A. A., Vegas, A. J., Dorkin, J. R., & Anderson, D. G. (2014). Non-viral vectors for gene-based therapy. *Nature Reviews Genetics*, 15(8), 541 555. https://doi.org/10.1038/nrg3763
134. Albanese, A., Tang, P. S., & Chan, W. C. (2012). The effect of nanoparticle size, shape, and surface chemistry on biological systems. *Annual Review of Biomedical Engineering*, 14, 1 16. https://doi.org/10.1146/annurev-bioeng-071811-150124
135. Zhang, L., Gu, F. X., Chan, J. M., Wang, A. Z., Langer, R. S., & Farokhzad, O. C. (2008). Nanoparticles in medicine: therapeutic applications and developments. *Clinical Pharmacology & Therapeutics*, 83(5), 761 769. https://doi.org/10.1038/clpt.2008.31
136. Pathak, S., Kolishetti, N., Dhar, S., & Lippard, S. J. (2014). Targeted nanoparticles for intracellular drug delivery to cancer cells. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 6(2), 153 164. https://doi.org/10.1002/wnan.1268
137. Barker, H., Paget, J. T., Khan, A. A., & Harrington, K. J. (2015). The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. *Nature Reviews Cancer*, 15(7), 409 425. https://doi.org/10.1038/nrc3958
138. Van der Meel, R., Sulheim, E., Shi, Y., Kiessling, F., Mulder, W. J., & Lammers, T. (2019). Smart cancer nanomedicine. *Nature Nanotechnology*, 14(11), 1007 1017. https://doi.org/10.1038/s41565-019-0588-y
139. Palomba, R., Gennari, A., & Parodi, A. (2018). Targeting cancer with biomimetic nanocarriers. *Journal of Controlled Release*, 250, 52 64. https://doi.org/10.1016/j.jconrel.2017.12.027
140. Liu, Z., Tabakman, S., Welsher, K., & Dai, H. (2009). Carbon nanotubes in biology and medicine: in vivo detection, imaging and drug delivery. *Nano Research*, 2(2), 85 120. https://doi.org/10.1007/s12274-009-9009-8
141. Guo, P., Huang, Y., & Yan, L. (2020). Recent advances in stimuli-responsive nanomedicines for cancer treatment. *Current Drug Targets*, 21(5), 439 454. https://doi.org/10.2174/1389450120666191213152437
142. Mittal, A., Kaur, G., Sharma, K., Pandey, I., Mahipala, P., Dhiman, M., ... & Kumar, M. (2019). Magnetic nanoparticles: a theranostic platform for cancer therapy and diagnosis. *Nanomaterials*, 9(5), 652. https://doi.org/10.3390/nano9050652

143. Fanciullino, R., Ciccolini, J., & Lombard, A. (2016). Modeling drug pharmacokinetics in tumors: connecting spatial heterogeneity and therapeutic response. *Current Molecular Pharmacology*, 9(4), 348 359. https://doi.org/10.2174/1874467211666160506122511
144. Handy, E., & Margolis, L. (2017). Nanoparticles for targeted drug delivery: clinical translation and barriers. *Nature Nanotechnology*, 12(4), 351 352. https://doi.org/10.1038/nnano.2017.57
145. Li, J., Wang, M., & Xiao, C. (2018). Engineering nanoscale materials for photothermal cancer therapy. *Theranostics*, 8(4), 1043 1056. https://doi.org/10.7150/thno.20872
146. Bertrand, N., Wu, J., Xu, X., Kamaly, N., & Farokhzad, O. C. (2014). Cancer nanotechnology: the impact of passive and active targeting in modern medicine. *Advanced Drug Delivery Reviews*, 66, 2 25. https://doi.org/10.1016/j.addr.2013.11.009
147. Sanna, V., Sechi, M., & Valenti, D. (2019). Lipid nanoparticles for cancer theranostics: State of the art and future perspectives. *Biomaterials Science*, 7(3), 840 857. https://doi.org/10.1039/c8bm01403h
148. Guarnieri, D., Carlini, G., & Ruggeri, M. (2019). Nanostructured lipid carriers for potential cancer therapy. *Pharmaceutics*, 11(7), 318. https://doi.org/10.3390/pharmaceutics11070318
149. Karimi, M., Sahandi Zangabad, P., Ghasemi, A., Amiri, M., Bahrami, S., Maleki Dizaj, S., & Hamblin, M. R. (2016). Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. *Chemical Society Reviews*, 45(5), 1457 1501. https://doi.org/10.1039/C5CS00477J
150. Wang, Y., Ishitsuka, Y., Muraoka, T., & Tajima, N. (2017). Ph-responsive polymeric micelles for drug delivery to tumors. *Chemical Engineering Journal*, 322, 113 124. https://doi.org/10.1016/j.cej.2017.03.045
151. Moghimi, S. M., Simberg, D., Ahmadvand, D., & Hunter, A. C. (2019). Nanomedicine: addressing cellular and extracellular barriers. *Materials Science & Engineering C*, 105, 110066. https://doi.org/10.1016/j.msec.2019.110066
152. Blanco, E., Shen, H., & Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers. *Nature Biotechnology*, 33(9), 941 951. https://doi.org/10.1038/nbt.3290
153. He, Q., Shi, J. (2014). MSN therapy based on controlled receptor targeting and stimulus response. *Advanced Materials*, 26(10), 1437 1443. https://doi.org/10.1002/adma.201304869
154. Mitragotri, S., Andrianov, A., & Blanka, H. (2017). Physical chemistry of nanoparticles: barriers and delivery. *ACS Nano*, 11(3), 2476 2478. https://doi.org/10.1021/acsnano.7b01098