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Smart Stimuli-Responsive Nanocarriers: Overcoming Biological Barriers in Solid Tumors

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Abstract

Multi-responsive nanocarriers have emerged as a promising platform in precision oncology, offering advanced capabilities for targeted, controlled, and stimuli-adaptive drug delivery. These systems are engineered to respond to multiple endogenous and exogenous stimuli within the Tumor Microenvironment (TME), including pH gradients, redox potential, enzymatic activity, hypoxia, and external physical triggers such as light, ultrasound, and magnetic fields. By integrating these responsive mechanisms, multi-functional nanocarriers can enhance tumor selectivity, improve deep tissue penetration, and enable on-demand drug release, thereby addressing major limitations of conventional chemotherapy and first-generation nanomedicine. Despite significant progress in material design, structural engineering, and preclinical validation, the clinical translation of multi-responsive nanocarriers remains limited. Major challenges include biological barriers such as rapid systemic clearance, abnormal tumor vasculature, elevated Interstitial Fluid Pressure (IFP), dense Extracellular Matrix (ECM), and tumor heterogeneity, as well as issues related to nanocarrier stability, large-scale reproducibility, and regulatory constraints. Additionally, discrepancies between preclinical models and human tumor biology further complicate successful clinical translation. Recent advances in biomimetic engineering, logic-gated delivery systems, and Artificial Intelligence (AI)-assisted nanocarrier design offer promising solutions to overcome these limitations. Furthermore, the development of personalized and multifunctional theranostic platforms is expected to play a key role in improving therapeutic outcomes. Multi-responsive nanocarriers represent a transformative approach in cancer therapy, with strong potential to enable highly precise and patient-specific treatment strategies. Continued interdisciplinary research is essential to bridge the gap between laboratory innovation and clinical application in precision oncology.

Keywords: Nanocarriers, Oncology, Tumor microenvironment, Biological barriers, Nanomedicine, Controlled drug release, Cancer therapy.

1 | Introduction

Precision oncology has redefined the conceptual framework of cancer therapy by transitioning from empirical, population-based treatment strategies to a more individualized approach grounded in the molecular and phenotypic heterogeneity of tumors [1–3]. This paradigm shift has been driven by advances in genomics, proteomics, and high-throughput sequencing technologies, enabling the identification of actionable mutations

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and patient-specific therapeutic targets [4]. Despite these achievements, the clinical translation of precision medicine remains significantly hindered by the lack of efficient drug delivery systems capable of ensuring selective accumulation and controlled release of therapeutic agents at tumor sites. Conventional systemic administration often leads to rapid drug clearance, nonspecific biodistribution, dose-limiting toxicity, and ultimately suboptimal therapeutic outcomes [5–11]. Within this context, nanotechnology has emerged as a transformative platform in the field of Nanomedicine, offering innovative solutions to longstanding challenges in cancer drug delivery. Nanocarriers including liposomes, polymeric nanoparticles, dendrimers, micelles, and inorganic nanomaterials have demonstrated significant potential due to their unique physicochemical properties, such as nanoscale size, high surface-to-volume ratio, tunable surface functionality, and the capacity for multifunctional integration. These characteristics facilitate improved pharmacokinetics, enhanced drug solubility, prolonged circulation time, and the possibility of both passive and active targeting [12–14]. Nevertheless, the clinical performance of first-generation nanocarriers has often fallen short of expectations, largely due to biological complexities such as heterogeneous vascular permeability, elevated Interstitial Fluid Pressure (IFP), and inefficient penetration into tumor tissues. The limitations associated with passive targeting strategies, particularly those relying on the Enhanced Permeability and Retention (EPR) effect, have prompted the development of more sophisticated and adaptive delivery systems [15]. In this regard, stimuli-responsive nanocarriers have gained considerable attention as intelligent systems capable of modulating drug release in response to specific physiological or externally applied triggers. These stimuli can be broadly categorized into endogenous factors such as pH gradients, redox potential, enzymatic activity, and hypoxia and exogenous triggers including temperature, light irradiation, magnetic fields, and ultrasound. By exploiting these stimuli, nanocarriers can achieve spatially and temporally controlled drug release, thereby enhancing therapeutic precision and minimizing systemic toxicity [16–18]. Among these advanced systems, multi-responsive nanocarriers represent a particularly promising class of next-generation drug delivery platforms. Unlike single-stimulus-responsive systems, multi-responsive nanocarriers are engineered to respond to multiple triggers either sequentially or synergistically, enabling a more precise adaptation to the dynamic and heterogeneous tumor environment [4], [7]. This multi-level responsiveness is especially advantageous in addressing the complexity of the Tumor Microenvironment (TME), which plays a critical role in tumor progression, metastasis, and therapeutic resistance. The TME is characterized by a multitude of abnormal physiological features, including acidic extracellular pH resulting from elevated glycolytic metabolism, hypoxic regions due to inadequate oxygen supply, overexpression of specific enzymes such as Matrix Metalloproteinases (MMPs), and altered redox homeostasis with increased intracellular glutathione levels. Additionally, the presence of dense extracellular matrices and stromal barriers significantly impedes nanoparticle penetration and distribution within tumor tissues [7–12]. These factors collectively contribute to the failure of many conventional and single-responsive delivery systems. The major endogenous and exogenous stimuli exploited in multi-responsive nanocarrier design, along with their mechanisms and key limitations, are summarized in *Table 1* [12–18]. In contrast, multi-responsive nanocarriers can be rationally designed to sequentially overcome these barriers for instance, by enabling pH-triggered surface charge conversion to enhance cellular uptake, followed by redox-sensitive drug release within the intracellular environment. The design and engineering of multi-responsive nanocarriers involve a complex interplay between material selection, structural architecture, and functional integration. Polymeric systems incorporating stimuli-cleavable linkers, lipid-based hybrid nanostructures, and inorganic platforms such as gold nanoparticles, mesoporous silica, and magnetic nanomaterials have all been extensively investigated. Advanced design strategies often incorporate phase-transition materials, gatekeeping mechanisms, and hierarchical structures that enable precise control over drug release kinetics. Furthermore, surface modification with targeting ligands such as antibodies, peptides, or small molecules facilitates active targeting by recognizing overexpressed receptors on cancer cells, thereby improving specificity and therapeutic efficacy. An important emerging direction in this field is the development of multifunctional or "theranostic" nanocarriers that integrate diagnostic and therapeutic capabilities within a single platform [19–21]. These systems enable real-time monitoring of drug delivery, biodistribution, and therapeutic response through imaging modalities such as Magnetic Resonance Imaging (MRI), fluorescence imaging, and Computed

