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Chapter 4: Stimuli-responsive nanoparticles: Controlled drug release strategies in tumor microenvironment

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Abstract

Stimuli-sensitive nanoparticles are emerging as a high-tech tool for advancing the controlled and targeted delivery of therapeutic drugs in the TME. The TME exhibits characteristic features such as acidic pH, higher glutathione concentrations, overexpressed enzymes, and hypoxia, and this can be exploited for the controlled release of therapeutic drugs. These intelligent nanoparticles are engineered in a manner that responds preferentially to some internal (endogenous) or external (exogenous) stimuli and therefore release therapeutic drugs in a controlled manner at the tumor site while suppressing systematic toxicity and side reactions. Representative examples for this platform are pH-sensitive, redox-sensitive, enzyme-sensitive, and temperature- or light-activated nanoparticles. Stimuli-sensitive systems enhance the accumulation and retention of anticancer drugs in tumor tissues and therefore improve treatment efficacy and clinical outcomes. This chapter identifies new methodologies, design parameters, and translational potential of stimuli-sensitive nanoparticles for cancer therapy and eliminating obstacles like tumor heterogeneity, biocompatibility, and regulatory hurdles.

Keywords: *Stimuli-responsive nanoparticles, tumor microenvironment, controlled drug release, targeted cancer therapy, tumor-targeted nanoparticles*.

1 Introduction

1.1 Overview of Cancer and the Tumor Microenvironment (TME)

Cancer continues as one of the pre-eminent world-wide causes of death. In 20, new cases exceeded 19 million and deaths approached 10 million (Zhou *et al*., 2022). Tumour microenvironment (TME), comprised of stromal cells, immune cells, the extracellular matrix, dysregulated vessels, and biochemical gradients, also delineate tumour growth. These characteristics, such as an acidic extracellular pH, reduced concentrations of oxygen, increased levels of ROS, increased levels of glutathione (GSH), and upregulated enzymes, distinguish tumour tissue from non-malignant tissue and enhance target drug delivery (Uthaman *et al*., 2018). The TME also makes drugs less effective, makes tumours different from each other, and makes it harder for drugs to get through physical barriers (Meng *et al*., 2024; Hou *et al*., 2025).

1.2 Limitations of Conventional Chemotherapy

A great deal of people use traditional chemotherapy, but it has problems like non-selective toxicity, poor water solubility, quick systemic clearance, and side effects that aren't related to the target. These problems make its therapeutic index lower (Zhou *et al*., 2022). Tumour heterogeneity and drug resistance mechanisms in the microenvironment, like the upregulation of efflux transporters and gene changes caused by low oxygen levels, make drugs work even less well (Meng *et al*., 2024). Also, the increased permeability and retention (EPR) effect, which helps passive nanocarrier accumulation, usually only lets a small amount of the dose (about 0.7% median) reach the tumour in people (Vagena *et al*., 2025).

1.3 Need for Targeted and Controlled Drug Delivery

It truly require drug delivery systems that are controlled and targeted and use natural TME cues to solve these problems. Stimuli responsive nanoparticles (srNPs) are a good choice because they stay stable while moving through the body and only release their payloads when they come into contact with TME-specific triggers like pH, redox potential, enzymes, hypoxia, and ROS. This makes them more tumor-specific, less harmful, better at getting through, and better at getting around resistance (Zhang *et al*., 2022).

2 Tumor Microenvironment: A Triggering Milieu

2.1 pH Gradient in Tumors

Aerobic glycolysis is how tumor cells get energy for themselves by taking in a lot of glucose from the TME. At the same time, it releases a lot of lactic acid, which makes the

TME acidic and low in glucose. Low pH in the TME makes tumor mesenchymal cells, especially immune cells, work less well, which makes the immune system weaker. For instance, lactic acids encourage tumor-associated macrophage M2 polarization and the growth of malignant tumors through the lactate-MCT-HIF1 axis, which is a key signaling pathway. The TME's low pH stops T cells from making NAD+, which is an important reductive equivalent. This pushes the mitochondrial tricarboxylic acid cycle (TCA) forward to make ATP, which stops T cells from working and making cytokines (Shi R, *et al*. 2020).

2.2 Redox Potential and Glutathione Levels

The tumor microenvironment (TME) has broken down redox homeostasis, mostly because there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, which are mostly glutathione (GSH). The redox potential is an important factor that controls many cellular processes, such as the growth, survival, spread, and resistance to chemotherapy of tumor cells (Trachootham *et al*., 2009; Sies & Jones, 2020). Redox regulation can happen by changing the activity of enzymes or at the level of transcription. Hydrogen peroxide (H_2O_2), a key ROS involved in redox signaling, affects the activity of different transcription factors in different organisms. In bacteria, these are OxyR and PerR; in yeast, they are Yap1, Maf1, Hsf1, and Msn2/4; and in mammalian cells, they are AP-1, NRF2, CREB, HSF1, HIF-1, TP53, NF-κB, NOTCH, SP1, and SREBP-1 (Veal *et al*., 2007; Holmström & Finkel, 2014). Thiol peroxidases are a key part of redox regulation. They can change protein cysteine residues into sulfenic acid (-SOH) forms, which act as molecular switches in redox signaling pathways (Poole, 2015). The Second Principle of the Redox Code says that "the redox proteome is organized through kinetically controlled sulfur switches linked to NAD and NADP systems." The hydrogen peroxide (H_2O_2) is a main oxidizing agent (Jones & Sies, 2015). Also, redox signaling is closely related to reactions that introduce and remove phosphate moieties from proteins. Oxidative inactivation significantly inhibits many protein tyrosine phosphatases (PTPs), some of which are phosphatase and tensin homolog (PTEN), Cdc25, and protein tyrosine phosphatase 1B (PTP1B). This results in an accumulation of the phosphorylated signaling proteins, subsequently shaping cellular decisions regarding their fate (Salmeen & Barford, 2005). Redox mechanisms also suppress the activity of Protein Phosphatase 1 (PP1) by oxidizing its catalytic metal center (Barford, 2004). The intracellular labile iron pool is also essential for modulating the redox signaling, mainly concerning the Fenton reaction and for increasing the oxidative signals that are mediated by H_2O_2 (Kruszewski, 2003). These mechanisms highlight the complexity and relevance of the redox potential and the glutathione levels in determining the behavior of the tumor and the efficacy of therapeutic approaches.

