Journal of Emerging Pharmaceutical and Medical Research (JEPMR)
ISSN: 3107-6726 | Vol. 02, Issue-02, May-Aug. 2026 | pp. 32-56

Recent Progress in Cancer Nanotheranostics: Multifunctional Platforms for Precision Oncology

Diksha khateek[1*], Disha Songara[1], Abhishek Singh[1], Anvesh Sharma[1]

[1]L.N. College of Pharmaceutical Studies, Indore, PIN: 453556, Madhya Pradesh, India

***Corresponding Author E-mail: kannojidiksha@gmail.com**

Abstract

Its value as a health burden is still important because cancer has been one of the leading causes in the world, where liver, lung, pancreatic, breast and brain cancers make up copious mortality and fatalities. Conventional diagnostic and therapeutic modalities are frequently faced with delayed detection, insufficient tumor specificity, systemic toxicity, and the development of therapeutic resistance, emphasizing an imperative to develop integrated and selective strategies. Consistent with the above-mentioned definition, this systematic review summarizes advances from 2020 to 2025 in almost five main types of nanotheranostics (i.e., nanostructures for simultaneous diagnosis and therapy) in cancer biology. Methods. A systematic literature search with PubMed, Scopus and Web of Science was conducted to identify any studies assessing the relationship between COVID-19 risk factors defined as a history of or concurrent chronic disease and COVID-19 infection or COVID-19-related mortality from January 2020 to June 2025. Inclusion Criteria: Eligible studies were defined as those reporting on nanoplatforms having both diagnostic imaging and therapeutic function in liver, lung, pancreatic, breast or brain tumors; Data extracted included nanomaterial composition, imaging modality, therapeutic mechanism and experimental outcomes, as well as physical indicators of translational feasibility. Results illustrate major advancements in metallic nanoparticles, polymeric and liposomal carriers, carbon-based nanomaterials and hybrid multifunctional systems that improve imaging sensitivity via different modalities including magnetic resonance imaging (MRI), positron emission tomography (PET), fluorescence and photoacoustic imaging while providing targeted therapeutic delivery through chemotherapy, photothermal therapy, photodynamic therapy and immunotherapy. Organ-targeting innovations such as blood-brain barrier–permeable carriers, inhalable nano-platforms, stroma-modulating systems and receptor-targeted constructs add to this precision. While preclinical and early clinical results have been promising, safety validation, regulatory approval, manufacture at scale and cost-effectiveness for healthcare delivery continue to pose challenges. Interdisciplinary collaboration and ongoing refinement of the technology are likely to foster clinical translation, paving the way toward global precision oncology.

Keywords: Nanotheranostics, multi-organ cancer, precision oncology, imaging-guided therapy, targeted drug delivery, clinical translation

Received: May 27, 2026 **Revised: June 18, 2026** **Accepted: July 21, 2026** **Published: Aug. 06, 2026**

DOI: https://doi.org/10.64474/3107-6726.Vol2.Issue2.3

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

1. Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, with the global incidence projected to rise significantly in the coming decades. Among the most challenging cancers are liver (hepatocellular carcinoma), lung, pancreatic, breast, and brain tumors, which collectively contribute to millions of deaths annually[1]. Lung cancer continues to hold the highest mortality rate, followed by liver and pancreatic cancers, both of which are often diagnosed at advanced stages. Breast cancer is the most prevalent malignancy among women, while brain tumors such as glioblastoma represent some of the most aggressive and treatment-resistant cancers[2] (Table 1)

Table 1. Global burden and key clinical challenges of the major cancer types addressed by nanotheranostics.

Cancer Type	Global Burden / Mortality Profile	Key Diagnostic Challenge	Key Therapeutic Challenge	Representative Nanotheranostic Focus
Liver (Hepatocellular Carcinoma)	High mortality; frequently compounded by underlying chronic liver dysfunction	Late-stage diagnosis; limited sensitivity of conventional MRI/CT/ultrasound for early lesions	Hepatic clearance of nanocarriers; systemic toxicity of agents such as sorafenib	Iron oxide- and liposome-based imaging-guided drug delivery
Lung	Highest cancer-related mortality worldwide	Advanced-stage detection with CT/PET; lack of sensitive circulating biomarkers	Rapid therapeutic resistance; systemic toxicity of chemotherapy	Liquid-biopsy nanoparticles; inhalable theranostic nanocarriers
Pancreatic	Among the most lethal malignancies; typically diagnosed at an advanced stage	Dense desmoplastic stroma limits imaging resolution and safe biopsy access	Poor drug/imaging-agent penetration through the fibrotic tumor microenvironment	Stroma-modulating and radiosensitizing nanoplatforms
Breast	Most prevalent malignancy among women	Heterogeneous receptor expression (e.g., HER2) complicates targeted imaging	Treatment resistance; need for real-time monitoring of therapeutic response	HER2-targeted, dual-mode imaging (MRI/fluorescence, PET/CT) nanoplatforms
Brain (Glioblastoma and other tumors)	Most aggressive and treatment-resistant tumor type	Blood-brain barrier (BBB) restricts both imaging-agent delivery and biopsy access	Extremely limited drug delivery across the BBB; frequent recurrence	BBB-penetrating, ligand-functionalized theranostic nanoparticles

Traditional methods, including imaging (CT, MRI, and PET) and systemic chemotherapy or radiotherapy, have improved outcomes but remain limited by delayed diagnosis, non-

specificity, toxicity, and drug resistance. Early detection is often hindered by the lack of sensitive biomarkers, while conventional treatments are plagued by systemic side effects and poor targeting efficiency. Furthermore, invasive biopsies are not always feasible for tumors located in sensitive regions such as the brain.The convergence of nanotechnology and theranostics has opened a transformative pathway in oncology[8]. Nanotheranostics are multifunctional nanosystems that integrate diagnostic imaging and therapeutic modalities into a single platform. These nanosystems can:

- Enhance imaging sensitivity and specificity (MRI, PET, fluorescence, photoacoustic imaging).
- Deliver drugs in a targeted manner, reducing systemic toxicity.
- Provide combinatorial therapies (chemotherapy, photothermal therapy, photodynamic therapy, and immunotherapy).
- Enable real-time monitoring of treatment response.

This paradigm shift from one-size-fits-all therapies to precision-guided, image-assisted treatments positions nanotheranostics as a frontier in personalized cancer management.

While numerous reviews exist for organ-specific nanotheranostic applications, there is limited systematic integration across multiple cancer types[9]. (Figure 1) Given the distinct biological barriers such as the dense stroma in pancreatic tumors or the blood brain barrier (BBB) in glooms comparing organ-specific advances can shed light on both universal design principles and unique therapeutic challenges. Between 2020 and 2025, nanotheranostic research has accelerated, yielding novel multifunctional nanoplatforms, translational models, and early-stage clinical applications [10].

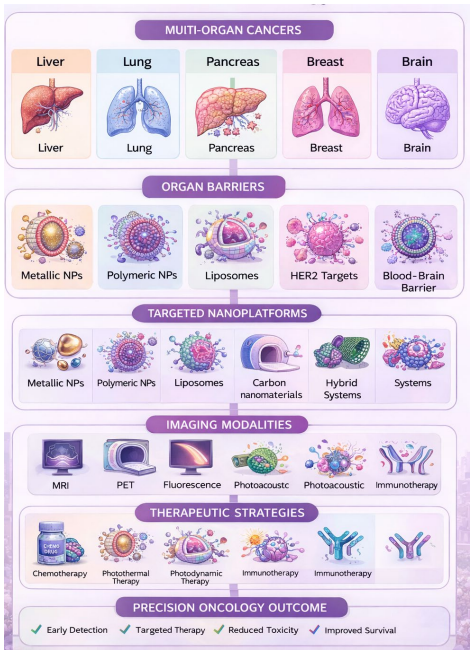

Figure 1. Organ-specific nanotheranostic strategies across major cancers. The schematic illustrates key biological barriers, nanoplatform types, imaging modalities, therapeutic

strategies, and pecision oncology outcomes associated with liver, lung, pancreatic, breast, and brain cancers.

2. Methodology

The data were collected from PubMed, Scopus and Web of Science relevant studies published between January 2020 and June 2025. We utilized keywords relevant to nanotheranostics, cancer and organ-specific cancers (liver, lung, pancreatic, breast and brain). The search was refined thanks to Boolean operators (AND, OR). Reference lists for selected papers were also checked. Only one peer-reviewed article published in English was included. We included studies that reported nanotheranostic systems with diagnostic and therapeutic components specific to liver, lung or pancreatic or breast or brain cancers. Laboratory and clinical studies were both included. Exclusion criteria included: reviews, editorials, conference abstracts and studies that did not specify combined diagnostic and therapeutic roles. Articles were excluded if they were not published in English, if their content reffered to another topic besides cancer or if the full text was unavailable. Methods: Two reviewers independently screened titles, abstracts and full texts. Relevant information like the cancer type, nanoplatform design, imaging mode, therapy type and study results were logged using a standardized format. Discrepancies between reviewers were discussed to arrive at a consensus. A summary of the collected data was created and grouped by type of cancer. Comparing nanoplatform designs, imaging modalities, therapeutic approaches and highlighting key findings allowed us to assess research trends and breakthroughs as well as current challenges in the field of nanotheranostics.