Tomography (CT). The incorporation of imaging agents alongside therapeutic payloads not only enhances treatment precision but also supports personalized treatment planning and adaptive therapy. Despite the significant progress achieved in the design and preclinical evaluation of multi-responsive nanocarriers, their clinical translation remains limited. Several critical challenges must be addressed to facilitate their successful integration into clinical practice. These include issues related to large-scale synthesis, batch-to-batch reproducibility, physicochemical stability, and regulatory compliance. Moreover, the complexity of these systems raises concerns regarding long-term toxicity, immunogenicity, and unexpected biological interactions. The discrepancy between preclinical models and human physiology further complicates the prediction of clinical outcomes, underscoring the need for more representative and predictive experimental models. In recent years, the integration of computational approaches, including Artificial Intelligence (AI) and Machine Learning (ML), has opened new avenues for the rational design and optimization of nanocarriers. These technologies enable the analysis of large datasets to identify optimal material compositions, predict biological interactions, and accelerate the development of highly efficient delivery systems. In parallel, advances in personalized medicine are facilitating the customization of nanocarrier design based on patient-specific tumor characteristics, thereby enhancing therapeutic efficacy and reducing adverse effects [18–21]. In this context, multi-responsive nanocarriers are poised to play a pivotal role in the future of precision oncology by providing adaptable, efficient, and highly targeted drug delivery solutions. However, achieving their full clinical potential requires a comprehensive understanding of their design principles, functional mechanisms, and translational challenges. This review aims to present an in-depth and critical overview of recent advances in multi-responsive nanocarriers for precision oncology, with a particular emphasis on rational design strategies, mechanisms of stimuli responsiveness, and barriers to clinical translation. By systematically analyzing current developments and identifying key knowledge gaps, this work seeks to contribute to the advancement of next-generation nanomedicine platforms capable of bridging the gap between laboratory innovation and clinical application.

Table 1. Major stimuli in multi-responsive nanocarriers for precision oncology.

Stimulus Type	Tumor Trigger	Mechanism	Key Advantage	Limitation
pH	Acidic tumor environment	Acid-labile bond cleavage/protonation	Site-specific drug release	Tumor heterogeneity
Temperature	Local hyperthermia	Polymer phase transition	Controlled release	Requires external stimulation
Redox	Elevated intracellular GSH levels	Disulfide bond cleavage	Efficient intracellular delivery	Possible off-target activation
Enzyme	Overexpressed enzymes	Enzymatic degradation	High specificity	Variability in enzyme expression
Hypoxia	Low oxygen levels	Hypoxia-sensitive activation	Targets resistant tumor regions	Complex design
External stimuli (light, magnetic)	Applied externally	Photo/magnetic activation	Precise spatiotemporal control	Limited tissue penetration
Multi-responsive	Multiple triggers	Combined/synergistic response	Enhanced targeting efficiency	Increased design complexity

2|Design Principles of Multi-Responsive Nanocarriers

The rational design of multi-responsive nanocarriers for precision oncology requires an intricate balance between structural stability in systemic circulation and stimuli-responsiveness within the pathological tumor environment. Unlike conventional delivery systems, these advanced platforms must remain inert under physiological conditions while being precisely activated in response to specific endogenous or exogenous triggers associated with the TME [20–22]. Achieving this dual functionality necessitates careful selection of materials, strategic architectural engineering, and integration of multiple functional components within a

single nanoscale system. A fundamental design strategy involves the incorporation of stimuli-cleavable chemical linkers within the nanocarrier framework. These linkers, such as hydrazone, disulfide, acetal, and imine bonds, enable selective disassembly of the nanostructure in response to specific physiological conditions. For instance, pH-sensitive linkers remain stable at physiological pH but undergo rapid cleavage in acidic TMEs or endo-lysosomal compartments, facilitating controlled intracellular drug release. Similarly, redox-sensitive disulfide bonds are cleaved in the presence of elevated intracellular glutathione levels, enabling selective cytosolic drug activation [21]. Another widely explored strategy is the development of core–shell and hierarchical nanostructures. In these systems, the outer shell typically provides systemic stability, stealth properties, and protection against premature degradation, while the inner core contains the therapeutic payload and responds to specific stimuli. This spatial organization allows sequential activation, where the nanocarrier first undergoes tumor accumulation, followed by microenvironment-triggered activation and intracellular drug release. Such hierarchical designs significantly enhance therapeutic precision and minimize off-target toxicity [10–14]. Polymeric materials represent one of the most versatile platforms for constructing multi-responsive nanocarriers. Smart polymers such as poly(N-isopropylacrylamide) (PNIPAM), poly(β-amino esters), and PEGylated copolymers can be engineered to respond to variations in pH, temperature, or redox conditions [2–5]. Their tunable physicochemical properties allow fine control over particle size, surface charge, and degradation kinetics. In addition, amphiphilic block copolymers facilitate self-assembly into micelles and vesicular structures, which are particularly useful for encapsulating hydrophobic anticancer drugs. Hybrid nanostructures combining organic and inorganic components have also gained significant attention due to their multifunctionality. For example, gold nanoparticles exhibit excellent photothermal conversion efficiency, while mesoporous silica nanoparticles provide high surface area and tunable pore sizes for drug loading. Magnetic nanoparticles further enable external guidance and magnetic hyperthermia applications [23]. When integrated with stimuli-responsive polymers, these systems can achieve synergistic multi-triggered responses, enhancing both targeting efficiency and therapeutic output. Surface functionalization plays a critical role in improving the biological performance of nanocarriers. Active targeting ligands such as antibodies, peptides, aptamers, and small molecules can be conjugated onto the nanocarrier surface to recognize overexpressed receptors on cancer cells, including folate receptors, transferrin receptors, and integrins. This active targeting approach enhances cellular uptake via receptor-mediated endocytosis and improves tumor accumulation beyond what is achievable through passive targeting alone. An emerging and highly promising direction in nanocarrier design is the development of programmable or logic-gated systems [16–18]. These systems are engineered to respond only when multiple conditions are simultaneously or sequentially satisfied, mimicking Boolean logic operations. For example, a nanocarrier may be designed to release its payload only under conditions of acidic pH AND high glutathione concentration, thereby significantly improving specificity and reducing premature drug leakage in normal tissues. Furthermore, the integration of diagnostic and therapeutic functionalities has led to the emergence of theranostic nanocarriers, which enable simultaneous imaging and treatment. The major design strategies for multi-responsive nanocarriers are summarized in *Table 2* [18–20]. These systems incorporate imaging agents such as gadolinium for MRI, fluorescent dyes for optical imaging, or radiolabels for Positron Emission Tomography (PET). This dual functionality allows real-time monitoring of biodistribution, tumor accumulation, and therapeutic response, providing critical feedback for personalized treatment strategies. Despite these advances, the rational design of multi-responsive nanocarriers remains a complex engineering challenge. The incorporation of multiple functional modules often leads to increased synthetic complexity, potential instability, and difficulties in large-scale reproducibility. Moreover, ensuring that all stimulus-responsive components function harmoniously without interfering with each other remains a significant scientific hurdle. Therefore, a deep understanding of material interactions, biological environments, and pharmacokinetic behavior is essential for successful translation [19–21].