2.3 Enzyme Overexpression

Tumor microenvironment (TME) is defined by its complex and dynamic nature, consisting of malignant cells, stromal fibroblasts, infiltrating immune cells, the extracellular matrix (ECM), and a variety of cytokines and signal molecules. An essential biochemical change in the TME is the overexpression of certain enzymes, allowing for tumor growth, angiogenesis, tissue invasion, metastasis, immune escape, and resistance to treatments (Hanahan & Weinberg, 2011; Quail & Joyce, 2013). Hypoxia, nutrient depletion, oxidants and acidosis common in the tumor niche increase the activity of these enzymes, that is, matrix metalloproteinases (MMPs), cathepsins, hyaluronidases, and some proteases (Vaupel & Multhoff, 2021). This dysregulatory enzymatic activity not only accelerates tumor growth but also creates a "biochemical triggering environment" that can be harnessed for the design of drug delivery vehicles responsive to certain stimuli (Bae & Park, 2011; Ryu *et al*., 2019). Employing these tumor-related enzymes as natural triggers is a highly promising tool for allowing for controlled release of drugs over time and space and consequently improving targeting specificity and off-target toxicity minimization. Researchers have engineered enzyme-sensitive prodrugs and nanocarriers that selectively cleave in the presence of the aberrant enzymes found in the TME and thus enhance the efficacy and specificity of treatments (Zhu *et al*., 2021).

2.4 Hypoxia and Other Stimuli

Hypoxia is one of the most prominent hallmarks of the tumor microenvironment (TME). This is a condition that develops when oxygen levels are reduced and cannot satisfy highly dividing cancer cells. The reduced supply of oxygen helps stabilize hypoxia-inducible factors (HIFs), particularly HIF-1α. In return, the factors upregulate the transcription of genes involved in angiogenesis (e.g., VEGF), glycolysis, metastasis, and chemotherapeutic and radioresistive resistance (Semenza, 2019; Muz *et al*., 2015). In addition, hypoxia initiates epithelial-to-mesenchymal transition (EMT), acidosis, and immune evasion, among other conditions, that stimulate tumor growth and lower treatment efficacy (Rankin & Giaccia, 2016). Beyond hypoxia, some other endogenous stimuli also exist in TME. They encompass elevated levels of reactive oxygen species (ROS), overexpressed enzymes such as matrix metalloproteinases (MMPs) and cathepsins, altered redox potential, high glutathione (GSH) levels, and low extracellular pH (Zhou *et al*., 2021; Wang *et al*., 2020). Such a platform of pathophysiological conditions provides for the development of drug delivery systems and nanocarrier systems that can be triggered by some stimuli. This facilitates charting the release of drugs at desired sites, therefore enhancing their efficacy and lower system-related toxicity (Dai *et al*., 2020). Focus on hypoxia and other tumor-specific stimuli provides

a potential method of circumventing drug resistance and enhanced specificity in cancer therapy.

3 Design and Classification of Stimuli-Responsive Nanoparticles

3.1 pH-Responsive Nanoparticles

Since the TME is highly acidic, pH-sensitive nanoparticles have gained immense focus in cancer therapy. The differential pH is one of the noteworthy points to consider while developing the systems. Normal tissue exhibits a pH level of approximately 7.4, while the extracellular pH in the TME ranges from around 5.8-7.2. In addition, the pH within organelles such as the endosomes and lysosomes ranges at approximately 5.5 and is thus much more acidic than that found in healthy tissue. This established pH window creates an effective tool for controlling and targeting drug release within the human body (Liu *et al*., 2020). Utilizing this tool, a variety of pH-sensitive nanocarrier systems emerged during the last decade, aiming toward spatiotemporal control in drug release in a more effective manner. Such technologies lead toward higher therapeutic output and reduced system-related rather than target-related side effects (Zhao *et al*., 2021). Of the materials, chitosan has emerged as a significant candidate for pH-sensitive applications that is a natural and naturally degradable polymer material that has a pKa of approximately 6.5. In slightly acidic conditions, chitosan becomes protonated and thus improves its solubility within aqueous conditions. This quality benefits particularly for a class of drug delivery systems that need pH sensitivity (Das *et al*., 2020). An illustrative one is the creation of a micellar-based chitosan-based system of nanocarriers by Das *et al*. (2020), through control of both the molecular weight of the chitosan and the feed-based PEG ratio. This nanocarrier demonstrated characteristic "off-on" behavior depending on pH change. It was stable and exhibited no leakage at a normal cellular level of pH, while it improved fast release of drugs in the mildly acidic environment characteristic of tumor cells (Tang *et al*., 2019). The systems are normally flexible due to a change from a hydrophobic to a hydrophilic condition that is reversible under acidic conditions. Nanocarrier (NC) systems that also incorporated ionizable carboxylic groups and changed once there was a change in pH levels also featured in the work of Tang *et al*. (2019). These phase transitions result in swelling of the nanocarrier, destabilization of the membrane, and ultimate release of the payload. Similarly, Zhao *et al*. (2016) also discussed several pH-sensitive nanoparticles that would alter their size and charge and other characteristics and thus deliver drugs into the tumors and eventually release inside cells.

3.2 Redox-Responsive Nanoparticles

Redox-sensitive nanocarriers (NCs) are an emerging approach for targeting cancer cells through the delivery of therapeutic agents because they target the unique redox environment inherent in cancer cells. Glutathione (GSH), a three-peptide that consists of glutamic acid, cysteine, and glycine, is responsible for maintaining the cellular redox balance. The linkage between glutamic acid and cysteinylglycine is achieved through its side chain at the N-terminus. Preservation of redox balance within cells is dependent on

the presence of GSH, and of relevance, cancer cells have much higher levels of intracellular GSH—some four times higher than that found in normal cells—which makes it a central trigger for release mechanisms sensitive to redox (Gawai *et al*., 2025). In multidrug-resistant tumor cells, the level of this peptide lies between 2 and 10 mM in the cytoplasm, and in the extracellular environment, it is only measured at a level of 2 to 20 μM. This contrast identifies GSH as a reliable biomarker for targeting tumors and for that reason is a component that is included in redox-sensitive nanoparticles that release therapeutic compounds solely at tumor cells (Li *et al*., 2020). To exploit those redox gradients, NCs often incorporate chemical groups like disulfide bonds, diselenide linkages, and manganese dioxide. These redox-sensitive building blocks cleave through reactions that exploit higher concentrations of GSH within cells, allowing the release of the payload of drugs and promoting the degradation process of those units. Accordingly, the redox-sensitive systems have shown significant potential for intracellular delivery of drugs in cancer treatment. Scientists have successfully synthesized many different nanoplatforms for drug release that are sensitive to redox conditions. These include liposomes, micelles, nanogels, and prodrug-based systems (Zhang *et al*., 2019). Also, redox-responsive inorganic nanoparticles have gotten a lot of attention because their physicochemical properties can be changed, they are easy to make and functionalize, and they could be used to monitor redox states in real time. These systems often have ligands that react to both reactive oxygen species (ROS) and GSH. This means that they can release drugs in two different ways (Li X. *et al*., 2021). The difference in redox potential between cancerous and normal tissues, as well as between intracellular and extracellular compartments, is a strong internal signal for tumor-targeted delivery systems. Continued progress in this area opens up new ways to make treatments more effective while reducing side effects that aren't related to the target.

