

Available online on 15.10.2026 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Stimuli-Responsive Nanocarriers in Oncology: Tumor Microenvironment Triggers, Overcoming Biological Barriers, and Clinical Reality

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Article Info:



Article History:

Received 28 July 2026
Reviewed 09 Sep 2026
Accepted 01 Oct 2026
Published 15 Oct 2026

Cite this article as:

Pan D, Sarkar S, Adhikary S, Mia A, Khandokar S, Das K, De B, Das M, Ghosh S, Stimuli-Responsive Nanocarriers in Oncology: Tumor Microenvironment Triggers, Overcoming Biological Barriers, and Clinical Reality, Journal of Drug Delivery and Therapeutics. 2026; 16(10) 194-198: DOI: <https://doi.org/10.22270/jddt.v16i10.8035>

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Abstract

Conventional anticancer nano-therapies often rely on passive accumulation through the enhanced permeability and retention (EPR) effect, resulting in insufficient penetration of tumor tissue and heterogeneous cellular uptake. Smart nanocarriers that are able to respond to specific stimuli through conformational, charge-reversal, or structural phase changes to improve targeting efficacy at the tumor site have been proposed as promising alternatives. These stimuli-responsive smart nanocarriers undergo conformational changes or transitions in charge, solubility, or structure when exposed to a specific triggering stimulus. Smart nanocarriers can be triggered by either endogenous biochemical perturbations associated with the tumor microenvironment or external ex vivo physical triggers. The former includes the extracellular and endosomal pH gradients, the increased intracellular glutathione redox potential, and dysregulated proteolytic enzymes in the tumor microenvironment, while the latter includes near-infrared light, alternating magnetic fields, and high-intensity focused ultrasound. This article reviews the fundamental bio responsive molecular mechanisms, nanocarrier types, clinical reality, translational barriers, and design-by-quality principles relevant to the development of responsive nanotherapeutics for clinical oncology.

Keywords: Stimuli-Responsive Nanocarriers, Tumor Microenvironment, Smart Drug Delivery, Redox Trigger, Endosomal Escape, Clinical Translation.

1. Introduction: The Need for Smart Delivery Systems

Despite significant progress in colloidal drug delivery systems over the past four decades, the therapeutic index of first-generation nanomedicines is limited by off-target biodistribution patterns, hepatic sequestration, and inadequate intratumoral bioavailability ^{1, 2}. Formulations based on passive targeting confront numerous biological barriers: dense extracellular matrix stroma, high interstitial fluid pressure (IFP) that hinders convective transport, aberrant fenestrations, and rapid opsonization by the reticuloendothelial system (RES) ³. In addition, a paradox is apparent in passive design: nanocarriers need to possess exceptional structural stability to avoid premature cargo leakage in circulation, but upon entering cancer cells, they must quickly release their bioavailable payload ⁴. To overcome this "carrier stability-versus-release dilemma," stimuli-responsive nanocarriers utilize smart chemical functionalities that

are inactive and intact under physiological homeostatic conditions (pH ~7.4, low reductive tension) but can trigger cargo release, surface de-shielding, or membrane permeabilization in response to pathological inputs ^{1, 5}.

2. Biochemical Anatomy of the Tumor Microenvironment (TME)

The metabolic aberrancies of solid tumors generate unique biochemical divergence from the normal tissues, resulting in distinctive stimuli:

- **Acidic Extracellular & Endosomal pH:** Hyperactive anaerobic glycolysis (the Warburg effect) and proton extrusion through vacuolar H⁺-ATPases acidify the tumor extracellular fluid (pH ~6.5-6.8). Following endocytosis, the luminal pH further decreases in early endosomes (pH 5.5-6.0) and lysosomes (pH 4.5-5.0), setting up steep proton gradients ⁶.
- **Intracellular Redox Gradient:** Intracellular glutathione (GSH) concentrations in malignant cells reach 2-10 mM, which can be up to 1,000-fold higher

than in non-malignant extracellular fluids (~2-20 μM), providing a robust cytosolic reducing trigger ⁷.

