RESEARCH PAPER

Stimuli-Responsive Nanocarriers for Targeted Drug Delivery: Design Strategies, Clinical Progress, and Translational Challenges

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Abstract
Stimuli-responsive nanocarriers represent one of the most sophisticated directions in targeted drug delivery because they are designed not merely to transport therapeutic agents, but to release them in response to specific biological or externally applied signals. Unlike conventional nanomedicines, which mainly depend on altered pharmacokinetics, passive accumulation, or surface-mediated targeting, stimuli-responsive systems integrate material engineering with disease microenvironment biology. These carriers can respond to endogenous stimuli such as acidic pH, redox gradients, enzymes, hypoxia, reactive oxygen species, adenosine triphosphate, and abnormal metabolic conditions, or to exogenous triggers such as temperature, light, magnetic fields, ultrasound, and electric fields. Their central objective is to maximize drug concentration at the pathological site while minimizing premature systemic leakage and off-target toxicity. This review critically examines the design principles, material platforms, release mechanisms, clinical progress, and translational limitations of stimuli-responsive nanocarriers for targeted drug delivery. Particular attention is given to pH-sensitive, thermosensitive, redox-responsive, enzyme-responsive, ultrasound-triggered, magnetic, light-activated, and multi-stimuli systems. The review also evaluates clinically advanced nanomedicines, including liposomal, albumin-bound, polymeric, and lipid-based formulations, while distinguishing between clinically approved nanomedicines and truly stimuli-responsive platforms still largely under investigation. Although several nanomedicines such as Doxil, Abraxane, Onivyde, Vyxeos, and Onpattro have demonstrated the clinical feasibility of nanoscale drug delivery, the clinical translation of stimuli-responsive systems remains limited by biological heterogeneity, weak predictability of the enhanced permeability and retention effect, complex manufacturing, incomplete safety profiling, regulatory uncertainty, and insufficient patient stratification. The future of this field will depend on simplified but programmable carrier design, clinically measurable biomarkers of responsiveness, scalable manufacturing, real-time imaging-guided delivery, and rational trial designs that select patients based on tumor biology rather than assuming uniform nanocarrier behavior. Stimuli-responsive nanocarriers therefore hold substantial promise, but their successful clinical translation requires a shift from highly complex laboratory prototypes toward reproducible, mechanism-driven, and clinically validated delivery technologies.

Keywords: stimuli-responsive nanocarriers; targeted drug delivery; smart nanomedicine; pH-responsive nanoparticles; redox-responsive systems; thermosensitive liposomes; nanomedicine translation; tumor microenvironment; controlled release; clinical nanomedicine

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1. Introduction

Targeted drug delivery has evolved from the simple concept of transporting drugs to a desired tissue into a more complex therapeutic strategy involving spatial, temporal, and biological control over drug release. Conventional systemic therapy, particularly in oncology, inflammatory diseases, and genetic disorders, is often limited by poor solubility, rapid clearance, non-specific biodistribution, systemic toxicity, multidrug resistance, and insufficient drug concentration at the pathological site [1]. Nanocarriers were introduced to address these limitations by improving drug stability, modifying pharmacokinetics, enhancing circulation time, increasing apparent solubility, protecting fragile therapeutic molecules, and altering tissue biodistribution. Approved nanomedicines have already demonstrated that nanoscale formulations can improve the therapeutic index of several drugs by changing their distribution and toxicity profiles rather than by discovering entirely new pharmacological targets. Clinical examples include liposomal doxorubicin, albumin-bound paclitaxel, liposomal irinotecan, liposomal cytarabine/daunorubicin, and lipid nanoparticle-based RNA therapeutics [2].

However, the first generation of nanomedicine relied heavily on passive targeting through the enhanced permeability and retention effect, commonly known as the EPR effect. The EPR concept proposes that nanoparticles preferentially accumulate in tumors because tumor vasculature is leaky and lymphatic drainage is impaired [3]. Although this principle is well supported in many preclinical models, its clinical reliability has been questioned because human tumors are heterogeneous in vascular density, perfusion, stromal pressure, lymphatic function, macrophage activity, and interstitial transport. Reviews on nanomedicine translation emphasize that EPR-mediated accumulation varies between tumor types, between patients, and even between lesions within the same patient. Therefore, a one-size-fits-all nanocarrier strategy is unlikely to produce consistent clinical benefit [4].

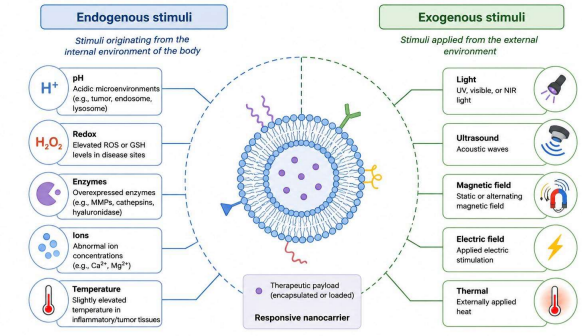

Figure 1. Schematic classification of endogenous and exogenous stimuli used in responsive nanocarrier design.

Stimuli-responsive nanocarriers emerged to overcome some of these limitations. Instead of relying only on passive deposition or ligand binding, these systems are engineered to undergo structural, chemical, or physical changes when exposed to specific triggers. These changes may include swelling, disassembly, bond cleavage, charge reversal, membrane destabilization, pore opening, drug diffusion, carrier degradation, or phase transition [5]. The stimulus may originate from the pathological microenvironment, such as acidic tumor extracellular pH, acidic endosomal or lysosomal pH, high intracellular glutathione, enzyme overexpression, reactive oxygen species, or hypoxia. Alternatively, the stimulus may be externally applied, such as localized hyperthermia, near-infrared light, ultrasound, magnetic field exposure, or radiation. In principle, this design permits more precise control over when and where the drug is released [6].

The significance of stimuli-responsive nanocarriers is especially high for diseases where the pathological tissue differs biochemically or physically from normal tissue. Tumors frequently exhibit acidic extracellular pH, abnormal protease activity, hypoxia, elevated reactive oxygen species, and altered redox balance. Inflamed tissues may show increased oxidative stress, enzyme activity, vascular permeability, and immune-cell infiltration [7]. Intracellular compartments such as endosomes and lysosomes possess acidic pH, while the cytosol contains higher reducing potential than extracellular fluids. These differences provide biological switches that can be exploited for controlled drug release. Nevertheless, the translation of this concept from experimental systems to clinical products remains difficult. Many stimuli-responsive systems show elegant responses under simplified laboratory conditions but fail to reproduce the same performance in the complex human body, where stimuli are spatially heterogeneous, temporally dynamic, and often insufficiently strong to activate carriers completely [8].