Table 2. Simplified design strategies for multi-responsive nanocarriers.

Design Strategy	Materials/Approach	Mechanism	Key Advantage	Main Limitation
Stimuli-cleavable linkers	Hydrazone, disulfide, acetal, imine bonds	Stimulus-triggered bond cleavage (pH, redox)	Site-specific drug release	Tumor heterogeneity
Core–shell structures	Lipid-polymer hybrids, layered nanoparticles	Sequential shell protection and core activation	High stability + controlled release	Synthetic complexity
Smart polymers	PNIPAM, PEGylated copolymers, poly(β-amino esters)	Stimuli-induced phase transition or degradation	Tunable responsiveness	Possible instability in vivo
Hybrid nanocarriers	Gold NPs, mesoporous silica, magnetic NPs + polymers	Multifunctional physical + chemical responsiveness	Combined therapy and imaging	Toxicity and clearance concerns
Active targeting ligands	Antibodies, peptides, aptamers, folate	Receptor-mediated endocytosis	Enhanced tumor specificity	Receptor heterogeneity
Logic-gated systems	DNA-based systems, polymer logic nanostructures	Multi-stimuli AND/OR activation	High selectivity	High design complexity
Theranostic systems	Gd^{3+}, fluorescent dyes, radiotracers	Integrated imaging + therapy	Real-time monitoring	Regulatory challenges

3 | Mechanisms of Stimuli Responsiveness in Tumor Microenvironment

The therapeutic performance of multi-responsive nanocarriers is fundamentally governed by their ability to sense and respond to specific physicochemical cues within the TME. These stimuli arise from the unique pathological features of solid tumors, including aberrant metabolism, hypoxia, abnormal vascular architecture, and dysregulated enzymatic activity. The integration of these cues into nanocarrier design enables spatiotemporally controlled drug release and significantly enhances therapeutic precision. One of the most extensively exploited endogenous triggers is the acidic pH characteristic of tumor extracellular space and intracellular endo-lysosomal compartments. Due to the Warburg effect, cancer cells exhibit elevated glycolytic activity, leading to excessive lactate production and extracellular acidification. pH-responsive nanocarriers exploit this gradient through acid-labile linkers or protonation-induced conformational changes, enabling selective drug release in tumor tissues while remaining stable in systemic circulation. Redox-responsive mechanisms represent another critical strategy, primarily based on the elevated intracellular concentration of glutathione (GSH) in cancer cells compared to normal tissues. Disulfide bond-containing nanostructures undergo cleavage in this reductive environment, triggering rapid payload release within the cytoplasm. This intracellular specificity significantly reduces off-target toxicity and enhances drug bioavailability at the site of action. As shown in *Fig. 1*, the responsiveness of nanocarriers to tumor-associated stimuli such as acidic pH and elevated glutathione enables cascade activation, resulting in controlled intracellular drug release. Enzyme-responsive systems further improve targeting specificity by exploiting the overexpression of tumor-associated enzymes such as MMPs, cathepsins, and hyaluronidases. These enzymes are actively involved in Extracellular Matrix (ECM) remodeling, tumor invasion, and metastasis. Nanocarriers designed with enzyme-cleavable peptide sequences or polymeric substrates can undergo site-specific degradation, facilitating deep tumor penetration and localized drug release. In addition to endogenous triggers, hypoxia represents a hallmark feature of solid tumors resulting from inadequate oxygen supply due to abnormal vasculature [2–5]. Hypoxia-sensitive nanocarriers are typically engineered using reduction-sensitive groups or hypoxia-activated prodrugs

that become active only under low oxygen conditions. This approach is particularly effective in targeting resistant tumor regions that are poorly accessible to conventional therapies. Exogenous stimuli such as light, magnetic fields, ultrasound, and temperature provide an additional layer of spatiotemporal control over drug release. For instance, Near-Infrared (NIR) light can induce photothermal or photodynamic effects in nanoparticles containing gold or organic photothermal agents. Similarly, magnetic nanoparticles can be guided externally and activated via alternating magnetic fields to generate localized hyperthermia. Ultrasound-responsive systems further enable deep tissue penetration and non-invasive activation of drug release. Importantly, these stimuli do not operate in isolation within the tumor environment. Instead, the TME presents a highly heterogeneous and dynamic landscape where multiple triggers coexist. This complexity has led to the development of multi-stage and cascade-responsive nanocarriers capable of sequential activation. For example, an initial pH-triggered surface charge reversal may enhance cellular uptake, followed by intracellular redox-triggered drug release, thereby maximizing therapeutic efficiency. Despite significant advances, challenges remain in achieving precise control over stimulus sensitivity and minimizing premature activation during circulation. Variability in tumor physiology, interpatient heterogeneity, and inconsistent stimulus intensity can significantly affect therapeutic outcomes. Therefore, a deeper understanding of TME dynamics and stimulus interplay is essential for the rational design of next-generation nanocarriers [10–13].

