Review Article

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Micelle-based nanoparticles with stimuli-responsive properties for drug delivery

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Abstract: Cancer treatment often causes adverse effects and toxicity, as chemotherapy drugs affect both cancerous and healthy cells. Scientists seek to target tumor cells specifically and minimize harm to normal cells. Smart nanoparticles (NPs) are a modern technique that can release drugs when triggered by internal or external stimuli, such as temperature, pH, ultrasound, *etc*. This review covers stimuli-responsive micelle-based nanoparticles (SRM-NPs), a promising drug delivery platform that can enhance drug efficacy and reduce toxicity. It discusses the recent developments and applications of SRM-NPs, their responsiveness to different stimuli, and their potential to overcome drug resistance and adaptive responses. It also addresses the challenges and issues related to their stability, reproducibility, biocompatibility, safety, and optimization. The study concludes that SRM-NPs have great potential for drug delivery, but more research and development are needed to improve their clinical utility.

Keywords: polymeric micelles, micelle NPs, cancer treatment, drug delivery, internal and external stimuli

1 Introduction

Cancer is a significant contributor to mortality rates [1,2] and poses a substantial obstacle to advancing life expectancy [3]. As per the GLOBOCAN digital repository, there is an anticipated rise in the occurrence of cancer every year [4], with a forecasted doubling of such incidence by the year 2050 [5]. The development of cancer treatments dates back to the early 1900s [3]. Several cancer treatment modalities exist, including chemotherapy, radiotherapy, surgery, hormone therapy, monoclonal antibodies, cell therapy, and gene therapy, as documented in sources [3,6,7]. Researchers in the scientific community have been conducting studies and creating therapeutic interventions involving chemotherapy for the treatment of cancer to enhance their effectiveness and minimize their adverse reactions [8]. Anticancer agents are employed to impede the growth and dissemination of cancer cells, given their capacity to disseminate to various organs within the circulatory system [7,9]. Most chemotherapy agents exhibit inadequate aqueous solubility [10], constraining their ability to traverse cellular membranes [11–13]. Additionally, it is frequently observed that these pharmaceutical compounds exhibit limited stability or undergo rapid metabolism [1,9]. One additional characteristic of these pharmaceuticals is their lack of ability to distinguish between normal and malignant tissues [2,14]. The administration of anticancer medications at high dosages is frequently associated with a range of adverse effects, including but not limited to anemia, fatigue, alopecia, anorexia, and other complications. Given the limited effectiveness of current chemotherapeutic agents, the need for improved cancer treatments with higher efficacy is imperative [2,4,7,9,15,16]. Therefore, the development of contemporary

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approaches is essential for addressing this issue. Although numerous chemotherapeutic agents are accessible, their effectiveness is restricted due to inadequate output [2]. Consequently, there is a pressing need for innovative methodologies to devise more efficacious cancer therapies [4].

Drug delivery is a method used to treat diseases by delivering medications to specific areas of the body [17–19]. The properties of agents can be improved by modifying their physicochemical and pharmacokinetic characteristics [20]. Additionally, drug delivery systems (DDS) can target medicines' entry into specific tissues [21]. The development of DDS began earlier than 1995, and significant progress has been made since then. The year 1995 witnessed a noteworthy achievement in the realm of drug delivery with the approval of the inaugural liposomal drug delivery system by the US Food and Drug Administration (FDA) [22]. A range of nanocarriers are employed in the field of drug delivery, such as liposomes [23], polymeric micelle (PMs) [24,25], metal nanoparticles (NPs) [26], mesoporous silica NPs [27], carbon nanotubes (CNTs) [28], dendrimer [29], exosomes [30,31], and mixed formulations utilizing albumin [20] (Table 1). The versatile physical and chemical characteristics, compatibility with biological systems, and capacity for degradation make polymers a popular choice for drug delivery applications. Micelles and liposomes play crucial roles as nanocarriers in delivering drugs. Liposomes, characterized by a water-filled core enclosed in a lipid bilayer, differ from micelles, which result from the self-assembly of amphiphilic molecules in a colloidal solution. Specifically, smaller and less stable than liposomes, micelles stand in contrast to the liposomes' greater flexibility and larger volume. Liposomes exhibit a superior carrying capacity, enabling them to transport various types of drugs concurrently. Clinical studies demonstrating the efficacy of both micelles and liposomes have validated their commendable biocompatibility. In the realm of polymeric NPs, micelles generally boast greater degradability. Despite discrepancies, micelles and polymeric NPs have effectively contributed to advancing DDS. Liposomes excel in stability and drug-loading capabilities, while micelles offer advantages such as smaller size, simplified manufacturing, and the potential for precise targeting and drug delivery. Micelles typically exhibit greater degradability and comparable biocompatibility and therapeutic efficacy compared to polymeric NPs [32,50]. It is possible to engineer carriers that can transport pharmaceutical agents, safeguard them from deterioration, and dispense them regulated upon exposure to different stimuli [51].