3.3. Enzyme-Responsive Nanoparticles

Enzyme-responsive NCs: The pathophysiology of many diseases, such as infection, inflammation, and cancer, is linked to the upregulation of several enzymes. These NCs can't be used to release drugs inside cells because most of the enzymes are present in similar amounts in both cancerous and normal cells (Zhang M, *et al*., 2022). However, enzyme-cleavable peptides can be used to make enzyme-triggered NC deshielding, which can eventually let the drug out. You can make enzyme-triggered NCs by changing the NC surface so that it can respond to the biocatalytic reaction of enzymes that are overexpressed in the extracellular microenvironment of cancer cells. For instance, matrix metalloproteinases (MMPs) and hyaluronidases (HAs) are two types of extracellular enzymes that are mostly overactive in tumors (McAtee CO, *et al*., 2014). Because of the changes that happen when a tumor grows, the levels of certain enzymes and proteins, like prostate-specific antigen, phospholipases, hyaluronidases, matrix metalloproteinases, and esterases, are much higher in tumor tissues than in healthy tissues. People have been paying more and more attention to enzyme-sensitive drug

delivery systems in recent years because they can release drugs at the right places when they come into contact with enzymes. As a result, a lot of enzyme-responsive nanoparticles have been designed, made, and used to control the release of drugs. Right now, the main focus of research on enzyme-responsive nanoparticles is on how they can release drugs at tumor sites (Zelzer M, *et al*., 2013; Harnoy AJ, *et al*., 2014). A group of nanoparticles that respond to enzymes showed that enzymes could break chemical bonds in the tumor microenvironment, but these bonds were stable while they were in the blood. The goal of cancer treatment is to break down chemical bonds with enzymes, which causes enzyme-responsive nanoparticles to break apart and release drugs (Zhao X, *et al*., 2021).

3.4. Thermo- and Photo-Responsive Systems

Thermoresponsive nanoparticles are attracting more and more attention because of their versatility and usability in a variety of fields, mainly the field of drug delivery. A very important factor to consider while determining the thermoresponsive behavior of a material is the low critical solution temperature (LCST). Thermoresponsive nanoparticles exist in a gel form above the LCST and switch into a solution form at temperatures lower than this (Castillo-Henríquez L, *et al*., 2021). In this way, it would be preferable for thermoresponsive nanocarrier LCSTs to lie in between body and room temperatures, allowing for efficient drug delivery. In the last decade, some thermoresponsive polymers like poly(N-vinylcaprolactam) (PVCL) and poly(N-isopropylacrylamide) (PNIPAAm) have found use (Sun Z, *et al*., 2020). Among them, PNIPAAm is the best-researched thermoresponsive polymer since it was first described in 1967. This polymer, in aqueous solutions, experiences a change from a hydrophobic into a hydrophilic character by a change in heat, and it dynamically responds for any change in temperature. Below the LCST, there is a solution state for PNIPAAm, while it shifts into a gel phase above this (Kozlovskaya V, *et al*., 2019). The phase change might be accounted for by the creation of hydrogen bonds among amide groups and water molecules. Because of the phase change characteristics of PNIPAAm, scientists have formatted heat-sensitive nanoparticles that have potential in drug delivery applications (Kozlovskaya V, *et al*., 2019; Luo G, *et al*., 2020; López Ruiz A, *et al*., 2022). Thermoresponsive nanocarriers release therapeutic content for a change in temperatures since they can manipulate solubility, modify hydrophile-hydrophobe balance, or change structural features depending on specified temperatures (López Ruiz A, *et al*., 2022). The lower critical solution temperature (LCST) for these nanocomposites means that there are elements of a solution that can gain homogeneity at a certain thermal limit. Thermosensitive polymers defined by an LCST, as well as stimuli-sensitive hydrogels that can avoid degrading drugs while having fast deactivation and activation, are potentially desirable drug delivery systems. In typical conditions, hydrogels can be injected through a viscous liquid form and later solidify into gels (Pasparakis G, *et al*., 2020).

3.5. Multi-Responsive (Dual or Multi-Trigger) Nanoparticles

Stimuli-sensitive polymeric nanoparticles showed increased release and improved anti-tumor activity of drugs, while the activity of drugs is altered depending on the type of stimulus, response rate, and location of triggered release of drugs. To further enhance drug release and therapeutic efficacy of nanoparticulate drugs, researchers have worked tirelessly for the development of advanced polymeric nanoparticles that respond towards more than one stimulus simultaneously. These stimuli include pH/temperature, pH/redox, pH/magnetic field, temperature/reduction, double pH, pH and diols, temperature/magnetic field, temperature/enzyme, temperature/pH/redox, temperature/pH/magnetic, pH/redox/magnetic, temperature/redox/guest molecules, and temperature/pH/guest molecules. It's important to note that the responses happen at the same time in the same place or one after the other in different places and/or compartments. These polymeric nanoparticles that respond to more than one stimulus could, on the one hand, give researchers more control over how drugs are delivered and released, which could make them more effective at fighting cancer in the lab or in the body. On the other hand, they could also make it easier to prepare nanoparticles and load drugs into them in mild conditions. For instance, researchers have made redox-sensitive drug release polymersomes from PEG–PAA–PNIPAAm triblock copolymers that respond to both temperature and reduction. They did this by raising the solution temperature above the polymers' lower critical solution temperature (LCST) and then crosslinking them with cystamine using carbodiimide chemistry. These crosslinked polymersomes were strong enough to withstand normal body conditions, but they broke apart quickly to release foreign proteins in cancer cells because redox reactions broke the crosslinks and disrupted the polymersomes. pH- and redox-dual-sensitive disulfide-crosslinked micelles were created to keep drugs from being released too soon into the blood, help drugs build up at the tumor site, and actively release drugs in the target tumor cells when the endo/lysosomal pH and intracellular reducing environment change (Cheng R, *et al*., 2013). These complicated nanoparticles were given the name "multifunctional nanoparticles" because they can do many things at once, such as deliver drugs, nucleic acids, peptides, and do optical imaging. One way to make targeted multifunctional nanoparticles was to change the surface of the parent nanoparticles by physically or covalently attaching affinity ligands that only bind to certain receptors on the target cell. These ligands could be imaging agents, stimuli-sensitive components, cell-penetrating agents, and so on, using a polymeric linker like polyethylene glycol (PEG) (Majumder J, *et al*., 2021). Stimuli-Responsive Nanoparticles in the Tumor Microenvironment is shown in Fig. 4.1