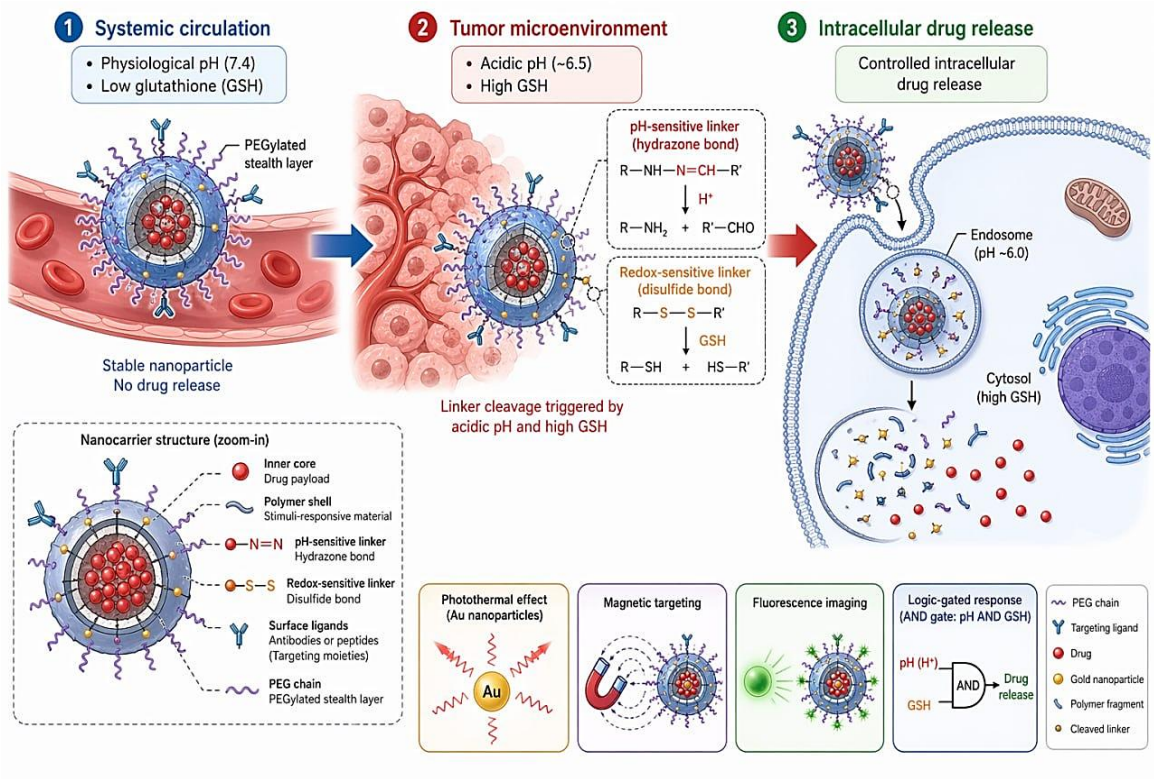

Fig 1. Schematic of multi-responsive nanocarriers showing stability in circulation and stimulus-triggered intracellular drug release in the tumor microenvironment.

4 | Biological Barriers Limiting Nanocarrier Delivery in Solid Tumors

Despite significant advances in the design of multi-responsive nanocarriers, their clinical efficacy remains substantially limited by a series of complex and interrelated biological barriers within solid tumors. These barriers operate at both systemic and local levels, collectively restricting nanoparticle circulation, tumor accumulation, deep tissue penetration, and effective intracellular drug delivery. A comprehensive understanding of these obstacles is essential for the rational design of next-generation nanomedicine platforms... Accordingly, the following sections systematically discuss the major biological barriers at systemic, tissue, and cellular levels [20–23].

4.1 | Systemic Clearance by the Mononuclear Phagocyte System

One of the earliest and most significant obstacles faced by nanocarriers after systemic administration is rapid recognition and clearance by the Mononuclear Phagocyte System (MPS), also known as the Reticuloendothelial System (RES). This system, primarily located in the liver, spleen, and lymph nodes, plays a critical role in eliminating foreign particles from circulation. Once administered intravenously, nanocarriers are immediately exposed to blood proteins that adsorb onto their surface, forming a protein corona. This opsonization process enhances recognition by macrophages and facilitates rapid phagocytic uptake. As a consequence, a substantial fraction of administered nanocarriers is sequestered before reaching the tumor site, significantly reducing bioavailability and therapeutic efficiency. Although surface modification strategies such as PEGylation, zwitterionic coatings, and biomimetic membranes have been developed to improve circulation time and reduce immune recognition, these approaches are not fully effective. In particular, the dynamic and patient-specific nature of protein corona formation continues to pose a major challenge, as it can alter nanoparticle identity, biodistribution, and targeting capability in unpredictable ways [19].

4.2 | Abnormal Tumor Vasculature and Limitations of the EPR Effect

At the tumor level, the vascular network represents a highly abnormal and dysfunctional system. Tumor blood vessels are characterized by chaotic architecture, irregular branching, discontinuous endothelial lining, and poor pericyte coverage. These abnormalities result in heterogeneous blood flow, creating regions of both excessive and insufficient perfusion within the same tumor mass. The EPR effect has long been considered the fundamental mechanism for passive nanoparticle accumulation in tumors. However, clinical and experimental evidence has demonstrated that the EPR effect is highly variable and often insufficient for reliable drug delivery in human tumors. Factors such as tumor type, size, location, and stage significantly influence vascular permeability. Moreover, high interstitial resistance and uneven vessel distribution further limit nanoparticle extravasation. As a result, only a small fraction of injected nanocarriers successfully accumulates in tumor tissue, leading to suboptimal therapeutic outcomes [21].