PMs, a subset of the nano-sized drug delivery system [31], have attracted more attention for cancer treatment than other nanocarriers due to their desirable characteristics. For instance, they are effective in transferring

Table 1: Comparison of different NP classes

Criteria	Micelles	Liposomes	Dendrimers	Metal-based NPs	CNTs	Quantum dots	Nab technology
Composition	Amphiphilic molecules	Phospholipids	Branched macromolecules	Metal oxides, metals, semiconductors	Carbon atoms	Semiconductor nanocrystals	Albumin protein bound to NPs
Size range (nm)	5–100	50–500	1–10	1–100	0.4–2	2–10	100–200
Drug loading	Moderate	High	High	Low	Low	Low	Moderate
Stability	High	Moderate	Moderate	Low to high	Moderate	Moderate	High
Biocompatibility	Moderate	High	Low	Varies	Low	Low	High
Applications	Drug delivery and imaging	Drug delivery and cosmetics	Gene delivery, drug delivery, and imaging	Catalysis, electronics, imaging, cancer therapy, and biosensors	Electronics, composites, energy storage	Bioimaging, diagnostics, solar cells	Drug delivery
Clinical status	In clinical trials	FDA-approved products	In preclinical research	In early development	In early development	In clinical trials	In clinical trials
Biodegradability	Biodegradable	Biodegradable	Biodegradable	Non-biodegradable	Non-biodegradable	Non-biodegradable	Biodegradable
Immunogenicity	Low	Low	Moderate	Varies	Moderate to high	Moderate	Low
References	[32–34]	[35,36]	[37,38]	[39–41]	[42,43]	[44–46]	[47–49]

hydrophobic drugs [52,53], have high biocompatibility, are low-cost, easy to prepare, have a high drug loading capacity [53], are small in size [54], have good solubility [55,56], can circulate in the blood for a long time [55,57], can respond to external stimuli, can efficiently deliver drugs to the target tissue, have controlled drug release [53], exhibit excellent performance [55], are stable [24], and have low toxicity [20]. PMs have a hydrophobic core that can load hydrophobic agents (drugs and/or targeting agents) and a hydrophilic shell that allows them to be water-soluble and durable [20,58–60]. Additionally, the hydrophilic shell of PMs can prevent protein adsorption on the external surface of the micelles, which allows for their purification [55]. The significance of NPs that are capable of responding to stimuli cannot be overstated [61].

This work explicitly discusses micelles that can respond to internal or external stimuli [62], aiming to present a thorough understanding of the possible uses of SRM-NPs as a drug delivery system and the issues related to their clinical application.

2 PMs

Nano-sized PMs are formed by the self-assembly of amphiphilic block copolymers in aqueous solutions and typically have a size between 10 and 100 nm [55]. Unlike bilayer vesicles, micelles are monolayered and composed of a hydrophobic inner core and hydrophilic outer shell. Various polymers can be used in the hydrophilic part, including polyvinylpyrrolidone, polytrimethylene carbonate, and poly(ethylene oxide) [63], but the most commonly used one is polyethylene glycol (PEG) [56]. Poly(propylene oxide), polyesters, or glycolic and lactic acid copolymers are hydrophobic components usually used in the inner core [56]. The structure of the polymers used and the solvent conditions, such as the temperature and pH of the environment, can cause variations in the shape of the micelles [64,65]. Micelles can be seen in rod-like, worm-like, and disc-like forms, although they are often spherical systems [22,64]. The morphology of micelles is essential as a nanocarrier during blood circulation and cellular uptake [66]. The surface characteristics of micelles are crucial in biological fluids. Micelles with a positive zeta potential tend to bind to non-specific proteins, leading to their accumulation [67,68]. Although the cell membrane has a slightly negative charge, positive NPs can be absorbed by cells more quickly than neutral or negative particles [69]. Therefore, this positive charge can enhance drug transfer through biological barriers and facilitate better interaction with epithelium [66,70], as observed in the administration of micelles *via* the oral route [71]. The use of a hydrophilic and neutral surface can increase the circulation time of micelles in the bloodstream by reducing the formation of the protein corona [72,73]. The surface chemistry of NPs and the electrostatic and van der Waals interactions between NPs, biomolecules, and cells are inevitable in biological environments and are related to cell internalization processes [74]. A timeline overview of the development of PMs has been presented in Figure 1.

One of the most important parameters for micelles is critical micelle concentration (CMC) because it represents the minimum concentration of polymer in the solution that leads to the formation of micelles. This factor indicates the thermodynamic stability of micelles. Above