3. Nanotheranostic Platforms: An Overview

Nanotheranostics represent an innovative class of nano systems that integrate diagnostic imaging and therapeutic functions into a single platform [11]. The versatility of these systems arises from the diversity of nanomaterials available and the ability to functionalize them with targeting ligands, imaging agents, and therapeutic payloads. Broadly, nanotheranostics can be classified into metallic nanoparticles, polymeric and liposomal nanocarriers, carbon-based nanomaterials, and hybrid/multifunctional systems**.** Each category offers unique physicochemical properties that can be exploited for precise cancer imaging and therapy. The following sections summarize their roles and mechanisms of action[12].

3.1 Types of Nanomaterials

3.1.1 Metallic Nanoparticles

Metallic nanoparticles, including gold, iron oxide, and silver nanoparticles**,** are among the most extensively investigated platforms. Gold nanoparticles (AuNPs) exhibit strong surface plasmon resonance properties, enabling their use in photo thermal therapy (PTT) and photoacoustic

imaging. Their surface can be readily functionalized with drugs, antibodies, or nucleic acids, making them adaptable for targeted cancer therapy[13]**.** Iron oxide nanoparticles (IONPs) serve as excellent magnetic resonance imaging (MRI) contrast agents and can be guided to tumor sites using external magnetic fields, thereby enhancing localized drug delivery. Silver nanoparticles, though less explored clinically due to toxicity concerns, have demonstrated intrinsic cytotoxic and antimicrobial activities, and when engineered appropriately, they can function as potent theranostic agents[14].

3.1.2 Polymeric and Liposomal Nanocarriers

Polymeric nanoparticles and liposomes provide biocompatibility and controlled drug release profiles. Polymeric nanocarriers such as poly (lactic-co-glycolic acid) (PLGA) or dendrimers can encapsulate hydrophobic and hydrophilic drugs simultaneously, offering dual- or multi-drug loading capabilities. Liposomes, on the other hand, are well-established nanocarriers approved for clinical use (e.g., liposomal doxorubicin)[15]. Their flexible bilayer structure enables co-delivery of chemotherapeutics with imaging agents, creating imaging-guided drug delivery systems. Modifications with polyethylene glycol (PEG) and targeting ligands extend their circulation half-life and tumor-specific accumulation via the enhanced permeability and retention (EPR) effect [16]**.**

3.1.3 Carbon-Based Nanomaterials

Carbon-based nanostructures such as grapheme, carbon nanotubes (CNTs), and carbon dots offer high surface-to-volume ratios, excellent electronic conductivity, and tunable optical properties. Graphene oxide (GO) provides a versatile platform for loading multiple drugs and imaging probes, while its photothermal conversion efficiency makes it suitable for PTT[17]. Carbon nanotubes penetrate cell membranes efficiently, serving as carriers for drugs and genes, and can also act as radiofrequency absorbers for hyperthermia therapy. Carbon dots are small (<10 nm) and exhibit inherent fluorescence, which facilitates real-time bioimaging along with drug delivery[18].

3.1.4 Hybrid and Multifunctional Systems

Recent advances have led to the design of hybrid nanotheranostic platforms that integrate two or more functional components into a single construct. For example, gold-coated iron oxide nanoparticles combine MRI contrast with photothermal properties, while liposome metallic hybrid**s** enable simultaneous controlled drug release and imaging[18]. Multifunctional nanosystems are increasingly being engineered for stimuli-responsive behavior**,** releasing therapeutic agents in response to pH, enzymes, or external triggers (light, magnetic field, and ultrasound). **(**Table 2) Such hybrid platforms offer the potential for real-time monitoring of therapy outcomes, reducing off-target effects and improving treatment precision[19].

Table 2. Classification of nanotheranostic platforms by nanomaterial type, imaging modality, and therapeutic mechanism.

Platform Category	Representative Nanomaterials	Imaging Modality	Therapeutic Mechanism	Distinguishing Feature
Metallic Nanoparticles	Gold nanoparticles; iron oxide nanoparticles	MRI; photoacoustic and surface plasmon resonance-based optical imaging	Photothermal therapy (PTT); carrier for targeted drug delivery	Strong imaging contrast combined with efficient light-to-heat conversion
Polymeric and Liposomal Nanocarriers	PLGA nanoparticles; polymeric micelles; liposomes	Fluorescence; MRI when co-loaded with contrast agents	Encapsulated chemotherapeutic delivery (e.g., sorafenib, doxorubicin) with controlled/targeted release	High biocompatibility; readily surface-modified with targeting ligands/antibodies
Carbon-Based Nanomaterials	Carbon nanotubes; graphene oxide; carbon nanodots	Fluorescence; photoacoustic imaging	Photothermal therapy via near-infrared (NIR) light absorption	High cell-membrane penetration efficiency
Hybrid / Multifunctional Systems	Gold-coated iron oxide nanoparticles; liposome-metal hybrids; stimuli-responsive composites	Combined/multi-modal (MRI, PET, fluorescence, photoacoustic)	Stimuli-responsive drug release triggered by pH, enzymes, light, magnetic field, or ultrasound	Enables real-time monitoring of therapy outcome and reduced off-target effects

3.2 Mechanisms of Action

The efficacy of nanotheranostic systems lies in their ability to diagnose, deliver therapy, and monitor response simultaneously**.**

3.2.1 Imaging Applications

Nanotheranostic platforms enable a spectrum of therapeutic strategies:

- Chemotherapy Delivery**:** Nanocarriers enhance tumor accumulation and reduce systemic toxicity.
- Photothermal Therapy (PTT)**:** Gold nanoparticles and graphene convert light energy into heat, selectively ablating cancer cells.
- Photodynamic Therapy (PDT)**:** Nanoparticles deliver photosensitizers that, upon light activation, generate reactive oxygen species to kill tumor cells.
- Immunotherapy**:** Some nanosystems are engineered to deliver immune checkpoint inhibitors or stimulate dendritic cells, enhancing antitumor immunity[20-21].

This dual functionality imaging plus therapy provides clinicians with the ability to tailor interventions, monitor therapeutic responses in real time, and adjust treatment strategies accordingly.

4. Organ-Specific Applications

4.1 Liver Cancer (Hepatocellular Carcinoma)

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and ranks among the leading causes of cancer-related deaths worldwide. Its high mortality is largely attributed to late-stage diagnosis, underlying liver dysfunction, and limited therapeutic options [26]. Conventional diagnostic imaging modalities such as MRI, CT, and ultrasound provide valuable information but often lack the sensitivity to detect early-stage disease or monitor therapeutic responses accurately. Nanotheranostics have emerged as a promising approach to overcome these limitations by integrating sensitive diagnostic imaging with localized and effective therapeutic strategies[27].

4.1.1 Progress in Imaging-Guided Nanotheranostics

Recent years have witnessed significant progress in imaging-guided nanoplatforms for HCC. Iron oxide nanoparticles remain the cornerstone for MRI-based diagnosis, offering excellent contrast for liver lesions. Functionalization with targeting ligands such as glypican-3 (GPC3) antibodies or folate has further improved tumor selectivity [28]. In parallel, ultrasound-responsive nanoparticles have been engineered to act as both contrast agents and therapeutic carriers, enabling real-time imaging-guided interventions. Dual-modality systems that combine MRI with fluorescence or photoacoustic imaging have also been developed to enhance sensitivity and precision in tumor localization[29].

4.1.2 Targeted Drug Delivery

Nanotheranostics have advanced the targeted delivery of frontline chemotherapeutics such as sorafenib and doxorubicin. Sorafenib, the standard systemic therapy for advanced HCC, suffers from poor bioavailability and off-target toxicity. Nanocarriers such as liposomes, PLGA nanoparticles, and polymeric micelles have been designed to encapsulate sorafenib and deliver it preferentially to tumor tissue, significantly enhancing therapeutic efficacy while reducing systemic side effects[30]. Similarly, doxorubicin-loaded nanoparticles, often surface-modified with targeting moieties like transferrin or lactobionic acid, have demonstrated superior tumor penetration and retention. The combination of imaging agents with these nanocarriers enables clinicians to track drug distribution in real time, paving the way for precision medicine.