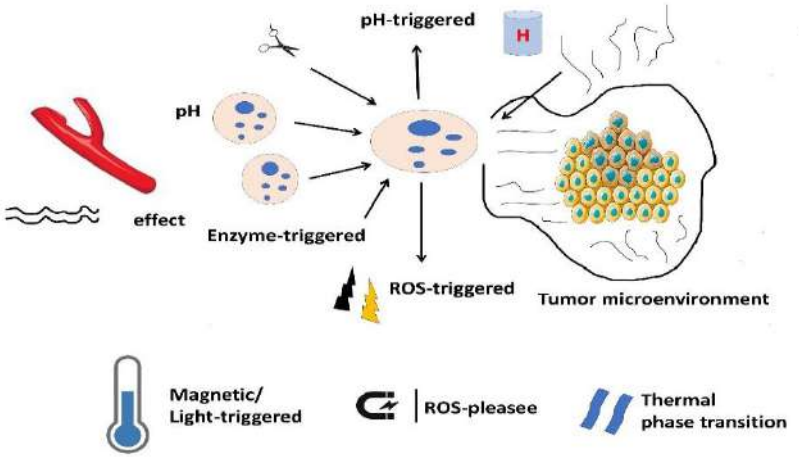

Fig. 4.1 Stimuli-Responsive Nanoparticles in the Tumor Microenvironment

Table 4.1: Types of Stimuli in Tumor Environment

Stimulus	**TME Characteristics**	**Responsive Materials/Therapies**	**Applications in Cancer Therapy**	**References**
pH	Acidic (pH ~6.5-6.9) due to Warburg effect	pH-sensitive polymers, liposomes (e.g., Doxil®)	Tumor-selective drug release, immunotherapy	(Heneberg P, 2022)
Redox	High GSH (2-10 mM vs. 2-20 μM in normal cells)	Disulfide-linked nanoparticles, ROS-generating agents	Targeted chemotherapy, ferroptosis induction	(Qin *et al.*, 2025)
Enzymes	Overexpressed MMPs, cathepsins, hyaluronidase	MMP-cleavable peptides, enzyme-activated prodrugs	Tumor-specific drug activation, imaging	(Piperigkou *et al.*, 2021)
Hypoxia	Low O_2 (<1% vs. 4-7% in normal tissue)	Hypoxia-activated prodrugs (e.g., evofosfamide)	Radiotherapy enhancement, bio reductive therapy	(Zhou *et al.*, 2022)
Temperature	Mild hyperthermia (~40-42°C) in tumors	Thermosensitive liposomes (e.g., Thermo Dox®)	Hyperthermia-assisted drug release, ablation	(Orel *et al.*, 2024)
Magnetic	Externally controllable via magnetic fields	SPIONs (superparamagnetic iron oxide nanoparticles)	Magnetic hyperthermia, MRI-guided drug delivery	(An *et al.*, 2023)

Light	Requires external NIR/UV activation	Photosensitizers (e.g., ICG, porphyrins), AuNPs	Photodynamic (PDT) & photothermal (PTT) therapy	(Zhao *et al*., 2020)
Ultrasound	Non-invasive, deep tissue penetration	Microbubbles, sonosensitizers (e.g., TiO_2)	Sonodynamic therapy (SDT), focused drug release	(Darvin ME, 2023)

4 Materials Used in Stimuli-Responsive Nanocarriers

4.1 Polymeric Nano Particle

These constituent polymers are generally divided into two categories in this chapter: synthetic polymers, which are made from monomers, and natural polymers, which are derived from natural products (Bhatia, S, 2016). Though they lack the tunability, batch-to-batch consistency, and variety of functionality found in synthetic polymers, natural polymers are typically non-toxic and biodegradable. In addition, the potential for further increasing the level of design complexity for nanoparticles continues to rise as polymer syntheses evolve over time (Satchanska *et al*., 2024). Synthetic polymer design has, very recently, become enabled for a new kind of control through advancements of RDRP methods such as ATRP, NMP, and RAFT. We have counted the various polymers utilized in nanoparticle preparation by type and starting from the lowest responsive polymers, i.e., the polyesters, vinyl polymers, poly (amino acids), and PEG derivatives, among many other varieties. Those that synthesize more complex nanoparticle preparations by virtue of stimuli-sensitive polymers come next. Of significant note is the observation that a very vast kind of polymer design is utilized for polymer nanoparticle preparation, and this kind continues increasing as RDRP methods become more in use (Grishin, D & Grishin, 2021).

4.1.1 Poly (amino acids) and Proteins

Poly (amino acids) (PAAs), a family of polymers that are made up of repeating amino acids, are one of the most prominent polymers for synthesizing polymeric nanoparticles. The fact that PAAs are present in a sizable portion of the currently developed clinically relevant polymeric nanoparticle designs emphasizes their importance. Solid-phase synthesis and ring opening polymerization (ROP) are two simple, well-researched, and economically feasible synthetic processes that produce PAAs, which are also functionally diverse, tunable, biocompatible, biodegradable, and versatile. Their constituents, amino acids, which are organic molecules with both amino and carboxylic functional groups as well as a side chain moiety specific to each amino acid, are the source of these alluring qualities. Twenty of the hundreds of naturally occurring amino acids make up the proteins that are present in the human body. PAAs are formed from this exclusive group of 20. The most widely used PAAs in the creation of polymeric nanoparticles for drug delivery are poly (glutamic acid) (PGlu), poly(L-lysine) (PLL), and poly (aspartic acid) (PAsp), among the many others (Kricheldorf *et al*., 2006).

4.1.2 Polysaccharides

Carbohydrate molecules joined by glycosidic bonds form polysaccharides, which are polymeric materials. Originating from renewable resources like plants, algae, and microbes, polysaccharides combine exceptional biocompatibility and biodegradability with a variety of functional groups that can be altered for precise medication delivery. Polysaccharides are also very adjustable. Their physicochemical characteristics, electrostatic charge, branching or linear architecture, and molecular weight all affect how well they deliver drugs (Prasher *et al*., 2021).

4.1.3 Glycopolymers

Glycopolymers, which are polymers with pendant groups of carbohydrates (saccharides), have drawn a lot of interest as potential drug delivery building blocks. When used as a shell component for nanoparticles, glycopolymers exhibit more complex behavior than PEG because of their variable hydrophilicity, which is dependent on the type of saccharide pendants they contain. Even when the polymers seem soluble in aqueous solutions, the strong intermolecular hydrogen bonds that form between glycopolymer chains can cause cross-linking, aggregation, and the formation of hydrogels (Oh *et al*., 2020). The ability of glycopolymers to bind to lectins makes them appealing and is a helpful characteristic for targeted drug delivery. But because glycopolymers share structural similarities with other natural polymers, their bioactivity can result in unintended interactions and a powerful immune response, which can drastically shorten the blood's circulation time (Stenzel *et al*., 2022).