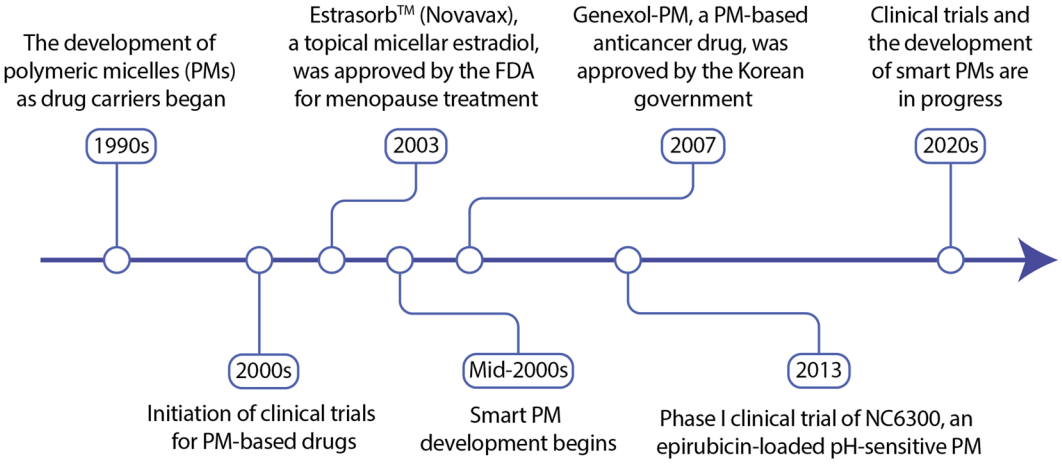

Figure 1: An overview of the development of PMs. Since their initiation in 1990, there have been significant advancements in PMs. Numerous clinical trials have been conducted, with many still in progress. Several PM-based drugs have received approval from the FDA and other regulatory bodies. Presently, there is a prevailing trend toward designing PMs that are responsive to multiple stimuli and targeted. The data presented in the figure were collected from various sources [5,75–79].

this concentration, copolymers begin to aggregate, and micelles are stable. At lower CMCs, amphiphilic molecules exist as separate surfactants, and micelles are not formed [80]. The characteristics of copolymers, such as the length of hydrophobic and hydrophilic parts, affect the CMC threshold value. For example, increasing the length of the hydrophobic part leads to more interactions between hydrophobic fragments, which reduces the CMC [81]. The surface tension method [82,83], light scattering method [84], and electrical conductivity method [85] are the most common CMC measurement methods.

Micelles can enter the cell or release the cargo outside the cell and cause the drug to accumulate in different places, such as the plasma membrane or different cell compartments [86,87]. Micelles are internalized mainly through endocytosis, which occurs when micelles interact with the cell membrane and transport within endosomes to the cytoplasm [88,89]. Most PMs are degraded in the plasma membrane or lysosomes; only a few can enter the cell intact [89]. After micelles are internalized through endocytosis, unimers reduce ATP by increasing membrane fluidity, which leads to a decrease in ATPase activity. This, in turn, enables a more accessible bypass of ATP-dependent efflux pumps, reducing drug and multidrug resistance (MDR) [90,91]. Moreover, MDR can be significantly reduced by conjugating molecules like quercetin that inhibit these pumps. The API can be physically entrapped or chemically conjugated to the micelle. The API loaded by the physical method is released by simple diffusion, whereas the chemically conjugated method requires a specific functional group of the API to establish a covalent bond with the hydrophobic portion of the micelles. This incorporation in the core causes the release of the API by surface erosion or complete degradation of the PM [92,93]. The advantages of polymer micelles have garnered much attention in recent years due to their ability to increase the stability and solubility of drugs compared to free drugs. This can be achieved by physically loading hydrophobic drugs or chemical conjugation. It is possible to design the size of micelles and increase their circulation time in the blood to prevent premature clearance of NPs smaller than 10 nm through renal glomeruli [56,94]. One of the key factors in increasing blood circulation time is increasing biodistribution, which can be achieved by the appropriate design of the molecular weight and size of micellar polymers. Meanwhile, the mononuclear phagocyte system (MPS, previously referred to as the reticuloendothelial system) in the liver and spleen can remove NPs larger than 100 nm from the blood circulation system. Therefore, an appropriate size range of 10–100 nm can prevent the rapid clearance of micelles from the body. Moreover, to avoid detection and removal by the MPS, the biocompatibility of micelles can be enhanced by utilizing biocompatible and hydrophilic polymers such as PEG [56,95–97].

In *in vivo* environments, the lack of stability of nanomaterials is one of the main challenges due to their interaction with plasma proteins, intense dilution, and pH shifts. These factors can cause premature cargo release and lead to undesired drug accumulation in non-target tissues. Micelles with a low CMC can maintain their stability even in very dilute conditions, and this advantage provides them with more opportunities to penetrate target tissues during blood circulation. This also increases the possibility of their accumulation in tumor tissue through the enhanced permeability and retention (EPR) effect [56,98,99]. The aforementioned features make micelles an intriguing option for drug delivery. The use of polymer micelles as a drug delivery system is based on their ability to transport hydrophobic and insoluble drugs, control drug release over a prolonged period, and target specific cells and organs. Since many anticancer agents have poor aqueous solubility, PMs are suitable for delivering them [56,100]. Compared to normal body cells, tumor cells have pH acidity, altered redox potential, and overexpressed proteins, and enzymes that can trigger drug release in these tissues. Micelles that can respond to these stimuli enable the controlled release of drugs and increase their effectiveness. Additionally, external stimuli such as light, temperature, and ultrasound (US) waves can be used to trigger drug release in the tumor area [101]. The aim of this article is to summarize and review the use of smart micelles in cancer treatment.