This review discusses the design strategies, material platforms, clinical progress, and translational challenges of stimuli-responsive nanocarriers [9]. It also emphasizes the gap between preclinical creativity and clinical feasibility, because many systems described as smart remain far from regulatory approval. A Q1-level review should not only describe the types of nanocarriers but also critically analyze why promising systems fail to translate, what clinical lessons can be learned from approved nanomedicines, and how future systems should be designed for realistic therapeutic impact [10].

2. Conceptual Basis of Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers are nanoscale delivery systems designed to remain relatively stable during circulation and release their payload preferentially after exposure to a defined trigger. The ideal system should satisfy several requirements [11]. First, it should

encapsulate or conjugate the therapeutic agent efficiently. Second, it should remain stable in blood to avoid premature drug leakage. Third, it should accumulate sufficiently at the disease site or enter target cells. Fourth, it should respond selectively to the intended stimulus. Fifth, it should release the drug at a rate compatible with pharmacological action. Finally, the carrier and its degradation products should be biocompatible, non-immunogenic, manufacturable, sterilizable, and reproducible [12].

The responsiveness of nanocarriers is usually achieved by incorporating stimulus-sensitive components into the carrier structure. These components may include acid-labile linkers, redox-cleavable disulfide bonds, enzyme-degradable peptides, thermosensitive lipids, pH-sensitive polymers, ROS-sensitive thioketal or boronic ester groups, photo-cleavable moieties, magnetothermal materials, gas-generating compounds, or ultrasound-sensitive shells. Depending on the design, the stimulus can trigger drug release by destabilizing the carrier, cleaving drug-linker bonds, changing hydrophilicity, altering surface charge, disrupting membranes, or generating local heat [13].

A key distinction must be made between targeting and release control. Targeting refers to the accumulation or binding of a carrier at a specific biological location, whereas stimuli-responsiveness refers to the activation or release behavior after exposure to a trigger [14]. A ligand-decorated nanoparticle may bind a receptor but may not be stimuli-responsive. Similarly, a pH-responsive nanoparticle may release drug in acidic tissue but may not actively target a receptor. The most advanced systems attempt to combine both properties, for example, a ligand-functionalized polymeric micelle that accumulates in tumors, undergoes charge reversal in acidic extracellular pH, enters cells through receptor-mediated endocytosis, and releases drug intracellularly in response to glutathione [15].

3. Classification of Stimuli-Responsive Nanocarriers

Stimuli-responsive systems may be classified according to the trigger responsible for carrier activation. The trigger may be generated by the disease microenvironment or applied externally by a clinician. **Table 1** summarizes the major classes, common design strategies, advantages, and limitations.

Table 1. Major stimuli used in responsive nanocarrier design [16,17,18,19,20].

Stimulus type	Typical trigger	Common design strategy	Main advantage	Major limitation
pH-responsive	Tumor acidity, endosomes, lysosomes	Acid-labile bonds, protonatable polymers, charge reversal	Useful for intracellular release	pH differences may be modest in vivo
Redox-responsive	High intracellular glutathione	Disulfide, diselenide, thioketal linkers	Strong intracellular/extracellular redox gradient	Variable redox state among tissues and diseases
Enzyme-responsive	MMPs, cathepsins, esterases, phospholipases	Peptide cleavage, enzyme-degradable polymers	Disease-associated specificity	Enzyme heterogeneity and off-target cleavage
ROS-responsive	Oxidative stress in tumors or inflammation	Thioketal, boronic ester, selenium/tellurium bonds	Useful in inflammatory and cancer microenvironments	ROS levels are dynamic and difficult to quantify
Hypoxia-responsive	Low oxygen in tumors	Nitroimidazole, azo bonds, hypoxia-activated prodrugs	Exploits tumor hypoxia	Hypoxia is spatially heterogeneous
Thermoresponsive	Local hyperthermia	Thermosensitive lipids and polymers	External control over release	Requires accurate heating at disease site
Light-responsive	UV, visible, NIR light	Photocleavable groups, photothermal agents	High spatial control	Limited tissue penetration and phototoxicity
Magnetic-responsive	Alternating magnetic field	Iron oxide or magnetic cores	Remote heating or guidance	Field penetration and heating control

				issues
Ultrasound-responsive	Focused ultrasound	Microbubbles, phase-change droplets, sonosensitive shells	Deep tissue penetration	Cavitation control and tissue safety
Multi-stimuli	pH + redox, pH + enzyme, heat + pH	Integrated responsive chemistry	Higher specificity	Increased complexity and regulatory burden

4. pH-Responsive Nanocarriers

pH-responsive nanocarriers are among the most extensively studied stimuli-responsive systems. Their design is based on pH differences between normal physiological fluids, tumor extracellular environments, and intracellular compartments [21]. Blood and normal tissues generally maintain a pH close to 7.4, whereas many solid tumors show mildly acidic extracellular pH due to high glycolytic metabolism, poor perfusion, lactate accumulation, and abnormal vascularization. After cellular uptake, nanoparticles may also encounter stronger acidity in endosomes and lysosomes. These pH gradients can be exploited for triggered release [22].

The most common pH-responsive strategies include acid-labile chemical bonds, protonation-induced swelling, charge conversion, and pH-mediated destabilization of lipid or polymeric membranes. Acid-labile bonds such as hydrazone, acetal, ketal, imine, cis-aconityl, and orthoester linkages can remain relatively stable at physiological pH but cleave under acidic conditions. Hydrazone bonds, for example, have been widely used to link doxorubicin to polymers or nanoparticles because they can hydrolyze in acidic intracellular compartments. Similarly, pH-sensitive polymers containing tertiary amines can become protonated in acidic environments, causing swelling, osmotic imbalance, or endosomal escape through the proton sponge effect [23].

A particularly important pH-responsive strategy is charge reversal. Many nanoparticles are coated with neutral or negatively charged surfaces to reduce protein adsorption and prolong circulation. However, negatively charged surfaces may reduce cellular uptake because cell membranes are also negatively charged. In acidic tumor environments, charge-reversal systems convert from neutral or negative to positive, enhancing interaction with tumor cells and improving internalization. This design attempts to balance long circulation with efficient cellular uptake [24].