4.1.4 Polyesters

It has adaptability, biodegradability, and biocompatibility, polyesters—polymers made up of repeating ester moieties—are among the most appealing and frequently used materials for creating polymeric nanoparticles for drug delivery. Polylactide or poly (lactic acid) (PLA), poly(glycolide) or poly (glycolic acid) (PGA), their copolymer poly(lactide-co-glycolide) (PLGA), and poly-(ε-caprolactone) (PCL) are the four most prominent polyesters available. In micelles, a type of nanoparticle in which the core and shell components are based on a single amphiphilic block copolymer, polyesters are commonly used as core components. Polyester core-based micelles typically use PEG as a shell and are already used in several FDA-approved products (Makadia *et al*., 2011).

4.1.5 Phosphate-Based Polymers

A class of polymers known as polyphosphoesters (PPEs) is biodegradable and adaptable, making it a good starting point for creating polymeric nanoparticles for drug delivery. Because poly(phosphonates) (PPNs) uses O-P linkages and have very strong backbone biodegradability, they are similar to PPEs and contribute to their versatility. The involved PPNs have a characteristic of solubility in water while bearing minimal cytotoxicity that can be contributed by the exhibited short alkyl side chains attached to

the phosphorus atom. The HeLa cells give no indication of cytotoxicity when treated with PPNs at concentrations as high as 1 mg/mL. The resultant polymers can be modulated for their hydrophilic characteristics through variations in alkyl chain lengths (Simon *et al*., 2011).

4.1.6 Vinyl Polymers

Vinyl polymers represent a distinct category of synthetic polymers synthesized from substituted vinyl monomers characterized by a carbon-based polymer backbone. Noteworthy among the various vinyl-based polymers that have garnered significant interest for applications in drug delivery are acrylates, methacrylates, acrylamides, and methacrylamides. Commonly utilized vinyl polymers include Poly(N-(2-hydroxypropyl) methacrylamide) (PHPMA), polystyrene (PS), poly(methyl methacrylate) (PMMA), poly(vinyl alcohol) (PVA), poly(butyl methacrylate) (PBMA), poly(2-hydroxyethyl methacrylate) (PHEMA), poly(hydroxyethyl acrylate) (PHEA), and poly(N, N-dimethylacrylamide) (PDMA) (Pereira *et al*., 2021).

4.1.7 Polyethyleneimine

Polyethyleneimine, a highly variable synthetic cationic polymer, is also highly researched today for many applications in drug delivery, particularly for gene delivery. This polymer can be broadly classified into two classes, i.e., branched polyethyleneimine (PEI) and linear polyethyleneimine. Typically, the preparation of linear PEI is initiated from the cationic ring-opening polymerization (ROP) of 2-oxazoline for the preparation of poly(2-oxazoline) (POx). POx thus prepared can further be hydrolyzed and yield linear PEI. Such a reaction may be in basic or acidic solution. The direct preparation of PEI that is branched has also been obtained by the cationic ROP of aziridine monomers (Englert *et al*., 2018).

4.1.8 Poly (ethylene glycol) and Alternatives

The main benefit of the synthetic polymer class known as poly (ethylene glycol) (PEG), also called poly (ethylene oxide) (PEO), is its high-water solubility. PEG is also very biocompatible and stable. According to the U.S. Food and Drug Administration (FDA), it is generally considered safe. PEG is a crucial component of polymeric nanoparticles and is sometimes referred to as the "gold standard" for nanomedicines because of these factors. PEG is actually used as a hydrophilic shell component in a sizable portion of all polymeric nanoparticles. This is because PEG (PEGylation) improves stability, reduces toxicity, prolongs retention during blood circulation by evading the immune system, and increases the EPR effect, all of which improve nanoparticle performance. The presence of a strong hydration shell at the water-PEG interface as a result of hydrogen bonding is frequently used to explain such "stealth" effects. The main mechanism by which this hydration shell reduces nonspecific protein adhesion is by acting as a steric barrier. which foreign material is recognized by the immune system. It is now evident that PEG

architecture (brush or linear), PEGylation density, and PEG chain molecular weight can all have a major impact on protein adsorption (Suk *et al*., 2016; Pelaz *et al*., 2015).

4.2. Liposomes and Micelles

Drugs, biomolecules, and imaging agents are transported into living cells using lipid carriers, such as liposomes or lipid nanoparticles (LNP). In recent years, cationic LNPs with small sizes and a high surface-to-volume ratio have been successfully used for COVID-19 vaccination. These LNPs can encapsulate negatively charged biomacromolecules like mRNA or plasmid DNA. The endosomal pathway's release of cargo molecules into the cytoplasm, where they can be sorted to the intended organelle to carry out their encoded functions, is the bottleneck of LNP application. One promising tactic to increase the effectiveness of drug delivery is to overcome endosomal uptake (Anselmo *et al*., 2021). Since the discovery that these nanoparticulate structures could self-assemble into vesicles, liposomes have been used for a variety of purposes that have always been improved. A liposome can enclose aqueous areas in a membrane that repels water. A different option is to dissolve hydrophobic substances into the membrane, which has two distinct characteristics and can hold both hydrophilic and hydrophobic molecules. The combination of a lipid bilayer with another bilayer, like the cellular membrane, leads to the movement of molecules towards the site of action. Macrophages in the body can target liposomes. Once internalized and further acted upon by macrophages, a certain stimulus initiates the release of drugs that are encapsulated. In a related aspect, administration of liposomes that are modified by certain ligands attached at the level of the liposome's surface promotes endocytosis. Another interesting use of liposomes for drug delivery is the method that has come to be termed lipofection, allowing for the uptake of DNA into a host cell (Dua *et al*., 2012). Because of their simplicity, ability to encapsulate and solubilize lipohpobic drugs at their core, and sensitivity towards biological stimuli through the enhancement of functional chemistry, micelles have emerged as very potential systems for delivering drugs. Micelles are solid, spherical-shaped nanoparticles that develop once an amphiphilic polymer enters into a process of self-assembly in aqueous solution. The copolymer that is used is often an AB diblock copolymer, whereby A and B denote the hydrophile and the lipophile segments, respectively (Zhang *et al*., 2014). Overall efficacy and preferable pharmacokinetic profile of these systems are frequently marred by a bodily barrier because of the non-specific disposition and fast clearance from the organism. Self-formation into spherical micelles happens at polymer concentrations in solution higher than the critical micellar concentration (CMC). These micelles are always in a state of dynamic equilibrium, which allows them to return to their unimeric form. These unimers can then attach to different components of the plasma, including albumin and other proteins, to further upset this equilibrium. The affinity of these unimers for these plasma constituents further promotes this binding (Lo *et al*., 2007).