4.1.3 Photothermal and Photodynamic Advances

The integration of photothermal therapy (PTT) and photodynamic therapy (PDT) into nanotheranostic designs has provided new therapeutic options for HCC. Gold nanoparticles, graphene oxide nanosheets, and carbon nanodots have been employed as photothermal agents, capable of converting near-infrared (NIR) light into localized heat to ablate tumor cells. PDT has similarly benefited from nanoparticle carriers that deliver photosensitizers such as chlorin e6 or indocyanine green (ICG) directly to the tumor site [31]. Multifunctional platforms combining chemotherapy with PTT or PDT have shown synergistic effects, overcome drug resistance and improving overall survival in preclinical liver cancer models.

4.1.4 Clinical and Preclinical Updates

Preclinical research has expanded rapidly, with numerous animal studies demonstrating enhanced therapeutic efficacy and safety of nanotheranostic approaches in HCC. Notably, iron oxide and liposomal nanoparticles carrying sorafenib have entered early-phase clinical trials, highlighting their translational potential. (Table 3) Clinical evaluations of ICG-loaded nanoparticles for fluorescence-guided liver cancer surgery have also shown encouraging results, improving tumor resection accuracy [32]. Despite these advances, challenges remain in addressing hepatic clearance, potential toxicity, and variability in patient liver function. Nevertheless, the convergence of nanotechnology with molecular imaging and targeted therapy is poised to transform HCC management in the coming decade[33]. (Figure 4)

Table 3. Preclinical and clinical progress of nanotheranostic platforms in hepatocellular carcinoma (liver cancer).

Development Stage	Nanoplatform / Agent	Targeting Strategy	Imaging Modality	Therapeutic Application	Reported Outcome
Imaging-guided diagnosis	Iron oxide nanoparticles	GPC3 antibody or folate functionalization	MRI	Tumor localization	Improved detection sensitivity for liver lesions
Imaging-guided diagnosis	Ultrasound-responsive nanoparticles	—	Ultrasound	Combined contrast agent / therapeutic carrier	Enables real-time image-guided intervention
Dual-modality imaging	MRI-fluorescence / MRI-photoacoustic hybrid systems	—	MRI + fluorescence or photoacoustic	Tumor localization	Enhanced sensitivity and precision
Targeted drug delivery	Liposomes, PLGA nanoparticles, polymeric micelles	Tumor accumulation (passive/enhanced permeability)	—	Sorafenib delivery	Enhanced efficacy; reduced systemic toxicity
Targeted drug delivery	Doxorubicin-loaded nanoparticles	Transferrin or lactobionic acid surface modification	—	Doxorubicin delivery	Superior tumor penetration and retention
Photothermal / photodynamic therapy	Gold nanoparticles; graphene oxide nanosheets; carbon nanodots	NIR light responsiveness	—	Photothermal therapy (PTT)	Localized tumor ablation
Photothermal / photodynamic therapy	Nanoparticles loaded with chlorin e6 or indocyanine green (ICG)	—	Fluorescence (ICG)	Photodynamic therapy (PDT)	Synergistic effect with chemotherapy; overcame

Development Stage	Nanoplatform / Agent	Targeting Strategy	Imaging Modality	Therapeutic Application	Reported Outcome
					drug resistance
Early-phase clinical translation	Iron oxide and liposomal nanoparticles carrying sorafenib	—	MRI	Chemotherapy	Entered early-phase clinical trials
Clinical translation	ICG-loaded nanoparticles	—	Fluorescence-guided surgery	Surgical resection guidance	Improved tumor resection accuracy

4.2 Lung Cancer

Lung cancer remains the leading cause of cancer-related mortality globally, with poor survival outcomes due to late-stage diagnosis and therapeutic resistance. Nanotheranostics have gained momentum in addressing these challenges by enabling early detection, targeted delivery, and combined therapies tailored to the tumor microenvironment.

4.2.1 Nanoparticles for Early Diagnosis (Liquid Biopsy Integration)

Traditional imaging (CT/PET) often identifies lung cancer only at advanced stages. Nanoparticles functionalized with tumor-specific markers have been developed for liquid biopsy integration**,** enabling detection of circulating tumor DNA (ctDNA), exosomes, and circulating tumor cells (CTCs)[40]**.** For instance, gold nanoparticles conjugated with DNA probes allow highly sensitive fluorescence and surface plasmon resonance-based detection of early-stage lung cancer biomarkers. These platforms provide a minimally invasive, rapid, and sensitive diagnostic alternative.

4.2.2 Tumor Microenvironment-Targeted Delivery

The lung tumor microenvironment (TME) is characterized by hypoxia, acidic pH, and immunosuppressive cells. Nanotheranostics designed with pH-sensitive, hypoxia-responsive, and redox-sensitive coatings have shown remarkable efficacy in releasing drugs selectively within the TME. For example, polymeric nanoparticles carrying doxorubicin and imaging agents have achieved deeper tumor penetration, improved MRI contrast, and minimized systemic toxicity[41].

4.2.3 Combined Chemo-Immunotherapy Nanoplatforms

Recent studies have demonstrated the use of multifunctional nanoplatforms that combine chemotherapy with immune checkpoint inhibitors**.** Nanoparticles delivering cisplatin along with PD-L1 blocking antibodies have enhanced immune cell infiltration and tumor regression. Real-time monitoring of drug release using fluorescence or MRI further strengthens their therapeutic applicability[42].

4.2.4 Advances in Inhalable Theranostic Nanocarriers

A unique approach for lung cancer is inhalable nanotheranostics, which enable direct deposition into the lungs, maximizing drug concentration at the tumor site while minimizing systemic exposure (Table 4). Inhalable liposomes and polymeric nanoparticles loaded with paclitaxel, coupled with fluorescent probes, have been developed for imaging-guided therapy. These advances hold promise for non-invasive and patient-friendly treatment regimens [43]. (Figure 4)

Table 4. Organ-targeted and inhalable nanotheranostic strategies in lung cancer.

Strategy	Nanoplatform	Targeting / Trigger	Imaging Component	Therapeutic Payload	Translational Relevance
Liquid biopsy-based early diagnosis	Gold nanoparticles conjugated with DNA probes	Tumor-specific ctDNA, exosome, and CTC markers	Fluorescence; surface plasmon resonance	Diagnostic only	Minimally invasive, rapid, and sensitive early detection
Tumor microenvironment (TME)-targeted delivery	Polymeric nanoparticles	pH-sensitive, hypoxia-responsive, redox-sensitive coatings	MRI contrast	Doxorubicin	Deeper tumor penetration; minimized systemic toxicity
Combined chemo-immunotherapy	Nanoparticles co-delivering chemotherapy and checkpoint inhibitors	PD-L1 immune checkpoint blockade	Fluorescence or MRI	Cisplatin + anti-PD-L1 antibody	Enhanced immune cell infiltration and tumor regression
Inhalable theranostic nanocarriers	Inhalable liposomes and polymeric nanoparticles	Direct pulmonary deposition	Fluorescent probes	Paclitaxel	Maximizes local drug concentration while minimizing systemic exposure; non-invasive, patient-

Strategy	Nanoplatform	Targeting / Trigger	Imaging Component	Therapeutic Payload	Translational Relevance
					friendly regimen

4.3 Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies due to its dense stromal barrier, late diagnosis, and resistance to therapy**.** Nanotheranostics provide unique opportunities to overcome these hurdles.

4.3.1 Overcoming Stromal Barriers with Nanotheranostics

The pancreatic TME is highly fibrotic, limiting drug penetration. Smart nanoparticles engineered with stromal-disrupting agents (e.g., hyaluronidase-loaded nanocarriers) have improved the accumulation of chemotherapeutics and imaging agents within tumors. Iron oxide-based nanoparticles, functionalized with stroma-targeting peptides, have also been used to enhance MRI visualization of PDAC [49].

4.3.2 Synergistic Therapies (Chemo-Radiotherapy with Nanoparticles)

Combination strategies using nanoparticles as radiosensitizers have gained traction. Gold nanoparticles improve tumor response to radiotherapy while also acting as PTT agents. Polymeric nanocarriers encapsulating gemcitabine combined with imaging probes have shown synergistic effects with radiotherapy, leading to improved survival in animal models.

4.3.3 Imaging-Guided Nanoparticle Delivery for Deep-Seated Tumors

Given the anatomical challenges of the pancreas, nanoplatforms designed for dual-mode imaging (MRI + PET/CT) facilitate precise localization and guided delivery. For instance, manganese oxide nanoparticles loaded with chemotherapeutics provide strong MRI contrast and controlled drug release. These imaging-guided systems are crucial for ensuring accurate delivery to deep-seated tumors [50].

