

Design and Research Progress of Microenvironment-Responsive Nanodrug Delivery Systems

Jiacheng Du

*School of Pharmacy, China Pharmaceutical University, Nanjing, China
17826069093@163.com*

Abstract. Microenvironment-responsive nanodrug delivery systems are engineered to convert pathological cues into controlled drug loading, transport, retention, activation, and release. Their design is based on the spatial and biochemical differences between diseased tissues and normal organs, including acidic pH, hypoxia, reductive gradients, elevated reactive oxygen species, abnormal enzyme expression, dense extracellular matrix, and inflammatory mediator enrichment. These endogenous signals can be used to destabilize nanocarriers, cleave chemical linkers, expose targeting ligands, switch surface charge, activate prodrugs, or promote tissue penetration. Compared with passive nanocarriers, responsive systems provide an additional level of control over pharmacokinetics and pharmacodynamics, but their performance depends on signal intensity, intratumoral heterogeneity, carrier stability, manufacturing reproducibility, and biological transport barriers. This review summarizes the principal carrier types used in microenvironment-responsive delivery, analyzes pH-, hypoxia-, redox-, and enzyme-responsive mechanisms, and discusses therapeutic applications in cancer, inflammatory diseases, infectious diseases, and other pathological contexts. Experimental and early translational data support responsive nanomedicine as a rational route for improving site-specific therapy, while indicating that clinical translation requires quantitative biomarker selection, simplified carrier architecture, standardized safety evaluation, and disease-specific validation of release mechanisms.

Keywords: Microenvironment-responsive nanomedicine, Nanodrug delivery, pH response, Hypoxia, Redox response

1. Introduction

Nanodrug delivery systems were developed to improve the solubility, circulation stability, biodistribution, and therapeutic index of bioactive agents whose free forms show rapid clearance or dose-limiting toxicity. Liposomes, polymeric nanoparticles, micelles, dendrimers, inorganic nanoparticles, biomimetic vesicles, protein nanocarriers, and hybrid nanostructures have all been used to alter drug exposure at tissue and cellular levels. In cancer and several nonmalignant diseases, however, passive accumulation alone rarely produces uniform drug distribution. Vascular permeability, lymphatic drainage, stromal density, macrophage uptake, interstitial pressure, lesion size, and patient-specific physiology can markedly alter carrier deposition. Responsive

nanomedicine addresses this limitation by integrating materials chemistry with local disease biology, so that the carrier changes its physicochemical state after encountering a defined pathological signal [1, 2].

The disease microenvironment provides several endogenous triggers for carrier activation. Solid tumors frequently contain extracellular acidosis, endosomal and lysosomal acidity, hypoxic zones, high intracellular glutathione, abnormal matrix metalloproteinase activity, hyaluronidase enrichment, oxidative stress, and immunosuppressive metabolites. Inflamed tissues display reactive oxygen and nitrogen species, proteases, acidic phagosomes, activated macrophages, and vascular adhesion signals. Bacterial infections and biofilms create localized acidity, pathogen-derived enzymes, toxins, dense polymeric matrices, and immune-cell-associated oxidative stress. These cues are not uniform, yet their magnitude often differs enough from healthy tissue to guide material design. Acid-labile linkers, protonatable polymers, nitroimidazole or azobenzene groups, disulfide and diselenide bonds, thioketal and boronate motifs, peptide substrates, and enzyme-degradable polysaccharides now serve as common building blocks for microenvironment-responsive delivery [3-6].

This review summarizes the design basis, response mechanisms, and therapeutic applications of microenvironment-responsive nanodrug delivery systems. The discussion emphasizes chemical triggers and disease-context requirements rather than presenting each carrier type as an isolated platform. Such an organization reflects the way responsive systems are designed in practice, where a material is selected only after the pathological trigger, intended drug, release site, administration route, and safety constraints have been defined. The review also considers translational issues, including heterogeneous trigger intensity, premature release, carrier complexity, scale-up, biomarker selection, and the need for release measurements that can be linked to therapeutic outcomes.

