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Multifunctional Nanosystems for Precision Oncology: Real-time Monitoring and Controlled Release for Tumor-specific Treatment

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Abstract

The rapid advancements in multifunctional nanosystems for precision oncology necessitate a comprehensive review to consolidate recent developments, evaluate their clinical potential, and address existing challenges. As cancer therapy shifts toward personalized approaches, integrating real-time monitoring and controlled drug release into a single platform has become critical for improving treatment efficacy and patient outcomes. This review highlights the urgent need to bridge the gap between innovative nanoplatforms and their clinical translation, emphasizing biocompatibility, scalability, and regulatory hurdles. This review provides key insights into the design and functionality of hybrid nanoparticles, nanogels, hydrogels, and magnetoliposomes, showcasing their ability to combine diagnostics and therapeutics for tumor-specific targeting. It explores stimulus-responsive mechanisms, such as pH, reactive oxygen species, and enzyme-triggered drug release, that enhance precision in oncology. Advanced real-time monitoring techniques, including fluorescence and magnetic resonance imaging (MRI)-based imaging, are examined for their role in optimizing treatment regimens. The review also discusses clinical studies demonstrating the efficacy of multifunctional nanosystems in overcoming multidrug resistance and improving therapeutic outcomes. Challenges such as biocompatibility, large-scale production, and regulatory barriers are critically analyzed to identify roadblocks in clinical adoption. Furthermore, the integration of nanosystems with immunotherapy and multimodal therapies is highlighted as a promising strategy for synergistic cancer treatment. Future research should focus on refining targeting strategies, improving biocompatibility, and developing standardized protocols for clinical application. The potential of organ-on-a-chip models to simulate tumor microenvironments and predict therapeutic responses warrants further exploration. Ultimately, this review underscores the transformative potential of multifunctional nanosystems in advancing precision oncology and calls for interdisciplinary efforts to accelerate their translation into clinical practice.

Keywords: Biocompatibility, Controlled drug release, Multifunctional nanosystems, Precision oncology, Real-time monitoring, Stimuli-responsive nanoplatforms, Targeted therapy, Theranostics

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Introduction

The development of multifunctional nanosystems for precision oncology has garnered significant attention due to their potential to enable real-time tumor monitoring and controlled, tumor-specific therapeutic delivery [1-4]. Recent studies highlight various nanoplatforms designed to integrate diagnostic and therapeutic functionalities, thereby advancing personalized cancer treatment. Hybrid nanoparticles have been extensively explored for their theranostic capabilities. Raka et al. [5] emphasized that hybrid nanoparticles can incorporate fluorescence dyes, MRI contrast agents, and positron emission tomography tracers, facilitating real-time monitoring of therapy response. The biocompatibility, stability, immunogenicity, and biosafety of these systems are critical factors for clinical translation, underscoring their multifunctional potential in cancer theranostics.

Similarly, the use of polyglycolic acid coated nanoparticles demonstrates promising advancements in integrating diagnostic and therapeutic functions within a single platform. Rizwan et al. [6] discussed how these nanoparticles enable real-time monitoring and treatment optimization, highlighting their role in safer and more personalized therapeutic approaches. The ability to monitor tumor progression dynamically allows for more precise adjustments in treatment regimens. Fluorescence-based nanosystems have also been developed for high-sensitivity tumor monitoring. Zhao et al. [7] introduce a fluorescence 'Trojan horse' nanosystem capable of detecting caspase-1 activity, a marker of apoptosis, while simultaneously delivering photothermal

therapy. This approach exemplifies how multifunctional fluorescence nanosystems can provide both diagnostic insights and therapeutic action, addressing challenges in precision oncology.

Magnetoliposomes and superparamagnetic nanogels further exemplify the integration of real-time monitoring with targeted delivery [8-10]. Veloso et al. [8] describe magnetoliposomes that enable precision targeting through external magnetic fields and controlled release via magnetic hyperthermia, offering spatiotemporal control over therapy. Similarly, Pareek et al. [11] review superparamagnetic nanogels that serve as dual diagnostic and delivery platforms, emphasizing their potential for clinical translation despite existing challenges. The incorporation of diagnostic imaging agents into hydrogels enhances tumor visualization and therapeutic monitoring. Lee et al. [12] highlight multifunctional hydrogels embedded with magnetic nanoparticles, fluorescent dyes, and radiolabeled isotopes, which collectively improve real-time imaging and treatment efficacy. These systems exemplify the convergence of diagnostic and therapeutic modalities within a biocompatible matrix.

Addressing the challenge of delivering multiple therapeutics with synchronized release, Liu et al. [13] focus on hybrid nanocarriers powered by functional nucleic acids. These platforms enable the co-delivery of hydrophilic and hydrophobic drugs with tumor-specific targeting, which is crucial for overcoming multidrug resistance and achieving precise combination therapy. Furthermore, the design of stimuli-responsive hybrid hydrogels offers tunable control over drug release and mechanical properties. Chang et al. [14] discussed how integrating nanomaterials with polymer networks can produce multifunctional platforms capable of real-time monitoring and combined chemo-immunotherapy, thus advancing the scope of personalized treatment strategies.

In summary, recent literature underscores the importance of multifunctional nanosystems that combine real-time monitoring with controlled, tumor-specific drug release. These platforms leverage diverse nanomaterials—ranging from hybrid nanoparticles and nanogels to hydrogels and magnetoliposomes—to enhance diagnostic accuracy, therapeutic precision, and clinical translatability in oncology. Continued innovation in this field aims to overcome current limitations and realize the full potential of nanotechnology in precision cancer therapy. The field of oncology is witnessing a transformative shift towards precision medicine, where treatment strategies are tailored to the individual characteristics of each patient's tumor. Multifunctional nanosystems have emerged as pivotal tools in this paradigm, offering capabilities for real-time monitoring and controlled release of therapeutic agents specifically targeting tumor cells. These nanosystems integrate diagnostic and therapeutic functionalities, enabling a more effective and personalized approach to cancer treatment.