4.4 Breast Cancer

Breast cancer is the most frequently diagnosed cancer worldwide. Nanotheranostics have focused on HER2-targeted therapies, dual-mode imaging, and treatment monitoring**.**

4.4.1 HER2-Targeted Nanotheranostics

HER2-overexpressing breast cancers benefit from nanoparticles functionalized with trastuzumab or HER2 aptamers. These nanoplatforms co-deliver drugs such as doxorubicin or paclitaxel while enabling MRI or fluorescence imaging, enhancing therapeutic specificity.

4.4.2 Dual-Mode Imaging (MRI/Fluorescence, PET/CT)

Gold nanoparticles and liposomes labeled with radioactive isotopes enable PET/CT-based tracking of tumor burden. Dual-mode imaging (e.g., MRI with near-infrared fluorescence) allows real-time assessment of drug biodistribution and therapeutic response [51].

4.4.3 Nanoplatforms for Monitoring Treatment Response

Carbon dots and polymeric nanoparticles conjugated with pH- or enzyme-sensitive probes provide dynamic monitoring of treatment response, including tumor shrinkage and drug resistance. This feedback mechanism enables adaptive treatment strategies.

4.5 Brain Tumors (Glioblastoma and Others)

Glioblastoma multiforme (GBM) is the most aggressive brain tumor, characterized by poor prognosis due to blood brain barrier (BBB) restrictions and therapy resistance. Nanotheranostics aim to bridge these gaps.

4.5.1 Blood Brain Barrier (BBB) Penetration Strategies

Nanoparticles modified with transferrin, lactoferrin, or angiopeptide ligands have shown enhanced BBB penetration. Exosome-based nanocarriers have also emerged as natural BBB-crossing vehicles for theranostics [52].

4.5.2 Theranostic Nanoparticles for Glioblastoma

Iron oxide nanoparticles conjugated with glioma-targeting peptides allow MRI visualization and localized delivery of temozolomide. Multifunctional nanoplatforms integrating PET/CT with drug delivery have shown promising results in extending survival in animal models.

4.5.3 Imaging-Guided Photothermal and Gene Therapy Approaches

Gold nanoshells and carbon-based platforms have been employed for NIR-based PTT, achieving selective glioblastoma ablation. Additionally, nanoparticles carrying gene-editing tools (CRISPR-Cas9, siRNA) allow simultaneous imaging and correction of tumor-driving mutations.

4.5.4 Nanoparticle-Assisted Radiosensitization

Gold and hafnium oxide nanoparticles act as potent radiosensitizers, amplifying radiation damage in glioblastoma cells. Imaging integration ensures precise localization of nanoparticles within the tumor before therapy [53].

5. Comparative Analysis across Organs

Nanotheranostics are a seductive promise: one platform that can both find and finish a tumor. In reality, however, the utility of any particular nanotheranostic design is shaped more by the *organ* than by the nanoparticle itself. This section synthesizes common challenges encountered across organs, contrasts two extremes (liver vs. brain), and identifies trends in whether researchers pursue universal (one-size-fits-many) versus organ-specific designs [54]. The goal is to make explicit where shared engineering solutions exist and where bespoke, organ-aware approaches are unavoidable.

5.1 Common Challenges in Multi-Organ Nanotheranostic Applications

Across liver, lung, pancreas, breast, and brain cancers, researchers repeatedly encounter several technical and translational obstacles. First, biodistribution and off-target accumulation remain persistent problems: nanoparticles introduced intravenously face opsonization, rapid clearance by the mononuclear phagocyte system (MPS), and sequestration in liver and spleen, which

reduces tumor uptake and raises safety concerns. Second, heterogeneous tumor microenvironments (TME) differences in vascular permeability, interstitial pressure, pH, and immune cell composition undermine predictable nanoparticle penetration and payload release [55]. Third, safety and long-term toxicity (material persistence, immunogenicity, and organ-specific toxicity) slow clinical translation and raise regulatory hurdles. Fourth, scalability and reproducibility of complex multifunctional constructs (hybrids, multilayered coatings, and ligand arrays) are nontrivial for manufacturing under GMP. Lastly, imaging therapy co-optimization is challenging: optimizing for maximal imaging contrast may conflict with optimal drug loading, release kinetics, or biodegradation profiles. These recurring barriers demand cross-disciplinary solutions spanning materials chemistry, pharmacology, regulatory science, and clinical trial design [56].

5.2 Differences Liver versus Brain (Accessibility, Microenvironment, Barriers)

Contrasting liver and brain cancers highlights how organ biology dictates nanotheranostic strategy. Liver (HCC) is comparatively *accessible* to nanoparticles delivered systemically: the organ's fenestrated sinusoidal endothelium and high perfusion often favor hepatic accumulation, which explains why many nanoparticles end up in the liver regardless of targeting. This is a double-edged sword: it facilitates delivery to hepatic tumors but increases off-target hepatic exposure and complicates dosage [57]. The liver microenvironment is also influenced by chronic disease (fibrosis, cirrhosis), which alters vascular architecture and nanoparticle transport. Thus, liver-directed nanotheranostics often exploit passive targeting (EPR) plus active targeting (GPC3, ASGPR ligands) and focus on controlling hepatic clearance and hepatotoxicity [58].

Brain tumors (e.g., glioblastoma), by contrast, are defined by *inaccessibility* the blood brain barrier (BBB) and blood tumor barrier (BTB) severely restrict nanoparticle entry. Successful strategies require either transiently disrupting the BBB (focused ultrasound, hyperosmotic agents), active receptor-mediated transcytosis (transferrin, angiopep), or leveraging endogenous carriers (exosomes). The brain TME is also highly immunosuppressive and spatially heterogeneous, necessitating precise intratumoral dosing and careful toxicity profiling to avoid neurotoxicity. Consequently, brain nanotheranostics prioritize BBB-penetrating ligands, minimized systemic exposure, and highly biocompatible, often degradable materials [59]. In short: the liver asks "how do we avoid killing the liver while exploiting its permissiveness?" while the brain asks "how do we get anything in there at all safely and selectively?" Those two constraints push design decisions in opposite directions.

5.3 Trends in Multi-Organ Targeting: Universal vs. Organ-Specific Designs

Two broad trends have emerged in the literature: (1) pursuit of universal, modular platforms that are tunable across organs, and (2) development of organ-specific, bespoke systems optimized for the unique biophysics and biology of a target site.Universal/modular platforms emphasize a common core (e.g., iron-oxide or polymeric core) with plug-and-play modules for imaging labels, targeting ligands, and therapeutic payloads. The attraction: simplified manufacturing pipelines, standardized safety profiles, and the ability to tailor modules to

different cancers without redesigning the entire nanoparticle [60]. These are particularly popular for diagnostic imaging agents (e.g., IONP cores used for MRI across liver, breast, and brain studies) and for immunomodulatory cargos that act systemically.Organ-specific systems, however, dominate where biological barriers are extreme (brain, pancreas) or where local delivery routes exist (inhalation for lung). These designs incorporate organ-aware features: enzyme-cleavable coatings for pancreatic stroma, mucus-penetrating and inhalable aerosols for lung tumors, hepatic-targeting ligands for HCC, and BBB-transcytosis ligands for brain tumors. Evidence increasingly supports that organ-specific tailoring yields superior target engagement and therapeutic indices for difficult sites, even if at higher development cost [61].A pragmatic strategy in the field is *hybridization*: start from a validated universal scaffold (for GMP/scale advantages) and add organ-specific modules to overcome local barriers. This balances translational feasibility with biological necessity.

5.4 Translational Implications and Clinical Priorities

Translational success will hinge on reconciling biological complexity with regulatory and manufacturing realities. For organs where passive accumulation is favorable (e.g., liver, breast), focus should be on safety optimization, predictable pharmacokinetics, and imaging biomarkers that demonstrate target engagement [62]. For organs with severe access barriers (brain, pancreas), early investment in robust preclinical models that mimic human barriers (orthotopic and large-animal models) and in translational delivery technologies (focused ultrasound, localized infusion, inhalation devices) is From a clinical-trial design perspective, imaging endpoints (real-time biodistribution, target saturation) can be used as early proof-of-concept biomarkers to de-risk therapeutics, enabling smaller, better-informed Phase I/II studies. Also, harmonizing characterization assays (size, charge, ligand density, release kinetics) across labs will accelerate regulatory dialogue [63].