2. Design basis of microenvironment-responsive nanodrug delivery systems

2.1. Main types of nanodrug delivery systems

Liposomes are among the most clinically established nanocarriers because their phospholipid bilayers can encapsulate hydrophilic cargo in the aqueous core and hydrophobic cargo in the membrane. Surface polyethylene glycol can extend circulation, while pH-sensitive lipids, fusogenic peptides, or cleavable coatings can promote endosomal escape and local release. Polymeric nanoparticles and polymeric micelles provide broader chemical flexibility because monomer composition, block length, crosslinking density, hydrophobicity, and linker chemistry can be tuned during synthesis. Micelles are suitable for hydrophobic drugs, whereas crosslinked polymer networks can improve stability during blood circulation. Dendrimers offer defined architecture and multiple functional groups, although cationic surface charge requires careful toxicity control. Albumin nanoparticles, exosomes, cell-membrane-coated particles, and other biomimetic systems use endogenous protein or membrane components to alter immune recognition and tissue interactions [1, 7].

Inorganic and hybrid nanoparticles extend the functional range of nanomedicine. Mesoporous silica nanoparticles provide high surface area and gateable pores for pH-, redox-, or enzyme-triggered release. Gold nanostructures, iron oxide nanoparticles, carbon-based materials, metal-organic frameworks, and Prussian blue nanozymes can combine drug delivery with imaging, photothermal conversion, catalytic activity, or reactive oxygen species modulation. Hybrid carriers integrate organic shells with inorganic cores or combine lipid, polymer, and biomimetic components to balance circulation stability with intracellular release. The increased functionality of hybrid

systems can support multimodal therapy, but each added component also increases characterization demands, batch variability risk, and regulatory complexity.

2.2. Mechanisms of microenvironment-responsive delivery

Microenvironment-responsive delivery is not limited to drug release. A pathological signal may change particle size, surface charge, hydrophilicity, ligand exposure, membrane fusion capacity, degradation rate, or prodrug activity. For example, acidic extracellular pH can detach protective shells and expose cationic or targeting groups, whereas lower endosomal pH can trigger polymer swelling, membrane destabilization, and lysosomal escape. Hypoxia can reduce nitroaromatic groups or cleave azo linkages, leading to carrier disassembly or prodrug activation. Intracellular glutathione can break disulfide-crosslinked networks after endocytosis, producing selective cytosolic release. Enzymes such as matrix metalloproteinases, hyaluronidase, cathepsins, phospholipases, and bacterial beta-lactamases can cleave substrates incorporated into the carrier scaffold or surface coating [8-10].

The response site determines the design of the chemical trigger. Extracellular activation is suitable when the objective is tissue penetration, exposure of targeting ligands, matrix remodeling, or local release into a lesion. Intracellular activation is preferable when the therapeutic agent is toxic in extracellular fluid or requires cytosolic, nuclear, mitochondrial, or lysosomal access. Multistage systems combine both levels. A large neutral particle may circulate stably, shrink in acidic tumor tissue, expose a penetrating surface after enzyme cleavage, and release drug in the reductive cytosol. These sequential designs can address multiple transport barriers, although their therapeutic gain must justify the added materials complexity.

2.3. Design strategies for microenvironment-responsive nanodrug delivery systems

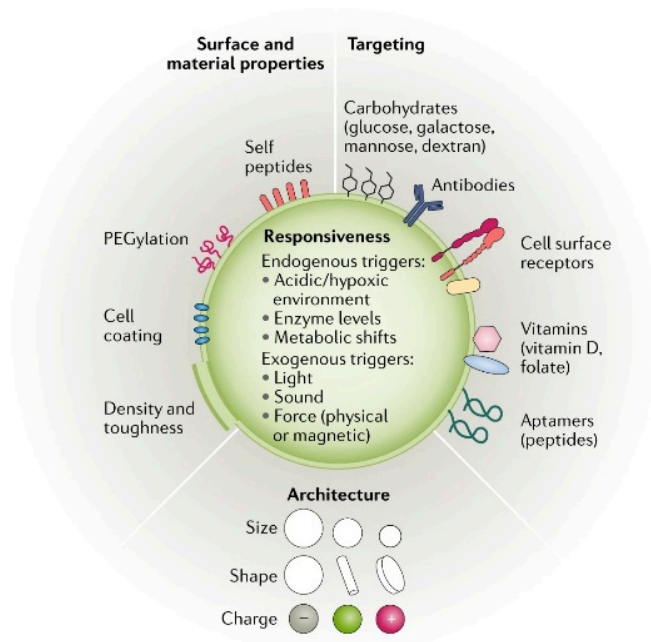


Figure 1. Key nanoparticle design features governing targeted and stimulus-responsive drug delivery [1]