- **Overexpressed Stromal Proteases:** Invasive tumor growth results in extensive expression of zinc-dependent matrix metalloproteinases (MMP-2, MMP-9), cathepsin B, and urokinase-type plasminogen activator (uPA), which degrade extracellular matrices, enabling tissue invasion ⁸.

3. Endogenous (Internal) Stimuli-Responsive Mechanisms

3.1. Acidic pH-Triggered Nanocarriers

pH-responsive nanosystems employ two main approaches for stimuli-responsive behavior: protonation-induced swelling/charge conversion and acid-labile covalent bond cleavage ^{5,6}.

- **Proton Sponge Effect & Charge Reversal:** Polymers with tertiary amines (e.g., poly(2-(diethylamino)ethyl methacrylate), PDEAEMA) or ionizable lipids possess a neutral surface at physiological pH to prolong vascular circulation. Endocytosis into early endosomes (pH ~6.0) leads to the protonation of amine moieties that buffer the lumen's low pH, resulting in passive chloride influx and osmotic swelling. This physical disruption of the endosomal membrane releases therapeutics into the cytosol [5, 9]. At the same time, charge-reversal coatings using acid-cleavable maleic acid derivatives (e.g., DMAA) shift from negative to positive surface potentials at pH 6.5, enabling electrostatic attachment to negatively charged cancer cell membranes ⁶.

- **Acid-Cleavable Covalent Linkers:** Acid-labile covalent bonds such as hydrazone, benzoic imine, acetal, ketal, and orthoester are used. Cis-aconityl groups are stabilized in plasma but hydrolyzed in acidic endolysosomes (pH 4.5-5.0). Hydrazone linkages are extensively used in polymer-drug conjugates and antibody-drug conjugates (ADCs) for rapid intracellular drug release ^{6,10}.

3.2. Redox & Glutathione (GSH)-Responsive Systems

Leveraging the imbalanced intracellular and extracellular glutathione (GSH) concentration, redox-responsive vectors utilize disulfide (-S-S-), diselenide (-Se-Se-), or thioether bonds in their polymeric backbone, core-crosslinked matrix, or prodrug pendants ⁷. Upon internalization into the cancer cell cytosol, the high GSH concentration rapidly reduces disulfide bonds into hydrophilic sulfhydryl (-SH) groups by thiol-disulfide exchange. The cleavage leads to the immediate dissolution of hydrophobic core domains, collapsing micelles or nanogels, and releasing cytotoxic molecules directly at intracellular target sites ^{7,11}.

3.3. Enzyme-Instructed Drug Release

Another approach uses sterically accessible peptide linkages that are specifically cleaved by overexpressed tumor proteases [8]. For example, the incorporation of the peptide sequence Pro-Val-Gly-Leu-Iso-Gly (which is selectively cleaved by MMP-2/9) or Gly-Phe-Leu-Gly (GFLG, digested by lysosomal Cathepsin B) enables

localized payload release. Indeed, enzymatic degradation of the outer PEG shields unveils hidden cell-penetrating peptides (e.g., TAT) and consequently enhances rapid cellular internalization restricted to the tumor milieu ^{8, 12}. These endogenous activation mechanisms ensure minimal systemic exposure, confining the active therapeutic window to the pathological site.

4. Exogenous (Externally Triggered) Systems

While endogenous stimuli are dictated by tumor physiology, which can present significant intra- and inter-patient heterogeneity, exogenously triggered platforms utilize non-invasive physical energy fields delivered from an external medical device to achieve precise, on-demand release kinetics ^{1,13}.

4.1. Photo-Responsive Nanocarriers (UV, Visible, and NIR)

Light-sensitive nanocarriers incorporate photochromic units that are capable of isomerization (e.g., azobenzene trans-cis transition), photo-induced irreversible bond cleavage (e.g., o-nitrobenzyl esters), or photo-crosslinking upon exposure to a specific wavelength of light ¹³. Near-infrared (NIR) light ($\lambda = 700\text{-}1000\text{ nm}$) is particularly advantageous for biological applications due to the reduced tissue scattering and hemoglobin absorption in the NIR-I and NIR-II optical windows, respectively, which enable enhanced subcutaneous energy penetration ¹⁴. Upon encapsulation of gold nanorods, carbon-based nanomaterials, or indocyanine green (ICG), NIR irradiation can be utilized to achieve:

- **Photothermal Therapy (PTT):** Localized hyperthermia ($> 42^\circ\text{C}$) disrupts thermo-sensitive membranes (e.g., DPPC bilayer) to initiate burst drug release while concurrently causing hyperthermic cancer cell ablation ^{13,14}.