6. Translational and Clinical Advances

6.1 Preclinical → Clinical Pipeline Updates

The past five years have seen a few nanotheranostic platforms progress from robust preclinical evidence into clinical testing, notably radiosensitizing nanoparticles and small multifunctional imaging therapy constructs. The hafnium-oxide nanoparticle NBTXR3 (radioenhancer) completed pivotal clinical studies in soft-tissue sarcoma and has multiple ongoing trials testing its activity with external beam radiation across different solid tumors, illustrating a clear preclinical-to-clinic trajectory for radiation-activated nanomaterials. Another high-profile example is AGuIX®, a gadolinium-based, ultrasmall nanoparticle designed to act as an MRI-visible radiosensitizer. AGuIX has progressed through phase 1/1b studies in brain tumors and brain metastases with encouraging safety and biodistribution data and is advancing into randomized phase-2 testing for glioblastoma and malignant gliomas it even received FDA fast-track designation in 2024 [65]. These moves exemplify how a clear mechanism (radiosensitization) + imaging readout (MRI) can fast-track translation.Beyond radiosensitizers, liposomal and polymeric nanocarriers with combined imaging labels and drugs continue to populate late preclinical pipelines; however, comparatively few

multifunctional theranostics have yet reached large multi-center Phase II/III trials. Recent reviews and meta-analyses note steady growth in preclinical sophistication (multimodal imaging, stimuli-responsive release, immune-modulating cargos) but a modest conversion rate to late-phase clinical testing [66].

6.2 Ongoing Clinical Trials Involving Nanotheranostics

Clinical trial registries and published phase I/II reports demonstrate an active, if selective, clinical agenda:

- NBTXR3 (hafnium oxide): Multiple trials (phase I III) across sarcoma, head and neck, lung and other solid tumors are testing intratumoral or intralesional NBTXR3 with radiotherapy; NBTXR3's randomized phase II/III soft-tissue sarcoma trial established proof-of-concept and has catalyzed broader testing in oncology.
- AGuIX (gadolinium nanoparticles): Phase 1b results in glioblastoma and brain metastases report broad intratumoral dispersion with no major AGuIX-related toxicity; larger randomized trials are ongoing and the agent has received FDA fast-track status for malignant gliomas.
- Additional small, early-phase studies are examining nanoparticle-enabled fluorescence agents for intraoperative guidance and inhalable nanoparticle formulations for lung cancer; however, many of these remain at pilot/Phase I stages. (See clinicaltrials.gov listings and recent trial reports [67].

6.3 Regulatory Hurdles and Safety Concerns

Regulatory agencies (FDA, EMA) have published guidance and horizon-scanning reports recognizing both the promise and the complexity of nanomedicines. regulatory challenges for nanotheranostics include heterogeneity of products, complex characterization requirements (size, surface chemistry, ligand density, batch-to-batch reproducibility), interdependence of imaging and therapeutic functions, and the need for robust nonclinical models that predict human biodistribution and long-term fate. The EMA's horizon-scanning and recent reviews emphasize the need for early engagement with regulators, standardized characterization assays, and clarity on safety end-points for nanoparticle persistence and immunotoxicity. Safety concerns remain front-and-center. Although several trials (for example, AGuIX phase 1b) reported no major nanoparticle-related toxicity at recommended doses and acceptable biodistribution, long-term retention (especially for non-biodegradable inorganic cores), potential for immunogenicity, and organ-specific toxicity (hepatic/splenic accumulation) are recurring issues that regulators scrutinize. Thorough pharmacokinetic, toxicokinetic and accumulation/clearance data are typically required before advancing to larger trials [68].

6.4 Cost-Effectiveness and Scalability Issues

From a practical, clinical-adoption perspective, two interlinked obstacles slow wider uptake: manufacturing scalability and cost-effectiveness. Multifunctional nanotheranostics often require multi-step, tightly controlled syntheses (core fabrication, surface functionalization, sterile fill/finish) that are difficult to scale under GMP without altering critical quality attributes. Reviews and industry analyses highlight that standardized, modular scaffolds

(platform cores that can be functionalized in downstream steps) are more likely to cross the "valley of death." Moreover, economic evaluations are scarce: while some nanomedicines (e.g., liposomal doxorubicin, nab-paclitaxel) have demonstrated cost-justified clinical benefits, the added complexity of theranostic agents (imaging+therapy) requires demonstration of not only clinical efficacy but also clear cost savings or value (for example, reduced re-operations, better patient selection for expensive therapies, or shorter hospital stays). Regulatory and reimbursement pathways remain immature for complex theranostic products, so developers must plan for health-economic evidence generation early [69].

7. Future Perspectives

The field of nanotheranostics has matured beyond proof-of-concept skeins of pretty TEM images; over the next decade it must deliver robustness, personalization, and responsible translation. Below I describe four converging directions likely to shape the landscape smart/stimuli-responsive systems, AI/ML integration, personalized nanomedicine, and ethical/societal concerns and close with pragmatic recommendations for researchers, funders, and regulators [70].

7.1 Smart and Stimuli-Responsive Nanotheranostics

The next generation of theranostic platforms will be *reactive* rather than passive. Stimuli-responsive systems tuned to endogenous cues (pH, redox potential, enzymatic activity, hypoxia) or exogenous triggers (light, ultrasound, magnetic fields) allow "on-demand" drug release and spatiotemporal control of therapy while minimizing off-target toxicity. Examples include pH-sheddable PEG coatings that expose targeting ligands in acidic TMEs, hypoxia-activated prodrug carriers, and magneto- or photo-responsive cores that combine localized heating with imaging readouts. Greater emphasis will be placed on modular chemistries that allow predictable, quantifiable response kinetics (release half-lives, trigger thresholds) and robust characterization under clinically relevant conditions (human plasma, diseased tissue explants). Engineering goals: high signal-to-noise in the diagnostic channel, a narrow trigger window to avoid premature activation, and reproducible manufacturing of responsive motifs [71].

technical priorities: develop standardized assays for trigger sensitivity; ensure stimuli are clinically deliverable (e.g., NIR light penetration, safe focused ultrasound parameters); and build biodegradable responsive linkers that leave minimal toxic residues.

7.2 AI and Machine Learning Integration for Imaging + Therapy Optimization

Artificial intelligence will move from novelty to necessity in nanotheranostics. Machine learning (ML) can accelerate everything from nanoparticle design (predicting biodistribution from physicochemical features) to image analysis (automated segmentation, quantifying intratumoral nanoparticle accumulation) and treatment optimization (adaptive dose timing based on intra-session imaging). Closed-loop systems that use real-time imaging data to update therapy parameters (laser power, drug release timing, and radiation dose) could dramatically increase therapeutic indices [72]. Digital twins computational patient models incorporating imaging, genomics, and nanoparticle PK/PD will enable in silico testing of nanotheranostic

regimens before patient exposure.Implementation needs: large, curated multimodal datasets (imaging + histopathology + PK) to train models; interpretability for clinical trust; and regulatory-acceptable validation pipelines for AI-driven medical devices. Also: guardrails against overfitting to animal-model data that do not translate to human physiology.

7.3 Personalized Nanotheranostics (Genomics + Nanomedicine)

This is the area in which nanotheranostics can truly be much more effective: personalization. An additional synergy would be to combine tumor genomics and single-cell profiling with either nanoparticle selection or functionalization to facilitate the matchmaking between a patient's molecular vulnerabilities ((personalized medicine and theranostics) and a spectrum of nanoplatform capabilities. Examples include the preferential delivery of ligand-functionalized carriers or hypoxia-activated prodrugs to tumors with defined surface-markers and/or associated microenvironmental signatures. For instance, adaptive designs may utilize patient-specific neoantigen peptides that mimic non-communicable infectious viruses for local vaccine-like immune priming in conjunction with imaging markers clearly demonstrating intratumoral targeting. Liquid biopsies will also be used in the context of personalized theranostics both to monitor minimal residual disease and to guide re-dosing decisions[73]. Barriers Addressed: logistics of just-in-time manufacturing, regulatory pathways for N-of-1 nano-products and stringent companion diagnostics to make sure the right nanoparticle hits the right tumor.

7.4 Ethical, Safety, and Societal Implications

With great nano-power comes great responsibility. Ethical and societal issues around nanotheranostics include equitable access (these are likely expensive initially), informed consent for multi-functional agents whose long-term biodisposition may be uncertain, and data privacy for AI models trained on sensitive imaging/genomic data. Safety concerns are not just toxicological; they include environmental fate of nanomaterials (manufacturing waste, excreted nanoparticles), potential for off-target immune modulation, and consequences of false-positive imaging leading to overtreatment. Public trust will hinge on transparent reporting of both benefits and adverse outcomes, long-term registries tracking patient outcomes and nanoparticle fate, and community engagement in study design for diverse populations. Regulatory-ethical recommendations: require environmental impact assessments, mandate long-term surveillance plans for persistent materials, and create clear frameworks for compassionate or experimental use of personalized nano-therapies [74].