4.3. Inorganic Nanoparticles (Gold, Silica, Iron oxide)

4.3.1. Gold NPs

Although GNPs come in a range of sizes from 2 to 100 nm, the most effective cellular uptake was observed in particle sizes between 20 and 50 nm. 40–50 nm particles have been shown to cause specific cell toxicity. These 40–50 nm particles readily recover from tumors after diffusing into them. Larger particles, such as those between 80 and 100 nm, on the other hand, do not diffuse into the tumor and remain close to the blood vessels. During their synthesis and functionalization with various groups, the size can be regulated. The conjugated nanoparticles' size varies (Pandey *et al*., 2016). The research community has focused a lot of attention on nanomaterials, particularly GNPs, in recent decades due to their distinct and different physical, chemical, photochemical, electronic, and optical properties that also differ from those of the material in its bulk states. High surface area-to-volume ratios, a surface plasmon resonance (SPR) effect, and high stability and chemical stability are some of GNPs' distinctive features. Besides that, GNPs also have the characteristics of biocompatibility, biological inertness, and compatibility for proteins, enzymes, and pharmaceutical agents. The applications of GNPs also reach a wide spectrum of medical areas, from drug and gene delivery, diagnostics, therapy, dentistry, tissue imaging, sensors and biosensors, through catalysis (Adekoya *et al*., 2018).

4.3.2. Fe_3O_4NPs

Fe3O4NPs can be readily synthesized by employing a sonochemical technique that promotes the decomposition of iron salts and other nanostructure precursors from an inorganic iron precursor by taking advantage of ultrasonic irradiation's very high temperatures and pressures. The iron salts' decomposition due to the higher temperatures caused by ultrasonic irradiation results in the production of Fe3O4NPs. In addition, the ultrasonic irradiation method enhances Fe3O4NPs' hydrophilic and monodisperse characteristics. Recent research has noted the successful preparation of Fe3O4 by exhibiting significant physicochemical features, including a high surface area and improved electron storage capacity, through a sonochemical method (Mukh-Qasem *et al*., 2005). The choice of nanoparticle size vis-a-vis the required magnetization of the particles is crucial, considering the significant effect nanoparticle size has on the magnetic and structural characteristics of Fe3O4NPs. The synthesis of Fe3O4NPs using ultrasonic treatment (40 kHz, 150 W) and a novel precipitating agent (ethylenediamine) via coprecipitation was successfully demonstrated by researchers (Boustani *et al*., 2020).

4.4. Hybrid Nano Structures

Nanoparticle Hybrids In order to create a complex, multipurpose design that shows promise as a drug delivery vehicle, hybrid nanoparticles combine various components. In the past ten years, thorough reviews of hybrid nanoparticles made entirely of organic

components, like lipid-polymer hybrid nanoparticles, have been published. Consequently, polymeric nanoparticles containing particular inorganic components will be the main topic of this section. These inorganic-based hybrid nanoparticles provide a flexible platform that can be customized to encapsulate, shield, and effectively deliver therapeutic agents to their intended targets by fusing the special qualities of various materials. However, due to the complexity of these hybrid designs, current research focuses on more basic aspects of
these resources. Although hybrid nanoparticles have proven to be highly effective in animal and in vitro models, further research is required to bring these advantages to clinical trials and beyond **(**Gao *et al*., 2022).

4.4.1. Preparation Methods

Surface Modification. The formation of a hybrid nanoparticle relies on the encapsulation of an inorganic core by one or more polymeric layers. Two distinct methods for the employment of the polymers on the core's surface follow. The first one is characterized by non-covalent forces, that is, by electrostatic attraction and hydrophobic forces. In this respect, for example, the layer-by-layer constructive approach, that is based on the deposition of charged polymers into a suspension of oppositely charged inorganic particles, has been extremely broadly applied for the formation of hybrid nanoparticles by means of precise control. This method offers the possibility for easy control of morphological features and polymeric thickness and, additionally, enhances the colloidal stability and the inorganic components' biocompatibility (Yi *et al*., 2018).

5 Mechanisms of Drug Release in TME

5.1 Triggered Degradation and Drug Unloading

Stimuli-sensitive nanoparticles (NPs) are designed to disintegrate only when exposed to certain physicochemical features of the tumor microenvironment (TME), e.g., acidic pH, higher levels of glutathione (GSH), reactive oxygen species (ROS), or enzymatic activity. These stimuli enable the breakup of nanocarriers, allowing for localized release of drugs at the tumor location while maintaining healthy tissue integrity. Poly(β-amino esters) and poly(lactic-co-glycolic acid) (PLGA), for example, have a faster rate of degradation under acidic conditions that are common in the extracellular matrix of tumors (pH~6.5) and intracellular vesicles, e.g., endosomes and lysosomes (pH~5.0). Tumoral acidic conditions promote polymer main chain or side chain ester hydrolysis, causing particle disintegration and eventual drug release (Yang *et al*., 2020). Overexpressed proteases in the TME, like matrix metalloproteinases (MMPs), help break down peptide linkers or polymeric shells in enzyme-sensitive systems. This starts drug release at a specific site (Li *et al*., 2021).

5.2 Swelling/Shrinking Mechanisms

Hydrogel-based drug delivery systems can swell or shrink in the TME in response to certain stimuli. This changes how quickly the drugs are released. This happens most often in polymers that have ionizable groups or that change phases when the pH, temperature, or redox state changes. One example is poly (acrylic acid)-based pH-responsive hydrogels, which stay collapsed at physiological pH (7.4) but swell in acidic conditions (pH <6.5). This lets drugs move through the expanded polymer network. The swelling happens because acidic parts of the molecule ionize, which causes electrostatic repulsion and water to flow in (Wang *et al*., 2019). Thermoresponsive polymers, on the other hand, shrink above their lower critical solution temperature (LCST), which pushes out trapped drugs. This is known as "thermal squeezing." In TME, systems like these can be turned on by local hyperthermia or inflammation that raises the temperature (Xie *et al*., 2023).