Design begins with matching the trigger to a measurable disease feature. A carrier intended for tumor acidosis should respond within the pH range present in extracellular tumor tissue or endolysosomal compartments rather than at an arbitrary acidic value. Hypoxia-responsive systems require attention to oxygen gradients, reductase expression, and the distance between perfused vessels and hypoxic regions. Redox-responsive systems must remain stable in plasma but disassemble in the intracellular glutathione-rich environment. Enzyme-responsive systems require substrate specificity because proteases and glycosidases are also present in normal tissues. Quantitative trigger mapping can limit overdesign and helps select the response threshold, linker density, and degradation kinetics.

Carrier stability and responsiveness must be balanced. Excessively labile linkers release drugs before reaching diseased tissue, whereas overstable systems fail to release the payload after accumulation. Particle size affects circulation, renal clearance, tissue penetration, macrophage uptake, and cellular internalization. Surface charge modulates protein adsorption, vascular transport, mucus penetration, and cell membrane interaction. Ligand decoration can improve cell recognition, but high ligand density may increase clearance or reduce tissue penetration. Drug loading, release rate, and carrier degradation products should be evaluated together because a responsive carrier is only therapeutically useful when activation leads to a pharmacologically meaningful concentration at the correct biological site.

Accordingly, rational responsive-nanocarrier design should integrate particle architecture, surface and material properties, targeting moieties, and stimulus responsiveness rather than optimizing these parameters independently (Fig. 1).

3. Response mechanisms of microenvironment-responsive nanodrug delivery systems

3.1. pH-responsive nanodelivery systems

pH-responsive nanodelivery exploits acidity gradients between blood, diseased extracellular tissue, and intracellular vesicles. Normal blood and most healthy extracellular fluids remain close to neutral pH, whereas solid tumors can show extracellular pH values near 6.5 to 6.9 because of glycolytic metabolism and insufficient perfusion. Endosomes and lysosomes are more acidic, providing a second activation step after cellular uptake. Acid-sensitive hydrazone, imine, acetal, ketal, orthoester, boronate, and cis-aconityl linkages are used to release drugs or detach shielding groups. Protonatable polymers containing tertiary amines can swell or disrupt endosomal membranes through osmotic and buffering effects. Acidic pH-responsive polymer nanoparticles have been used to deliver immune agonists and anticancer agents, illustrating how pH activation can combine release with immune modulation [11].

The main design challenge is separating tumor extracellular activation from endosomal activation. Systems that respond at pH 6.8 may release cargo in acidic tumor regions but risk activation in inflamed or ischemic tissue. Systems that respond mainly below pH 5.5 are more stable during tissue transport but require efficient cellular uptake. Charge-reversal coatings provide an intermediate strategy. A near-neutral or anionic carrier can reduce nonspecific blood interactions, then convert to a cationic surface under mild acidity to increase tumor cell association. pH-responsive systems have also been applied to infection, where acidic abscesses, biofilms, and phagosomes can trigger antibiotic or photosensitizer release [12, 13].

3.2. Hypoxia-responsive nanodelivery systems

Hypoxia is a hallmark of many solid tumors and arises from abnormal vasculature, rapid oxygen consumption, and poor perfusion. It promotes angiogenesis, invasion, immune suppression, and resistance to radiotherapy and chemotherapy. Hypoxia-responsive nanodelivery uses reduced oxygen tension and reductase activity to activate chemical groups such as nitroimidazole, nitrobenzyl, azobenzene, quinone, and tirapazamine-like motifs. Reduction can increase hydrophilicity, cleave linkers, destabilize amphiphilic assemblies, or convert a prodrug into a cytotoxic species. Nanomedicine strategies can also modulate hypoxia itself by carrying oxygen, generating oxygen catalytically, normalizing vasculature, or combining hypoxia-activated therapy with photodynamic, radiotherapeutic, or immunotherapeutic approaches.