8. Conclusion

Nanotheranostics represent one of the most revolutionary frontiers in oncology by providing a single platform that integrates early, sensitive and specific diagnosis with targeted, multimodal therapy. Advances in liver, lung, pancreatic, breast and brain cancers over five years have demonstrated the potential but complexity of these nanosystems. We contrast universal design principles of modular nanocarriers with multifunctional imaging–therapy integration against organ-specific challenges such as the blood–brain barrier in glioblastoma or the stromal barrier in pancreatic cancer. There is strong preclinical evidence, but translation into clinical practice

is more prudent; only a small number of nanotheranostics (i.e. NBTXR3, AGuIX) have reached late-stage trials. One of the hurdles is long-term safety, manufacturability, regulatory ambiguity and cost-effectiveness. However, timely advancement within the discipline via stimuli-responsive designs, AI-driven optimization and personalized nanomedicine promises a near future for image-guided, patient-specific cancer treatment to enter routine clinical care. Simply put, nanotheranostics are transitioning from bench to bedside but success will rely on utilizing synergistic interdisciplinary efforts, a uniform standard of assessment and ethical governance. If these challenges can be overcome, then this may herald the transition of nanotheranostics from a novel experimental field into a key pillar of precision oncology during the next decade.

9. References

1. Akhtar, M., Haider, A., Rashid, S., & Al-Nabet, A. (2019). Paget's "seed and soil" theory of cancer metastasis: An idea whose time has come. *Advances in Anatomic Pathology, 26*(1), 69–74. https://doi.org/10.1097/PAP.0000000000000229
2. Anani, T., Rahmati, S., Sultana, N., & David, A. E. (2021). MRI-traceable theranostic nanoparticles for targeted cancer treatment. *Theranostics, 11*(2), 579–601. https://doi.org/10.7150/thno.51718
3. Ban, J., Fock, V., Aryee, D. N. T., & Kovar, H. (2021). Mechanisms, diagnosis and treatment of bone metastases. *Cells, 10*(11), 2944. https://doi.org/10.3390/cells10112944
4. 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
5. Björnmalm, M., Thurecht, K. J., Michael, M., Scott, A. M., & Caruso, F. (2017). Bridging bio-nano science and cancer nanomedicine. *ACS Nano, 11*(10), 9594–9613. https://doi.org/10.1021/acsnano.7b04855
6. Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 74*(3), 229–263. https://doi.org/10.3322/caac.21834
7. Celin, M. R., Simon, J. C., Krzak, J. J., Fial, A. V., Kruger, K. M., Smith, P. A., & Harris, G. F. (2020). Do bisphosphonates alleviate pain in children? A systematic review. *Current Osteoporosis Reports, 18*(5), 486–504. https://doi.org/10.1007/s11914-020-00617-x
8. Chen, H., Wang, D., Yao, Y., Xiao, Y., Zhao, Z., Zhang, Z., Liu, S., Wang, X., Yang, S., Huang, P., & Huang, Z. (2024). Leukemia cell hitchhiking hypoxia responsive nanogel for improved immunotherapy of acute myeloid leukemia. *Advanced Functional Materials.* Advance online publication. https://doi.org/10.1002/adfm.202407890

9. Chen, J. H., Huang, W. C., Bamodu, O. A., Chang, P. M., Chao, T. Y., & Huang, T. H. (2019). Monospecific antibody targeting of CDH11 inhibits epithelial-to-mesenchymal transition and represses cancer stem cell-like phenotype by up-regulating miR-335 in metastatic breast cancer, in vitro and in vivo. *BMC Cancer, 19*, 634. https://doi.org/10.1186/s12885-019-5835-y
10. Chen, Q., Liang, C., Wang, X., He, J., Li, Y., & Liu, Z. (2014). An albumin-based theranostic nano-agent for dual-modal imaging guided photothermal therapy to inhibit lymphatic metastasis of cancer post-surgery. *Biomaterials, 35*(34), 9355–9362. https://doi.org/10.1016/j.biomaterials.2014.07.051
11. Craciun, I., Gunkel-Grabole, G., Belluati, A., Palivan, C. G., & Meier, W. (2017). Expanding the potential of MRI contrast agents through multifunctional polymeric nanocarriers. *Nanomedicine, 12*(7), 811–827. https://doi.org/10.2217/nnm-2016-0371
12. Du, Y., Liang, X., Li, Y., Sun, T., Xue, H., Jin, Z., & Tian, J. (2018). Liposomal nanohybrid cerasomes targeted to PD-L1 enable dual-modality imaging and improve antitumor treatments. *Cancer Letters, 414*, 230–238. https://doi.org/10.1016/j.canlet.2017.11.032
13. Estelrich, J., Sánchez-Martín, M. J., & Busquets, M. A. (2015). Nanoparticles in magnetic resonance imaging: From simple to dual contrast agents. *International Journal of Nanomedicine, 10*, 1727–1741. https://doi.org/10.2147/IJN.S76501
14. Gerratana, L., Fanotto, V., Bonotto, M., Bolzonello, S., Minisini, A. M., Fasola, G., & Puglisi, F. (2015). Pattern of metastasis and outcome in patients with breast cancer. *Clinical & Experimental Metastasis, 32*(2), 125–133. https://doi.org/10.1007/s10585-015-9697-2
15. Hofbauer, L. C., Bozec, A., Rauner, M., Jakob, F., Perner, S., & Pantel, K. (2021). Novel approaches to target the microenvironment of bone metastasis. *Nature Reviews Clinical Oncology, 18*(8), 488–505. https://doi.org/10.1038/s41571-021-00498-0
16. Ibrahim, A., Scher, N., Williams, G., Sridhara, R., Li, N., Chen, G., Leighton, J., Booth, B., Gobburu, J. V., Rahman, A., & Pazdur, R. (2003). Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. *Clinical Cancer Research, 9*(7), 2394–2399.
17. Jeon, M., Halbert, M. V., Stephen, Z. R., & Zhang, M. (2021). Iron oxide nanoparticles as T1 contrast agents for magnetic resonance imaging: Fundamentals, challenges, applications, and prospectives. *Advanced Materials, 33*(10), 1906539. https://doi.org/10.1002/adma.201906539
18. Kim, J., Lee, N., & Hyeon, T. (2017). Recent development of nanoparticles for molecular imaging. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 375*(2107), 20170022. https://doi.org/10.1098/rsta.2017.0022
19. Kievit, F. M., Stephen, Z. R., Veiseh, O., Arami, H., Wang, T., Lai, V. P., Park, J. O., Ellenbogen, R. G., Disis, M. L., & Zhang, M. (2012). Targeting of primary breast

cancers and metastases in a transgenic mouse model using rationally designed multifunctional SPIONs. *ACS Nano, 6*(3), 2591–2601. https://doi.org/10.1021/nn204873h

20. Khan, A. U., Khan, M., Cho, M. H., & Khan, M. M. (2020). Selected nanotechnologies and nanostructures for drug delivery, nanomedicine and cure. *Bioprocess and Biosystems Engineering, 43*(8), 1339–1357. https://doi.org/10.1007/s00449-020-02338-y
21. Li, J., Ge, Z., Toh, K., Liu, X., Dirisala, A., Ke, W., Wen, P., Zhou, H., Wang, Z., Xiao, S., … & Chen, Y. (2021). Enzymatically transformable polymersome-based nanotherapeutics to eliminate minimal relapsable cancer. *Advanced Materials, 33*, e2105254. https://doi.org/10.1002/adma.202105254
22. Li, J., Kataoka, K. (2021). Chemo-physical strategies to advance the in vivo functionality of targeted nanomedicine: The next generation. *Journal of the American Chemical Society, 143*(2), 538–559. https://doi.org/10.1021/jacs.0c10559
23. Liu, Y., Huo, Y., Yao, L., Xu, Y., Meng, F., Li, H., Sun, K., Zhou, G., Kohane, D. S., & Tao, K. (2019). Transcytosis of nanomedicine for tumor penetration. *Nano Letters, 19*(11), 8010–8020. https://doi.org/10.1021/acs.nanolett.9b02816
24. Liu, X., Zheng, Y., Wang, Q., Zhao, L., Zhang, Z., Wang, H., Yang, Y., Song, N., Xiang, J., Shen, Y., & Chen, J. (2023). Artificially reprogrammed stem cells deliver transcytosable nanocomplexes for improved spinal cord repair. *Journal of Controlled Release, 364*, 601–617. https://doi.org/10.1016/j.jconrel.2023.03.035
25. Lim, E. K., Kim, H. O., Jang, E., Park, J., Lee, K., Suh, J. S., Huh, Y. M., & Haam, S. (2011). Hyaluronan-modified magnetic nanoclusters for detection of CD44-overexpressing breast cancer by MR imaging. *Biomaterials, 32*(32), 7941–7950. https://doi.org/10.1016/j.biomaterials.2011.07.014
26. Lu, Z., Zou, J., Li, S., Topper, M. J., Tao, Y., Zhang, H., Jiao, X., Xie, W., Kong, X., Vaz, M., & Zhang, Y. (2020). Epigenetic therapy inhibits metastases by disrupting premetastatic niches. *Nature, 579*(7800), 284–290. https://doi.org/10.1038/s41586-020-2080-2
27. Mosafer, J., Abnous, K., Tafaghodi, M., Mokhtarzadeh, A., & Ramezani, M. (2017). In vitro and in vivo evaluation of anti-nucleolin-targeted magnetic PLGA nanoparticles loaded with doxorubicin as a theranostic agent for enhanced targeted cancer imaging and therapy. *European Journal of Pharmaceutics and Biopharmaceutics, 113*, 60–74. https://doi.org/10.1016/j.ejpb.2017.03.008
28. Mostov, K. E., & Simister, N. E. (1985). Transcytosis. *Cell, 43*(3), 389–390. https://doi.org/10.1016/0092-8674(85)90139-2
29. Mu, C. F., Shen, J., Liang, J., Zheng, H. S., Xiong, Y., Wei, Y. H., & Li, F. (2018). Targeted drug delivery for tumor therapy inside the bone marrow. *Biomaterials, 155*, 191–202. https://doi.org/10.1016/j.biomaterials.2017.11.029