- **Photodynamic Therapy (PDT):** Light excitation of photosensitizers generates reactive singlet oxygen (O_2), which chemically peroxidizes lipid bilayers to release trapped payloads while inducing severe oxidative damage to adjacent tumor vessels ¹⁴.

4.2. Magnetic Field & Ultrasound Triggers

- **Alternating Magnetic Field (AMF):** Superparamagnetic iron oxide nanoparticles (SPIONs, Fe_3O_4) subjected to high-frequency AMF convert electromagnetic energy into localized heat through Néel and Brownian relaxation mechanisms. This localized thermal energy cleaves thermo-labile crosslinkers (e.g., azo-initiators) to release encapsulated payloads without damaging non-target tissues ¹.

- **High-Intensity Focused Ultrasound (HIFU):** Achieves deep anatomical penetration using thermal and non-thermal acoustic cavitation. Acoustic radiation forces generate localized microstreaming and transient shear stresses that rupture microbubbles or cause phase shifts in nanoemulsions to accelerate vascular extravasation through dense desmoplastic tumor stroma ¹⁶.

5. Multi-Stimuli Responsive (Smart "AND/OR" Logic) Vectors

Single-stimulus nanosystems can be non-specifically triggered by minor physiological changes in non-target inflamed tissues. To address this, advanced nanoplateforms incorporate multiple-responsive logic gates ("AND" / "OR" Boolean operators) to boost delivery specificity^{1, 17}. In the particular case of an "AND" logic vector, both acidic extracellular conditions (pHe 6.5) to remove the PEG shell and high intracellular

GSH (10 mM) to break the core disulfide bonds are required. This ensures that cytotoxic drugs remain intact until complete cellular internalization occurs¹⁷.

6. Clinical Translation Landscape & Trial Reality

Despite thousands of successful laboratory studies, only a small fraction of stimuli-responsive nanocarriers have successfully navigated through regulatory approvals and advanced clinical trials^{2, 18}.

Table 1: Selected Stimuli-Responsive Nanotherapeutics in Clinical Evaluation

Product / Agent	Carrier Architectur	Stimulus Mechanism	Clinical Indication	Current Phase / Outcome
ThermoDox® ¹	Lyso-thermosensitive liposome (LTSL)	Hyperthermia ($\geq 40-42^{\circ}\text{C}$) via RFA / MR HIFU	Hepatocellular carcinoma, breast cancer metastases	Phase III completed; achieved rapid localized intravascular drug release but failed to reach overall survival primary endpoints in unstratified patient cohorts.
Opaxio™ (Xyotax) ²⁰	Poly-L-glutamic acid paclitaxel conjugate	Enzymatic (Cathepsin B proteolysis)	Ovarian, non-small cell lung cancer (NSCLC)	Phase III completed; it demonstrated significantly reduced systemic neurotoxicity and bone marrow suppression compared to conventional Paclitaxel.
NanoTherm® ¹⁵	Aminosilane-coated iron oxide (Fe_3O_4)	Exogenous Alternating Magnetic Field (AMF)	Recurrent Glioblastoma multiforme, prostate cancer	EMA approved (CE marked); it generates interstitial magnetic hyperthermia to induce direct tumor cell ablation and sensitize radiochemotherapy.
Patisiran (Onpattro) ^{5, 9}	Ionizable lipid nanoparticle (LNP)	pH-dependent protonation (pH < 6.0) in endosomes	Hereditary Transthyretin Amyloidosis (hATTR)	FDA Approved: Validated the safety and clinical feasibility of tertiary amine-driven endosomal escape for clinical systemic macromolecular delivery.
CybreXa (CBX-12) ²¹	pH-low insertion peptide (pHLIP) conjugate	Acidic extracellular pH (pHe < 6.5) folding	Advanced solid tumors (colorectal, ovarian)	Active Phase I/II clinical trials exploit pH-driven transmembrane insertion to deliver cytotoxic topoisomerase-1 inhibitors independently of receptor overexpression.