Despite strong experimental support, pH-responsive delivery faces several translational obstacles. The extracellular pH difference between tumor and normal tissue is often modest, usually not as sharp as in buffer-based experiments [25]. Tumor acidity is also heterogeneous, meaning that some tumor regions may activate the carrier while others may not. Furthermore, endosomal release does not guarantee cytosolic delivery; drugs may remain trapped in lysosomes or undergo degradation. Therefore, clinically relevant pH-responsive systems should be tested under realistic pH gradients, serum conditions, three-dimensional tumor models, and orthotopic or patient-derived models rather than only in acidic buffer solutions [26].

5. Redox-Responsive Nanocarriers

Redox-responsive nanocarriers are designed around differences in oxidative and reductive potential between extracellular and intracellular environments. The intracellular cytosol contains higher levels of reducing agents such as glutathione compared with extracellular fluids. This gradient makes redox-responsive systems attractive for intracellular drug release, especially for cytotoxic drugs, nucleic acids, and protein therapeutics that must act inside cells [27].

The most widely used redox-sensitive linkage is the disulfide bond. Disulfide-containing polymers, crosslinkers, or drug conjugates remain relatively stable in extracellular environments but are cleaved in the reducing intracellular environment. When disulfide bonds are broken, the carrier may disassemble, release the drug, expose functional groups, or reduce crosslinking density. Diselenide and ditelluride bonds have also been explored because they may respond to both reductive and oxidative stimuli, although their safety and translational maturity remain lower than disulfide systems [28].

Redox-responsive nanocarriers are particularly relevant for gene delivery. Small interfering RNA, messenger RNA, plasmid DNA, and antisense oligonucleotides are vulnerable to enzymatic degradation and require intracellular delivery [29]. Redox-cleavable cationic polymers can condense nucleic acids during circulation but release them inside the cytosol after disulfide reduction, potentially reducing long-term cationic toxicity. Lipid nanoparticles used for RNA delivery are not always described as classical redox-responsive systems, but their clinical success has strengthened confidence in nanoscale intracellular delivery platforms. Patisiran, marketed as Onpattro, is an FDA-approved lipid nanoparticle-based siRNA therapy for hereditary transthyretin-mediated amyloidosis, demonstrating that nanocarrier-mediated RNA delivery can be clinically successful when the formulation, disease target, and regulatory pathway are well aligned [30].

The main challenge with redox-responsive systems is biological variability. Glutathione concentration differs between cell types, disease stages, tumor regions, and intracellular compartments. Premature reduction may also occur in certain pathological environments. Additionally, excessive reliance on intracellular reduction assumes that the nanocarrier has already crossed biological barriers,

reached the right tissue, entered target cells, escaped endosomes, and avoided clearance. Therefore, redox-responsiveness should be viewed as one step in a multi-barrier delivery process rather than a complete targeting solution [31].

6. Enzyme-Responsive Nanocarriers

Enzyme-responsive nanocarriers use disease-associated enzymatic activity as a trigger for drug release. Many pathological tissues overexpress specific enzymes, including matrix metalloproteinases, cathepsins, hyaluronidase, phospholipases, esterases, caspases, beta-glucuronidase, and alkaline phosphatase. These enzymes can cleave peptide linkers, degrade polymer shells, digest extracellular matrix components, or convert prodrugs into active molecules [32].

In cancer, matrix metalloproteinases are frequently associated with invasion, angiogenesis, metastasis, and extracellular matrix remodeling. Nanocarriers containing MMP-cleavable peptides can remain shielded during circulation but expose cell-penetrating peptides or release drugs after enzymatic cleavage in the tumor microenvironment. Cathepsins, especially cathepsin B, are lysosomal proteases often exploited for intracellular drug release after endocytosis. Hyaluronidase-responsive systems are also important because hyaluronic acid can serve both as a CD44-targeting ligand and as an enzyme-degradable carrier material [33].

The major conceptual strength of enzyme-responsive systems is biological specificity. Unlike pH or redox changes, which may occur in many tissues, enzyme expression can be more closely associated with disease phenotype. However, enzyme activity is not uniform across patients or lesions. Enzyme expression in biopsy tissue may not accurately represent enzyme activity throughout the tumor. Moreover, enzymes are also present in normal physiological processes, creating possible off-target activation. Therefore, enzyme-responsive nanocarriers require careful validation using activity-based assays, patient-derived samples, and biomarker-guided clinical designs [34].

7. Thermoresponsive Nanocarriers

Thermoresponsive nanocarriers respond to temperature changes, usually through phase transition, membrane destabilization, or polymer collapse. They are especially attractive because temperature can be externally controlled using localized hyperthermia, radiofrequency ablation, focused ultrasound, microwave heating, or magnetic hyperthermia. Thermosensitive liposomes are the most clinically advanced thermoresponsive platform [35].

The best-known example is ThermoDox, a lysolipid-containing thermosensitive liposomal doxorubicin formulation designed to release doxorubicin rapidly when exposed to mild hyperthermia. The concept is clinically elegant: the formulation circulates systemically but releases drug locally when the tumor region is heated. In hepatocellular carcinoma, ThermoDox was evaluated with radiofrequency ablation in large clinical studies. The Phase III HEAT trial did not meet its primary endpoint, and the later OPTIMA trial was also unsuccessful, leading to major disappointment in the clinical development of this platform [36].

The ThermoDox experience is highly instructive. It shows that a scientifically sound stimuli-responsive mechanism does not automatically translate into clinical success. The outcome depends on thermal dose, heating duration, tumor geometry, vascular perfusion, intratumoral drug penetration, procedural standardization, and patient selection. If insufficient tissue volume reaches the required temperature for adequate time, drug release may be incomplete or uneven. Conversely, excessive heating may damage surrounding tissue. Thermoresponsive systems therefore require integration of drug formulation, device performance, imaging, temperature monitoring, and interventional technique. This makes them scientifically powerful but operationally complex [37].

Thermoresponsive polymers, such as poly(N-isopropylacrylamide)-based materials, have also been studied. These polymers undergo a lower critical solution temperature transition, changing from hydrophilic to hydrophobic above a threshold temperature. However, concerns about biodegradability, toxicity, and clinical manufacturability have limited their translation. Future thermoresponsive systems may need to focus on simpler lipid-based designs, image-guided heating, and combination protocols where heat itself contributes therapeutic benefit [38].