3 Smart micelles

3.1 Ligand-mediated targeting

Cancerous cells express certain biomarkers on their surface that are involved in cell reproduction, intercellular interactions, and signal transduction. Examples of such biomarkers include membrane proteins and growth and transcription factors. Using these biomarkers makes it possible to create targeted binding conditions for cancer cells, making treatments more effective and less toxic (Figure 2) [102]. Since one of the challenges in DDS is related to the ability of the drug to penetrate cells, carriers are often modified with ligands to target cancer cell receptors [103]. Ligand-mediated targeting is a widely used approach to improve the specificity of drug delivery to desired sites. By modifying the surface of smart micelles with specific ligands, they can selectively bind to receptors or proteins that are overexpressed on the surface of target cells. This targeted interaction enhances the effectiveness of cellular uptake and therapeutic

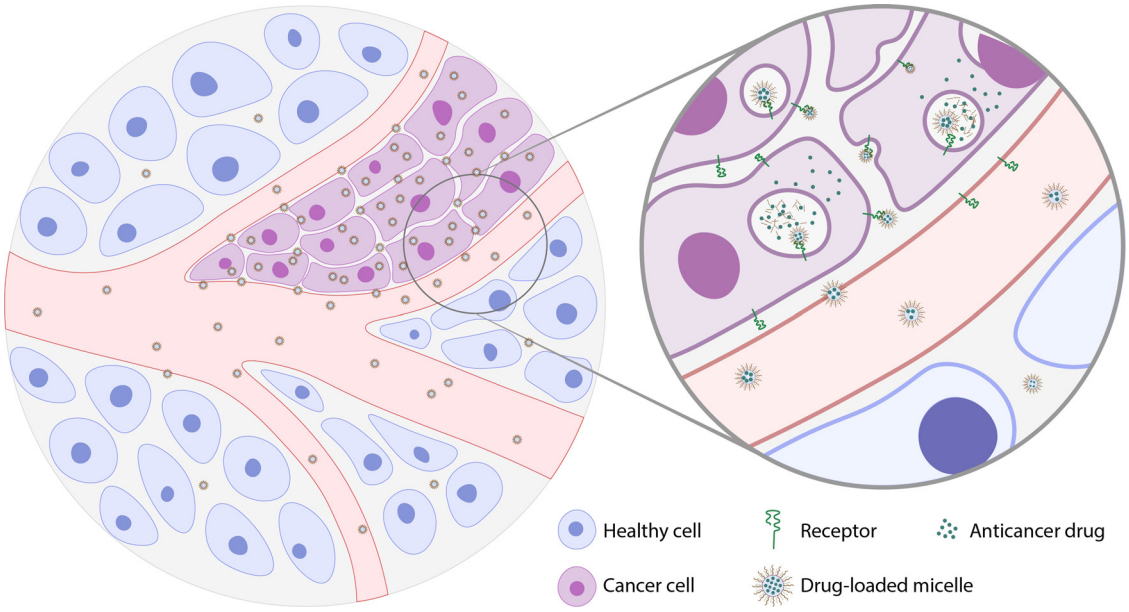

Figure 2: Ligand-targeted micelles. Different ligands are used to target overexpressed biomarkers and receptors on the surface of cancer cells. These micelles circulate in the body and bind to the overexpressed receptors of cancer cells. This way, micelles can accumulate only in cancerous tissue without harming healthy cells. Then, micelles enter the cancer cells through ligand-mediated endocytosis, releasing their cargo in lysosomes and eventually killing the cell.

interventions [104]. One of the ligands that can be used to modify carriers for targeted drug delivery is aptamers. Aptamers are single-stranded oligonucleotides that can bind to cancer cell receptors with high affinity when placed on the surface of carriers. For instance, the DNA aptamer S2.1 can target MUC1 (mucin 1) on the surface of cancerous cells, such as ovarian and breast cancer cells. In melanoma cancer, RNA aptamer 9.8 has been shown to effectively target the CD134 (OX40) receptor [102]. Cholesterol is another example of a ligand that can be used, as it is naturally present in animal cell membranes and plays a role in membrane fluidity. As a result, it is readily available and has a low cost.

Furthermore, several types of molecules based on steroids can be derived from cholesterol for this purpose [103]. Polysaccharides are another type of modification that can be used. Chitosan, for example, is commonly utilized due to its adhesive properties, lack of toxicity or harmful effects on biological functions, and ability to be biodegradable in the environment [105]. Hyaluronic acid (HA) is another example of a polysaccharide used for drug delivery due to its biocompatibility and biodegradability. Many tumor cells express the CD44 receptor on their cell surface, which can bind to HA. Therefore, HA is often used for targeting cancer cells. During cell reproduction, folic acid (FA) is a crucial substance for base synthesis, and as a result, many cancer cells, such as lung, kidney, and breast cancer, express FA on their surfaces. Compared to healthy cells, tumor tissue overexpresses the folate receptor (FR), leading to increased uptake of FA [106]. Zhang *et al.* synthesized polyethylene oxide and polycaprolactone (PEO–PCL) micelles and loaded docetaxel inside them, which is used for prostate cancer. Subsequently, they modified the surface of the micelles with the *N*-[*N*-[(*S*)-1,3-dicarboxypropyl]carbamoyl]-(*S*)-lysine (DCL) ligand, which targets prostate membrane antigen, and the TAT peptide (HIV-1 TAT protein peptide). The modifications mentioned in the study did not disrupt the structure of the PEO–PCL micelles due to their weight. The DCL ligand was used to target prostate cancer cells, while the TAT peptide was used to facilitate the transit of the micelles through the cell membrane. The study showed that these modifications improved the effectiveness of prostate cancer treatment [107]. In another study conducted by Kalinova and Dimitrov, a poly(2-hydroxyethyl methacrylate)-*b*-poly(L-lysine) block copolymer was synthesized, and curcumin (Cur) was loaded into it. The copolymer was then modified with poly(ethylene glycol)-*b*-poly(L-aspartic acid) copolymer to improve its targeting and durability [108]. Zhang *et al.* implied in their article that using the CD44 receptor and FR simultaneously as a ligand can not only facilitate cell infiltration but also make cargo release more challenging. Some nanocarriers are designed with the ability to respond to extrinsic or intrinsic stimuli to address this issue [106].

