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Smart Nanoparticles in Oncology: Enhancing Drug Delivery and Efficacy

Siri Goud Cheruku[1*], Deepna Reddy Patlolla[2], Parth Sandeep Lele[3*] and Gandikota Renu[4]

[1]Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, Telangana, India
[2]Kakatiya Medical College, Warangal, Telangana, India
[3]Terna Medical College, Mumbai, Maharashtra, India
[4]Government Medical College, Suryapet, Telangana, India

Abstract

Cancer remains a leading global health challenge, necessitating innovative therapies to overcome limitations like drug resistance and systemic toxicity. Smart nanoparticles have emerged as a promising solution, offering targeted and stimuli-responsive approaches to enhance treatment precision. This review highlights the urgent need to consolidate recent advancements and address gaps in translating nanotechnologies from bench to bedside. The review explores diverse types of smart nanoparticles, including polymeric, metallic, and lipid-based systems, and their mechanisms of action, such as passive/active targeting and stimuli-responsive drug release. Key insights include their applications in drug delivery, imaging, and overcoming biological barriers, supported by preclinical and clinical successes in breast, pancreatic, and lung cancers. Challenges like biocompatibility and scalability are critically analyzed, alongside strategies to optimize nanoparticle design and functionality. The integration of theranostics and artificial intelligence is emphasized as a transformative approach for personalized oncology. Future prospects lie in advancing multifunctional nanoparticles, refining manufacturing processes, and fostering interdisciplinary collaborations to accelerate clinical adoption. With continued innovation, smart nanoparticles hold immense potential to revolutionize cancer therapy, improving efficacy while minimizing adverse effects. This review underscores their pivotal role in shaping the next generation of precision oncology.

Keywords: Cancer therapy, Drug delivery, Nanomedicine, Oncology, Stimuli-responsive, Targeted therapy, Theranostics

Correspondence to: Siri Goud Cheruku and Parth Sandeep Lele, Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, Telangana, India and Terna Medical College, Mumbai, Maharashtra, India.

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Introduction

Smart nanoparticles represent a cutting-edge approach in oncology, offering a promising avenue for precise and personalized cancer therapy [1-3]. Smart nanoparticles are engineered to respond to specific biological cues or external stimuli, enhancing the delivery and efficacy of anticancer agents while minimizing side effects [4-6]. The integration of nanotechnology in cancer treatment has led to significant advancements in drug delivery systems, enabling targeted therapy that spares healthy cells and focuses on tumor cells [7-9]. This approach not only improves the therapeutic index of anticancer drugs but also addresses challenges such as drug resistance and tumor heterogeneity.

The recent literature underscores the significant advancements in the development and application of smart nanoparticles for cancer therapy, highlighting their potential to revolutionize oncological treatments [10, 11]. These nanocarriers encompass a diverse array of materials, including polymeric nanoparticles, dendrimers, micelles, liposomes, protein-based nanoparticles, and inorganic structures such as mesoporous silica, gold, and iron oxide nanoparticles [10]. Their design aims to address critical challenges in cancer treatment, such as drug solubility, targeted delivery, and minimizing off-target effects [11].

Targeted therapy is a prominent focus, with smart nanoparticles engineered to recognize and bind specific biomarkers on cancer cells and within the tumor microenvironment (TME) [12-14]. For instance, TME-responsive nanoparticles leverage the unique features of tumor tissues, such as abnormal pH and enzyme expression, to enhance selective drug release and improve therapeutic efficacy [10]. This approach is particularly promising in the context of breast cancer, where nanostrategies are designed to respond to the TME, thereby increasing treatment precision and reducing systemic toxicity [10].

In addition to conventional delivery, smart nanoparticles are being integrated into immunotherapeutic strategies, with polymeric systems playing a role in modulating immune responses against tumors [15]. The ability to functionalize nanoparticles with targeting ligands, such as surface biomarkers and intracellular markers, further enhances their specificity and therapeutic potential [16]. Moreover, theranostic applications—combining therapy and diagnostics-are gaining traction, enabling real-time tracking of treatment and monitoring of tumor

response [17]. In the realm of central nervous system cancers like glioblastoma, nanoparticles facilitate molecular targeting across the blood-brain barrier, offering new avenues for effective drug delivery in otherwise challenging environments [18]. Similarly, in liver cancer, smart microbeads and nanoparticles are being explored for interventional embolization, aiming to improve localized treatment outcomes [19, 20].

Despite these promising developments, challenges remain in translating these nanotechnologies into clinical practice. Issues such as biocompatibility, stability, and large-scale manufacturing are acknowledged, alongside the need for comprehensive evaluation of safety and efficacy [11]. Nonetheless, ongoing research continues to refine nanoparticle design, targeting strategies, and functionalization techniques, paving the way for more effective and personalized cancer therapies [10].

In summary, the current body of research demonstrates that smart nanoparticles hold considerable promise for enhancing cancer diagnosis, targeted drug delivery, and combination therapies, with ongoing efforts aimed at overcoming existing limitations to facilitate clinical translation [10, 11]. The integration of nanotechnology into oncology has revolutionized cancer diagnosis and treatment, leading to the development of smart nanoparticles [21, 22]. These nanoparticles are engineered to respond to specific biological stimuli, enhancing their efficacy in targeting cancer cells while minimizing side effects [23, 24]. This article explores the various types of smart nanoparticles, their mechanisms of action, and their applications in oncology.