30. Mu, Q., Wang, H., & Zhang, M. (2017). Nanoparticles for imaging and treatment of metastatic breast cancer. *Expert Opinion on Drug Delivery, 14*(2), 123–136. https://doi.org/10.1080/17425247.2016.1230052
31. Paolillo, M., & Schinelli, S. (2019). Extracellular matrix alterations in metastatic processes. *International Journal of Molecular Sciences, 20*(20), 4947. https://doi.org/10.3390/ijms20204947
32. Park, S. H., Keller, E. T., & Shiozawa, Y. (2018). Bone marrow microenvironment as a regulator and therapeutic target for prostate cancer bone metastasis. *Calcified Tissue International, 102*(2), 152–162. https://doi.org/10.1007/s00223-017-0367-0
33. Patel, S., Kim, J., Herrera, M., Mukherjee, A., Kabanov, A. V., & Sahay, G. (2019). Brief update on endocytosis of nanomedicines. *Advanced Drug Delivery Reviews, 144*, 90–111. https://doi.org/10.1016/j.addr.2019.10.005
34. Peinado, H., Zhang, H., Matei, I. R., Costa-Silva, B., Hoshino, A., Rodrigues, G., Psaila, B., Kaplan, R. N., Bromberg, J. F., Kang, Y., … & Lyden, D. (2017). Pre-metastatic niches: Organ-specific homes for metastases. *Nature Reviews Cancer, 17*(5), 302–317. https://doi.org/10.1038/nrc.2017.6
35. Peiris, P. M., Deb, P., Doolittle, E., Doron, G., Goldberg, A., Govender, P., Shah, S., Rao, S., Carbone, S., Cotey, T., … & Zuckerman, D. (2015). Vascular targeting of a gold nanoparticle to breast cancer metastasis. *Journal of Pharmaceutical Sciences, 104*(8), 2600–2610. https://doi.org/10.1002/jps.24435
36. Rizvi, S. A. A., & Saleh, A. M. (2018). Applications of nanoparticle systems in drug delivery technology. *Saudi Pharmaceutical Journal, 26*(1), 64–70. https://doi.org/10.1016/j.jsps.2017.09.005
37. Salerno, M., Cenni, E., Fotia, C., Avnet, S., Granchi, D., Castelli, F., Micieli, D., Pignatello, R., Capulli, M., Rucci, N., … & Baldini, N. (2010). Bone-targeted doxorubicin-loaded nanoparticles as a tool for the treatment of skeletal metastases. *Current Cancer Drug Targets, 10*(6), 649–659. https://doi.org/10.2174/156800910793190090
38. Satriyo, P. B., Bamodu, O. A., Chen, J. H., Aryandono, T., Haryana, S. M., Yeh, C. T., Chao, T. Y., … & Fang, T. H. (2019). Cadherin 11 inhibition downregulates β-catenin, deactivates the canonical WNT signalling pathway and suppresses the cancer stem cell–like phenotype of triple negative breast cancer. *Journal of Clinical Medicine, 8*(1), 148. https://doi.org/10.3390/jcm8010148
39. Sheth, V., Wang, L., Bhattacharya, R., Mukherjee, P., & Wilhelm, S. (2021). Strategies for delivering nanoparticles across tumor blood vessels. *Advanced Functional Materials, 31*(21), 2007363. https://doi.org/10.1002/adfm.202007363
40. Shi, Y., van der Meel, R., Chen, X., & Lammers, T. (2020). The EPR effect and beyond: Strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. *Theranostics, 10*(17), 7921–7924. https://doi.org/10.7150/thno.48114

41. Shao, H., & Varamini, P. (2022). Breast cancer bone metastasis: A narrative review of emerging targeted drug delivery systems. *Cells, 11*(3), 388. https://doi.org/10.3390/cells11030388
42. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209–249. https://doi.org/10.3322/caac.21660
43. Tao, J., Diao, L., Chen, F., Shen, A., Wang, S., Jin, H., Cai, D., & Hu, Y. (2021). pH-sensitive nanoparticles codelivering docetaxel and dihydroartemisinin effectively treat breast cancer by enhancing reactive oxidative species-mediated mitochondrial apoptosis. *Molecular Pharmaceutics, 18*(1), 74–86. https://doi.org/10.1021/acs.molpharmaceut.0c00887
44. Tuma, P., & Hubbard, A. L. (2003). Transcytosis: Crossing cellular barriers. *Physiological Reviews, 83*(3), 871–932. https://doi.org/10.1152/physrev.00029.2002
45. Tu, Q., Zhang, J., Fix, A., Brewer, E., Li, Y. P., Zhang, Z. Y., & Chen, J. (2009). Targeted overexpression of BSP in osteoclasts promotes bone metastasis of breast cancer cells. *Journal of Cellular Physiology, 218*(1), 135–145. https://doi.org/10.1002/jcp.21539
46. Vega, F., Medeiros, L. J., Lang, W. H., Mansoor, A., Bueso-Ramos, C., & Jones, D. (2002). The stromal composition of malignant lymphoid aggregates in bone marrow: Variations in architecture and phenotype in different B-cell tumours. *British Journal of Haematology, 117*(3), 569–576. https://doi.org/10.1046/j.1365-2141.2002.03566.x
47. Vijayaraghavalu, S., Gao, Y., Rahman, M. T., Rozic, R., Sharifi, N., Midura, R. J., & Labhasetwar, V. (2020). Synergistic combination treatment to break cross talk between cancer cells and bone cells to inhibit progression of bone metastasis. *Biomaterials, 227*, 119558. https://doi.org/10.1016/j.biomaterials.2019.119558
48. Waks, A. G., & Winer, E. P. (2019). Breast cancer treatment: A review. *JAMA, 321*(3), 288–300. https://doi.org/10.1001/jama.2018.19323
49. Wang, B., Hu, S., Teng, Y., Chen, J., Wang, H., Xu, Y., Wang, K., Xu, J., Cheng, Y., & Gao, X. (2024). Current advance of nanotechnology in diagnosis and treatment for malignant tumors. *Signal Transduction and Targeted Therapy, 9*, 200. https://doi.org/10.1038/s41392-024-00462-7
50. Wang, G., Gao, W., Zhang, X., & Mei, X. (2016). Au nanocage functionalized with ultra-small Fe_3O_4 nanoparticles for targeting T1-T2 dual MRI and CT imaging of tumor. *Scientific Reports, 6*, 28258. https://doi.org/10.1038/srep28258
51. Wang, L., Zhao, C., Lu, L., Jiang, H., Wang, F., & Zhang, X. (2023). Transcytosable peptide-paclitaxel prodrug nanoparticle for targeted treatment of triple-negative breast cancer. *International Journal of Molecular Sciences, 24*(6), 4646. https://doi.org/10.3390/ijms24064646