The utilization of ligand-mediated targeting in smart micelles poses challenges, primarily stemming from the limited availability and specificity of suitable ligands for target cells. Additionally, incorporating ligands onto micelle surfaces

can alter their physicochemical properties, potentially influencing stability, drug loading capacity, and release kinetics [109,110]. The variability and potential mutation of target cells and receptor downregulation further complicate ligand-mediated targeting. These factors can impact the effectiveness of targeted drug delivery by influencing the interaction between ligands and receptors. Consequently, the development of ligand-mediated targeting strategies should consider these challenges and strive to offer adaptable and resilient approaches to overcome them [109,110]. Table 2 presents a summary of ligands used in the preparation of targeted micelles.

3.2 SRM

Stimuli-responsive systems operate based on the physicochemical changes, instability, and disintegration of NPs in response to stimuli [111–113]. Stimuli can be classified as internal or external. Internal stimuli include redox reactions [114], changes in pH [115], enzymes, and reactive oxygen species (ROS) [116] (Figure 3). External stimuli include light [117], temperature [28], US, and magnetic field [62] (Figure 4).

3.2.1 Internal stimuli

3.2.1.1 pH-responsive PMs

pH-responsive PMs are a class of polymeric materials that demonstrate a reversible chemical response to alterations in the pH of their surrounding environment. These materials have significant applications in DDS, where they can trigger drug release in response to pH changes specific to certain biological conditions, such as tumor tissues or inflamed regions. By harnessing pH responsiveness, PMs enable a more controlled and targeted drug release, thereby enhancing the effectiveness of drug therapies while reducing the potential for undesirable side effects [118–120]. Some special properties of tumor cells include a high level of enzymes [121], high temperature [101], hypoxia [122], low pH [123], an eminent measure of lactate, and a light level of glucose [124]. Among the stimuli, pH is utilized more frequently than other stimuli for DDS. The pH of cancer cells is lower than that of normal cells due to the Warburg effect, ranging from 6.5 to 7.2 [125]. The Warburg effect is induced by the tendency of cancer cells to favor aerobic glycolysis in the cytosol over the citric acid cycle and oxidative phosphorylation in mitochondria for energy production. This metabolic pathway leads to the generation of lactate, consequently causing the surrounding environment to become more acidic [124]. This acidic pH allows drug-loaded delivery to the cancer site [126]. Consequently, drug-loaded distribution occurs at cancer sites [127]. There are two reasons for drug release: the first is related to the deprotonation [128] or protonation of a particular group and disintegration [129], while the second is related to the destruction of pH-sensitive bonds [101], such as acetal, hydrazine, *cis*-aconityl [127], methyl maleate [124], and ketal [130]. Domiński *et al.* synthesized nanocarriers by combining poly(ethylene glycol) with poly[R,S]-3-hydroxybutyrate and inserting the hydrazone bond between them, which imparted self-assembling properties to the resulting micelles. The diblock copolymer used in this approach is biodegradable and has a diameter of approximately 55 nm. Doxorubicin (DOX) was conjugated with 8-hydroxyquinoline glucose and galactose and loaded in the core of the micelles as an anticancer drug. The authors observed that the micelles remained stable at pH 7.4. However, the hydrazone bond was destroyed at acidic pH, leading to micelle disintegration and cargo release [131]. Ameli and Alizadeh synthesized micelle-based NPs with pH-sensitive properties by combining cyclodextrin and copolymers to deliver capecitabine (CAP) for colon cancer treatment. The release of CAP was studied at various pH levels, and it was finally demonstrated that the micelles completely disintegrated at a pH of 7.4 [132]. Table 3 presents a compilation of selective pH-sensitive polymers that have been investigated for cancer remedies. Liu *et al.* designed a pH-sensitive amphiphilic block copolymer, poly(acrylic acid)-*b*-polycaprolactone (PAA-*b*-PCL) micelle, and loaded it with Gambogenic acid (GNA). They then studied its effects on cancer, both *in vitro* and *in vivo*. Given the positive results obtained, they asserted that this type of system holds potential for future cancer treatment.

3.2.1.2 Redox-responsive PMs

It has been observed that various types of cancer cells persist and proliferate by elevating the production of ROS. In response, cells increase the production of GSH to counteract and neutralize ROS [148]. GSH serves as an endogenous reducing agent in the human body [28] and possesses antioxidant properties [149]. It plays a role in preventing the aggregation of ROS in diseased cells through its thiol group [128]. Due to their stable blood circulation, some redox-responsive nanocarriers have been designed to control cargo release [150].