Types of Smart Nanoparticles

Smart nanoparticles have emerged as a transformative tool in oncology, offering innovative solutions for cancer diagnosis and treatment [25]. These nanoparticles are engineered to respond to specific biological cues or external stimuli, enhancing the precision and efficacy of cancer therapies [26, 27]. They can be classified into various types, each with unique properties and mechanisms of action that make them suitable for different therapeutic and diagnostic applications (Table 1). Smart nanoparticles can be classified based on their composition and functionality. Common types include polymeric nanoparticles, liposomes, dendrimers, and metal-based nanoparticles such as gold and iron oxide nanoparticles [28-30]. Below is an overview of the different types of smart nanoparticles used in oncology and their functions.

Polymeric nanoparticles are designed to carry and release therapeutic agents in response to specific stimuli such as pH, temperature, or enzymatic activity. Polymeric nanoparticles are biocompatible and stable, making them ideal for drug delivery systems. They can be engineered to respond to specific stimuli, allowing for controlled drug release at the tumor site [10, 15]. These nanoparticles are used in cancer immunotherapy to enhance the specificity and efficacy of immune responses against tumors [15]. For instance, Sun and Zhong [31] discussed the development of biological stimuli-sensitive polymer prodrugs that enhance tumor-specific drug delivery by utilizing the unique microenvironment of tumors, such as mild acidity and overexpressed enzymes.

Gold nanoparticles have gained significant attention due to their biocompatibility and ability to selectively target tumor cells. Gerosa et al. [32] highlights the promising applications of gold nanoparticles in oncology, emphasizing their low toxicity and high selectivity in targeting cancer cells. Furthermore, gold nanoparticles are widely used due to their ease of functionalization and ability to enhance imaging contrast, making them useful in both therapeutic and diagnostic applications [33, 34]. Similarly, iron oxide nanoparticles are utilized for their magnetic properties, which facilitate targeted drug delivery and imaging [35]. Iron oxide nanoparticles are particularly valuable in magnetic resonance imaging (MRI) and magnetic hyperthermia therapy, where they can be guided to the tumor site using an external magnetic field [34, 36].

Liposomes are spherical vesicles that can encapsulate both hydrophilic and hydrophobic drugs, providing a versatile platform for drug delivery. They enhance the bioavailability and reduce the systemic toxicity of anticancer agents [33, 37]. These nanoparticles can be functionalized with ligands for targeted delivery, improving the accumulation of drugs in tumor tissues [10]. Quantum dots are semiconductor nanoparticles that offer high fluorescence, making them excellent for imaging applications. They can be used to track the distribution and accumulation of drugs in real-time [33, 37]. Carbon nanotubes have a high surface area and can be used to deliver drugs, genes, or proteins directly to cancer cells, enhancing the therapeutic index [10, 37].

Table 1: Types of smart nanoparticles and their applications in oncology.

Category	Sub-type	Size range (nm)	Stimuli-responsive properties	Drug loading capacity	Targeting mechanism	Clinical stage	Advantages	Limitations	Key applications
Polymeric	Poly(lactic-co-glycolic acid)	50 to 200	pH, enzymes	High (10 to 20%)	Passive/ Active	Phase II-III	Biodegradable, Food and Drug Administration (FDA)-approved	Burst release	Chemotherapy, immunotherapy
	Poly(ethylene glycol)–poly(lactic acid) (PEG-PLA)	20 to 100	Temperature	Moderate (5 to 15%)	Active	Phase I-II	Long circulation	Complex synthesis	Targeted drug delivery
Lipid-based	Liposomes	80 to 150	pH	High (15 to 25%)	Passive/ Active	Marketed (Doxil)	Low toxicity	Stability issues	Doxorubicin N (DOX) delivery
	Solid lipid nanoparticles	50 to 120	Temperature	Moderate (5 to 10%)	Passive	Phase II	Improved stability	Low drug loading	Breast cancer
Metallic	Gold nanoparticles	10 to 100	Light	Low (1 to 5%)	Active	Phase I-II	Photothermal therapy	Potential toxicity	Imaging, hyperthermia
	Iron oxide nanoparticles	10 to 50	Magnetic field	Moderate (5 to 10%)	Passive/ Active	Marketed (Ferumoxytol)	MRI contrast	Aggregation issues	Theranostics
Inorganic	Mesoporous silica	50 to 200	pH	Very high (20 to 30%)	Active	Preclinical	High surface area	Slow degradation	Gene delivery
	Carbon nanotubes	1 to 100	NIR	Moderate (5 to 15%)	Active	Preclinical	Photothermal	Toxicity concerns	Brain tumors
Biological	Exosomes	30 to 150	Biological cues	Low (1 to 5%)	Active	Phase I	Natural targeting	Low yield	Immunotherapy
	Albumin nanoparticles	20 to 150	pH	Moderate (10 to 15%)	Passive/ Active	Marketed (Abraxane)	FDA-approved	Cost	PTX delivery

Dendrimers are highly branched, tree-like structures that can carry multiple drug molecules. Their surface can be modified to improve solubility and targeting capabilities, making them effective in delivering anticancer drugs [10, 38]. Mesoporous silica nanoparticles, these nanoparticles have a large surface area and pore volume, allowing for high drug loading capacity. They can be engineered to release drugs in response to specific stimuli, such as pH changes in the TME [10].