7. Critical Limitations & Translational Bottlenecks

Significant translational barriers are highlighted by the transition gap between preclinical publication and commercial approval^{2, 18}.

• **Biological heterogeneity:** Tumor grades, metastatic locales, and patient subpopulations all have different physiological triggers. In poorly vascularized locations, the slight pH difference between normal blood (7.4) and tumor stroma (~6.8) frequently causes sluggish, partial medication action^{2, 6}.

• **Manufacturing complexity (CMC bottlenecks):** Complex conjugation methods, multi-step chemical syntheses, and purification procedures are necessary for multi-stimuli structures. It remains difficult to

guarantee batch-to-batch consistency in particle size, drug encapsulation, and ligand orientation under current Good Manufacturing Practice (cGMP) rules¹⁸.

• **Immunogenicity and material biocompatibility:** Reactive degradation fragments, uncleavable synthetic polymers, or cationic intermediates that cause long-term organ toxicity or complement activation-related pseudoallergy (CARPA) can be generated by responsive cleavage^{11, 18}.

• **Physical trigger penetration limits:** Photo-triggered therapies are restricted to superficial, accessible lesions because exogenous energy sources, including NIR light, undergo rapid optical attenuation in human tissues (> 3-5 cm)^{13, 14}.

8. Comprehensive Future Perspectives

Several fields must come together to effectively convert stimuli-responsive nanomedicines into useful clinical oncology:

• **Companion Theranostics & Patient Stratification:** Future clinical trials should use diagnostic imaging (PET, SPECT, chemical exchange saturation transfer MRI) instead of generic patient enrollment. Patients most likely to benefit from responsive nano systems will be identified by pre-screening them for tissue acidity, local perfusion, or target enzyme expression ^{1,2}.

• **Biomimetic Cell-Membrane Cloaking & Synthetic Biology:** While retaining precise intracellular stimuli-triggered release mechanisms, camouflaging intelligent responsive cores with cell membranes derived from erythrocytes, leukocytes, or platelets confers endogenous CD47 "don't eat me" signaling and homologous homing, leading to immune evasion ¹⁸.

• **Artificial Intelligence & Continuous Microfluidic Manufacturing:** Machine learning algorithms enable the prediction of multi-stimuli cleavage kinetics, polymer-drug compatibility, and stability. Embracing continuous-flow microfluidic platforms informed by Quality-by-Design paradigms will engender robust large-scale manufacturing amenable to minimal batch-to-batch variability ^{5,18}.

• **Deep-Tissue Energy Transduction:** Emerging physical trigger modalities, including X-ray-enabled photodynamic excitation and focused shockwaves, are being developed. Wirelessly controlled bio-electronic implantable transducers are being created to activate therapeutics deep within anatomical viscera while avoiding inadvertent energy deposition in healthy parenchyma ^{14,16}.

9. Conclusion

Stimuli-responsive nanocarriers represent a new paradigm in pharmaceutical oncology, offering opportunities to go beyond traditional colloidal carriers and create intelligent therapeutics capable of actively controlling drug release in a stimulus-dependent manner. Such control relies on bio-labile chemical switches that can be triggered only in specific pathological environments to allow either an explosive release of the payload or its gradual release into the targeted area.

However, the clinical translation landscape teaches one crucial lesson. No matter how beautiful the solutions at the lab bench may be, they often fail to exhibit the desired effect in the diverse settings of the clinical environment. To overcome the translational barrier, it is essential to switch to more clinically viable and less complex systems that can be produced in an operationally robust manner using the principles of QbD and have a demonstrated safety profile. Ideally, these systems should incorporate a companion theranostic diagnostic. In the future, with a greater understanding of the tumor microenvironment and the availability of cGMP-compatible microfluidic manufacturing, smart nanocarriers will finally overcome the formidable

translational divide and bring personalized cancer medicine to the clinic.

Conflicts of Interest: None

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