Redox-responsive PMs are a class of polymeric materials that demonstrate sensitivity to changes in the redox state of their surroundings. These PMs undergo reversible chemical transformations upon exposure to reactive

Table 2: Summary of ligands used in the preparation of targeted micelles

Ligand type	Subclass	Advantages	Disadvantages	Ref.
Small organic molecule	FA	Improved tumor targeting and reduced side effects	May have limited efficacy in tumors with low FR expression	[224]
	Galactose	Enables targeted delivery of drugs to the liver	Potential for off-target effects in other tissues expressing asialoglycoprotein receptors	[225]
Peptide	cRGD	Improved tumor targeting and reduced side effects	Limited specificity and potential for off-target effects	[226]
	NGR	Enhances tumor accumulation and penetration	Relatively short circulation time *in vivo*	[227]
	Lyp-1	Enables specific delivery of micelles to the lymphatic system	May require additional targeting moieties for deeper tissue penetration	[228]
Monoclonal antibody	Anti-MDA2	Holds promise for monitoring high-risk atherosclerosis	Further validation in larger animal models and humans needed	[229]
	Anti-CTLA4	Demonstrated clinical efficacy in various cancers	Can cause severe immune-related adverse events	[230]
	Anti-Her2	Improved targeted delivery and reduced side effects compared to traditional chemotherapy	May cause cardiotoxicity and other adverse events	[231]
Folate conjugate	FA	Improved tumor targeting and reduced side effects	Limited specificity due to FR expression in some healthy tissues, such as kidneys and placenta	[232,233]
	Folate-PEG (FA-PEG)	Reduced systemic toxicity and prolonged therapeutic efficacy	Potential for reduced targeting efficiency compared to unmodified folate due to PEG shielding effect	[234,235]
	5-Methyltetrahydrofolate (5-MTHF)	Improved safety profile and targeting specificity	Requires further development for scalable and cost-effective synthesis	[236,237]
	Folate-decorated PMs	Versatile platform for targeted drug delivery with potential for multi-modality therapy	Requires careful design and optimization of micelle structure and folate conjugation to achieve optimal targeting and drug release	[238,239]
Carbohydrate	Glucose	Efficient targeting of cancer cells with minimal impact on healthy tissues	Limited specificity due to GLUT expression in various cell types	[240]
	Dextran	Biocompatible and biodegradable, providing sustained drug release	Can be susceptible to enzymatic degradation *in vivo*	[241]
Aptamer	AS1411	Improved tumor targeting and reduced side effects	Limited specificity due to nucleolin expression in some healthy tissues	[242]

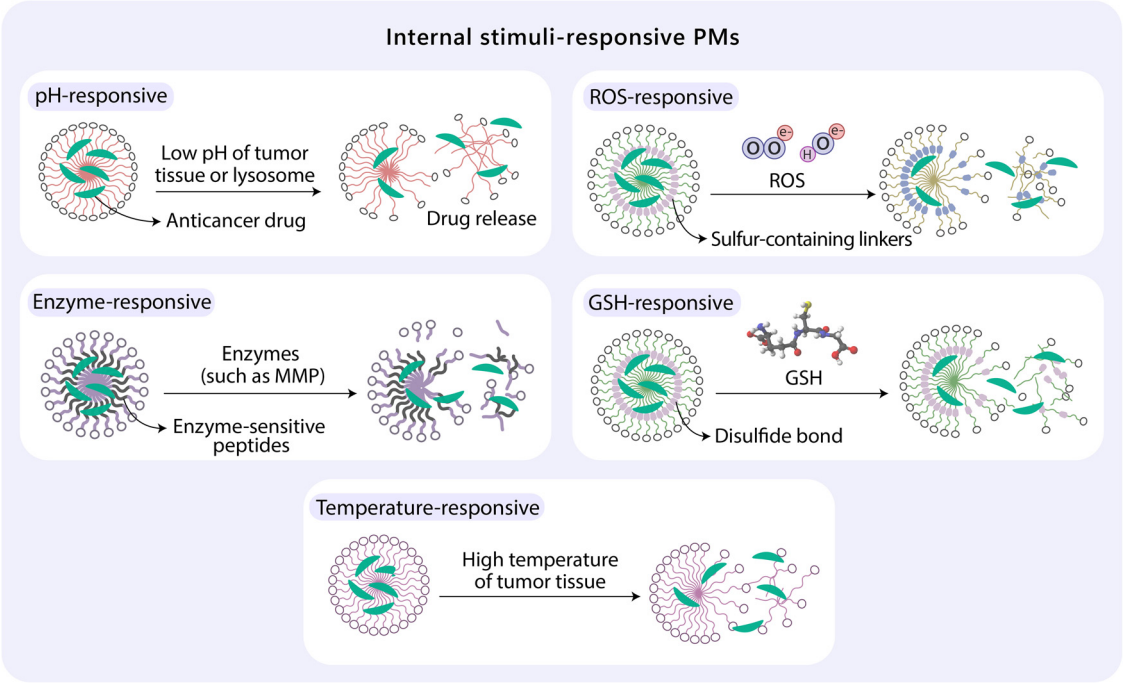

Figure 3: Internal SRMs. Micelles can be designed to respond to different intrinsic stimuli and release their cargo at the activation site. Internal stimuli can be natural characteristics of cancer cells, such as low pH and high levels of ROS, glutathione (GSH), and some enzymes (*e.g.*, matrix metalloproteinases: MMPs) and high temperature.

molecules like oxygen or hydrogen peroxide. In the context of drug delivery, redox-responsive PMs can be engineered to release drugs in response to variations in the redox environment of specific pathological tissues, including tumors or inflamed areas [101,151]. This unique property of redox-responsive PMs holds significant promise for achieving precise and targeted drug delivery, enabling enhanced therapeutic outcomes. By harnessing the redox responsiveness of these PMs, researchers are exploring innovative strategies to optimize drug release and improve treatment efficacy while minimizing off-target effects [152].