Hypoxia-responsive delivery requires spatial precision because hypoxia is heterogeneous within tumors. A carrier that releases only in severely hypoxic zones may not affect better-oxygenated proliferative margins, whereas oxygen-consuming therapies can worsen hypoxia and reduce treatment efficacy if not combined rationally. Biomimetic and catalytic systems, including erythrocyte-membrane-coated metal-organic frameworks and other oxygen-modulating platforms, have been studied to alter tumor metabolism and local oxygen availability [14]. The clinical translation of hypoxia-responsive systems will likely depend on imaging or biomarker selection, since patients with low hypoxic burden may not benefit from this response mechanism.

3.3. Redox-responsive nanodelivery systems

Redox-responsive nanodelivery uses differences in oxidative and reductive states across biological compartments. The cytosol and nucleus contain higher glutathione concentrations than extracellular fluids, and many tumor cells have altered thiol metabolism. Disulfide bonds are widely used to crosslink micelles, attach drugs, cap mesoporous pores, or connect hydrophilic and hydrophobic blocks. After endocytosis, intracellular glutathione cleaves disulfide bonds and accelerates carrier disassembly. Diselenide bonds, tellurium-containing motifs, ferrocene groups, thioketals, and arylboronate structures expand the redox-responsive toolbox by responding to reductive or oxidative environments. Redox-responsive micelles and mesoporous silica systems have shown selective drug release in cancer models, including triple-negative breast cancer and carbonic anhydrase IX-associated tumor targeting [15, 16]. For example, LHRH-targeted disulfide-crosslinked micelles combine receptor-mediated cellular uptake with GSH-triggered micelle disassembly, enabling selective intracellular paclitaxel release in triple-negative breast cancer cells (Fig. 2).

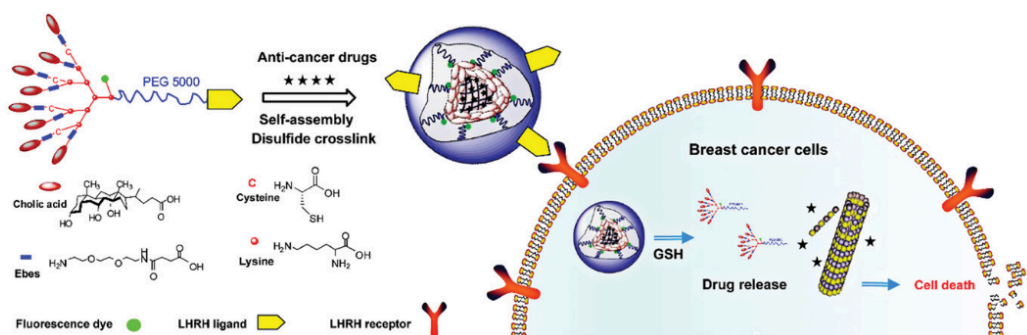


Figure 2. LHRH-targeted disulfide-crosslinked micelles enable GSH-triggered drug release in triple-negative breast cancer [15]

Oxidation-responsive systems are particularly relevant to inflammatory diseases and infections, where macrophages, neutrophils, damaged epithelia, and bacteria-associated immune reactions generate reactive oxygen species. Thioketal, thioether, selenium, poly(propylene sulfide), bilirubin, and boronate-containing materials can undergo oxidation-driven cleavage or polarity changes. Reactive oxygen species-responsive hyaluronic acid-bilirubin nanoplateforms and cascade nanocarriers have been investigated for inflammatory tissue therapy, showing how oxidative microenvironments can be used for both drug release and inflammation modulation [17, 18]. The same trigger must be calibrated carefully because systemic oxidative stress, ischemia-reperfusion injury, and normal phagocyte activity can also activate oxidation-sensitive materials.