In summary, smart nanoparticles represent a significant advancement in cancer therapy, offering targeted, efficient, and less toxic treatment options. However, ongoing research and development are crucial to overcoming existing challenges and fully realizing their potential in clinical applications.

Mechanisms of Action

Smart nanoparticles operate through various mechanisms that enhance their therapeutic efficacy. Smart nanoparticles can function with tumor-specific ligands, such as antibodies or peptides, to enhance targeting and uptake by cancer cells [10, 39]. By bypassing efflux pumps and targeting cancer stem cells, nanoparticles can overcome multidrug resistance, a significant hurdle in cancer treatment [38]. Smart nanoparticles are used in cancer theranostics, combining therapeutic and diagnostic capabilities. They can be engineered for multimodal imaging and therapy, providing real-time monitoring of treatment efficacy [40, 41]. They achieve this through various mechanisms, including passive and active targeting, as well as smart activation triggered by internal and external factors.

Passive targeting

This approach primarily relies on the enhanced permeability and retention (EPR) effect, which allows nanoparticles to accumulate in tumor tissues more effectively than in normal tissues. The EPR effect is a result of the abnormal and leaky vasculature present in tumors, coupled with poor lymphatic drainage, which facilitates the retention of nanoparticles [42, 43]. Passive targeting is a cornerstone of nanoparticle-based cancer therapies, offering a means to improve the specificity and reduce the systemic toxicity of anticancer drugs [38]. This method is widely used in conventional nanoparticle formulations. The EPR effect is a passive process that does not require specific interactions between the nanoparticles and tumor cells, making it a widely applicable strategy for various types of nanoparticles, including liposomes, dendrimers, and polymeric nanoparticles [44, 45].

The size, shape, and surface charge of nanoparticles significantly influence their ability to exploit the EPR effect. Typically, nanoparticles ranging from 10 to 200 nm in size are optimal for passive targeting, as they can navigate through the leaky vasculature of tumors while avoiding rapid clearance by the reticuloendothelial system [43]. Surface modifications, such as PEGylation, can enhance the circulation time of nanoparticles in the bloodstream, further improving their accumulation in tumor tissues [43]. While passive targeting offers a promising approach to enhance the delivery of anticancer agents, it is important to consider the limitations and variability associated with this strategy. The heterogeneity of tumor vasculature and TME can lead to inconsistent drug delivery and therapeutic outcomes.

Active targeting

Active targeting involves the functionalization of nanoparticles with ligands that specifically bind to receptors overexpressed on cancer cells [46, 47]. This approach increases the specificity of drug delivery, reducing off-target effects. Functionalization of nanoparticles with ligands such as antibodies or peptides enables them to bind specifically to tumor cells, enhancing targeting accuracy [10]. Active targeting involves the conjugation of nanoparticles with ligands such as antibodies, peptides, aptamers, and small molecules that specifically bind to receptors overexpressed on cancer cells. Examples include transferrin, folate, and various antibodies that target specific tumor antigens [48, 49]. Once the ligand binds to its target receptor on the cancer cell surface, the nanoparticle is internalized through receptor-mediated endocytosis, facilitating the delivery of the therapeutic payload directly into the cancer cells [50].

Kenchegowda et al. [51] discussed various smart nanocarriers that utilize active targeting mechanisms to enhance therapeutic outcomes. While active targeting mechanisms in smart nanoparticles offer significant promise for improving cancer therapy, it is essential to address the challenges associated with their clinical translation.

Stimuli-responsive release

Stimuli-responsive nanoparticles are designed to release their therapeutic payload in response to specific environmental triggers, such as changes in pH, temperature, or the presence of certain enzymes [52-54]. Huang et al. [55] describes a hybrid nanoparticle platform that responds to the TME, enabling controlled release of chemotherapeutic agents while simultaneously providing imaging capabilities.

Internal triggering mechanisms

- pH sensitivity: Smart nanoparticles can be engineered to respond to the acidic environment of tumors. For instance, lipid-polypeptide hybrid nanoparticles undergo phase transitions at different pH levels, enhancing cellular uptake and drug release within the TME [39].
- Enzyme and redox sensitivity: These nanoparticles can be activated by specific enzymes or redox conditions prevalent in tumors, allowing for targeted drug release [56].
- Hypoxia: Some nanoparticles are designed to respond to the low oxygen levels in tumors, triggering drug release or other therapeutic actions [56].

External triggering mechanisms

- Temperature and light: Nanoparticles can be activated by external stimuli such as heat or light, which can induce drug release or enhance therapeutic effects. For example, magnetically responsive nanoparticles use magnetic fields to generate heat and release drugs [57].
- Ultrasound and magnetic fields: These external factors can be used to control the release of drugs from nanoparticles, providing a non-invasive method to enhance treatment precision [56].

In summary, in contrast to traditional therapies, smart nanoparticles offer a more targeted and efficient approach to cancer treatment, potentially reducing side effects and improving patient outcomes. Smart nanoparticles can be used in combination with other therapies, such as immunotherapy or chemotherapy, to enhance overall treatment efficacy [38]. Nanozymes, these are nanoparticles that mimic enzyme activity and can modulate the TME to enhance therapeutic outcomes [58]. However, the complexity of their design and the need for precise control over their activation and targeting mechanisms present significant challenges that must be overcome to fully realize their potential in clinical settings.

Applications for Oncology

The applications of smart nanoparticles in oncology are vast, ranging from drug delivery to imaging and diagnostics [59-61].