Consequently, through the utilization of redox-responsive carriers in conditions rich in redox agents like GSH, the disulfide bond is disrupted. This results in the release of the loaded drug, specifically targeting and destroying cancer cells [149]. Zhou *et al.* demonstrated that under GSH conditions, the disulfide bond is broken, leading to the release of paclitaxel (PTX) from redox-responsive diP-PSSP micelles [153].

Pang *et al.* synthesized three types of micelles containing NPDOX and F-NPDOX without ditelluride bonds and F-TeNPDOX with ditelluride bonds. They loaded DOX in each of them and examined *in vitro* loading release in 20 mM phosphate buffer at pH 7.4 and 37°C in the presence or absence of 10 mM GSH. They found that the release of DOX from F-TeNPDOX was approximately 76.71 ± 2.8% after 24 h in the presence of GSH, whereas it was 26.87 ± 2.06% after 72 h in the absence of GSH. On the other hand, the release of the drug from NPDOX and F-NPDOX micelles was slow. Thus, they concluded that the rapid drug release occurred due to the breakage of ditelluride bonds under redox conditions [154]. Table 4 presents a compilation of selective redox-responsive micelles that have been studied for cancer therapy applications.

Yu *et al.* synthesized redox-sensitive AS1411 aptamer-modified chondroitin sulfate A-ss-deoxycholic acid (ACSSD) micelles, loaded with doxorubicin, and tested them *in vivo* in mice. The results indicated that this system can be used to treat lung metastasis with minimal toxicity [170].

3.2.1.3 Enzyme-responsive PMs

Enzymatic polymers belong to a class of NPs that exhibit sensitivity to biological factors. These biomolecule-sensitive nanocarriers find utility in both therapeutic and diagnostic applications as they respond to stimuli inherent in living systems or arising from cellular signaling. Bioresponsive polymer systems release their payload by binding to biologically relevant entities that share complementary functional groups with them. Examples of this polymer class include ATP-responsive polymers, glucose-sensitive polymers, and antigen-responsive polymers [171].

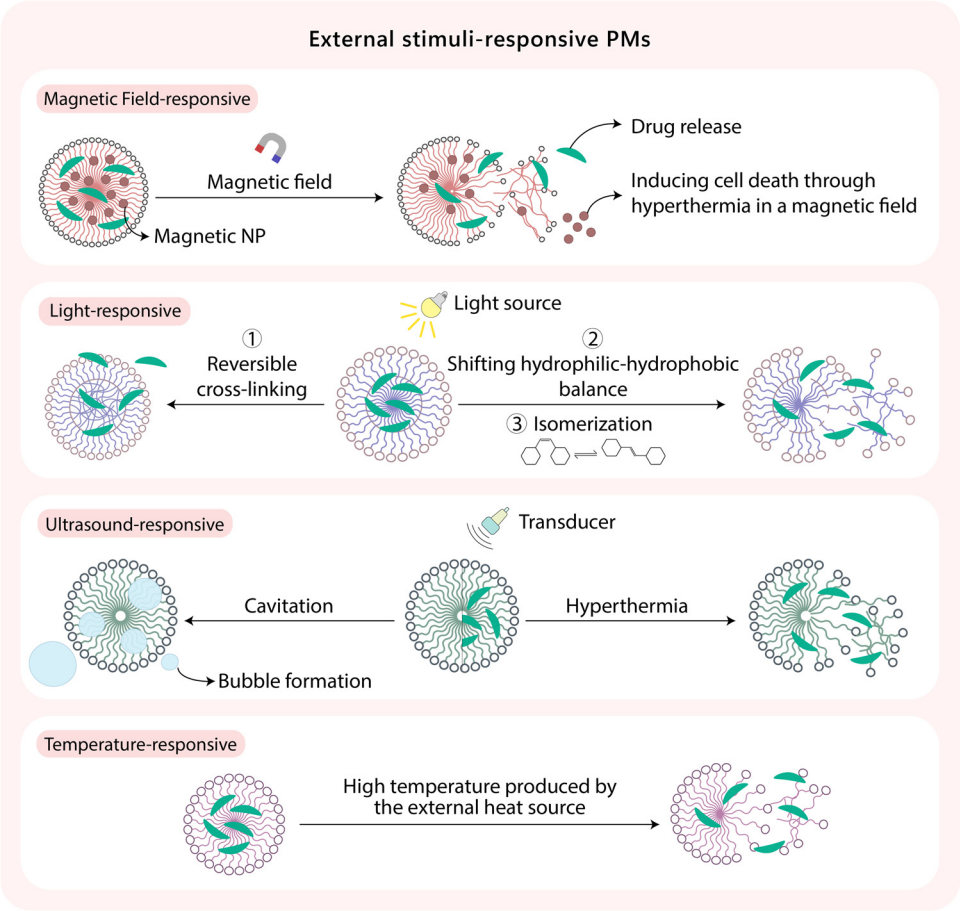

Figure 4: External SRMs. External stimuli, such as magnetic fields, light, and US, can control micelle aggregation and cargo release. Temperature is regarded as both an external and internal stimulus because tumor tissues have higher temperatures than healthy tissue within the same organ, while temperature can also be applied from outside the body with a heat source.