52. Wang, Y., Jia, J., Wang, F., Fang, Y., Yang, Y., Zhou, Q., Yuan, W., Gu, X., Hu, J., & Yang, S. (2024). Pre-metastatic niche: Formation, characteristics and therapeutic implication. *Signal Transduction and Targeted Therapy, 9*, 236. https://doi.org/10.1038/s41392-024-01221-w
53. Yip, R. K. H., Rimes, J. S., Capaldo, B. D., Vaillant, F., Mouchemore, K. A., Pal, B., Chen, Y., Surgenor, E., Murphy, A. J., Anderson, R. L., … & Snowden, S. (2021). Mammary tumour cells remodel the bone marrow vascular microenvironment to support metastasis. *Nature Communications, 12*, 6920. https://doi.org/10.1038/s41467-021-27216-9
54. Zhang, Z., Wang, T., Yang, R., Fu, S., Guan, L., Hou, T., Mu, W., Pang, X., Liang, S., & Liu, Y. (2020). Small Morph nanoparticles for deep tumor penetration via caveolae-mediated transcytosis. *ACS Applied Materials & Interfaces, 12*(35), 38499–38511. https://doi.org/10.1021/acsami.0c10624
55. Chen, Q., Liang, C., Wang, C., & Liu, Z. (2015). An imagable and photothermal "Abraxane-like" nanodrug for combination cancer therapy to treat subcutaneous and metastatic breast tumors. *Advanced Materials, 27*(5), 903–910. https://doi.org/10.1002/adma.201404824
56. Zheng, X. C., Ren, W., Zhang, S., Zhong, T., Duan, X. C., Yin, Y. F., Xu, M. Q., Hao, Y. L., Li, Z. T., Li, H., … & Li, H. (2018). The theranostic efficiency of tumor-specific, pH-responsive, peptide-modified, liposome-containing paclitaxel and superparamagnetic iron oxide nanoparticles. *International Journal of Nanomedicine, 13*, 1495–1504. https://doi.org/10.2147/IJN.S155627
57. Zhang, X., Li, D., Wang, W., Zheng, X., Zhang, C., Jin, Y., Meng, S., Li, J., Dai, R., Kang, W., … & Li, J. (2024). A novel NIR-II FL/PA imaging-guided synergistic photothermal-immune therapy: Biomineralizing nanosystems integrated with anti-tumor and bone repair. *Materials Today Bio, 26*, 101052. https://doi.org/10.1016/j.mtbio.2023.101052
58. Bose, R. J. C., Uday Kumar, S., Zeng, Y., Afjei, R., Robinson, E., Lau, K., Bermudez, A., Habte, F., Pitteri, S. J., Sinclair, R., … & Sinclair, R. (2018). Tumor cell-derived extracellular vesicle-coated nanocarriers: An efficient theranostic platform for the cancer-specific delivery of anti-miR-21 and imaging agents. *ACS Nano, 12*(11), 10817–10832. https://doi.org/10.1021/acsnano.8b04848
59. Pourtau, L., Oliveira, H., Thevenot, J., Wan, Y., Brisson, A. R., Sandre, O., Miraux, S., Thiaudiere, E., & Lecommandoux, S. (2013). Antibody-functionalized magnetic polymersomes: In vivo targeting and imaging of bone metastases using high-resolution MRI. *Advanced Healthcare Materials, 2*(11), 1420–1424. https://doi.org/10.1002/adhm.201300127
60. Qiao, H., Cui, Z., Yang, S., Ji, D., Wang, Y., Yang, Y., Han, X., Fan, Q., Qin, A., Wang, T., … & Wang, T. (2017). Targeting osteocytes to attenuate early breast cancer bone

metastasis by theranostic upconversion nanoparticles with responsive plumbagin release. *ACS Nano, 11*(7), 7259–7273. https://doi.org/10.1021/acsnano.7b02023

61. Zhang, Y., Wang, Y., Zhu, A., Yu, N., Xia, J., & Li, J. (2024). Dual-targeting biomimetic semiconducting polymer nanocomposites for amplified theranostics of bone metastasis. *Angewandte Chemie International Edition, 63*(5), e202310252. https://doi.org/10.1002/anie.202310252
62. Ross, M. H., Esser, A. K., Fox, G. C., Schmieder, A. H., Yang, X., Hu, G., Pan, D., Su, X., Xu, Y., Novack, D. V., … & Novack, D. V. (2017). Bone-induced expression of integrin β3 enables targeted nanotherapy of breast cancer metastases. *Cancer Research, 77*(22), 6299–6312. https://doi.org/10.1158/0008-5472.CAN-17-0706
63. Fox, G. C., Su, X., Davis, J. L., Xu, Y., Kwakwa, K. A., Ross, M. H., Fontana, F., Xiang, J., Esser, A. K., Cordell, E., … & Novack, D. V. (2021). Targeted therapy to β3 integrin reduces chemoresistance in breast cancer bone metastases. *Molecular Cancer Therapeutics, 20*(6), 1183–1198. https://doi.org/10.1158/1535-7163.MCT-20-1095
64. Thamake, S. I., Raut, S. L., Gryczynski, Z., Ranjan, A. P., & Vishwanatha, J. K. (2012). Alendronate-coated poly(lactic-co-glycolic acid) nanoparticles for active targeting of metastatic breast cancer. *Biomaterials, 33*(27), 7164–7173. https://doi.org/10.1016/j.biomaterials.2012.06.032
65. He, Y., Huang, Y., Huang, Z., Jiang, Y., Sun, X., Shen, Y., Chu, W., & Zhao, C. (2017). Bisphosphonate-functionalized coordination polymer nanoparticles for the treatment of bone metastatic breast cancer. *Journal of Controlled Release, 264*, 76–88. https://doi.org/10.1016/j.jconrel.2017.08.013
66. Chen, S. H., Liu, T. I., Chuang, C. L., Chen, H. H., Chiang, W. H., & Chiu, H. C. (2020). Alendronate/folic acid-decorated polymeric nanoparticles for hierarchically targetable chemotherapy against bone metastatic breast cancer. *Journal of Materials Chemistry B, 8*(17), 3789–3800. https://doi.org/10.1039/D0TB00469J
67. Pang, Y., Fu, Y., Li, C., Wu, Z., Cao, W., Hu, X., Sun, X., He, W., Cao, X., Ling, D., … & Ling, D. (2020). Metal-organic framework nanoparticles for ameliorating breast cancer-associated osteolysis. *Nano Letters, 20*(2), 829–840. https://doi.org/10.1021/acs.nanolett.9b04853
68. Au, K. M., Satterlee, A., Min, Y., Tian, X., Kim, Y. S., Caster, J. M., Zhang, L., Zhang, T., Huang, L., & Wang, A. Z. (2016). Folate-targeted pH-responsive calcium zoledronate nanoscale metal-organic frameworks: Turning a bone antiresorptive agent into an anticancer therapeutic. *Biomaterials, 82*, 178–193. https://doi.org/10.1016/j.biomaterials.2015.12.032
69. Ramanlal Chaudhari, K., Kumar, A., Megraj Khandelwal, V. K., Ukawala, M., Manjappa, A. S., Mishra, A. K., Monkkonen, J., & Ramachandra Murthy, R. S. (2012). Bone metastasis targeting: A novel approach to reach bone using zoledronate anchored PLGA nanoparticle as carrier system loaded with docetaxel. *Journal of Controlled Release, 158*(3), 470–478. https://doi.org/10.1016/j.jconrel.2011.12.031

70. Hatami, E., Bhusetty Nagesh, P. K., Chowdhury, P., Elliot, S., Shields, D., Chand Chauhan, S., Jaggi, M., & Yallapu, M. M. (2019). Development of zoledronic acid-based nanoassemblies for bone-targeted anticancer therapy. *ACS Biomaterials Science & Engineering, 5*(5), 2343–2354. https://doi.org/10.1021/acsbiomaterials.9b00341
71. Ye, W. L., Zhao, Y. P., Li, H. Q., Na, R., Li, F., Mei, Q. B., Zhao, M. G., & Zhou, S. Y. (2015). Doxorubicin-poly(ethylene glycol)-alendronate self-assembled micelles for targeted therapy of bone metastatic cancer. *Scientific Reports, 5*, 14614. https://doi.org/10.1038/srep14614
72. Wu, H., Luo, Y., Xu, D., Ke, X., & Ci, T. (2020). Low molecular weight heparin modified bone-targeting liposomes for orthotopic osteosarcoma and breast cancer bone metastatic tumors. *International Journal of Biological Macromolecules, 164*, 2583–2597. https://doi.org/10.1016/j.ijbiomac.2020.08.132
73. Zhao, Y.P., Ye, W.L., Liu, D.Z., Cui, H., Cheng, Y., Liu, M., Zhang, B.L., Mei, Q.B., & Zhou, S.Y. (2017). Redox and pH dual sensitive bone targeting nanoparticles to treat breast cancer bone metastases and inhibit bone resorption. *Nanoscale, 9*, 6264–6277. https://doi.org/10.1039/C7NR01478K
74. Bussard, K.M., Gigliotti, C.M., Adair, B.M., Snyder, J.M., Gigliotti, N.T., Loc, W.S., Wilczynski, Z.R., Liu, Z.K., Meisel, K., Zemanek, C., *et al.* (2021). Preferential uptake of antibody targeted calcium phosphosilicate nanoparticles by metastatic triple negative breast cancer cells in co-cultures of human metastatic breast cancer cells plus bone osteoblasts. *Nanomedicine, 34*, 102383. https://doi.org/10.1016/j.nano.2021.102383