4.3 | Elevated Interstitial Fluid Pressure

Another major physical barrier within solid tumors is elevated IFP. This condition arises due to a combination of leaky vasculature, absence of functional lymphatic drainage, and rapid tumor cell proliferation. The resulting pressure gradient between tumor interstitium and surrounding tissues significantly hinders convective transport of nanocarriers. Unlike normal tissues, where fluid exchange is balanced, tumors maintain a nearly uniform and elevated IFP throughout the tumor core. This eliminates the driving force required for inward nanoparticle transport, causing most nanocarriers to remain localized near blood vessels. Consequently, deep tumor penetration is severely restricted, limiting access to hypoxic and poorly vascularized tumor regions, which are often the most resistant to therapy [20].

4.4 | Dense Extracellular Matrix and Stromal Resistance

The ECM represents a highly structured and physically restrictive barrier composed of collagen fibers, fibronectin, hyaluronic acid, and proteoglycans. In many solid tumors, particularly desmoplastic tumors such as pancreatic ductal adenocarcinoma, the ECM becomes excessively dense and fibrotic, forming a rigid barrier that physically obstructs nanoparticle diffusion. This dense stromal architecture not only limits passive diffusion but also increases interstitial resistance and reduces pore size within the TME. Additionally, interactions between ECM components and tumor-associated fibroblasts further reinforce structural rigidity, creating a dynamic barrier that continuously adapts to tumor progression. As a result, nanocarriers often exhibit perivascular accumulation with minimal penetration beyond the tumor periphery [19].

4.5 | Tumor Heterogeneity and Microenvironmental Variability

Tumor heterogeneity represents one of the most complex challenges in nanomedicine. Solid tumors exhibit profound spatial and temporal heterogeneity in terms of oxygen concentration, pH levels, enzyme expression, metabolic activity, and receptor distribution. This variability leads to inconsistent behavior of stimuli-responsive nanocarriers within different tumor regions. For instance, acidic pH and hypoxic conditions may be present only in localized tumor zones, resulting in partial or uneven activation of pH- or hypoxia-responsive systems. Similarly, heterogeneous expression of surface receptors limits the efficiency of active targeting strategies. This intra-tumoral variability not only reduces overall therapeutic efficacy but also contributes to the emergence of drug-resistant tumor subpopulations [21].

4.6 | Intracellular Trafficking Barriers and Endosomal Entrapment

Following cellular uptake, nanocarriers are typically internalized through endocytic pathways and sequestered within endosomes and lysosomes. While this process enables cellular entry, it also presents a major barrier to effective drug delivery, as therapeutic payloads often remain trapped and are eventually degraded by lysosomal enzymes. Efficient endosomal escape is therefore essential for successful cytoplasmic or nuclear drug delivery. However, most nanocarriers lack intrinsic escape mechanisms, resulting in limited intracellular bioavailability. Strategies such as proton sponge effect, membrane-disruptive peptides, and pH-responsive swelling have been explored to address this limitation, yet achieving consistent and efficient endosomal escape remains a significant challenge [16].

4.7 | Integrated and Hierarchical Nature of Biological Barriers

Importantly, these biological barriers do not act independently but rather function in a highly interconnected and hierarchical manner. Systemic clearance, vascular abnormalities, elevated interstitial pressure, ECM density, and intracellular trafficking collectively form a multi-level defense system that severely restricts nanocarrier performance. Therefore, successful nanomedicine design must adopt a holistic approach that considers all stages of delivery from systemic circulation to intracellular release as a continuous and interdependent process. Addressing only a single barrier is insufficient; instead, integrated strategies targeting multiple levels of obstruction are required to achieve meaningful clinical translation [17–20].

5 | Strategies to Overcome Biological Barriers in Solid Tumors

Overcoming the multifaceted biological barriers that limit nanocarrier performance in solid tumors requires a paradigm shift from single-function delivery systems toward highly integrated, adaptive, and multistage nanoplatforms. Given that obstacles exist at systemic, tissue, and cellular levels, successful strategies must address each barrier in a coordinated manner rather than independently. Accordingly, contemporary nanomedicine design increasingly focuses on systems that combine immune evasion, tumor targeting, deep tissue penetration, stimuli-responsiveness, and intracellular delivery within a unified framework [14–17]. These strategies are often inspired by the dynamic and heterogeneous nature of the TME, enabling spatiotemporally controlled therapeutic action (*Fig. 2*).

5.1 | Prolonged Systemic Circulation and Immune System Evasion

A primary prerequisite for effective tumor delivery is prolonged blood circulation, which increases the probability of nanocarrier accumulation at tumor sites. To achieve this, various surface engineering approaches have been developed to minimize recognition by the MPS. Polyethylene Glycol (PEG) remains the most widely used stealth coating due to its hydrophilicity and ability to reduce protein adsorption; however, its clinical limitations, including accelerated blood clearance upon repeated administration, have motivated the development of alternative strategies. Zwitterionic coatings, biomimetic cell membranes, and "self" recognition strategies represent next-generation approaches to immune evasion. In particular, coating nanoparticles with erythrocyte, platelet, or cancer cell membranes provides a biologically camouflaged surface

that reduces opsonization and enhances circulation stability. These biomimetic systems not only prolong half-life but also introduce additional functionalities such as homologous targeting and immune modulation [15–18].

5.2 | Improved Tumor Accumulation and Vascular Transport

Efficient tumor accumulation depends on successful navigation through abnormal and heterogeneous tumor vasculature. One strategy to enhance vascular transport involves optimizing nanoparticle physicochemical properties such as size, shape, and surface charge. Smaller nanoparticles (<100 nm) generally exhibit improved extravasation through leaky tumor vessels, while anisotropic shapes (rod- or disk-like structures) may enhance margination and vascular wall interaction. Active vascular targeting strategies further improve tumor accumulation by targeting endothelial markers such as VEGFR, integrins, and selectins. In addition, tumor-penetrating peptides (e.g., iRGD) can facilitate transvascular transport via receptor-mediated transcytosis pathways. External physical stimuli, including ultrasound and magnetic fields, have also been employed to transiently increase vascular permeability, thereby enhancing localized nanoparticle deposition within tumor tissues [21].