5.3 Bond Cleavage Mechanisms (Hydrazone, Disulfide, etc.)

Chemical bond cleavage mechanisms are a common way to control and target drug release in the TME. The labile linkages, hydrazone, disulfide, imine, and thioether bonds, characterize the properties of nanocarriers. Hydrazone, disulfide, thioether, and boronic ester bonds are specific examples of stimuli-sensitive linkages also commonly utilized in nanoparticle-entrapped drug delivery systems for a controlled and targeted release of drugs inside the TME. It is established that hydrazone bonds are of acid-labile characteristics, stable at the physiological pH (7.4), while easily cleaving under mildly acidic conditions (pH < 6.8). This property allows for drug conjugates or prodrugs equipped with hydrazone to release their therapeutic payload exclusively in acidic organelles like endosomes and lysosomes after cellular uptake. Accordingly, it reduces early release and promotes efficient drug delivery inside cells (Zhang *et al*., 2019). In contrast, disulfide bonds cleave under reduced conditions and therefore work efficiently for drug release inside cells since tumor cells contain highly increased levels of glutathione (GSH) relative to the exterior environment (around 10 mM in contrast to 2 μM). Once the nanoparticles accumulate inside the reductive intracellular environment of cancer cells, disulfide linkages engage in thiol-disulfide exchange reactions and lead to a fast disintegration of the carrier and controlled release of the attached drug (Liu *et al*., 2020). Thioether and boronic ester bonds also display ROS sensitivities, especially hydrogen peroxide (H_2O_2), often found at higher concentrations inside the TME. In the presence of ROS species, the bonds cleave under oxidation-labile bonds, giving rise to the release of therapeutic compounds that are either encapsulated or conjugated. Responsive capacity for oxidative stress is demonstrated to be particularly effective for targeted drug delivery for chemotherapeutic drugs and immune modulators into localized sites of inflamed or oxidized tumors and therefore elevating their specificity

and efficacy (Chen *et al*., 2021). Mechanisms of controlled drug release from stimuli-responsive nanoparticles in the tumor microenvironment are shown in fig. 4.2

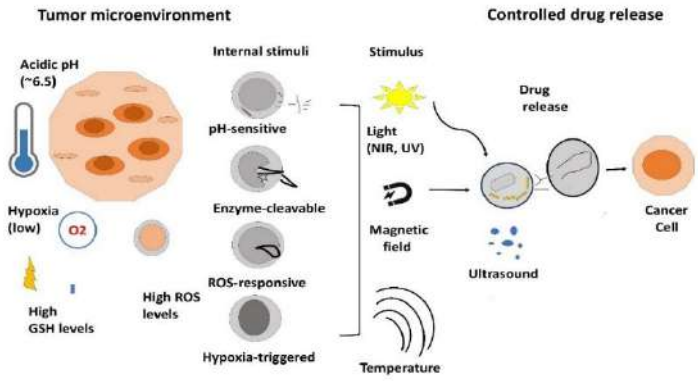

Fig. 4.2 Mechanisms of controlled drug release from stimuli-responsive nanoparticles in the tumor microenvironment

6 Preclinical and Clinical Applications

6.1 In Vitro and In Vivo Studies

Extensive in vitro cell culture models and in vivo animal experiments are used in the preclinical validation of stimuli responsive nanoparticles (srNPs). Under regulated pH, redox, enzyme, or ROS conditions, in vitro tests evaluate cytotoxicity, cellular uptake, endosomal escape, and stimulus-triggered release. Then, biodistribution, pharmacokinetics, tumour inhibition, and systemic toxicity are assessed in vivo in murine models (Zhou *et al*., 2022). For example, compared to free drug and spared normal cells, pH-responsive MSNs capped with acetal linkers and targeting ligands demonstrated >8-fold higher osteosarcoma cell cytotoxicity in vitro (Martínez-Carmona *et al*., 2018). Biomimetic nanoparticles, such as erythrocyte-membrane-coated PCL nanoparticles loaded with paclitaxel, have been used in in vivo studies. These nanoparticles have been shown to significantly increase circulation half-life (~5.8×), achieve >90% tumour suppression, and decrease capture by RES cells. P. Chowdhury (2020). Additionally, under magnetic guidance, redox/pH dual sensitive nanomicelles enhanced tumour accumulation and achieved synergistic magnetothermal chemotherapy efficacy (pH-triggered release + magnetic field) (Dutta Gupta *et al*., 2024). All of these studies show improved tumour cytotoxicity, controlled release, precise stimulus activation, and cross-system biocompatibility.

6.2 Tumor Targeting and Accumulation

The EPR effect, which is made stronger by tumour vascular fenestrations and the lack of lymphatic clearance, is mostly what causes srNPs to build up in tumours. This has been reviewed in depth by Zhu and Torchilin (2013). Stimuli-responsive design makes this even better by only activating at the TME, which encourages disassembly or charge conversion to increase cellular uptake and penetration (Su *et al*., 2023). Active targeting also uses ligand decoration. For example, lectin-modified MSNs were taken up more by osteosarcoma cells that had too much sialic acid, which made them more specific and better at getting to tumours while having less of an effect on healthy cells (Martinez Carmona *et al*., 2018). Magnetic fields combined with pH-sensitive release in hybrid systems have been shown to improve site-specific delivery and therapy outcomes (magnetothermal chemotherapy) (Moorcroft, *et al*., 2018).

6.3 Case Studies and Clinical Trials

Most srNP systems are still in the preclinical stage, but a few have moved on to early-phase trials. Liposomal formulations, like pH-sensitive liposomal doxorubicin prodrugs, have been tested in people. They aren't strictly srNPs, but they show how stimuli-responsive approaches can be used in real life (Lee & Thompson, 2017). In early tests, immunoliposomes linked to tumor-specific antibodies are being combined with pH or temperature stimuli to lower systemic toxicity and increase tumour specificity. Magnetic-targeted nanocarriers that are meant to be guided by magnets are also being tested in clinical trials for delivering drugs to specific sites in solid tumours (Li *et al*., 2022). Clinical translation is still limited, but several FDA-approved nanoparticle drugs, like Doxil® and Abraxane®, show that the platform has potential. Stimuli-responsive versions are being tested in translational studies to combine controlled release with established safety profiles for nanocarriers (Du *et al*., 2015; Thomas *et al*., 2020).

Table: 4.2 Clinical Stimuli-Responsive Nanomedicine

Name/Code	Nanoparticle Type	Stimulus	Clinical Stage	Indication & Outcome	Reference
Doxil®/Caelyx®	PEGylated liposomal doxorubicin	pH (passive EPR effect)	FDA-approved (1995)	Ovarian cancer, Kaposi's sarcoma; reduced cardiotoxicity	(Barenholz YC, 2021)
ThermoDox®	Thermosensitive liposomes (lysolipid-based)	Temperature (hyperthermia)	Phase III (HEAT trial)	Hepatocellular carcinoma; improved drug	(Lyon *et al*., 2024)

				release with RF ablation	
MM-398 (Onivyde®)	Liposomal irinotecan	Enzymatic (TME MMPs)	FDA-approved (2015)	Pancreatic cancer; prolonged survival	(Chiang *et al.*, 2025)
NBTXR3	Hafnium oxide nanoparticles	Radiation (external)	Phase III	Locally advanced soft-tissue sarcoma; radiosensitization	(Le *et al.*, 2025)
AuroLase®	Gold nanoshells (SiO_2-Au)	Light (NIR)	Phase I/II	Head/neck cancer; photothermal ablation	(Kadria-Vili *et al.*, 2024)
Ferumoxytol (Feraheme®)	SPIONs (iron oxide)	Magnetic (MRI-guided)	Off-label use	Glioblastoma; imaging + hyperthermia	(Si *et al.*, 2024)
PK2	Galactosamine-PHPMA-doxorubicin	pH/enzyme (lysosomal)	Phase II (discontinued)	Liver cancer; targeted delivery	(Avramovic *et al.*, 2020)
STING-agonist NPs	Polymer nanoparticles	Redox (high GSH)	Preclinical	Immunotherapy; enhanced T-cell infiltration	(Wang-Bishop *et al.*, 2023)
Sonosensitizer TiO_2 NPs	Titanium dioxide NPs	Ultrasound (SDT)	Preclinical	Breast cancer; ROS generation for apoptosis	(Qin *et al.*, 2022)
Hypoxia-activated NPs	Prodrug-loaded micelles	Hypoxia	Phase I/II (e.g., TH-302)	Pancreatic cancer; bioreductive cytotoxicity	(Li *et al.*, 2021)