Multifunctional Nanoplatforms

Multifunctional nanoplatforms are designed to combine various diagnostic and therapeutic agents into a single system. According to Wang et al. [15], these platforms must exhibit biocompatibility, smart delivery mechanisms, and the ability to respond to specific tumor microenvironment stimuli. Recent advancements have categorized multifunctional nanoplatforms based on their functionalities, including enhanced targeted delivery, specific recognition, controlled release, multimodal diagnosis, and real-time tracking of therapeutic effects. One of the most promising strategies for enhancing the accuracy of multifunctional nanoplatforms is the development of endogenous stimuli-responsive systems. These systems can be activated by specific conditions within the tumor microenvironment, such as pH changes or the presence of certain biomarkers. For instance, Zuo et al. [16] introduced a DNA-hybrid-gated nanoprobe capable of monitoring microRNA levels while simultaneously delivering drugs in response to specific biomarker concentrations. This dual functionality allows for precise therapeutic interventions tailored to the tumor's molecular profile.

Nanoplatforms can be designed for theranostic applications, combining therapeutic and diagnostic functions to monitor treatment efficacy in real-time. Gold nanoclusters and other nanomaterials serve as imaging agents, drug carriers, and therapeutic agents, facilitating targeted delivery and enhanced imaging of tumors [17]. Near-infrared imaging and photoacoustic imaging are examples of how nanoplatforms can be used for non-invasive tumor detection and monitoring [18]. Micelles, with their hydrophobic core and hydrophilic shell, are effective for the co-delivery of drugs and genes, providing a synergistic anticancer effect. They can be modified with ligands to enhance selectivity and are capable of responding to various stimuli, such as pH and light, for targeted therapy [19]. Metal-organic frameworks are highly versatile due to their customizable shape, adjustable diameter, and high porosity, making them ideal for drug delivery and cancer therapy. They have been employed in various therapeutic methods, including starvation therapy, chemodynamic therapy, and phototherapy, to improve treatment efficacy and reduce side effects [20, 21]. Metal-organic frameworks can be functionalized to enhance their biocompatibility and target specificity, allowing for more precise delivery of therapeutic agents to tumor sites [22].

pH-responsive (Table 1) and reactive oxygen species (Table 2) controlled nanoplatforms, these nanoplatforms utilize pH-responsive mechanisms to release therapeutic agents specifically in the acidic tumor microenvironment, enhancing tumor uptake and minimizing systemic toxicity. The generation of reactive oxygen species and controlled release of carbon monoxide can induce apoptosis and improve therapeutic outcomes, as demonstrated by the IL@CPP or carbon monoxide system [59]. Such systems combine photodynamic therapy with chemodynamic therapy and carbon monoxide therapy, offering a multifaceted approach to cancer treatment [59]. Multifunctional nanoplatforms can address the challenge of multidrug resistance in cancer by enhancing the delivery and efficacy of photodynamic therapy and chemotherapy. These platforms can be engineered to bypass drug efflux transporters, which are often responsible for resistance, thereby improving the therapeutic index of anticancer drugs [60].

While multifunctional nanoplatforms offer promising advancements in precision oncology, challenges remain in their clinical translation. Issues such as large-scale production, long-term biocompatibility, and regulatory approval need to be addressed to fully realize their potential in clinical settings. Additionally, the complexity of tumor biology and the heterogeneity of cancer types necessitate the development of tailored nanoplatforms for specific applications. Nonetheless, the ongoing research and development in this field hold great promises for improving cancer treatment outcomes and patient quality of life.

Real-time Monitoring Techniques

Real-time monitoring of therapeutic responses is crucial for optimizing treatment regimens. Wang et al. [61] developed a caramelized nanotheranostic system that integrates MRI capabilities with drug delivery. This system not only facilitates the controlled release of doxorubicin but also allows for real-time imaging of tumor

Table 1: pH-responsive multifunctional nanoplatforms for controlled release.

Nanocarrier type	Release conditions	Drug type	pH responsive material	Biological model
Nanoparticles [23]	pH < 5.5	Doxorubicin, α-PCNA aptamer	AS1411 aptamer	MCF-7 and 4T1 cells
Nanoparticles [24]	pH < 6.0	Mitoxantrone	Poly(2-(diisopropylamino)ethylmethacrylate)	MCF-7 and MCF-10A cells, mice
Vesicle [25]	Endosomal pH	Double stranded DNA	Imidazolic side chains	MCF-7 and KB cells
Micelles [26]	pH < 6.0	Doxorubicin	Hydrazone bond	A549 cancer cells and Kunming mice
Bio-metal-organic framework [27]	pH < 6.8	Doxorubicin	Chitosan	MCF-7 cells
Mesoporous silica nanoparticles [28]	pH < 6.8	Ibuprofen	Chitosan	Hep-G2 cells, mice
Mesoporous silica nanoparticles [29]	pH < 5.5	Doxorubicin	Chitosan/poly (methacrylic acid)	HeLa cells
Mesoporous silica nanoparticles [30]	pH < 5.0	Doxorubicin	ZnO nanolids	HeLa cells
Mesoporous silica nanoparticles [31]	pH < 6.0	Doxorubicin	β-Cyclodextrin	THP-1 and KB-31cells
Nanoparticles [32]	pH < 6.0	Daunorubicin hydrochloride and Mitoxantrone	Metalion-ligand coordination-bonds	N/A
Mesoporous silica nanoparticles [33]	pH < 6.3	Ibuprofen	Chitosan	N/A
Core-shell Fe_3O_4@mSiO_2 nanoparticles [34]	pH < 5.8	Doxorubicin	Chitosan	HepG2
Litchi-like Fe3O4@Fe-MOF [35]	pH < 5.0	Doxorubicin	Hydroxyapatite	HeLa cells
Mesoporous silica nanoparticles [36]	pH < 6.5	Doxorubicin	Poly(2-(pentamethyleneimino)ethyl methacrylate)	HeLa cells
Mesoporous silica nanoparticles [37]	pH < 5.0	Doxorubicin	Polydopamine	MCF7, MDA-MB-231 cells, Nude mice
Mesoporous silica nanoparticles [38]	pH < 5.5	Doxorubicin	Dextran	HeLa cells
Mesoporous silica nanoparticles [39]	pH < 5.3	Doxorubicin	β-cyclodextrin	HeLa and HepG2 cells
Nanoparticles [40]	pH < 5.0	Docetaxel	Acetal group	N/A
Core-shell nanoparticles [41]	pH < 5.3	Doxorubicin	Polypyrrole	HepG2 cells and mice

Table 2: Reactive oxygen species responsive multifunctional nanoplatforms and their response mechanism.