8. Light-Responsive Nanocarriers

Light-responsive nanocarriers offer high spatial and temporal precision because light can be applied at a defined location and time. These systems may use photocleavable bonds, photosensitizers, photothermal agents, upconversion nanoparticles, gold nanostructures, carbon-based materials, or semiconductor nanoparticles. Light exposure can trigger drug release through bond cleavage, heat generation, reactive oxygen species production, membrane disruption, or structural transformation [39].

Near-infrared light is generally preferred for biomedical applications because it penetrates tissue more effectively than ultraviolet or visible light and causes less photodamage. Photothermal systems convert light into heat, which can induce local hyperthermia and drug release. Photodynamic systems generate reactive oxygen species after light activation, producing direct cytotoxicity and sometimes enhancing release from ROS-sensitive carriers. Combined photothermal-photodynamic-chemotherapy platforms have received substantial preclinical attention [40].

However, the clinical translation of light-responsive nanocarriers is limited by tissue penetration depth, light dosimetry, tumor accessibility, potential phototoxicity, and complexity of device-drug combinations. Superficial tumors, accessible lesions, intraoperative settings, dermatological diseases, ophthalmic diseases, and endoscopic applications may be more realistic early

indications than deep metastatic tumors. For deep tissues, light-responsive systems may require optical fibers, endoscopic devices, or upconversion technologies, each adding regulatory and procedural complexity [41].

9. Magnetic-Responsive Nanocarriers

Magnetic-responsive nanocarriers generally incorporate magnetic materials such as iron oxide nanoparticles. They can be used for magnetic targeting, magnetic resonance imaging, magnetothermal release, or combined diagnostic and therapeutic applications. Under an alternating magnetic field, magnetic nanoparticles can generate heat, which may induce drug release from thermosensitive carriers or directly damage tumor cells through magnetic hyperthermia [42].

Magnetic systems are attractive because magnetic fields can penetrate tissue more deeply than light. They also permit imaging-guided delivery when the magnetic component provides MRI contrast. However, magnetic targeting in humans is difficult because the magnetic force must overcome blood flow, tissue depth, and complex vascular geometry. Superficial or localized disease may be more suitable than deep disseminated disease. Another challenge is ensuring uniform heating without damaging healthy tissue. Magnetic nanoparticle dose, field strength, frequency, biodistribution, clearance, and long-term iron metabolism must be carefully controlled [43].

10. Ultrasound-Responsive Nanocarriers

Ultrasound-responsive nanocarriers are gaining attention because ultrasound can penetrate deep tissues and can be focused noninvasively. Ultrasound may trigger drug release through cavitation, acoustic droplet vaporization, mechanical disruption, membrane permeabilization, or localized heating. Common platforms include microbubbles, nanobubbles, phase-change droplets, liposomes, polymeric nanoparticles, and gas-generating systems [44].

One key advantage of ultrasound is that it can enhance both carrier release and tissue permeability. Focused ultrasound can temporarily disrupt biological barriers, including tumor vasculature and the blood-brain barrier, thereby improving local delivery. This makes ultrasound-responsive systems highly relevant for brain tumors, neurodegenerative diseases, and deep solid tumors. However, controlling cavitation is difficult. Stable cavitation may improve delivery, whereas inertial cavitation may cause tissue injury. Ultrasound parameters such as frequency, duty cycle, intensity, exposure time, and microbubble concentration must be optimized. Clinical translation will require standardized protocols and real-time monitoring [45].

11. Multi-Stimuli Responsive Nanocarriers

Multi-stimuli responsive nanocarriers are designed to respond to more than one trigger. Examples include pH/redox, pH/enzyme, pH/temperature, redox/ROS, magnetic/thermal, and light/pH systems. The purpose is to increase specificity by requiring sequential or combined activation. For example, a carrier may remain stable in blood, become positively charged in acidic tumor extracellular pH, enter cells, and release drug in response to intracellular glutathione. Another system may release partially under tumor acidity and fully after external ultrasound [46].

Multi-stimuli systems are conceptually powerful because diseases are rarely defined by a single abnormal signal. Tumors, for example, may be acidic, hypoxic, enzyme-rich, and redox-altered at the same time. Combining stimuli can increase precision and reduce premature release. However, complexity is a double-edged sword. Every additional responsive component increases manufacturing difficulty, analytical characterization burden, regulatory uncertainty, batch variability, and safety concerns. A highly complex formulation may perform impressively in animal experiments but become impractical for scale-up. Therefore, future multi-stimuli systems should be designed with translational simplicity: each responsive element must have a clear purpose, measurable activation threshold, and clinically relevant contribution [47].

12. Material Platforms Used in Stimuli-Responsive Drug Delivery

Liposomes are among the most clinically successful nanocarrier platforms. They are vesicular systems composed of phospholipid bilayers surrounding an aqueous core. Hydrophilic drugs can be loaded into the aqueous interior, whereas hydrophobic drugs can be incorporated into the lipid bilayer. Liposomes can be PEGylated to prolong circulation and modified with ligands or stimuli-responsive lipids. Clinically approved liposomal products demonstrate the translational strength of this platform. Doxil was the first FDA-approved nanodrug and established the clinical value of PEGylated liposomal doxorubicin. Vyxeos is a liposomal combination of cytarabine and daunorubicin designed to maintain a synergistic drug ratio. Onivyde is a PEGylated liposomal irinotecan formulation approved in cancer therapy [48].

For stimuli-responsive delivery, liposomes can be engineered to respond to pH, heat, enzymes, ultrasound, or light. Thermosensitive liposomes remain the most mature example. However, liposomal systems may suffer from drug leakage, complement activation-related pseudoallergy, accelerated blood clearance after repeated dosing, and challenges in sterilization and long-term stability [49].

Polymeric nanoparticles and micelles provide high structural flexibility. They can be designed using biodegradable polymers such as PLGA, PEG-PLA, PEG-PCL, chitosan, dextran, poly(amino acids), and polypeptides. Stimuli-responsive linkers can be incorporated into polymer backbones, side chains, crosslinkers, or drug conjugates. Polymeric micelles are particularly useful for poorly soluble hydrophobic drugs because they contain a hydrophobic core and hydrophilic shell [50].

Dendrimers are highly branched, monodisperse macromolecules with controlled size, internal cavities, and multiple surface functional groups. Their architecture allows drug encapsulation, conjugation, targeting ligand attachment, and stimuli-responsive modification. pH-sensitive dendrimers can release drugs in acidic endosomes, while redox-sensitive dendrimers can use disulfide linkers for intracellular release. Despite their precision, dendrimers face toxicity concerns, especially cationic surface toxicity, as well as scale-up and regulatory challenges [51].