5.3 | Overcoming Interstitial Transport Barriers and Enhancing Deep Tumor Penetration

Once nanoparticles extravasate into tumor tissue, their further diffusion is hindered by elevated IFP and dense ECM. To address this limitation, ECM modulation strategies have been widely investigated. Enzymatic degradation using hyaluronidase, collagenase, or MMP-responsive systems can reduce stromal density and facilitate deeper nanoparticle penetration. Another effective strategy involves charge-switchable nanocarriers that remain neutral or negatively charged in systemic circulation but convert to a positively charged state in the acidic TME. This enhances electrostatic interactions with negatively charged cellular membranes, improving retention and uptake. Additionally, size-shrinking systems that disassemble or contract upon tumor entry allow improved diffusion into poorly accessible tumor regions, including hypoxic cores [22].

5.4 | Cascade and Multi-Stage Stimuli-Responsive Systems

Given the heterogeneous nature of tumors, single-stimulus systems often fail to achieve consistent activation. To overcome this, cascade-responsive nanocarriers have been developed that undergo sequential activation in response to multiple endogenous stimuli. For example, initial pH-triggered destabilization may expose hidden ligands or functional groups, followed by redox-triggered intracellular drug release.

Such hierarchical systems mimic logical progression through biological barriers, ensuring that each functional component is activated only when the nanocarrier reaches the appropriate microenvironment. This improves spatial precision, reduces premature drug leakage, and enhances overall therapeutic efficacy. Multi-stage systems can also integrate endogenous triggers (pH, hypoxia, enzymes) with exogenous stimuli (light, magnetic fields) to further enhance control [23].

5.5 | Active Targeting and Ligand-Mediated Cellular Uptake

Active targeting strategies significantly enhance nanocarrier selectivity by exploiting receptor-ligand interactions. Common targeting ligands include antibodies, peptides, aptamers, and small molecules such as folate or transferrin. These ligands bind to overexpressed receptors on cancer cells, promoting receptor-mediated endocytosis and improving intracellular uptake.

However, tumor heterogeneity and dynamic receptor expression remain major challenges. In response, dual-targeting and multi-ligand systems have been developed to improve robustness across different tumor regions. Furthermore, stimuli-triggered exposure of targeting ligands ensures that binding occurs only within the TME, minimizing off-target interactions in healthy tissues [14].

5.6 | Overcoming Intracellular Trafficking and Endosomal Escape Barriers

After cellular internalization, nanocarriers are typically trapped within endosomal and lysosomal compartments, where acidic and enzymatic conditions can degrade therapeutic payloads. To overcome this barrier, several endosomal escape strategies have been developed.

Proton sponge materials such as Polyethylenimine (PEI) induce osmotic swelling and membrane rupture, enabling cytosolic release. Alternatively, membrane-disruptive peptides and pH-responsive polymers can destabilize endosomal membranes under acidic conditions. Some systems also employ Reactive Oxygen Species (ROS)-generating components or photochemical internalization to facilitate endosomal escape. Efficient intracellular delivery remains particularly critical for gene therapy, siRNA, and protein-based therapeutics [18].

5.7 | Integrated Multistage and Biomimetic Delivery Platforms

The most advanced strategy involves integrating multiple functional mechanisms into a single multistage nanoplatform. These systems are designed to sequentially respond to systemic circulation conditions, tumor microenvironmental cues, and intracellular triggers. For example, a biomimetic nanoparticle may first evade immune clearance, then accumulate in tumor tissue, subsequently penetrate deep into the ECM, and finally release its payload in response to intracellular stimuli.

This hierarchical design significantly improves therapeutic precision and efficiency while reducing systemic toxicity. However, challenges remain in terms of synthetic complexity, scalability, reproducibility, and regulatory approval. Nevertheless, multistage and biomimetic systems represent a highly promising direction for bridging the gap between preclinical success and clinical translation [21].