Nanocarrier type	Release conditions	Drug type	Ros-responsive materials	Mechanisms (Reactive oxygen species induced)	Biological model
RGD–PEG–TK–PLGA polymer [42]	KO_2 (50 - 100 mM)	Doxorubicin and alpha-TOS	Poly(lactic-co-glycolic acid)	Bond cleavage	Cal27 cells and Balb/c mice
Polymeric micelles [43]	H_2O_2: 3.3 vol% 3-Morpholinosydnonimine (SIN-1): 1 - 100 mM Peroxynitrite: 1 - 100mM	Nile red and DiO	Poly(propylene sulfide)	Hydrophobic-hydrophilic transition	RAW 264.7 cells
Polymersomes [44]	H_2O_2: 1 mM at 37°C	Double-quenched green bovine serum albumin or Doxorubicin	Hydrophobic boronic ester	Hydrophobic-hydrophilic transition	EL4 T cell and mice
Cytotoxin epothilone B [45]	H_2O_2: 100 μM at 37°C	Epo B and Cy5.5	Thioketal	Bond cleavage	PC-3, HCT116 cancer cells, L929 normal cells, mice
Polypeptide-based block copolymer micelles [46]	H_2O_2: 500 mM at 25°C	Nile Red	Thioether	Hydrophobic-hydrophilic transition	B16F10 and L929 cells
Fe3O4@OANPs [47]	H_2O_2: 133 μM	5-FLU	Chitosan	Bond cleavage	A549, HeLa S3, MCF-7 and IMR-90 cells
Amphiphilic block copolymer [48]	H_2O_2: 100 mM for CPT and 0.1 mM for Lapa at 37°C	β-lapachone and Camptothecin	Thioketal linkers	Bond cleavage	4T1 or NIH-3T3 cells, mice
PTX-S-MAL prodrug nanoparticles [49]	H_2O_2: 1 mM	PTX	Thioether linker	Bond cleavage	4T1, NIH/3T3 cells and mice
Polymeric nanoparticles [50]	H_2O_2: 100 mM	Docetaxel	Thioether	Hydrophobic-hydrophilic transition	CT-26 cells and mice
Polymeric aggregates [51]	H_2O_2: 0.1% v/v	Doxorubicin	Selenium-containing polymers	Hydrophobic-hydrophilic transition	-
Nanogel [52]	H_2O_2: 10 mM	Doxorubicin	Selenium-containing polymers	Hydrophobic-hydrophilic transition	A549 and HEK293 cells
Ferrocene nanoparticles [53]	H_2O_2: 0.4 M	Nile red	Ferrocene-containing polymers	Hydrophobic-hydrophilic transition	NIH 3T3 fibroblast cells
Spherical aggregates [54]	H_2O_2: 100 mM	-	Tellurium-containing polymers	Hydrophobic-hydrophilic transition	-
Polymeric nanoparticles [55]	O_2^-: 0.2 mM	siRNA	Poly(thioketal)	Degradation	RAW 264.7 macrophages and mice
Polymeric scaffolds [56]	H_2O_2: 0.2% v/v	-	Poly(thioketal)	Degradation	RAW 264.7 macrophages and Sprague-Dawley rats
Polymeric nanoparticles [57]	H_2O_2: 50 μM	Nile red	Phenylboronic acid and ester-containing polymers	Degradation	dMPRO cells
Polymeric scaffolds [58]	SIN-1: 1 mM H_2O_2: 5 mM	-	Poly(proline)	Degradation	immortalized bone-marrow-derived macrophages

responses, thereby enhancing the therapeutic efficacy against triple-negative breast cancer. Fluorescence-based systems have also gained traction for their ability to provide real-time feedback on treatment efficacy. Zhao et al. [7] presented a fluorescence nanosystem designed for monitoring caspase-1 activity, a critical marker in assessing tumor responses to therapy. This system enables precise tracking of reactive oxygen species generation, thereby facilitating timely adjustments to treatment protocols.

The NanoTrackThera platform utilizes fluorescence and photoacoustic imaging to monitor tumor biomarker changes in real-time during combined immunotherapy and photothermal therapy. This dual detection capability allows for precise feedback on treatment efficacy, enhancing the therapeutic outcome for non-small cell lung cancer models [62]. The near infra-red ratiometric fluorescent nanoplatform employs dual fluorescent probes to monitor the efficacy of sonodynamic therapy by tracking singlet oxygen generation. This method provides a consistent reflection of treatment efficacy through changes in fluorescence signals, offering a reliable real-time monitoring strategy [63]. Mesoporous silica nanoparticles are used for 'on-demand' drug release, triggered by tumor markers such as survivin mRNA. The fluorescence resonance energy transfer strategy enables real-time monitoring of drug release, ensuring that therapeutic agents are delivered precisely when needed, minimizing toxicity to healthy cells [64]. Gold nanoparticles serve as vehicles for controlled drug release and photothermal therapy, with their optical properties allowing for real-time monitoring of disease progression and therapeutic response. This dual functionality supports precision oncology by tailoring treatments to individual patient needs [65].

Multifunctional nanomicelles incorporate pH-activatable fluorescent probes and near infra-red photosensitizers for targeted cancer imaging and therapy. They enable real-time visualization of the treatment process by lighting up lysosomes and reflecting cellular status, thus providing molecular information for precise therapy [66]. Nanotheranostics-based imaging approach integrates molecular imaging with therapeutic monitoring, offering insights into tumor shrinkage, metastasis, and apoptosis. It supports the evaluation of therapeutic responses and side effects, guiding treatment adjustments in real-time [67]. While these techniques offer significant advancements in precision oncology, challenges such as biocompatibility, toxicity, and regulatory hurdles remain. Addressing these issues is crucial for the successful translation of these technologies into clinical practice. Future research should focus on improving the safety profiles of these nanoplatforms and developing standardized protocols for their use in diverse clinical settings [68, 69].

In summary, real-time monitoring techniques in multifunctional nanoplatforms are revolutionizing precision oncology by enabling dynamic and personalized treatment strategies. These technologies not only enhance therapeutic efficacy but also minimize adverse effects, paving the way for more effective cancer management. However, ongoing research and development are essential to overcome existing challenges and fully realize the potential of these innovative approaches in clinical applications.