3.4. Enzyme-responsive nanodelivery systems

Enzyme-responsive nanodelivery converts disease-associated catalytic activity into carrier degradation, gate opening, ligand exposure, or prodrug activation. Matrix metalloproteinases are frequently upregulated in invasive tumors and inflamed tissues, making peptide substrates for MMP-2, MMP-9, and membrane-type MMPs common design elements. MMP-responsive nanoparticles can enhance penetration, release cytotoxic drugs, or expose imaging signals after reaching enzyme-rich lesions. Gelatin nanoparticles and peptide-linked systems have been used for breast cancer, pancreatic cancer, and metastatic tumor models, while reviews of MMP-responsive delivery emphasize the need for substrate specificity and in vivo enzyme validation [19-21].

Other enzyme triggers broaden disease coverage. Hyaluronidase-responsive systems use degradation of hyaluronic acid shells to increase tumor penetration, release drugs, or expose cationic cores. Cathepsin-sensitive linkers exploit lysosomal protease activity after endocytosis. Phospholipase-, esterase-, and beta-glucuronidase-responsive systems have been used in inflammation and tumor therapy. In bacterial infection, beta-lactamase, gelatinase, lipase, phosphatase, and pathogen-associated enzymes can trigger antibiotic release or activate photothermal and photodynamic components. Gelatinase-responsive nanogels and beta-lactamase-responsive hydrogels demonstrate the relevance of pathogen- or lesion-specific enzymatic activation in infected wounds and resistant bacterial environments [22].

4. Applications of microenvironment-responsive nanodrug delivery systems in disease treatment

4.1. Applications in cancer therapy

Cancer therapy remains the principal application field for microenvironment-responsive nanodrug delivery. Tumor acidosis, hypoxia, reductive intracellular conditions, abnormal protease activity, and dense extracellular matrix create several opportunities for sequential delivery. Responsive systems have been used to deliver chemotherapeutic agents, photosensitizers, immune agonists, nucleic acids, checkpoint blockade modulators, and combinations of these modalities. In breast cancer, pH-responsive and TME-responsive nanoformulations have been developed to enhance drug accumulation, trigger release, remodel immune responses, or overcome resistance [5, 6]. In bladder, pancreatic, colorectal, and glioblastoma models, multistage carriers have been designed to cross biological barriers and release payloads under local stimuli [4, 23, 24].

Combination therapy is a major direction in tumor-responsive nanomedicine. A single carrier can co-deliver chemotherapy and phototherapy agents, release immunostimulatory molecules after acidic activation, or remodel hypoxia to improve radiotherapy and immunotherapy. Nanomedicine

has also been investigated for improving cancer immunotherapy by increasing antigen presentation, changing myeloid cell phenotypes, and reducing off-target immune toxicity [25]. Translational progress remains constrained by interpatient heterogeneity, limited tumor penetration, mononuclear phagocyte clearance, scale-up, and the difficulty of demonstrating that the intended microenvironment trigger is responsible for clinical benefit. Release biomarkers and patient selection assays will shape the next stage of tumor-responsive nanomedicine development.

4.2. Applications in inflammatory disease therapy

Inflammatory diseases provide endogenous triggers that differ from those in tumors. Activated immune cells produce reactive oxygen and nitrogen species, secrete proteases, acidify intracellular vesicles, and express adhesion receptors that alter vascular and tissue transport. Responsive systems for inflammatory bowel disease, cardiovascular inflammation, alcoholic liver disease, intervertebral disc degeneration, and autoimmune-like tissue injury have used pH, reactive oxygen species, enzyme activity, and macrophage-associated signals to localize drug action [18, 26, 27]. Oral delivery adds another layer of design because carriers must tolerate gastric acid and digestive enzymes before responding to intestinal inflammation. For example, ROS-cleavable mPEG-TK-PLGA:PLGA nanoparticles developed for oral teduglutide delivery showed rapid gastrointestinal transport and reached the colon within 15 min after administration in DSS-induced colitis mice (Fig. 3).