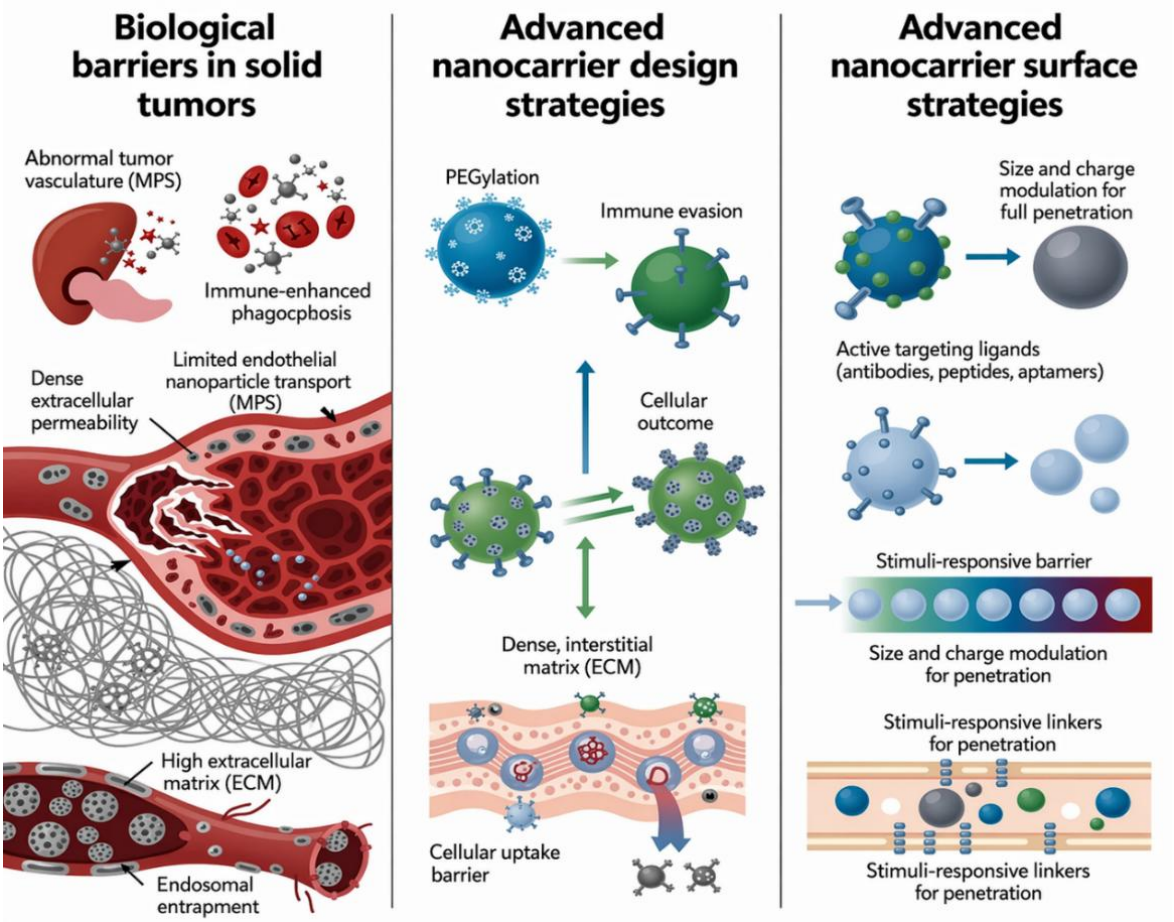

Fig 2. Approaches to overcome biological barriers in solid tumors.

6 | Clinical Translation Challenges and Regulatory Barriers

Despite the remarkable progress in the design of multi-responsive nanocarriers and their demonstrated efficacy in preclinical tumor models, successful clinical translation remains limited. A combination of scientific, technical, regulatory, and manufacturing challenges hinders the transition from laboratory-scale innovation to clinically approved nanomedicine. These barriers collectively contribute to the well-known "valley of death" in nanomedicine development, as summarized in *Fig. 3*, where many promising systems fail to progress beyond early-stage studies [17–20]. One of the most fundamental challenges lies in the lack of reproducibility and standardization in nanocarrier synthesis. Many multi-responsive systems involve complex multi-step fabrication processes, including surface functionalization, polymer conjugation, and incorporation of multiple functional components. These processes often result in batch-to-batch variability in physicochemical properties such as particle size distribution, surface charge, drug loading efficiency, and stimuli-responsiveness. Even minor variations in synthesis conditions can significantly alter biological behavior, making large-scale reproducibility difficult to achieve under Good Manufacturing Practice (GMP) conditions. In addition, the physicochemical stability of nanocarriers in biological environments remains a major concern. Upon exposure to blood plasma, nanoparticles undergo rapid adsorption of proteins, leading to the formation of a protein corona that can dramatically alter their identity, biodistribution, and targeting performance. This dynamic transformation is difficult to predict in vitro, and often leads to discrepancies between preclinical and clinical outcomes [12]. Furthermore, instability during storage, aggregation under physiological conditions, and premature drug leakage further compromise clinical applicability. Another major barrier is the limited predictive power of current preclinical tumor models. Most studies rely on simplified in vitro cell cultures or murine xenograft models, which fail to fully recapitulate the complexity of human tumors. Differences in tumor vasculature, immune system interactions, ECM composition, and interpatient heterogeneity significantly affect nanocarrier performance [13]. As a result, many nanomedicine systems that demonstrate strong therapeutic efficacy in animal models fail to reproduce similar outcomes in human clinical trials. From a regulatory perspective, multi-responsive nanocarriers face additional challenges due to their structural complexity and multifunctional nature. Regulatory agencies such as the FDA and EMA require comprehensive evaluation of safety, pharmacokinetics, toxicity, and long-term biodistribution. However, the presence of multiple active components, stimuli-responsive mechanisms, and potential degradation products complicates safety assessment [18]. The lack of standardized regulatory guidelines specifically tailored for advanced nanomedicines further delays clinical approval processes. Toxicological evaluation represents another critical hurdle. While many nanocarriers are designed to be biocompatible, their long-term fate in the human body is often poorly understood. Issues such as chronic accumulation in vital organs, immunogenicity, unexpected metabolic degradation, and potential off-target effects remain insufficiently characterized. In particular, inorganic nanoparticles may raise concerns regarding non-biodegradability and long-term toxicity, especially when used in repeated dosing regimens. Manufacturing scalability also represents a significant translational bottleneck. While laboratory-scale synthesis allows precise control over nanocarrier properties, scaling up production while maintaining identical structural and functional characteristics is extremely challenging. Parameters such as mixing conditions, reaction kinetics, and purification processes must be tightly controlled to ensure consistency, which is often difficult in industrial settings. Finally, economic and commercialization factors further limit clinical translation. The high cost of raw materials, complex fabrication processes, and stringent regulatory requirements increase the overall development cost of nanomedicines [23]. In addition, uncertainty regarding clinical success and market acceptance reduces industrial investment in advanced multi-responsive systems. Collectively, these challenges highlight that the successful clinical translation of multi-responsive nanocarriers requires not only scientific innovation but also advances in manufacturing technology, standardized characterization protocols, predictive preclinical models, and clear regulatory frameworks. Addressing these limitations will be essential to bridge the gap between bench-side research and bedside application, ultimately enabling the realization of precision nanomedicine in oncology.