Controlled Release Mechanisms

The ability to control the release of therapeutic agents is a cornerstone of effective cancer treatment. Zeng et al. [70] highlighted the importance of developing nanosystems that can release drugs in response to specific stimuli, such as pH or temperature changes. Their study demonstrated that a double-triggering caramelized nanotheranostic system could achieve significant drug release under acidic conditions typical of the tumor microenvironment, thereby enhancing the therapeutic impact while minimizing systemic toxicity. Hybrid nanoparticles have emerged as a versatile platform for achieving synchronized delivery of multiple therapeutic agents. Raka et al. [5] emphasized the potential of hybrid nanocarriers to combine hydrophilic and hydrophobic drugs, enabling a more comprehensive approach to overcoming multidrug resistance in cancer treatment. These carriers can be engineered to respond to tumor microenvironment specific cues, ensuring that drug release is both targeted and controlled.

pH-responsive nanoplatforms exploit the acidic microenvironment of tumors to trigger drug release. For instance, copper peroxide nanoparticles decompose under acidic conditions to release H_2O_2 and Cu^{2+}, which further trigger the release of carbon monoxide and reactive oxygen species, enhancing oncotherapy efficacy [23]. Another example involves mesoporous silica nanoparticles functionalized with disulfide bonds that cleave in acidic endosomal pH, releasing doxorubicin specifically within cancer cells [71]. Nanoplatforms can also utilize reactive oxygen species and redox conditions for controlled release. The presence of reactive oxygen species in the tumor microenvironment can trigger the release of therapeutic agents, as seen in systems where reactive oxygen species generation leads to the rapid intracellular release of carbon monoxide, promoting apoptosis [23]. Redox-sensitive coatings, such as MnO_2 nanosheets, dissociate in the presence of glutathione, releasing drugs like doxorubicin and enhancing MRI signals, thus providing both therapeutic and diagnostic capabilities [72].

Near-infrared light is used to control drug release in some nanoplatforms. For example, Fe_3O_4@$mSiO_2$ nanoparticles gated by a lipid bilayer release drugs upon near infra-red irradiation, which increases the permeability of the lipid bilayer, allowing for precise control over drug delivery [73]. Photoinitiated crosslinking in micellar systems provides stability in circulation and allows for rapid drug release upon exposure to specific light wavelengths, offering a spatiotemporal control over drug delivery [74]. Multifunctional nanoplatforms often incorporate targeting ligands, such as aptamers or folate, to enhance specificity towards cancer cells. This targeting capability is combined with controlled release mechanisms to ensure that drugs are delivered precisely to tumor sites, minimizing effects on healthy tissues [71, 72]. Metal-organic frameworks and other nanoparticle systems are designed to exploit enhanced permeability and retention effect, further improving localization and accumulation in tumor tissues [22, 68].

While multifunctional nanoplatforms offer significant advantages in precision oncology, challenges remain in optimizing their design for clinical applications. Issues such as biocompatibility, potential toxicity, and regulatory hurdles need to be addressed to ensure safe and effective use in patients. Additionally, the integration of diagnostic and therapeutic functions in a single platform, known as theranostics, holds promise for real-time monitoring of treatment efficacy, but requires further development to overcome current limitations. As research progresses, these nanoplatforms are expected to play a crucial role in advancing personalized cancer therapy.

Clinical Studies

Multifunctional nanoplatforms are emerging as a transformative approach in precision oncology, offering the potential to enhance both the diagnosis and treatment of cancer. These platforms integrate various therapeutic and diagnostic functions into a single system, aiming to improve the specificity and efficacy of cancer treatments

while minimizing side effects. The development and clinical translation of these nanoplatforms are supported by a range of studies exploring different materials and strategies.

A study by Zhao et al. [75] successfully developed an arsenic trioxide-based multifunctional drug delivery system. This system was designed to efficiently deliver arsenic trioxide for cancer therapy and enable real-time monitoring of its release and delivery *in vivo* (Figure 1). The system utilized water-insoluble manganese arsenite complexes (an arsenic trioxide prodrug) loaded into hollow silica nanoparticles, creating a pH-sensitive delivery system. Acidic stimuli triggered the simultaneous release of manganese ions and arsenic trioxide. This release dramatically increased the T1 signal, allowing for real-time visualization and monitoring of arsenic trioxide release and delivery through bright signal imaging. The smart multifunctional drug delivery system significantly improved the efficacy of arsenic trioxide. It strongly inhibited the growth of solid tumors. Crucially, these therapeutic benefits were achieved without adverse side effects. In summary, the paper reports the successful creation and evaluation of a novel drug delivery system for arsenic trioxide that not only enhances its anti-cancer effectiveness and tumor inhibition but also provides a real-time monitoring capability for arsenic trioxide release, all while maintaining a favorable safety profile.

A study Lai et al. [76] detailed the development and evaluation of a novel adenosine triphosphate responsive drug delivery system utilizing mesoporous-silica-coated multicolor up conversion nanoparticles (UCNP@MSN). The system allows for real-time monitoring of drug release through ratiometric luminescence changes (Figure 2). Loading anticancer drugs like doxorubicin or camptothecin into the UCNP@MSNs led to luminescence resonance energy transfer from the UCNP (donor) to the drugs (acceptor), resulting in quenching