Drug delivery

Smart nanoparticles are primarily used for targeted drug delivery, allowing for the efficient transport of chemotherapeutic agents directly to tumor sites [62, 63]. This targeted approach minimizes systemic toxicity and enhances therapeutic efficacy. For example, Saharkhiz et al. [64] presents a novel pH-responsive niosome formulation for DOX delivery, demonstrating significant cytotoxic effects against breast cancer cells.

Smart nanoparticles are designed to deliver drugs directly to tumor sites, maximizing local drug concentration and reducing systemic toxicity [65, 66]. They achieve this through mechanisms such as the EPR effect and active targeting via ligands like antibodies and peptides [10, 38]. These nanoparticles can be engineered to respond to internal stimuli (e.g., pH, enzymes) or external stimuli (e.g., temperature, magnetism), allowing for controlled drug release at the tumor site [10, 67]. Examples include micelle-based nanoparticles that release drugs in response to pH changes, and iron oxide nanoparticles used for magnetic hyperthermia and targeted drug delivery [67, 68].

Imaging and diagnostics

In addition to drug delivery, smart nanoparticles are employed in molecular imaging and diagnostics. Up-conversion luminescent nanoparticles have shown promise in cancer diagnosis due to their unique luminescent properties, enabling sensitive detection of cancer biomarkers [69]. Smart nanoparticles enhance imaging techniques such as MRI and photoacoustic imaging, providing detailed insights into tumor biology and aiding in precise tumor localization [41, 68]. Theranostic nanoparticles combine therapeutic and diagnostic functions, enabling simultaneous cancer treatment and monitoring. For instance, hybrid nanoparticles like IO@MnO_2@DOX facilitate both imaging and drug delivery, enhancing the synergistic effects of chemotherapy and hyperthermia [41]. Furthermore, magnetic nanoparticles are utilized for rapid detection and *in situ* diagnosis in clinical oncology, providing a safer and faster alternative to traditional methods [35].

Furthermore, smart nanoparticles can bypass multidrug resistance mechanisms by targeting cancer stem cells and avoiding efflux pumps, which are common barriers in conventional chemotherapy [38]. Selenium nanoparticles, for example, have shown promise in activating apoptotic pathways in cancer cells, thereby enhancing the efficacy of anticancer drugs [70]. The large surface area of nanoparticles allows for the encapsulation of multiple therapeutic agents and functionalization with various biosubstrates, such as DNA and RNA, enhancing their multifunctionality and biocompatibility [25, 40]. Biologically derived nanoparticles offer advantages in terms of reduced toxicity and ease of production compared to those produced by conventional methods [40]. The continued advancement of smart nanoparticles holds the promise of revolutionizing cancer treatment, offering more effective and personalized therapeutic options for patients.

Clinical Studies

Smart nanoparticles have emerged as a promising tool in oncology, offering innovative solutions for cancer therapy through enhanced drug delivery systems [71]. These nanoparticles are designed to respond to specific biological cues, allowing for precise targeting and controlled drug release within the TME. The clinical studies and trials of smart nanoparticles in oncology focus on their ability to improve therapeutic outcomes by overcoming traditional treatment limitations such as non-specific targeting and drug resistance (Table 2). This section will explore the various aspects of smart nanoparticles in oncology, including their design, functionality, and clinical applications.

A study by Kaushal et al. [72] focused on using 'smart' nanoparticles to deliver anti-RhoC silencing RNA (siRNA) to breast cancer cells, specifically SUM149 and MDA-MB-231 cell lines. These

Table 2: Clinical advancements and challenges of smart nanoparticles.

Application area	Nanoparticle type	Current status	Key challenges	Clinical benefits	Ongoing trials	Regulatory hurdles	Manufacturing complexity	Cost considerations	Future directions	Notable examples
Chemotherapy	Liposomal DOX	Marketed (since 1995)	Cardiotoxicity management	Reduced side effects	NCT04591184	Established pathway	Moderate	High (~$5,000/ dose)	Combination therapies	Doxil, Myocet
	Polymeric nanoparticles	Phase III (Breast cancer)	Scalability issues	Targeted delivery	NCT03948698	Characterization standards	High	Very high	Personalized medicine	BIND-014
Immunotherapy	Gold nanoparticles	Phase II (Melanoma)	Immune activation control	Enhanced checkpoint inhibition	NCT04240639	Novel mechanisms	Very high	Extremely high	Neoantigen vaccines	AuroLase
Gene therapy	Lipid nanoparticles	Marketed (COVID vaccines)	Tissue specificity	Rapid development	NCT05262530	Established for vaccines	Moderate	Moderate	Cancer vaccines	Onpattro
Theranostics	Iron oxide nanoparticles	Phase II (Glioblastoma)	Imaging resolution	Diagnosis + treatment	NCT03494712	Dual approval needed	High	High	Image-guided surgery	Ferumoxytol
Photothermal	Gold nanorods	Phase I (Prostate)	Laser penetration depth	Minimally invasive	NCT04240639	Device combination	Extreme	Extreme	Outpatient procedures	AuroShell
Brain delivery	Polymeric nanoparticles	Preclinical (GBM)	BBB penetration	Localized effect	-	Novel endpoints	Very high	-	Convection-enhanced delivery	-
Combination	Hybrid nanoparticles	Phase I (Pancreatic)	Drug interactions	Synergistic effects	NCT05652148	Complex approvals	Extreme	-	Nanococktails	CRLX101
Diagnostics	Quantum dots	Preclinical	Toxicity concerns	Multiplex imaging	-	Safety thresholds	High	-	Intraoperative imaging	-
Vaccines	Virus-like nanoparticles	Phase II (HPV+)	Stability	Strong immune response	NCT05262530	Similar to biologics	Moderate	-	Cancer prevention	Gardasil