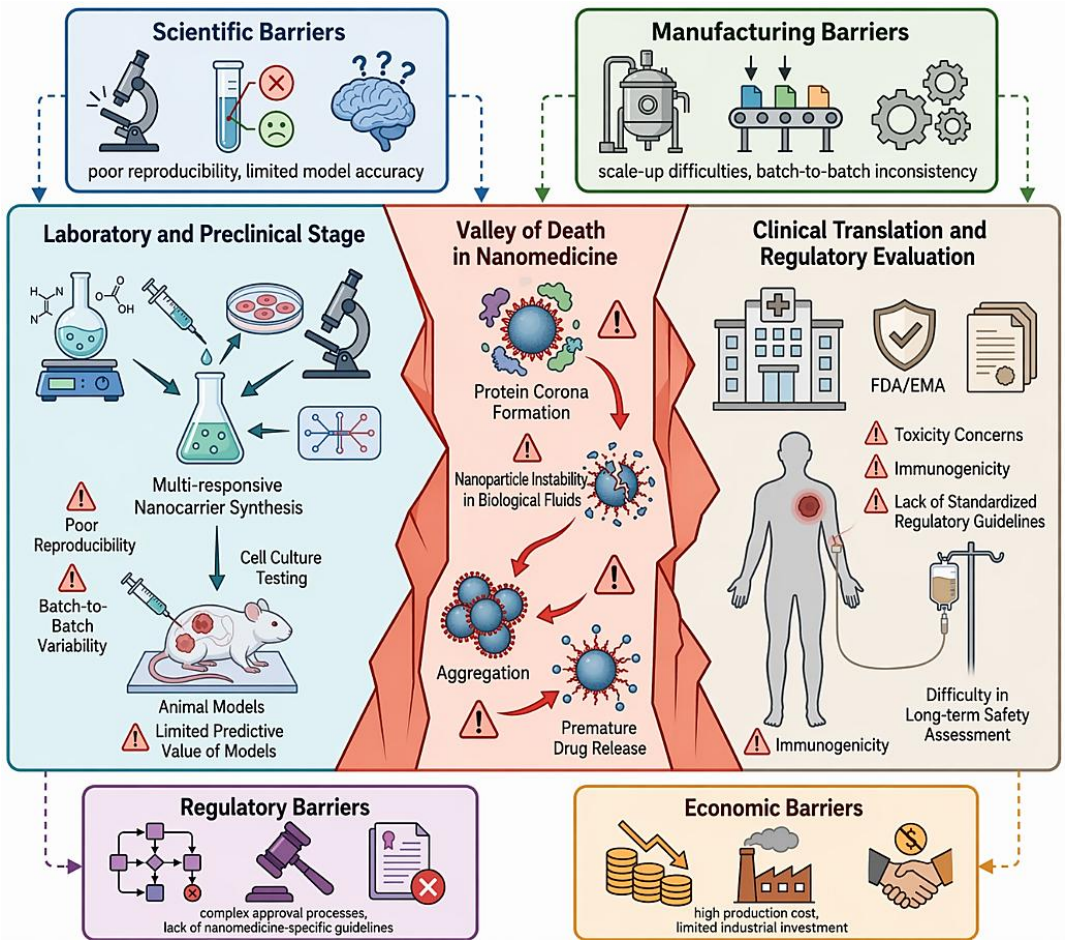

Fig 3. Overview of translational and regulatory challenges limiting the clinical application of multi-responsive nanocarriers, including scientific, manufacturing, and economic barriers.

7 | Conclusion

The field of multi-responsive nanocarriers for precision oncology has undergone remarkable evolution over the past decade, transitioning from simple passive delivery systems to highly sophisticated, stimuli-adaptive, and multifunctional platforms. Despite significant preclinical progress, the clinical translation of these systems remains limited, highlighting the need for new conceptual and technological advances that bridge the gap between laboratory research and real-world therapeutic application. One of the most promising future directions lies in the development of truly intelligent and adaptive nanocarriers capable of dynamic decision-making in response to complex tumor microenvironmental cues. Instead of relying on single or even dual-stimulus responsiveness, next-generation systems are expected to integrate multi-input logic operations and feedback-regulated drug release. Such systems could mimic biological decision-making processes, enabling autonomous regulation of therapeutic activity based on real-time environmental changes within tumors. In parallel, the integration of AI and ML into nanocarrier design is expected to significantly accelerate innovation in this field. Data-driven approaches can facilitate the prediction of nanomaterial biological interactions, optimize physicochemical parameters, and identify optimal combinations of materials and targeting strategies. By leveraging large-scale datasets from preclinical and clinical studies, AI-guided nanomedicine design may reduce trial-and-error experimentation and improve translational success rates. Another important future direction involves the development of highly biomimetic and personalized nanocarriers. The use of cell membrane coatings derived from erythrocytes, platelets, immune cells, or even patient-specific tumor cells offers a powerful strategy to enhance immune evasion and targeting specificity. Furthermore, the emergence of personalized medicine approaches suggests that future nanocarriers may be tailored to individual patient tumor profiles, including genetic mutations, receptor expression patterns, and microenvironmental

characteristics, thereby maximizing therapeutic efficacy while minimizing adverse effects. Advances in spatiotemporal control of drug delivery also represent a critical area of development. The combination of endogenous and externally applied stimuli, such as pH, hypoxia, enzymes, light, ultrasound, and magnetic fields, enables highly precise control over therapeutic activation. Future systems are expected to incorporate multi-modal triggering mechanisms with improved tissue penetration and minimal invasiveness, allowing for on-demand drug release at specific tumor sites. From a translational perspective, addressing current limitations in manufacturing scalability, reproducibility, and regulatory standardization will be essential. The development of robust, cost-effective, and reproducible synthesis methods compatible with GMP standards will play a central role in enabling clinical adoption [20]. In addition, the establishment of standardized characterization protocols and regulatory frameworks specifically designed for complex nanomedicines is urgently needed to streamline approval processes. Despite these challenges, the convergence of nanotechnology, materials science, computational modeling, and molecular medicine provides an unprecedented opportunity to revolutionize cancer therapy. Multi-responsive nanocarriers hold the potential to transform oncology from conventional systemic treatment approaches into highly precise, adaptive, and patient-specific therapeutic strategies. In conclusion, multi-responsive nanocarriers represent a powerful and rapidly evolving platform in precision oncology. While significant barriers remain in terms of clinical translation, continued interdisciplinary research and technological innovation are expected to drive this field toward practical clinical applications [23]. Ultimately, the successful integration of intelligent nanocarriers into cancer therapy may enable more effective, safer, and personalized treatment strategies, significantly improving patient outcomes in the future.

Authors' Contributions

The author was responsible for all stages of the research and manuscript preparation and approved the final version.

Data Availability

All data are included in the text.

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Conflict of Interest

There are no competing interests to declare.

Consent for Publication

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants performed by the author.

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