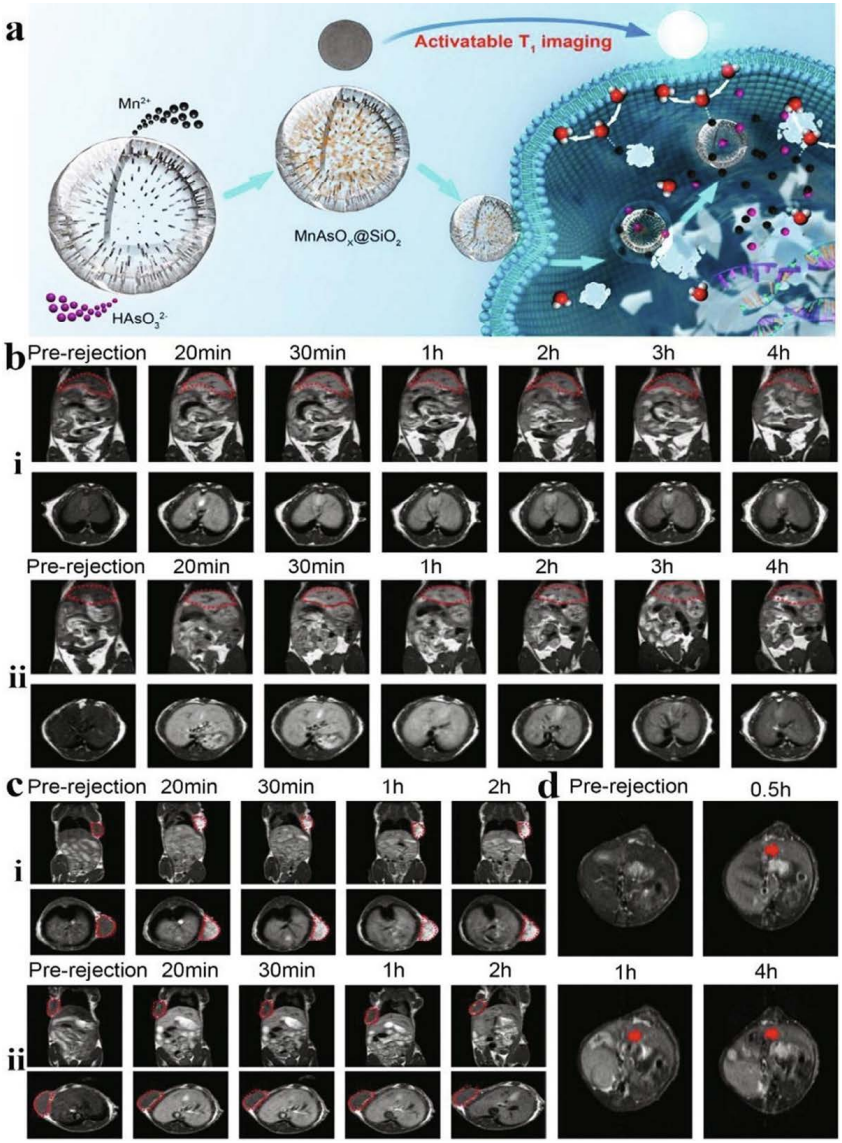

Figure 1: (a) A schematic illustration of hollow silica nanoparticles designed for co-loading arsenic trioxide, enabling real-time tracking of drug release within cells through activatable T1-weighted MRI. **(b)** *In vivo* T1-weighted MRI (coronal and transverse views) showing real-time drug release monitoring in the livers of healthy BALB/c mice. **(c)** T1-weighted MRI for tumor diagnosis and real-time drug release tracking in BALB/c mice with subcutaneous H22 tumors after intravenous injection of (i) manganese arsenite complexes@silica-GSH and (ii) manganese arsenite complexes@silica at various time points. and **(d)** Transverse plane T1-weighted MRI for tumor detection and real-time drug release assessment in BALB/c mice with orthotopic H22 liver tumors following manganese arsenite complexes@silica-GSH injection. The orthotopic liver tumors are marked by red arrows [75].

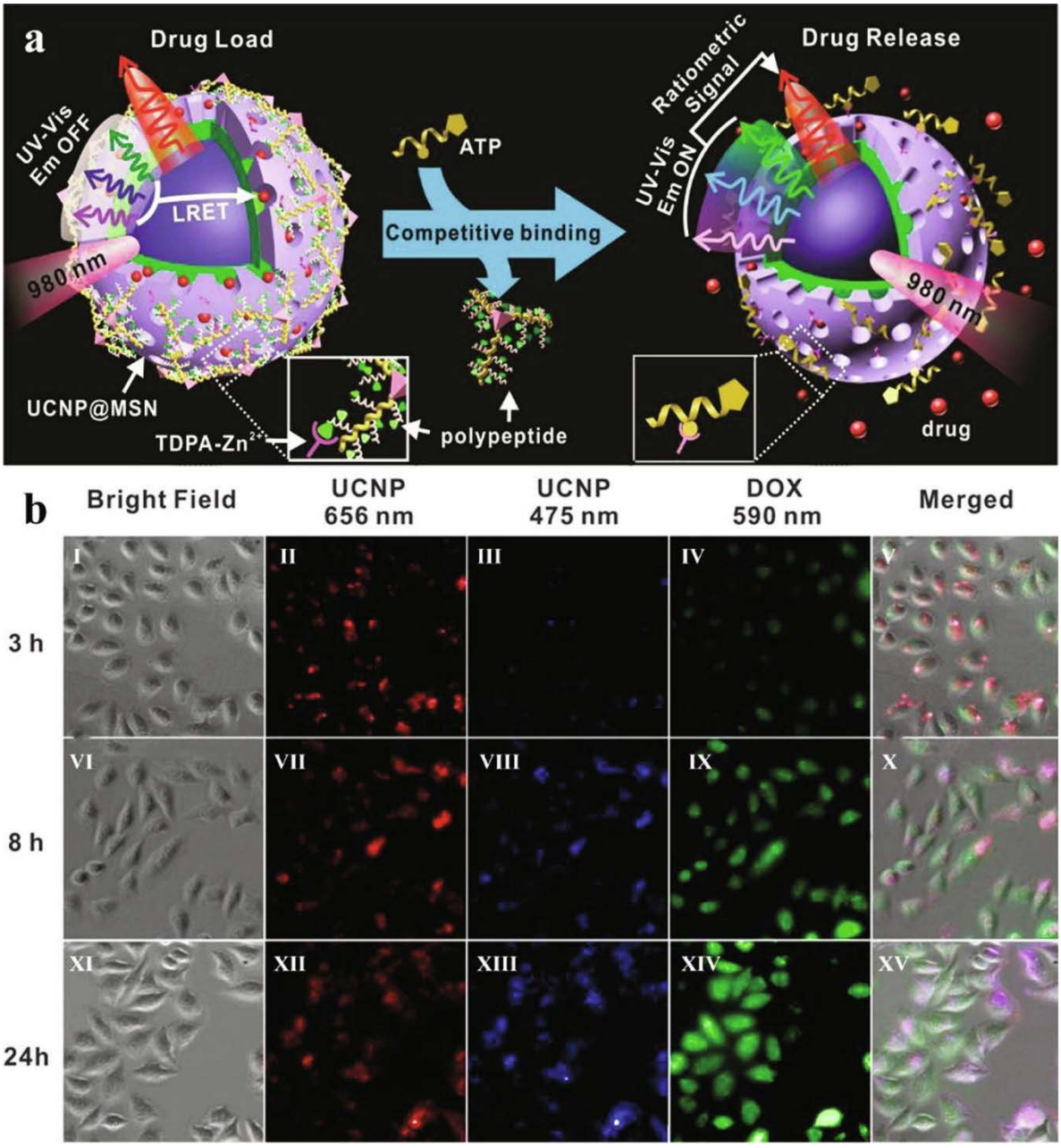

Figure 2: (a) Schematic illustration of adenosine triphosphate responsive drug release from TDPA-Zn^{2+}-UCNP@MSNs encapsulated by a polypeptide, enabling real-time monitoring. **(b)** Fluorescence microscopy images showing the time-dependent changes (3, 8, and 24 h) in UCNP and DOX emission signals in HeLa cells after treatment with G2d2-coated TDPA-Zn^{2+}-UCNP@MSNs [76].