nanoparticles were made from a biodegradable, pH-sensitive polymer based on β-cyclodextrin (βCD) and were designed to enhance the delivery of siRNA into the cytoplasm of cancer cells. The researchers found that the smart anti-RhoC particles effectively entered the cells and released their siRNA cargo into the cytoplasm. This was confirmed by observing a significant reduction in RhoC protein levels: a 100% reduction in SUM149 cells and a 90% reduction in MDA-MB-231 cells. The treatment with anti-RhoC particles led to a notable decrease in the invasive and migratory capabilities of the cancer cells. Specifically, the invasion of SUM149 cells was reduced by 40% and that of MDA-MB-231 cells by 47%. Additionally, the motility of SUM149 cells decreased by 60% and that of MDA-MB-231 cells by 57%. The study also demonstrated that the smart particles did not affect the expression of RhoA, another protein similar to RhoC, indicating that the effects observed were specific to RhoC knockdown. This specificity is crucial for minimizing potential side effects on healthy cells. The researchers concluded that these smart anti-RhoC particles have significant therapeutic potential for inhibiting the spread of aggressive breast cancer cells. They suggested that these particles could also be used to deliver other siRNA molecules targeting different Rho-GTPases to further enhance their effectiveness in cancer treatment [72].

A study by Yumuk et al. [73] presented several significant findings regarding the use of smart polymeric nanocarriers for delivering miRNA in the treatment of triple-negative breast cancer (TNBC). The research demonstrated that the developed smart polymeric nanocarriers could effectively transport miRNA to breast cancer cells. The import percentages of BT-549 and MDA-MB-231 cells were over 35% and 55%, respectively, indicating a successful delivery mechanism. Fluorescence microscopy results showed that FAM-labelled miRNAs reached the interior of the cells within 4 h. This rapid uptake suggests that the nanocarriers facilitate efficient cellular entry without causing enzymatic degradation of the miRNA. The study established that the inhibitor miRNA and smart nanocarriers formed a complex at a 2/1 N/P ratio, while mimic miRNA and negative miRNA formed an 8/1 complex. Additionally, FAM-labelled negative miRNA and smart nanocarriers formed a complex at a 16/1 N/P ratio. These ratios are crucial for optimizing the delivery system. The research emphasized the importance of optimizing the physicochemical characteristics of smart nanocarriers, including size, surface charge, and stability, to enable efficient delivery and controlled release of miRNA. The results indicated that the polymeric miRNA delivery systems hold promise for improving the precision, efficacy, and safety of treatments for TNBC. This suggests a potential shift in therapeutic strategies for managing this aggressive cancer subtype [73].

A study by Luo et al. [41] presents several significant findings regarding the developed smart nanoparticles, specifically the superparamagnetic iron oxide, manganese dioxide, and DOX (IMD) hybrid nanoparticles. The IMD nanoparticles demonstrated efficient T2-T1 MRI and switchable photoacoustic imaging. This dual imaging capability is crucial for enhancing the precision of tumor diagnosis and monitoring treatment responses. The nanoparticles were designed to respond to the TME, leading to the degradation of IMD and the subsequent release of DOX. This feature allows for targeted drug delivery, enhancing the effectiveness of chemotherapy. The IMD nanoparticles exhibited excellent heating properties when exposed to an alternating magnetic field. This characteristic is essential for the application of magnetic hyperthermia, which can synergistically enhance the effects of chemotherapy. The combination of magnetic hyperthermia and chemotherapy using the IMD nanoparticles resulted in a significant synergistic effect. This means that the combined treatment was more effective at inhibiting tumor growth than either treatment alone. *In vivo* experiments showed that the IMD nanoparticles significantly inhibited tumor growth in tumor-bearing mice. Importantly, this treatment was associated with negligible side effects, indicating a favorable safety profile for potential clinical applications. The study concludes that the smart IMD nanoparticles have the potential to serve as integrated diagnostic nanoprobes, facilitating both tumor diagnosis and therapeutic intervention, which is a promising advancement in cancer precision medicine. These results highlight the innovative approach of using smart nanoparticles for enhanced cancer treatment through multimodal imaging and targeted therapy [41].

A study by Gonzalez-Valdivieso et al. [74] presents several significant findings regarding the use of smart nanoparticles for delivering an Akt inhibitor in pancreatic cancer therapy. The self-assembling genetically engineered polymeric nanoparticles, made from elastin-like recombinamers, were successfully created. These nanoparticles had an average size of 73 ± 3.2 nm, which is suitable for cellular uptake and drug delivery. The uptake of these nanoparticles by pancreatic cancer cells (specifically PANC-1 and patient-derived xenograft models) was measured using flow cytometry. The results indicated effective cellular uptake, and confocal microscopy revealed that the nanoparticles localized primarily in lysosomes. The study demonstrated that the nanoparticles carrying the Akt inhibitor significantly reduced metabolic activity and cell viability in a time- and dose-dependent manner. This suggests that the nanoparticles effectively deliver the drug and exert a therapeutic effect on the cancer cells. The nanoparticles inhibited the phosphorylation and activation of the Akt protein, which is crucial for cancer cell survival and proliferation. This inhibition subsequently blocked the NF-κB signaling pathway, leading to the activation of caspase 3-mediated apoptosis, a process that results in programmed cell death. *In vivo* assays indicated that the elastin-like recombinamers-based nanoparticles were effective for drug delivery, demonstrating a long circulation time in the bloodstream and minimal toxicity. This highlights their potential as a safe and effective treatment option for pancreatic cancer. These results collectively suggest that the smart nanoparticles developed in this study could significantly improve therapeutic strategies for pancreatic cancer by effectively delivering the Akt inhibitor and inducing cancer cell death [74].