Inorganic materials such as mesoporous silica nanoparticles, gold nanoparticles, iron oxide nanoparticles, calcium phosphate nanoparticles, carbon dots, graphene oxide, and upconversion nanoparticles offer unique optical, magnetic, thermal, or structural properties. Mesoporous silica nanoparticles can load large amounts of drug within pores and use pH-, enzyme-, or redox-sensitive gatekeepers. Gold nanoparticles are useful for photothermal release. Iron oxide nanoparticles support magnetic targeting and hyperthermia. Calcium phosphate nanoparticles dissolve in acidic environments and are attractive for gene delivery. However, inorganic systems often raise concerns regarding long-term biodistribution, biodegradation, tissue retention, immune interaction, and chronic toxicity [52].

Lipid nanoparticles have gained major clinical importance because of RNA therapeutics and vaccines. Their success demonstrates that nanocarriers can deliver fragile nucleic acids in humans when formulation design, disease biology, and clinical endpoints are appropriate. LNPs typically contain ionizable lipids, helper phospholipids, cholesterol, and PEG-lipids. Ionizable lipids are especially important because they remain relatively neutral at physiological pH but become protonated in acidic endosomes, facilitating endosomal escape. This makes many LNPs functionally pH-responsive at the intracellular level, although they are often discussed separately from classical stimuli-responsive nanocarriers [53].

13. Clinical Progress of Nanocarrier-Based Drug Delivery

The clinical success of nanomedicine is real but selective. Several nanocarrier-based products have reached approval, particularly liposomal, albumin-bound, polymeric, and lipid-based systems. However, the number of truly stimuli-responsive nanocarriers approved for routine clinical drug delivery remains limited. Most approved nanomedicines improve pharmacokinetics, reduce toxicity, or enable delivery of difficult molecules, rather than relying on a sophisticated disease-triggered release mechanism [54].

Current reviews of clinical cancer nanomedicines emphasize that nanomedicine has become part of cancer therapy, but clinical success is uneven and depends strongly on formulation simplicity, therapeutic context, and measurable benefit over existing standards. The most important lesson for stimuli-responsive nanocarriers is that clinical translation requires more than innovative chemistry. A formulation must solve a real clinical problem, be manufacturable at scale, demonstrate safety, show superiority or meaningful added value, and fit into practical treatment workflows [55].

Table 2. Selected clinically relevant nanomedicines and lessons for stimuli-responsive systems. [56,57,58,59]

Product/platform	Carrier type	Payload	Key clinical lesson
Doxil/Caelyx	PEGylated liposome	Doxorubicin	Long-circulating liposomes can reduce selected toxicities and alter biodistribution
Abraxane	Albumin-bound nanoparticle	Paclitaxel	Nanocarriers can improve delivery of poorly soluble drugs without toxic solvents
Onivyde	PEGylated liposomal formulation	Irinotecan	Liposomal encapsulation can improve pharmacokinetics and clinical utility
Vyxeos	Liposomal combination	Cytarabine + daunorubicin	Nanocarriers can preserve synergistic drug ratios
Onpattro	Lipid nanoparticle	siRNA	Nanocarriers can clinically deliver nucleic acids
ThermoDox	Thermosensitive liposome	Doxorubicin	Stimuli-responsive success depends on device-drug-procedure integration
BIND-014	Targeted polymeric nanoparticle	Docetaxel	Active targeting may require biomarker-based patient selection

14. Translational Challenges

Many nanocarriers are still designed under the assumption that they will accumulate in tumors through the EPR effect. However, human tumors differ greatly in vascular permeability, stromal density, perfusion, lymphatic drainage, and immune-cell uptake. Dense extracellular matrix, high interstitial fluid pressure, and poor vascular perfusion can prevent deep nanoparticle penetration. This means that nanoparticles may accumulate near blood vessels but fail to reach distant tumor cells. The clinical heterogeneity of EPR remains one of the most important barriers in nanomedicine translation [60].

Stimuli-responsive systems assume that the target stimulus is sufficiently present at the disease site. In reality, tumor acidity, enzyme activity, hypoxia, ROS levels, and redox gradients are heterogeneous. A pH-responsive carrier may work in one tumor region but not another. An enzyme-responsive system may work in patients with high enzyme activity but fail in patients with low expression. Therefore, clinical trials should not treat responsiveness as universal. Biomarker-based selection is essential [61].

A major problem in responsive nanocarrier design is balancing stability and release. If the carrier is too unstable, drug leaks during circulation, causing systemic toxicity. If it is too stable, insufficient drug is released at the target site. Many preclinical studies report high release in acidic or reducing buffers but do not adequately test serum stability, protein corona effects, shear stress, storage stability, or repeated freeze-thaw effects.

After entering blood, nanoparticles interact with plasma proteins, forming a protein corona. This corona can change size, charge, receptor recognition, immune clearance, cellular uptake, and biodistribution. It may mask targeting ligands or alter the intended stimulus-response behavior. Therefore, nanocarriers characterized only in water or buffer may behave differently in vivo [62].

Nanoparticles are often cleared by macrophages in the liver, spleen, and bone marrow. PEGylation can reduce clearance, but repeated administration may trigger anti-PEG antibodies or accelerated blood clearance. Surface charge, particle size, shape, rigidity, hydrophobicity, and protein corona composition influence immune recognition [63].

Laboratory-scale nanocarriers are often prepared in small batches using methods that are difficult to scale. Clinical translation requires reproducible particle size, polydispersity, drug loading, encapsulation efficiency, release profile, sterility, endotoxin control, residual solvent control, and long-term stability. Multi-component stimuli-responsive systems are particularly difficult because small changes in synthesis can alter responsiveness [64].

Regulatory agencies require clear characterization of composition, mechanism, pharmacokinetics, biodistribution, toxicity, degradation, impurities, and manufacturing consistency. Stimuli-responsive systems may be considered combination products if they require external devices such as ultrasound, laser, magnetic field, or hyperthermia equipment. This adds regulatory complexity because both the drug and device must be evaluated [65].

Many nanocarriers perform well in subcutaneous mouse tumor models but fail clinically. Subcutaneous tumors do not fully reproduce human tumor architecture, immune environment, stromal barriers, vascular heterogeneity, or metastatic disease. More predictive models include orthotopic tumors, genetically engineered mouse models, patient-derived xenografts, organoids, tumor-on-chip systems, and immunocompetent models [66].