of the UV-vis emission of UCNP. The near infra-red emission of the UCNP remained constant and served as an internal reference for tracking and imaging. Upon adenosine triphosphate triggered drug release, the luminescence resonance energy transfer diminished, leading to an enhancement in the UV-vis emission of UCNP. A linear correlation was established between the amount of released drug and the ratiometric signal of the UCNP, enabling real-time monitoring of drug release kinetics. The polypeptide-wrapped TDPA-Zn^{2+}-UCNP@MSNs demonstrated negligible cytotoxicity in HeLa cells, confirming their biocompatibility. Targeted delivery was achieved using folic acid-modified polypeptides, showing selective uptake by HeLa cells (which overexpress folate receptors) but not by MCF-7 cells (which lack folic acid receptor). *In vitro* real-time monitoring in HeLa cells showed that after 3 h, most drug delivery systems were entrapped in endosomes with limited doxorubicin release. As time progressed (8 and 24 h), a time-dependent enhancement of fluorescence intensity (590 nm) and diffuse dispersion of doxorubicin within the cancer cells were observed, indicating adenosine triphosphate triggered release. The recovery of UCL signal at 475 nm was clearly detectable, further confirming the adenosine triphosphate triggered release and the capability of the drug delivery system to monitor drug release in real-time. In conclusion, the study successfully developed an adenosine triphosphate responsive UCNP@MSN-based drug delivery system capable of long-term tracking and real-time monitoring of drug delivery *in vitro*. The

system's mechanism, based on competitive binding and luminescence resonance energy transfer, allows for flexible modulation of specificity and sensitivity, making it a promising platform for cancer therapy and neuroscience applications. The multi-emission peaks of UCNPs enable real-time monitoring for various drugs with different UV-vis absorption properties.

A study by Ma et al. [77] focused on engineering a stable nanocomposite, Zr-metal-organic frameworks-quercetin, for dual sensitization in radiotherapy, aiming to overcome hypoxia-induced resistance in tumor tissues. Nanocomposite exhibited excellent potential for radiotherapy sensitization characteristics. This was observed through both *in vitro* and *in vivo* experiments. The evaluation methods included γ-H_2AX immunofluorescence staining and colony assays, which confirmed the sensitizing effects. The decomposition product from nanocomposite was found to suppress carbonic anhydrase IX expressions. This mechanism helps alleviate resistance induced by the hypoxic environment within tumors. Quercetin, encapsulated within the nanocomposite structure, played a crucial role in boosting the overall sensitivity of tumor tissues to radiation therapy. The combined action of suppressing carbonic anhydrase IX and boosting sensitivity by quercetin led to improved cell apoptosis from radiation. The treatment showed no significant systemic toxicity during its application. The therapeutic outcome was assessed in animal models, indicating a promising approach for cancer treatment in the field of radiation therapy. In summary, the paper successfully demonstrated that the nanocomposite can effectively enhance radiotherapy by addressing hypoxia and increasing tumor cell sensitivity, all while maintaining a favorable safety profile.

A research study by Shabana et al. [78] focused on developing and evaluating a pH-sensitive multi-ligand gold nanoplatform (THZN) designed to target carbonic anhydrase IX and enhance the delivery of doxorubicin to hypoxic tumor spheroids, thereby overcoming hypoxia-induced chemoresistance. HT-29 colorectal cancer cells, used as a tumor hypoxia model, showed significantly higher expression of carbonic anhydrase IX under hypoxic conditions compared to normoxic conditions. While LA-decorated Au NPs (Au NPs-LA) were taken up in large amounts under normoxic conditions, their uptake was diminished under hypoxic conditions. Importantly, Au NPs decorated with short carbonic anhydrase inhibitor ligands (Au NPs-LA-CAI) showed increased uptake under hypoxic conditions compared to normoxia, demonstrating a statistically significant increase in uptake versus non-targeted Au NPs-LA under hypoxia. PEGylated Au NPs (Au NPs-LA-PEG2000) showed very low uptake in both normoxic and hypoxic conditions due to steric stabilization. However, when carbonic anhydrase inhibitor ligands were introduced on PEGylated Au NPs (Au NPs-LA-PEG2000-CAI), a small uptake was observed under normoxic conditions, attributed to carbonic anhydrase IX mediated endocytosis. Crucially, Au NPs-LA-PEG2000-carbonic anhydrase inhibitor showed significantly higher cell uptake under hypoxic conditions versus normoxia, correlating with high carbonic anhydrase IX expression and carbonic anhydrase IX mediated endocytosis. The release of doxorubicin from the nanoplatforms (NTHZN and THZN) was confirmed to be pH dependent. At pH 5.5 (mimicking late endosomes), there was a rapid burst release of Dox (almost 80% after 4 h and 98% after 24 h), whereas at pH 7.4, the release rate was very slow (<20% after 4 hours and 23% after 24 h). Free doxorubicin showed reduced cytotoxicity under hypoxic conditions compared to normoxic conditions. The Dox-loaded nanoplatforms with an amide linker did not show additional cytotoxic effects due to the linker's stability. In contrast, the Dox formulations with a pH-labile hydrazone group (NTHZN and THZN) showed improved cytotoxicity, attributed to the fast cleavage of the acid-sensitive hydrazone linker in the late endosome, liberating free Dox. Most significantly, the carbonic anhydrase IX targeted THZN formulations exhibited superior cytotoxic effects compared to NTHZN, especially under hypoxic conditions. This enhanced toxicity reverses the hypoxia-induced chemoresistance observed with free Dox and non-targeted nanoparticles. Improved Tumor Penetration: In tumor spheroids, free doxorubicin was confined to the periphery, likely due to its lipophilicity and partial protonation in the mild acidic hypoxic environment. The NTHZN nanoplatform showed better tumor penetration than free Dox. However, the THZN nanoplatform demonstrated superior tumor penetration and doxorubicin delivery compared to both NTHZN and free Dox. Quantitative assessment showed that the THZN nanoplatform delivered almost 2.5 times more doxorubicin into tumor spheroids than both NTHZN and free Dox treatments. This highlights the potentiating role of carbonic anhydrase IX in enhancing the uptake of targeted formulations and increasing the amount of free drug released inside tumor cells. In summary, the optimized THZN nanoplatform effectively targets carbonic anhydrase IX, enhances doxorubicin delivery, and overcomes hypoxia-induced chemoresistance in tumor cells and spheroids, demonstrating better tumor penetration and increased drug accumulation compared to free doxorubicin. This technology represents a promising approach to improve chemotherapy outcomes in solid tumors.