A study by Bryant et al. [75] presents significant findings regarding the use of magnetoelectric nanoparticles in targeting and eradicating cancer cells, specifically in a pancreatic adenocarcinoma murine model. The application of magnetoelectric nanoparticles resulted in a mean tumor volume reduction of three-fold when compared to control groups. Specifically, the treatment tumors showed a reduction of 62.3% versus 188.7% in the control group, with a statistically significant p-value of less than 0.001. In a longitudinal confirmatory study, 35% of the mice treated with activated magnetoelectric nanoparticles achieved a durable complete response, lasting for 14 weeks after a single treatment. This indicates the potential for long-term effectiveness of magnetoelectric nanoparticles in cancer therapy. The degree of tumor volume reduction was found to correlate with a decrease in MRI $T2^*$ relaxation time ($r = 0.351$; $p = 0.039$). This suggests that magnetoelectric nanoparticles not only serve as a treatment but also have predictive capabilities regarding treatment outcomes based on MRI. Importantly, the study reported no discernable toxicities associated with the use of magnetoelectric nanoparticles at any time point during the study. Histopathological analysis of major organs showed no adverse effects, indicating that magnetoelectric nanoparticles are a noninvasive

alternative for cancer treatment. Magnetoelectric nanoparticles leverage the magnetoelectric effect to create local electric fields in response to an external magnetic field. This mechanism allows for the induction of irreversible electroporation in cancer cell membranes, leading to targeted cell death. These results highlight the promising potential of magnetoelectric nanoparticles as a novel theranostic agent in cancer treatment, combining effective targeting and monitoring capabilities without significant side effects [75].

A study by Zhang et al. [76] successfully developed a smart two-dimensional supraparticle, named CM-DOX-GMNPs, which combines a core of gold nanorods and manganese dioxide nanosheets with a shell made from cancer cell membranes. This design aims to enhance tumor targeting and improve imaging and therapy for cancer. The CM-DOX-GMNPs demonstrated effective tumor-specific targeting capabilities. The cancer cell membrane coating improved the nanoparticles' stability and allowed them to better recognize and bind to cancer cells, leading to increased internalization within these cells. *In vitro* studies showed that the CM-DOX-GMNPs had a high drug loading efficiency of approximately 12.1% for DOX, a common chemotherapy drug. Nanoparticles released about 44.8% of the drug in a controlled manner, which is beneficial for targeted therapy. The combination of chemotherapy and photothermal therapy using these nanoparticles resulted in significant tumor growth inhibition *in vivo*. Mice treated with CM-DOX-GMNPs and exposed to near-infrared laser showed over 70% cell death, indicating a strong therapeutic effect. The CM-DOX-GMNPs also served as effective contrast agents for MRI. The presence of Mn^{2+} ions, released from the MnO_2 nanosheets, enhanced the MRI signal, allowing for better visualization of tumors. In terms of safety, the CM-GMNPs exhibited good biocompatibility, with minimal toxicity observed in mice. The body weight of treated mice remained stable, and no significant organ damage was noted in histological examinations. Overall, the results indicate (Figure 1) that CM-DOX-GMNPs provide a promising approach for cancer diagnosis and treatment, combining imaging and therapy in a single platform, which could help overcome challenges faced by traditional cancer treatments [76].

A study by Jin et al. [77] successfully developed polymeric nanoparticles that can co-deliver the chemotherapy drug paclitaxel (PTX) and survivin siRNA, which is designed to silence a gene that helps cancer cells survive. This co-delivery system showed promising results in treating lung cancer. The nanoparticles had a mean size of 82.4 nm and a zeta potential of 4.1 mV, which are optimal for passive targeting tumors. This size helps the nanoparticles to accumulate in tumor tissues effectively due to the EPR effect. The nanoparticles demonstrated a drug loading efficiency of 6.04% and were stable in serum, maintaining their size and structure over 24 h. At a lower pH (5.5), which simulates the acidic environment of tumor cells, the nanoparticles released PTX more effectively compared to a neutral pH (7.4). After 72 h, about 86% of PTX was released at pH 5.5, compared to 55% at pH 7.4. The co-delivery of PTX and siRNA significantly improved the anticancer effects. The NPs effectively knocked down survivin mRNA and protein levels in A549 lung cancer cells, leading to enhanced cell death. The combination treatment resulted in a much lower cell viability compared to treatments with either PTX or siRNA alone. *In vivo* studies showed that the nanoparticles accumulated in tumor sites and inhibited tumor growth, extending the survival rate of mice with lung cancer. The combination of PTX and survivin siRNA was more effective than either treatment alone (Figure 2), indicating a synergistic effect. Overall, the study concluded that the polyethyleneimine-block-polylactic acid (PEI-PLA)/poly(ethylene glycol)-block-poly(L-aspartic acid sodium salt) (PEG-PAsp) based co-delivery system is a promising approach for cancer therapy, combining the benefits of chemotherapy and gene silencing to improve treatment outcomes [77].