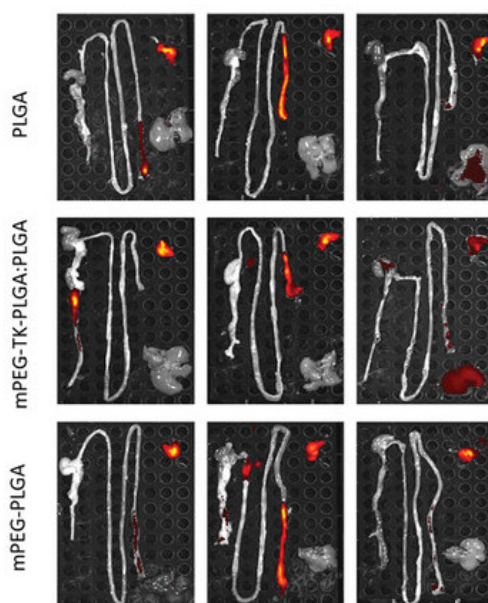


Figure 3. Gastrointestinal distribution of PLGA, ROS-cleavable mPEG-TK-PLGA:PLGA, and mPEG-PLGA nanoparticles 15 min after oral administration [8]

The therapeutic logic in inflammation differs from that in cancer. Instead of maximizing cytotoxic release, many systems aim to suppress pathological cytokine production, promote macrophage repolarization, protect epithelial barriers, reduce oxidative injury, or deliver biologics locally. Reactive oxygen species-responsive carriers are attractive because oxidative stress can both trigger release and act as a therapeutic target. The main risk is nonspecific activation in tissues with physiological immune surveillance. Inflammatory diseases also often fluctuate over time, so a

responsive carrier may need to match disease stage and activity rather than a fixed anatomical location.

4.3. Applications in infectious disease therapy

Infectious lesions contain microenvironmental features that can be used for selective delivery, including acidic biofilm matrices, bacterial enzymes, pathogen-derived toxins, local hypoxia, and immune-cell-derived reactive oxygen species. Biofilms create a diffusion barrier that reduces antibiotic penetration and protects bacteria from host immunity. pH-responsive vesicles, zwitterionic antimicrobial nanoparticles, silver metal-organic frameworks, antimicrobial peptide nanogels, and beta-lactamase-responsive hydrogels have been used to improve drug retention and trigger release at infected sites [22, 28]. Some platforms combine antimicrobial chemotherapy with photothermal therapy, photodynamic therapy, catalytic reactive oxygen species generation, or immune modulation.

The infection setting imposes safety and resistance-related constraints. Materials should avoid subtherapeutic antibiotic release that could favor resistance, should not intensify damaging inflammation, and should remain active in pus, mucus, necrotic tissue, and biofilm matrices. Carrier design also needs to account for bacterial species, enzyme expression, lesion pH, and host immune status. Infection-responsive nanomedicine has a clearer translational path when linked to defined indications such as cutaneous wounds, diabetic ulcers, implant biofilms, *Helicobacter pylori* infection, or localized abscesses, where the trigger and administration route can be measured directly.

4.4. Applications in other diseases

Microenvironment-responsive delivery is also being extended to cardiovascular, neurological, metabolic, ocular, and degenerative diseases. Cardiovascular lesions may contain oxidative stress, activated endothelium, inflammatory macrophages, acidic ischemic regions, and protease activity, enabling responsive delivery of anti-inflammatory, antioxidant, or anti-thrombotic agents [26]. Intervertebral disc degeneration and osteoarthritis involve low pH, oxidative stress, enzyme activity, and extracellular matrix remodeling, which have been used to guide local or injectable nanocarrier design [27]. In neurological disease, blood-brain barrier transport and disease heterogeneity remain major obstacles, but multistage nanomedicine concepts are being applied to glioblastoma and may inform other brain disorders [23].

Across these non-oncological indications, the strongest rationale comes from local delivery settings where the pathological trigger can be measured and the therapeutic window is narrow. Intra-articular, intradiscal, ocular, topical, inhaled, and oral administration may reduce systemic exposure and allow carrier design to reflect the local microenvironment. The same principles apply to gene therapy and protein delivery, where lipid nanoparticles and polymeric systems can be modified for selective release or endosomal escape [29]. Disease-specific transport barriers, not material novelty alone, should determine whether a responsive nanocarrier is preferable to a conventional formulation.