Research by Wang et al. [79] investigated the development and efficacy of antisense oligonucleotide-laden UiO-66@Au (UAAP) nanohybrids for enhanced radiotherapy against hypoxic tumors, specifically triple-negative breast cancer. The key results demonstrate the successful synthesis, characterization, and therapeutic potential of these nanohybrids both *in vitro* and *in vivo*. Hypoxic MDA-MB-231 cells, which typically up-regulate CA IX and HIF-1α, showed significant inhibition of both proteins when treated with UAAP NPs. The dual-inhibition strategy, involving PTA (exogenous) and ASO (endogenous), resulted in 68% inhibition of CA IX and 79% inhibition of HIF-1α protein expression. UAAP + RT treatment significantly increased DNA damage, as evidenced by γ-H2AX foci, showing a 10.9-fold increase compared to UAP NPs alone and 21% higher than UAP+RT. The UAAP-treated cells exhibited a higher G2/M phase proportion, which is a radiosensitive phase of the cell cycle. Clonogenic survival assays confirmed potent radiosensitization, with UAAP+RT leading to only 11.53% cell survival, indicating high-performance radiosensitization. Flow cytometry showed that UAAP NPs induced 28.12% apoptotic cells, which was significantly higher than control or UAP NPs. UAAP NPs demonstrated significant tumor accumulation due to the enhanced permeability and retention effect, with strong fluorescence signals observed in tumors. ICP-MS analysis confirmed higher Zr content in tumors compared to other organs, supporting effective accumulation and stable retention. *In vivo* studies showed that UAAP+RT treatment resulted in the smallest tumor volume and highest tumor inhibition rate (93.48%) among all groups, demonstrating a synergistic effect of radiosensitization and dual CA IX inhibition. Histopathological examination revealed more fragmented cell nuclei and increased apoptotic cells in the UAAP+RT group, along with reduced Ki67 (proliferation marker) and lower CA IX and HIF-1α expression. The nanohybrids exhibited high physiological stability and biocompatibility, with no obvious body weight changes or destruction in major organs, and normal serum biochemistry and blood routine parameters. In conclusion, the UAAP nanohybrids represent a promising therapeutic platform that effectively combines dual CA IX

inhibition and radiosensitization, leading to significant anti-tumor effects in hypoxic TNBC models, highlighting its potential for clinical application in managing hypoxic tumors. This strategy offers a robust approach to overcome radioresistance by alleviating hypoxia and enhancing the sensitivity of tumor cells to radiation.

A study by Li et al. [80] investigated the synthesis and application of cyanine (Cy) embedded within zeolitic imidazolate framework-8 (Cy@ZIF-8) nanoparticles for antitumor photothermal therapy and near infra-red imaging. The key results demonstrate the therapeutic and diagnostic potential of these novel nanocarriers. The Cy@ ZIF-8 nanoparticles exhibited good water solubility and excellent photostability, addressing limitations of free Cy dye. The synthesized Cy@ZIF-8 NPs displayed strong near infra-red absorbance and a great photothermal conversion efficiency, which are crucial for effective photothermal therapy. The Cy@ZIF-8 NPs were found to efficaciously inhibit tumor growth. This indicates their potential as an effective agent for anticancer photothermal therapy. The nanoparticles demonstrated outstanding near infra-red imaging capacity, both *in vitro* and *in vivo*. This suggests their utility as a theranostic agent, combining therapy with imaging for guided treatment. The work successfully demonstrated the theranostic value of Cy@ZIF-8 NPs for imaging-guided photothermal therapy. This also encourages further research into other phototherapy agents embedded in ZIF-8 composites for improved anticancer photothermal therapy. In summary, the paper highlights the successful development of Cy@ZIF-8 nanoparticles as a promising platform for imaging-guided photothermal therapy, overcoming the inherent limitations of free Cy dye while providing effective tumor inhibition and imaging capabilities.

A study by Zhao et al. [81] focused on developing a novel approach to enhance T cell-mediated cancer immunotherapy by reprogramming lysosomes within CD8+ T cells. A lysosome-targeting nanoparticle (LYS-NP) was successfully developed. This nanoparticle is composed of a mineralized metal-organic framework coupled with a CD63-aptamer, which targets lysosomes. The metal-organic framework, synthesized from Zn^{2+} and dimethylimidazole, demonstrated good protein encapsulation capabilities and acid sensitivity, making it suitable as a lysosomal delivery vector. Calcium carbonate was utilized to induce metal-organic framework mineralization, which improved the composite material's stability for encapsulating therapeutic proteins and provided synergistic calcium ions. Before mineralization, therapeutic proteins crucial for tumor targeting, specifically perforin and granzyme B, were preloaded into the metal-organic framework. T cells were pretreated with processed tumor-specific antigens. This step aimed to activate the T cells or induce memory, thereby facilitating the T cell receptor for the release of the therapeutic proteins upon lysosome reprogramming. The study confirmed a significant enhancement in breast cancer control when using T cells recombined with LYS-NPs. This demonstrates the effectiveness of the developed LYS-NP in improving the antitumor function of T cells. In summary, the paper successfully developed a LYS-NP that can deliver therapeutic proteins like perforin and granzyme B to T cells, leading to a significant improvement in breast cancer control by enhancing the T cells' antitumor effects.