Challenges and Future Perspectives

Despite the promising advancements in smart nanoparticles for oncology, several challenges remain. These include the need for a comprehensive understanding of nano-bio interactions, the complexities of clinical translation, and the potential for off-target effects. As highlighted by Tiwari et al. [45], ongoing research is essential to address these challenges and optimize the design of smart

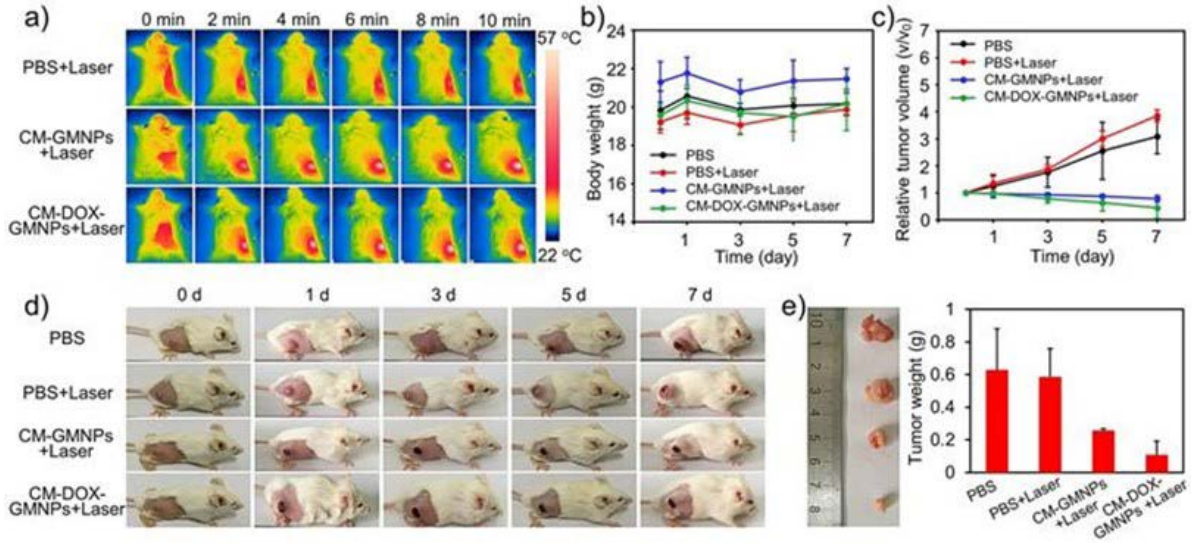

Figure 1: (a) Infrared thermographic images of 4T1 breast tumor-bearing mice treated with phosphate buffer saline (PBS), CM-GMNPs and CM-DOX-GMNPs in the presence of near infrared (NIR) laser at different irradiation times. **(b)** Body weight changes and **(c)** relative tumor volume of 4T1 breast tumor-bearing mice treated with PBS, PBS+NIR laser, CM-GMNPs+NIR laser and CM-DOX-GMNPS+NIR laser within 7 days. **(d)** Photographs of the mice in different groups. **(e)** The photograph and corresponding weight of tumors which were collected on the 7th day [76].