15. Future Directions

The future of stimuli-responsive nanocarriers should move toward clinically realistic design. First, carrier systems should be simplified. A nanocarrier with five responsive components may look innovative but may be impossible to manufacture reproducibly. Second, responsiveness must be matched to measurable patient biomarkers. For example, enzyme-responsive carriers should be tested in patients whose tumors show high activity of the target enzyme. Third, imaging should be integrated into nanomedicine development. Companion imaging can help determine whether the carrier reaches the tumor before therapy is administered. Fourth, clinical trials should be designed around mechanism-based selection rather than broad unselected populations.

Another important direction is the development of theranostic nanocarriers, which combine therapy and diagnostic imaging. These systems can help monitor biodistribution, accumulation, release, and treatment response. Imaging-guided drug delivery may be especially valuable for externally triggered systems such as thermosensitive, magnetic, light-responsive, and ultrasound-responsive platforms.

Artificial intelligence and computational modeling may also improve nanocarrier design by predicting formulation behavior, drug release, biodistribution, toxicity, and patient-specific response. However, computational models must be trained on high-quality experimental and clinical data. Poor-quality data will generate unreliable predictions.

Finally, regulatory translation will require stronger standardization. Researchers should report nanoparticle size distribution, zeta potential, morphology, drug loading, release kinetics, serum stability, protein corona behavior, storage stability, sterilization method, endotoxin levels, hemocompatibility, immunotoxicity, and batch-to-batch reproducibility. Without such reporting, even scientifically exciting systems may fail to move beyond preclinical publication.

16. Conclusion

Stimuli-responsive nanocarriers represent a powerful and intellectually mature approach to targeted drug delivery. Their ability to respond to disease-associated or externally applied triggers allows a level of control that conventional formulations cannot achieve. pH-responsive, redox-

responsive, enzyme-responsive, thermoresponsive, light-responsive, magnetic, ultrasound-triggered, and multi-stimuli systems have demonstrated remarkable preclinical promise. However, the clinical translation of these systems remains limited. Approved nanomedicines prove that nanoscale delivery can succeed, but most approved products are not highly complex stimuli-responsive systems. The field must therefore learn from both successes and failures.

The major barriers include heterogeneous disease biology, variable EPR effect, premature leakage, immune clearance, protein corona formation, insufficient tissue penetration, manufacturing complexity, regulatory uncertainty, and weak clinical trial design. The next generation of stimuli-responsive nanocarriers should be simpler, safer, biomarker-guided, image-trackable, and manufacturable. Instead of designing carriers only for impressive laboratory responsiveness, researchers should design them for clinical decision-making, patient selection, reproducible manufacturing, and measurable therapeutic superiority. If these challenges are addressed, stimuli-responsive nanocarriers may become an important foundation for precision drug delivery in cancer, inflammatory disease, neurological disorders, genetic diseases, and beyond.

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References

1. Allen, T. M., & Cullis, P. R. (2013). Liposomal drug delivery systems: From concept to clinical applications. *Advanced Drug Delivery Reviews, 65*(1), 36–48. https://doi.org/10.1016/j.addr.2012.09.037
2. Anselmo, A. C., & Mitragotri, S. (2016). Nanoparticles in the clinic. *Bioengineering & Translational Medicine, 1*(1), 10–29. https://doi.org/10.1002/btm2.10003
3. Autio, K. A., Dreicer, R., Anderson, J., Garcia, J. A., Alva, A., Hart, L. L., Milowsky, M. I., Posadas, E. M., Ryan, C. J., Friedlander, T. W., Shore, N., Beer, T. M., Kopp, H. G., Fong, L., et al. (2018). Safety and efficacy of BIND-014, a docetaxel nanoparticle targeting prostate-specific membrane antigen for patients with metastatic castration-resistant prostate cancer. *JAMA Oncology, 4*(10), 1344–1351.
4. Bae, Y. H., & Park, K. (2011). Targeted drug delivery to tumors: Myths, reality and possibility. *Journal of Controlled Release, 153*(3), 198–205. https://doi.org/10.1016/j.jconrel.2011.06.001
5. Barenholz, Y. (2012). Doxil®—The first FDA-approved nano-drug: Lessons learned. *Journal of Controlled Release, 160*(2), 117–134. https://doi.org/10.1016/j.jconrel.2012.03.020
6. Bertrand, N., Wu, J., Xu, X., Kamaly, N., & Farokhzad, O. C. (2014). Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. *Advanced Drug Delivery Reviews, 66*, 2–25. https://doi.org/10.1016/j.addr.2013.11.009
7. Bobo, D., Robinson, K. J., Islam, J., Thurecht, K. J., & Corrie, S. R. (2016). Nanoparticle-based medicines: A review of FDA-approved materials and clinical trials to date. *Pharmaceutical Research, 33*, 2373–2387. https://doi.org/10.1007/s11095-016-1958-5
8. Chen, X., Zhang, Y., Wang, Y., & Wang, J. (2022). Stimuli-responsive image-guided nanocarriers as smart drug delivery systems. *Expert Opinion on Drug Delivery, 19*(11), 1385–1401.
9. Danhier, F. (2016). To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine? *Journal of Controlled Release, 244*, 108–121. https://doi.org/10.1016/j.jconrel.2016.11.015
10. de la Rica, R., Aili, D., & Stevens, M. M. (2012). Enzyme-responsive nanoparticles for drug release and diagnostics. *Advanced Drug Delivery Reviews, 64*(11), 967–978. https://doi.org/10.1016/j.addr.2012.01.002
11. Dou, Y., Hynynen, K., & Allen, C. (2017). To heat or not to heat: Challenges with clinical translation of thermosensitive liposomes. *Journal of Controlled Release, 249*, 63–73. https://doi.org/10.1016/j.jconrel.2017.01.025
12. Fang, J., Nakamura, H., & Maeda, H. (2011). The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Advanced Drug Delivery Reviews, 63*(3), 136–151. https://doi.org/10.1016/j.addr.2010.04.009
13. Fleige, E., Quadir, M. A., & Haag, R. (2012). Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: Concepts and applications. *Advanced Drug Delivery Reviews, 64*(9), 866–884. https://doi.org/10.1016/j.addr.2012.01.020
14. Gabizon, A., Shmeeda, H., & Barenholz, Y. (2003). Pharmacokinetics of pegylated liposomal doxorubicin: Review of animal and human studies. *Clinical Pharmacokinetics, 42*(5), 419–436.