5. Conclusions and outlook

Microenvironment-responsive nanodrug delivery systems use pathological chemical and biological gradients to regulate carrier behavior after administration. pH, hypoxia, redox state, reactive oxygen species, and enzyme activity can be translated into linker cleavage, carrier swelling, shell

detachment, charge reversal, pore opening, prodrug activation, or matrix degradation. These mechanisms are relevant to tumor therapy, inflammatory disease, infection, and several localized degenerative disorders. The therapeutic value of a responsive system depends on whether the selected trigger is sufficiently strong, spatially restricted, durable, and connected to the required release site.

Several design issues will shape the next stage of this field. Trigger thresholds need to be quantified in patient-relevant tissues rather than inferred from simplified in vitro buffers. Carrier architecture should be simplified where possible, because multi-component systems increase manufacturing and regulatory burdens. Release assays should distinguish extracellular activation from intracellular activation and should be linked to pharmacodynamic outcomes. For clinical translation, microenvironment biomarkers, imaging readouts, and companion stratification methods will determine whether a carrier is matched to the lesion it is designed to treat. Responsive nanomedicine is most likely to advance when material design, disease biology, and therapeutic decision-making are developed as a single experimental system.

References

- [1] Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R. (2021). Engineering precision nanoparticles for drug delivery. *Nature Reviews Drug Discovery*, 20(2), 101–24.
- [2] Xie, F., Wang, M., Chen, Q., et al. (2022). Endogenous stimuli-responsive nanoparticles for cancer therapy: From bench to bedside. *Pharmacological Research*, 186, 106522.
- [3] Meng, W., Huang, L., Guo, J., Xin, Q., Liu, J., & Hu, Y. (2024). Innovative nanomedicine delivery: Targeting tumor microenvironment to defeat drug resistance. *Pharmaceutics*, 16(12).
- [4] Fakhri, S., Moradi, S. Z., Faraji, F., et al. (2023). Current advances in nanoformulations of therapeutic agents targeting tumor microenvironment to overcome drug resistance. *Cancer Metastasis Reviews*, 42(3), 959–1020.
- [5] Velapure, P., Kansal, D., & Bobade, C. (2024). Tumor microenvironment-responsive nanoformulations for breast cancer. *Discover Nano*, 19(1), 212.
- [6] Cao, Y., Meng, F., Cai, T., et al. (2024). Nanoparticle drug delivery systems responsive to tumor microenvironment: Promising alternatives in the treatment of triple-negative breast cancer. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 16(2), e1950.
- [7] Guo, J., & Huang, L. (2020). Membrane-core nanoparticles for cancer nanomedicine. *Advanced Drug Delivery Reviews*, 156, 23–39.
- [8] Barros, A. S., Pinto, S., Viegas, J., et al. (2024). Orally delivered stimulus-sensitive nanomedicine to harness teduglutide efficacy in inflammatory bowel disease. *Small*, 20(45), e2402502.
- [9] Guo, F., Du, Y., Wang, Y., et al. (2024). Targeted drug delivery systems for matrix metalloproteinase-responsive nanoparticles in tumor cells: A review. *International Journal of Biological Macromolecules*, 257(Pt 1), 128658.
- [10] Pan, Y., Liu, L., Mou, X., & Cai, Y. (2023). Nanomedicine strategies in conquering and utilizing the cancer hypoxia environment. *ACS Nano*, 17(21), 20875–924.
- [11] Kim, H., Sehgal, D., Kucaba, T. A., Ferguson, D. M., Griffith, T. S., & Panyam, J. (2018). Acidic pH-responsive polymer nanoparticles as a TLR7/8 agonist delivery platform for cancer immunotherapy. *Nanoscale*, 10(44), 20851–62.
- [12] Obuobi, S., Ngoc Phung, A., Julin, K., Johannessen, M., & Škalko-Basnet, N. (2022). Biofilm responsive zwitterionic antimicrobial nanoparticles to treat cutaneous infection. *Biomacromolecules*, 23(1), 303–15.
- [13] Li, Y., Liu, G., Wang, X., Hu, J., & Liu, S. (2016). Enzyme-responsive polymeric vesicles for bacterial-strain-selective delivery of antimicrobial agents. *Angew Chem Int Ed Engl*, 55(5), 1760–4.
- [14] Zhang, L., Wang, Z., Zhang, Y., et al. (2018). Erythrocyte membrane cloaked metal-organic framework nanoparticle as biomimetic nanoreactor for starvation-activated colon cancer therapy. *ACS Nano*, 12(10), 10201–11.
- [15] Xiao, K., Liu, Q., Suby, N., et al. (2021). LHRH-targeted redox-responsive crosslinked micelles impart selective drug delivery and effective chemotherapy in triple-negative breast cancer. *Adv Healthc Mater*, 10(3), e2001196.
- [16] Chen, M., Hu, J., Wang, L., et al. (2020). Targeted and redox-responsive drug delivery systems based on carbonic anhydrase IX-decorated mesoporous silica nanoparticles for cancer therapy. *Sci Rep*, 10(1), 14447.