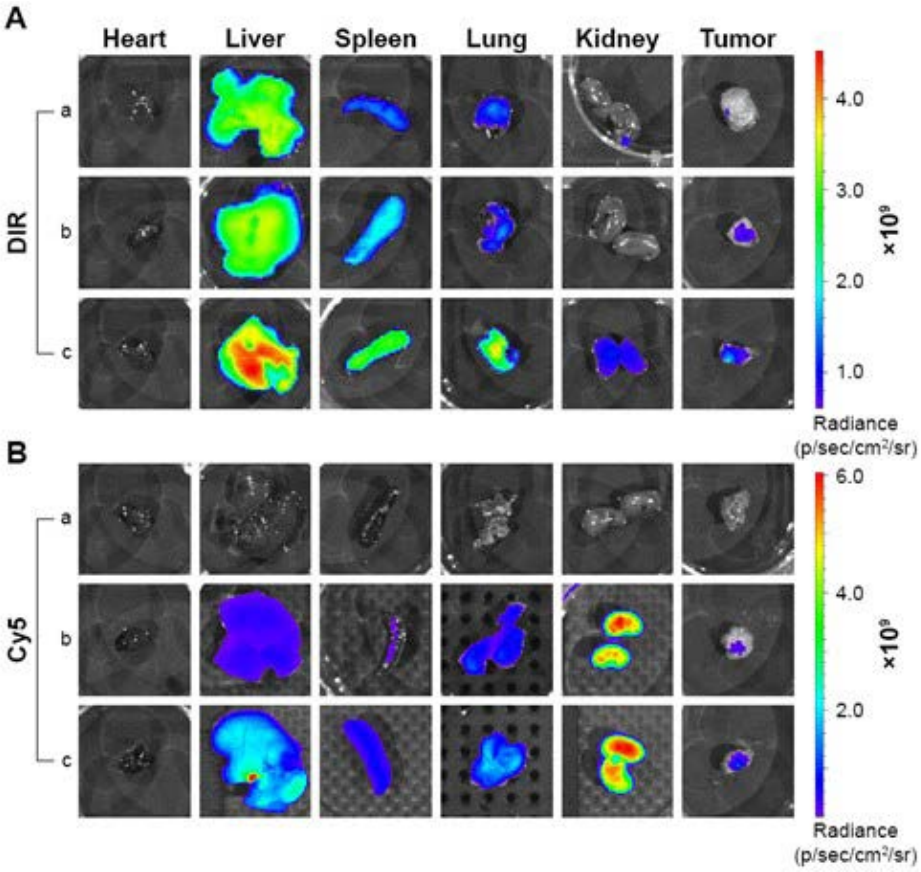

Figure 2: Fluorescence images of organs and tumors in A549 tumor-bearing mice 24 h after intravenous injection of complex nanoparticles (DIR = 50 μg/kg, siRNA^{Cy5} = 2 mg/kg) (n = 3). **(A)** Fluorescence image of DIR channel**: (a)** DIR; **(b)** PEI-PLA/DIR/siRNA^{Cy5}; and **(c)** PEI-PLA/DIR/siRNA^{Cy5}/PEG-PAsp. **(B)** Fluorescence image of Cy5 channel: **(a)** siRNA^{Cy5}; **(b)** PEI-PLA/DIR/siRNA^{Cy5}; and **(c)** PEI-PLA/DIR/siRNA^{Cy5}/PEG-PAsp [77].

nanoparticles for clinical applications. While smart nanoparticles hold great promise in oncology, there are challenges related to their biocompatibility, potential toxicity, and large-scale manufacturing. Continuous research is needed to address these issues and improve the safety and efficacy of nanoparticle-based therapies [33, 38]. Additionally, the integration of artificial intelligence with smart nanoparticles could further enhance personalized cancer treatment by optimizing drug delivery and therapeutic outcomes [10].

Current challenges

- Biocompatibility and toxicity: Ensuring that nanoparticles are biocompatible and do not induce adverse immune responses is a significant challenge. The potential toxicity of nanoparticles, especially when used in high doses or over extended periods, remains a concern that needs to be addressed through rigorous preclinical and clinical testing [78].

- Scalability and manufacturing: The production of nanoparticles at a scale suitable for clinical use while maintaining consistency and quality is challenging. The complexity of nanoparticle synthesis and the need for precise control over their physicochemical properties complicate large-scale manufacturing [78, 79].

- Regulatory approval: The regulatory landscape for nanoparticles is still evolving, and gaining approval for new nanoparticle-based therapies can be a lengthy and complex process. This is due to the need for comprehensive safety and efficacy data, which can be difficult to obtain given the novel nature of these technologies [78, 80].

- Biological barriers: Nanoparticles must overcome various biological barriers to effectively deliver drugs to tumor sites. These include the blood-brain barrier, TME, and the body's immune system, which can hinder the delivery and efficacy of nanoparticle-based therapies [79, 81].

- Clinical translation: Despite promising preclinical results, challenges such as patient-specific responses, regulatory hurdles, and large-scale manufacturing need to be addressed for clinical application [82].

Future directions

- Multifunctional nanoparticles: The development of nanoparticles that can perform multiple functions, such as drug delivery, imaging, and therapy, is a promising direction. These multifunctional systems can enhance treatment efficacy and provide real-time monitoring of therapeutic outcomes [10, 78].

- Artificial intelligence integration: The use of artificial intelligence to design and optimize nanoparticles for specific cancer types and patient profiles is an emerging area. AI can help in predicting nanoparticle behavior, optimizing drug loading, and personalizing treatment plans [10].

- Theranostic applications: Combining therapeutic and diagnostic capabilities in a single nanoparticle platform, known as theranostics, is a growing field. This approach allows for simultaneous treatment and monitoring of cancer, potentially improving patient outcomes [25].

- Interdisciplinary collaboration: Strengthening collaborations between researchers in nanotechnology, oncology, and regulatory science is crucial for advancing the field. Such collaborations can facilitate the translation of laboratory findings into clinical applications and help navigate regulatory challenges [83].

While smart nanoparticles hold immense potential in revolutionizing cancer therapy, it is important to consider the broader context of their application. The development of these nanoparticles must be accompanied by rigorous clinical testing to ensure their safety and efficacy [84]. Additionally, the integration of smart nanoparticles with other therapeutic modalities, such as immunotherapy and gene therapy, could further enhance their effectiveness [85]. As research progresses, addressing the challenges of clinical translation and regulatory approval will be crucial in realizing the full potential of smart nanoparticles in oncology.

Conclusion

Smart nanoparticles represent a transformative advancement in oncology, offering targeted drug delivery, enhanced therapeutic efficacy, and reduced systemic toxicity. Their ability to respond to specific biological cues or external stimuli enables precise treatment of cancer cells while sparing healthy tissues, addressing challenges such as drug resistance and tumor heterogeneity. Clinical studies have demonstrated their potential in improving imaging, diagnostics, and combination therapies, with promising results in breast, pancreatic, and lung cancers. Despite challenges in biocompatibility, scalability, and regulatory approval, ongoing research and interdisciplinary collaboration are paving the way for their clinical translation. The integration of multifunctional designs, artificial intelligence, and theranostic applications holds immense promises for revolutionizing personalized cancer therapy, ultimately improving patient outcomes and quality of life.

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Conflict of Interest

None.

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