A study by Li et al. [82] demonstrated the successful design and application of a nanoscale metal-organic frameworks-based vaccine, highlighting its synergistic effects with programmed cell death 1 (PD-1) blockade therapy to enhance anti-tumor immunity. The study developed an ultrafast, low-temperature, and universal self-assembly method to integrate immunology-associated large molecules into metal-organic framework gated mesoporous silica nanoparticles, forming cancer vaccines. Core mesoporous silica nanoparticles were found to act as an intrinsic immunopotentiator, providing space to accommodate antigens and soluble immunopotentiators. The metal-organic framework gatekeeper component of the vaccine protects its interior contents from robust and off-target release, ensuring controlled delivery. A combination of the metal-organic framework gated mesoporous silica cancer vaccines with systemic PD-1 blockade therapy generated synergistic effects that significantly potentiated anti-tumor immunity. This combination therapy allowed for a substantial reduction in the effective dose of an anti-PD-1 antibody, requiring as low as 1/10 of the dose typically used for PD-1 blockade monotherapy in E.G7-OVA tumor-bearing mice. The combination therapy elicited robust adaptive OVA-specific CD8+ T-cell responses in the mice. The treatment was effective in reversing the immunosuppressive pathway within the tumor microenvironment. The synergistic approach induced durable tumor suppression in the E.G7-OVA tumor model. In summary, the paper successfully demonstrates a novel nanoscale vaccine platform that, when combined with PD-1 blockade, dramatically improves anti-tumor immune responses and allows for a significant reduction in the required dose of anti-PD-1 therapy, offering a promising strategy for more effective and cost-efficient cancer treatment.

Research by Wu et al. [83] proposed a novel approach to tumor starvation therapy by introducing a 'nano-enabled energy interrupter'. The proposed energy interrupter effectively leads to preferential tumor systemic energy exhaustion. This indicates a targeted effect on tumor cells, aiming to deprive them of necessary energy for survival and growth. The mechanism behind this energy exhaustion is synergistic, involving two main components: (i) The interrupter utilizes Zn^{2+} interference to inhibit glycolysis, a crucial metabolic pathway for energy production in cancer cells and (ii) It also achieves tumor-specific depletion of GLUT1 (glucose transporter 1), which is activated by Zn^{2+}. GLUT1 is essential for glucose uptake by tumor cells, and its depletion further starves the cells. A significant result of this therapy is that it achieves tumor systemic energy exhaustion without causing obvious side effects. This suggests a potentially safer therapeutic strategy compared to conventional treatments that often come with severe systemic toxicities. In summary, the paper introduces a promising 'nano-enabled energy interrupter' that effectively starves tumors by inhibiting glycolysis and depleting GLUT1, all while showing a favorable safety profile with no apparent side effects.

Challenges and Future Directions

Despite the promising advancements in multifunctional nanosystems, several challenges remain. Issues related to biocompatibility, scalability, and long-term safety profiles must be addressed to facilitate clinical translation. As highlighted by Gupta et al. [84], ongoing research is focused on optimizing the design and functionalization of nanosystems to enhance their therapeutic efficacy while minimizing adverse effects. The integration of multifunctional nanosystems with immunotherapy represents a promising avenue for enhancing treatment outcomes. El-Tanani et al. [85] discussed how electrically active biomaterials can modulate the tumor microenvironment to improve drug delivery and enhance the efficacy of immunotherapeutic agents. This synergistic approach could pave the way for more effective cancer treatments that leverage the body's immune response.

Challenges

- Biocompatibility and toxicity: Ensuring that nanoparticles

are biocompatible and non-toxic is a significant challenge. Many nanoparticles can induce immune responses or accumulate in non-target tissues, leading to potential side effects [68, 86].

- Scalability and reproducibility: The production of nanoparticles at a scale suitable for clinical use while maintaining consistency and quality is difficult. Techniques like high-pressure homogenization and media milling are being explored to address these issues, but reproducibility remains a concern [51].

- Regulatory approval: The path to regulatory approval for multifunctional nanoplatforms is complex, requiring extensive testing to demonstrate safety and efficacy. This process can be lengthy and costly, delaying the availability of new treatments [68, 86].

- Targeting and delivery: Achieving precise targeting of cancer cells while avoiding healthy tissues is crucial. Current strategies involve ligand-receptor targeting and exploiting enhanced permeability and retention effect, but these methods are not always effective across different tumor types [68, 88].

Future directions

- Advanced targeting strategies: Research focuses on developing more sophisticated targeting mechanisms, such as active targeting using monoclonal antibodies and surface functionalization of nanoparticles to improve specificity and reduce off-target effects [89, 90].

- Multimodal therapies: Combining multiple therapeutic modalities, such as photothermal, photodynamic, and immunotherapy, within a single nanoplatform can enhance treatment efficacy and overcome resistance mechanisms in tumors [91].

- Integration with diagnostic tools: The development of theranostic platforms that combine therapeutic and diagnostic capabilities is a promising area. These systems allow for real-time monitoring of treatment efficacy and can be tailored to individual patient needs [68, 89].

- Organ-on-a-chip models: To better predict human responses, organ-on-a-chip models are being developed to simulate the tumor microenvironment and test the efficacy of nanoplatforms in a controlled setting [92].

While the potential of multifunctional nanoplatforms in precision oncology is immense, it is essential to address the challenges of clinical translation. The integration of advanced targeting strategies and multimodal therapies, along with improved diagnostic capabilities, could significantly enhance the effectiveness of cancer treatments. However, the complexity of tumor biology and the variability in patient responses necessitate continued research and innovation in this field.

Conclusion

The development of multifunctional nanosystems represents a transformative advancement in precision oncology, offering unparalleled capabilities for real-time tumor monitoring and controlled, tumor-specific therapeutic delivery. By integrating diagnostic and therapeutic functionalities into a single platform, these nanosystems enable personalized treatment strategies that enhance therapeutic efficacy while minimizing adverse effects. The diverse array of nanoplatforms-including hybrid nanoparticles, nanogels, hydrogels, and magnetoliposomes-demonstrates remarkable potential in overcoming challenges such as multidrug resistance and tumor heterogeneity. However, the clinical translation of these innovations requires addressing critical issues related to biocompatibility, scalability, and regulatory approval. Continued research and interdisciplinary collaboration are essential to optimize these systems for widespread clinical use, ensuring they meet safety and efficacy standards.

Looking ahead, the future of multifunctional nanosystems lies in the integration of advanced targeting strategies, multimodal therapies, and real-time diagnostic tools. Combining these approaches with emerging technologies like organ-on-a-chip models and immunotherapy could further enhance treatment precision and patient outcomes. Despite the existing challenges, progress in this field underscores the immense potential of nanotechnology to revolutionize cancer therapy. As innovations continue to bridge the gap between laboratory research and clinical application, multifunctional nanosystems are poised to play a pivotal role in the era of precision medicine, ultimately improving the quality of life for cancer patients worldwide.

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None.

Conflict of Interest

None.

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