- [17] Wang, Y., Pu, M., Yan, J., et al. (2023). 1,2-Bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid acetoxymethyl ester loaded reactive oxygen species responsive hyaluronic acid-bilirubin nanoparticles for acute kidney injury therapy via alleviating calcium overload mediated endoplasmic reticulum stress. *ACS Nano*, 17(1), 472–91.
- [18] Liu, F., Wang, X., Ren, M., et al. (2024). A shielded cascade of targeted nanocarriers spanning multiple microenvironmental barriers for inflammatory disease therapy. *J Nanobiotechnology*, 22(1), 789.
- [19] Chen, X., Zou, J., Zhang, K., et al. (2021). Photothermal/matrix metalloproteinase-2 dual-responsive gelatin nanoparticles for breast cancer treatment. *Acta Pharmaceutica Sinica B*, 11(1), 271–82.
- [20] Yin, N., Yu, H., Zhang, X., & Lv, X. (2020). Enhancement of pancreatic cancer therapy efficacy by type-1 matrix metalloproteinase-functionalized nanoparticles for the selective delivery of gemcitabine and erlotinib. *Drug Design, Development and Therapy*, 14, 4465–75.
- [21] Li, M., Wang, X., Wang, C., et al. (2022). Antimicrobial peptide-loaded gelatinase-responsive photothermal nanogel for the treatment of Staphylococcus aureus-infected wounds. *ACS Biomaterials Science & Engineering*, 8(8), 3463–72.
- [22] Alkekhia, D., LaRose, C., & Shukla, A. (2022). β -Lactamase-responsive hydrogel drug delivery platform for bacteria-triggered cargo release. *ACS Applied Materials & Interfaces*, 14(24), 27538–50.
- [23] Sun, Q., Zhou, Z., Qiu, N., & Shen, Y. (2017). Rational design of cancer nanomedicine: Nanoproperty integration and synchronization. *Advanced Materials*, 29(14).
- [24] Zhang, S., Zhang, H., Song, P., Wang, D., & Wang, Y. (2023). Colorectal cancer therapy mediated by nanomedicines. *Chemical Communications (Cambridge)*, 59(30), 4423–35.
- [25] Martin, J. D., Cabral, H., Stylianopoulos, T., & Jain, R. K. (2020). Improving cancer immunotherapy using nanomedicines: Progress, opportunities and challenges. *Nature Reviews Clinical Oncology*, 17(4), 251–66.
- [26] Liu, Y., Li, C., Yang, X., Yang, B., & Fu, Q. (2024). Stimuli-responsive polymer-based nanosystems for cardiovascular disease theranostics. *Biomaterials Science*, 12(15), 3805–25.
- [27] Tang, J., Luo, Y., Wang, Q., Wu, J., & Wei, Y. (2024). Stimuli-responsive delivery systems for intervertebral disc degeneration. *International Journal of Nanomedicine*, 19, 4735–57.
- [28] Zhou, D., Zhang, Z., Qiu, B., et al. (2022). Ultrasound-activated persistent luminescence imaging and bacteria-triggered drug release for Helicobacter pylori infection theranostics. *ACS Applied Materials & Interfaces*, 14(23), 26418–30.
- [29] Witzigmann, D., Kulkarni, J. A., Leung, J., Chen, S., Cullis, P. R., & van der Meel, R. (2020). Lipid nanoparticle technology for therapeutic gene regulation in the liver. *Advanced Drug Delivery Reviews*, 159, 344–63.