15. Ganta, S., Devalapally, H., Shahiwala, A., & Amiji, M. (2008). A review of stimuli-responsive nanocarriers for drug and gene delivery. *Journal of Controlled Release, 126*(3), 187–204. https://doi.org/10.1016/j.jconrel.2007.12.017
16. Gradishar, W. J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P., Hawkins, M., & O'Shaughnessy, J. (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil–based paclitaxel in women with breast cancer. *Journal of Clinical Oncology, 23*(31), 7794–7803. https://doi.org/10.1200/JCO.2005.04.937
17. Hare, J. I., Lammers, T., Ashford, M. B., Puri, S., Storm, G., & Barry, S. T. (2017). Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. *Advanced Drug Delivery Reviews, 108*, 25–38. https://doi.org/10.1016/j.addr.2016.04.025
18. Hatakeyama, H. (2017). Recent advances in endogenous and exogenous stimuli-responsive nanocarriers for drug delivery and therapeutics. *Chemical and Pharmaceutical Bulletin, 65*(7), 612–617.
19. Hu, Q., Katti, P. S., & Gu, Z. (2014). Enzyme-responsive nanomaterials for controlled drug delivery. *Nanoscale, 6*(21), 12273–12286. https://doi.org/10.1039/C4NR04249B
20. Jain, R. K., & Stylianopoulos, T. (2010). Delivering nanomedicine to solid tumors. *Nature Reviews Clinical Oncology, 7*(11), 653–664. https://doi.org/10.1038/nrclinonc.2010.139
21. Jia, Y., Wang, X., Hu, D., Wang, P., Liu, Q., Zhang, X., Jiang, J., Liu, X., Sheng, Z., Liu, B., & Zheng, H. (2023). Approved nanomedicine against diseases. *Pharmaceutics, 15*(3), 774.
22. Kapalatiya, H., Raval, J. P., & Murthy, R. S. R. (2022). Enzyme-responsive smart nanocarriers for targeted drug delivery in cancer therapy. *Drug Discovery Today, 27*(7), 1945–1963.
23. Kim, J., Lee, J., Kim, Y. M., Kim, H., Park, D., Kim, K., & Kwon, I. C. (2023). Perspectives for improving the tumor targeting of nanomedicine via the EPR effect. *Journal of Pharmaceutical Investigation, 53*, 1–16.
24. Kobayashi, H., Watanabe, R., & Choyke, P. L. (2014). Improving conventional enhanced permeability and retention effect: What is the appropriate target? *Theranostics, 4*(1), 81–89. https://doi.org/10.7150/thno.7193
25. Lancet, J. E., Uy, G. L., Cortes, J. E., Newell, L. F., Lin, T. L., Ritchie, E. K., Stuart, R. K., Strickland, S. A., Hogge, D., Solomon, S. R., et al. (2018). CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukemia. *Journal of Clinical Oncology, 36*(26), 2684–2692. https://doi.org/10.1200/JCO.2017.77.6112
26. Li, D., Li, J., Wang, Y., & Mehta, J. L. (2020). Redox-responsive self-assembled nanoparticles for cancer therapy. *Current Drug Metabolism, 21*(8), 575–587.
27. Li, M., Zhao, L., Zhang, T., & Liu, W. (2020). Enzyme-responsive nanoparticles for anti-tumor drug delivery. *Frontiers in Chemistry, 8*, 647.
28. Liu, M., Du, H., Zhang, W., & Zhai, G. (2017). Internal stimuli-responsive nanocarriers for drug delivery. *Materials Science and Engineering: C, 71*, 1267–1280.
29. Maeda, H. (2015). Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity. *Advanced Drug Delivery Reviews, 91*, 3–6. https://doi.org/10.1016/j.addr.2015.01.002
30. Maeda, H., Wu, J., Sawa, T., Matsumura, Y., & Hori, K. (2000). Tumor vascular permeability and the EPR effect in macromolecular therapeutics: A review. *Journal of Controlled Release, 65*(1–2), 271–284.
31. Majumder, J., Minko, T., & others. (2020). Multifunctional and stimuli-responsive nanocarriers for targeted therapeutic drug delivery. *Nanomaterials, 10*, 1–34.
32. Mi, P. (2020). Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. *Theranostics, 10*(10), 4557–4588. https://doi.org/10.7150/thno.38069
33. Miele, E., Spinelli, G. P., Miele, E., Tomao, F., & Tomao, S. (2009). Albumin-bound formulation of paclitaxel: Abraxane® ABI-007 in the treatment of breast cancer. *International Journal of Nanomedicine, 4*, 99–105.
34. Moghimi, S. M., & Szebeni, J. (2003). Stealth liposomes and long circulating nanoparticles: Critical issues in pharmacokinetics, opsonization and protein-binding properties. *Progress in Lipid Research, 42*(6), 463–478.
35. Mollazadeh, S., Mackiewicz, M., & Yazdimamaghani, M. (2021). Recent advances in the redox-responsive drug delivery nanoplatforms: A chemical structure and physical property perspective. *Materials Science and Engineering: C, 118*, 111536.
36. Mura, S., Nicolas, J., & Couvreur, P. (2013). Stimuli-responsive nanocarriers for drug delivery. *Nature Materials, 12*(11), 991–1003. https://doi.org/10.1038/nmat3776
37. Nakamura, Y., Mochida, A., Choyke, P. L., & Kobayashi, H. (2016). Nanodrug delivery: Is the enhanced permeability and retention effect sufficient for curing cancer? *Bioconjugate Chemistry, 27*(10), 2225–2238.