7 Challenges and Limitations

7.1 Tumor Heterogeneity and Variable Stimuli

Tumour heterogeneity is still a major problem. Different levels of pH, redox state, enzyme expression, ROS, and hypoxia inside tumours cause srNPs to be activated in different ways in different patients and tumour regions. Targeting receptor-ligand strategies also have problems with expression levels, which makes active targeting

platforms less useful. Strategies that target generalised TME features, like acidity and hypoxia, try to fix this, but heterogeneity still causes uneven release profiles (Suvac *et al*., 2025).

7.2 Biocompatibility and Safety Concerns

Many srNP constructs look safe in vitro, but we need to carefully check their long-term biocompatibility, immunogenicity, and off-target toxicity. Functionalised mesoporous silica nanoparticles, for instance, have shown that immune cells respond less to inflammation, but the immunotoxicity and organ clearance in living organisms depend a lot on the formulation (Yousefiasl *et al*., 2025). Biomimetic coatings, like erythrocyte membranes, can lower RES uptake, but they are hard to make and could cause immune reactions, which makes safety even harder. Regulatory bodies want a lot of toxicology profiling, like studies on genotoxicity, biodegradation kinetics, and chronic exposure. These studies are still not very well developed for many srNPs. (Guo *et al*., 2021).

7.3 Manufacturing, Scalability, and Regulatory Hurdles

Making large amounts of reproducible srNPs is hard because you have to make sure that each batch is the same, control the stimuli-responsive triggers, and sterilise them without changing how they work. The fact that multi-component designs (like dual stimuli systems or biomimetic coatings) are so complicated makes it even harder to translate them into industry. There aren't any standard regulatory pathways for stimulus-responsive modalities yet. It's hard to prove that they are both safe and effective when activation is limited to tumour tissue. Good Manufacturing Practices (GMP) say that tuning the physico-chemical properties (size, charge, and linkage stability) must be done very carefully. Regulatory agencies place a lot of importance on analytical characterisation, stability, and impurity control, which are very hard to meet for complex srNP constructs (Su *et al*., 2023).

8 Future Perspectives and Opportunities

8.1 New Trends in Smart Nanomedicine

New research in smart nanomedicine is looking at next-generation multifunctional platforms that can be programmed to respond to both internal and external stimuli (Zhou *et al*., 2023). Recent advances use mechanisms that cause ferroptosis to work together with pH-sensitive carriers, ROS generation, and glutathione depletion to treat drug-resistant tumours. For instance, Yang *et al*. (2024) created a hyperbranched polyglycerol (HDP ss) nanoplatform that delivered both sorafenib and siNRF2 at the same time. This led to about 94% tumour inhibition by overproducing ROS and depleting GSH, which got around ferroptosis resistance (Liu & Yuan, 2025).

At the same time, more and more studies are looking into how multimodal external stimuli like photothermal, ultrasound, and magnetic fields can activate release and improve tumour penetration. A platform made of copper sulphide nanosheets combined photothermal therapy and chemotherapy under NIR irradiation to work together to get rid of breast tumours. Systems that respond to ultrasound speed up both the accumulation and release rates (Zeng *et al*., 2024).

8.2 Working with immunotherapy and theranostics

Combining nanoparticles that respond to stimuli with immunotherapy and theranostics is becoming a strong model. Nanoparticles designed to cause immunogenic cell death (ICD) and immune checkpoint inhibitors (like PD 1/PD L1 blockade) can turn "cold" tumours into "hot," immunoresponsive ones. This boosts anti-tumor immunity right in the tumour microenvironment by releasing both ICD inducers and immunomodulators in a controlled way (Banstola *et al*., 2021). Theranostic nanomedicine combines drug delivery with diagnostic imaging in the field of imaging. Magnetic nanoparticles make it possible to track things in real time with MRI and magnet-guided photothermal or chemodynamic therapy. Data-driven feedback systems and hybrid physics–AI models are making it more likely that smart theranostic control will be possible (Kim *et al*., 2024). Combining smart srNPs with immunotherapy and theranostic abilities is a very powerful way to do precision oncology.

8.3 Personalized Nanomedicine Methods

Using patient-specific TME profiles to create personalized nanomedicine is becoming a major area of research. Molecular Cancer (2025) talks about TME heterogeneity, which includes differences in pH, enzyme levels, and hypoxia, and how these differences affect how well drugs work. It argues for personalized design based on tumor-specific parameters to make sure that treatment is the same for all patients (Zhang *et al*., 2022). Scientists are developing modular systems that can alter their sizes, deshield polyethylene glycols (PEGs), or alter charges based on tumor microenvironment (TME) stimuli for enhanced penetration and uptake within various tumor microenvironments (Sabit *et al*., 2025).

Conclusion

Stimuli-sensitive nanoparticles also provide a new era of targeted cancer treatment due to their promise of enabling practitioners a high level of control over the timing of release of drugs within the tumor microenvironment (TME), characterized by its unique and dynamic attributes. In addition to taking advantage of the specific physiology and pathology of the TME, i.e., acidic pH, increased redox potential, overexpressed enzymes, and increased levels of reactive oxygen species, advanced nanocarriers release

drugs by design at defined sites and regulate their release. This form of targeting not only optimizes the potency of anticancer drugs but also inhibits the system-wide toxicity and side effects common to conventional chemotherapies. Furthermore, due to the modularity of the nanoparticles, it is possible to alter their physicochemical attributes and responsiveness finely and consequently make them suited for a vast array of medical applications, e.g., combination therapies and immunotherapies. Due to the ongoing nature of investigations into polymer chemistry, nanotechnology, and bioengineering, it is increasingly feasible to translate stimuli-sensitive platforms into practical applications. But problems like scalability, reproducibility, and long-term safety still need to be worked out. Overall, stimuli-responsive nanoparticles seem like a promising and flexible way to get around the problems that cancer treatment has right now. This could lead to more personalized, effective, and less invasive treatments.

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