https://doi.org/10.1021/acs.bioconjchem.6b00437

38. Namiot, A., Sokolowska, E., & Zawadzka, K. (2023). Clinical trials and FDA-approved nanoparticle drugs for cancer therapy. *International Journal of Molecular Sciences, 24*(1), 787.
39. Nichols, J. W., & Bae, Y. H. (2014). EPR: Evidence and fallacy. *Journal of Controlled Release, 190*, 451–464. https://doi.org/10.1016/j.jconrel.2014.03.057
40. Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology, 2*(12), 751–760. https://doi.org/10.1038/nnano.2007.387
41. Raza, A., Rasheed, T., Nabeel, F., Hayat, U., Bilal, M., & Iqbal, H. M. N. (2019). Redox-responsive nano-carriers as tumor-targeted drug delivery systems. *European Journal of Medicinal Chemistry, 157*, 705–715.
42. Regenold, M., Kuehl, P. J., Haemmerich, D., & others. (2022). Turning down the heat: The case for mild hyperthermia and thermosensitive liposomes. *International Journal of Hyperthermia, 39*(1), 103–117.
43. Rwei, A. Y., Wang, W., & Kohane, D. S. (2015). Photoresponsive nanoparticles for drug delivery. *Nano Today, 10*(4), 451–467.
44. Shahriari, M., Zahiri, M., Abnous, K., Taghdisi, S. M., Ramezani, M., & Alibolandi, M. (2019). Enzyme responsive drug delivery systems in cancer treatment. *Journal of Controlled Release, 308*, 172–189.
45. Shan, X., Gong, X., Li, J., Wen, J., Li, Y., & Zhang, Z. (2022). Current approaches of nanomedicines in the market and various stages of clinical translation. *Acta Pharmaceutica Sinica B, 12*(7), 3028–3048.
46. Shi, J., Kantoff, P. W., Wooster, R., & Farokhzad, O. C. (2017). Cancer nanomedicine: Progress, challenges and opportunities. *Nature Reviews Cancer, 17*(1), 20–37. https://doi.org/10.1038/nrc.2016.108
47. Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians, 73*(1), 17–48. Use only if you discuss cancer burden/background.
48. Subhan, M. A., Yalamarty, S. S. K., Filipczak, N., Parveen, F., & Torchilin, V. P. (2021). Recent advances in tumor targeting via EPR effect for cancer treatment. *Journal of Personalized Medicine, 11*(6), 571.
49. Tak, W. Y., Lin, S. M., Wang, Y., Zheng, J., Vecchione, A., Park, S. Y., Chen, M. H., Wong, S., Xu, R., Peng, C. Y., et al. (2018). Phase III HEAT study adding lyso-thermosensitive liposomal doxorubicin to radiofrequency ablation in patients with unresectable hepatocellular carcinoma lesions. *Clinical Cancer Research, 24*(1), 73–83.
50. Torchilin, V. P. (2014). Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. *Nature Reviews Drug Discovery, 13*(11), 813–827. https://doi.org/10.1038/nrd4333
51. Von Hoff, D. D., Mita, M. M., Ramanathan, R. K., Weiss, G. J., Mita, A. C., Lorusso, P. M., Burris, H. A., Hart, L. L., Low, S. C., Parsons, D. M., et al. (2016). Phase I study of PSMA-targeted docetaxel-containing nanoparticle BIND-014 in patients with advanced solid tumors. *Clinical Cancer Research, 22*(13), 3157–3163.
52. Wang-Gillam, A., Li, C. P., Bodoky, G., Dean, A., Shan, Y. S., Jameson, G., Macarulla, T., Lee, K. H., Cunningham, D., Blanc, J. F., et al. (2016). Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy. *The Lancet, 387*(10018), 545–557. https://doi.org/10.1016/S0140-6736(15)00986-1
53. Wilhelm, S., Tavares, A. J., Dai, Q., Ohta, S., Audet, J., Dvorak, H. F., & Chan, W. C. W. (2016). Analysis of nanoparticle delivery to tumours. *Nature Reviews Materials, 1*, 16014. https://doi.org/10.1038/natrevmats.2016.14
54. Xu, L., Li, H., Wang, R., & Li, J. (2024). Redox-responsive polymeric nanoparticles for nucleic acid delivery and cancer therapy: Progress, opportunities and challenges. *International Journal of Pharmaceutics, 650*, 123654.
55. Yang, Y., Wang, Z., Huang, L., & Shao, K. (2022). Recent advances in redox-responsive nanoparticles for cancer therapy. *Journal of Nanobiotechnology, 20*, 381.
56. Zhang, P., Zhai, Y., Cai, Y., Zhao, Y., & Li, Y. (2019). Nanomedicine-based immunotherapy for the treatment of cancer metastasis. *Advanced Materials, 31*(49), 1904156.
57. Cai, R., Chen, C., & Ke, P. C. (2019). Roles of the protein corona in nanomedicine. *Advanced Materials, 31*(45), 1805740. https://doi.org/10.1002/adma.201805740
58. Chen, Z., Wang, Z., Gu, Z., & others. (2022). Harnessing protein corona for biomimetic nanomedicine applications. *Biomimetics, 7*(3), 126. https://doi.org/10.3390/biomimetics7030126
59. Geers, B., Lentacker, I., Sanders, N. N., Demeester, J., Meairs, S., & De Smedt, S. C. (2011). Self-assembled liposome-loaded microbubbles: The missing link for safe and efficient ultrasound-triggered drug-delivery.

Journal of Controlled Release, 152(2), 249–256. https://doi.org/10.1016/j.jconrel.2011.02.024

60. Hughes, G. A. (2005). Nanostructure-mediated drug delivery. *Nanomedicine: Nanotechnology, Biology and Medicine, 1*(1), 22–30. https://doi.org/10.1016/j.nano.2004.11.009
61. Kumari, R., Sunil, D., & Ningthoujam, R. S. (2020). Hypoxia-responsive nanoparticle based drug delivery systems in cancer therapy: An up-to-date review. *Journal of Controlled Release, 319*, 135–156. https://doi.org/10.1016/j.jconrel.2019.12.030
62. Mahmoudi, M., Landry, M. P., Moore, A., & Coreas, R. (2023). The protein corona from nanomedicine to environmental science. *Nature Reviews Materials, 8*, 422–438. https://doi.org/10.1038/s41578-023-00552-2
63. Mamnoon, B., Feng, L., Froberg, J., Choi, Y., Sathish, V., Mallik, S., & others. (2020). Hypoxia-responsive, polymeric nanocarriers for targeted drug delivery to estrogen receptor-positive breast cancer cell spheroids. *Molecular Pharmaceutics, 17*(11), 4312–4322. https://doi.org/10.1021/acs.molpharmaceut.0c00772
64. Rapoport, N. (2012). Phase-shift, stimuli-responsive perfluorocarbon nanodroplets for drug delivery to cancer. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 4*(5), 492–510. https://doi.org/10.1002/wnan.1176
65. Rwei, A. Y., Wang, W., & Kohane, D. S. (2015). Photoresponsive nanoparticles for drug delivery. *Nano Today, 10*(4), 451–467. https://doi.org/10.1016/j.nantod.2015.06.004
66. Zeng, Y., Ma, J., Zhan, Y., Xu, X., Zeng, Q., Liang, J., & Chen, X. (2018). Hypoxia-activated prodrugs and redox-responsive nanocarriers. *International Journal of Nanomedicine, 13*, 6551–6574. https://doi.org/10.2147/IJN.S173722