Enzymes have various biological and metabolic functions, and their deficiencies can cause pathological states and illnesses. Cancer cells exhibit high proliferation, the development of blood vessels, invasion, and metastasis due to the overexpression of many types of enzymes, such as proteases, peptidases, lipases [101], phospholipases, hydrolases, glucosidases [62], oxidoreductases, and trypsin [128]. Enzymes can also serve as effective triggers for cargo release [172]. Several types of polymeric nanocarriers have been designed to release drugs in response to the presence of enzymes. Drug release can occur through shell subversion and disintegration or regulation of the surface properties of the nanocarriers through physicochemical variations [62]. Enzymatic degradation can be modulated by changing the hydrophobicity and amphiphilicity of the carrier [173]. Proteases are considered the most important among different enzymes [128].

MMPs are endopeptidase enzymes that function in the extracellular matrix [62]. MMPs are well known for their tumor prognostication properties. They are often overexpressed in various types of cancers and are associated with tumor growth, invasion, and metastasis. The expression level of MMPs in tumors can be used as a prognostic factor for cancer progression and patient survival [128]. MMP plays a role in metastasis and is highly expressed in tumor cells. This is the reason that loading release is controlled by MMP usage, especially MMP2 and MMP9 [127]. For example, Wan *et al.* fabricated the TPGS3350-GPLGVR (D-α-tocopherol PEG 3350 succinate-Gly-Pro-leu-Gly-Val-Arg) micelle that was sensitive to MMP-9 and folate-DEVD micelle (folate-Asp-Glu-Val-Asp), which was sentient toward caspase-3. They loaded DOX into the micelles, dissolved them in a phosphate-buffered solution (PBS), and added MMP-9. Next they incubated the solution at 37°C for 0, 2, 4, 8, 16, and 24 h. They observed that MMP-9 affected the GPLGVR peptide in cancerous cells and eliminated the outer layer of TPGS3350. Therefore, the micelles were able to penetrate the tumor tissue due to the exposed folate-targeting molecule. The DEVD peptide was then intercepted due to the presence of caspase-3 in cancer cells, resulting in the delivery of DOX from the micelles [174].

Table 3: Selected pH-sensitive polymers for cancer remedy

Polymer	Drug load	Cancer type	Result	Reference
DSPE-PEG/OA6	DOX	Breast	With pH reduction, drug release increased	[133]
mPEG-*b*-PAE	PTX/DOX	Multiple	With pH decline, zeta-potential growth and pH sensibility increased	[134]
PLGA-D-P	DOX	Multiple	With pH decrease to 5.0, DOX release is at ~80%	[135]
DA-P-SS-T/C6	PTX	Lung	Declining pH and zeta-potential variation augmented drug delivery	[136]
TPGS, PBLG, TPH, and TPM	DOX	Lung	Framework transformation enabled DOX release	[137]
HA-Cur-TPGS	DAS	Liver	With pH reduction, drug release is enhanced	[138]
HDO-NPs	DAS	Breast	After 48 h, moiety release was ~50%; the ligand was CD44	[139]
Polycarboxylate-PEG	Lysozyme protein	Breast cancer	Improved release upon cell uptake	[140]
Polyhistidine-polyglutamate	Granzyme B	Murine melanoma cells (melanoma)	Improved anti-tumor efficiency	[141]
PDHA-PEG	Irinotecan and imiquimod	Colorectal	Amplifies anti-tumor immunity	[142]
PMPC-*b*-P(DEGMA-*co*-FPMA)	Tirapazamine	Hela and HepG2	Precise delivery and enhance the therapeutic effect	[143]
PEG-*b*-HES-*b*-PLA	Emodin	Breast cancer	Good thermal stability and pH responsiveness	[144]
P(PAA-*co*-GLU)	DOX and imiquimod	4T1 (breast cancer)	Effective tumor inhibition, and fewer adverse effects	[145]
P(DMAEMA-*co*-MaPCL)	DOX	HeLa and MCF-7 cells	Efficiently suppresses the proliferation of tumor cells	[146]
HA-Cur polymer	Dasatinib	HepG2	Accumulates efficiently at the tumor site and reduces the toxic side effects	[138]
$P2VP_{90}$-*b*-PEO_{398}	Cur and 5-Fluorouracil	Human dermal fibroblasts adult cell line (HDFa)	Increase release efficiency	[147]

Barve *et al.* synthesized a cabazitaxel-loaded micelle comprising cholesterol-PLGVRK-PEG2000 (Pro-Leu-Gly-Val-Arg-Lys). They dissolved the micelles in PBS and added human MMP-2 protein. They found that cabazitaxel diffusion occurred in the presence of 200 ng/mL MMP-2. When MMP-2 was present, the drug release was about 80% after 24 h, whereas in the absence of MMP-2, the drug release was approximately 10%. In summary, the PLGVRK linker was broken upon encountering MMP-2, causing the micelle structure to collapse and the cabazitaxel to be released [175]. The synthesis of PEG–MMP2-cleavable peptide–phosphatidylethanolamine (PEG-pp-PE) micelles, responsive to MMP2, has shown promise. The utilization of this model is anticipated to be beneficial for targeting resistant cancer cells *in vivo* [176].

3.2.1.4 Temperature-responsive PMs

Temperature-responsive DDS are designed to release drugs in response to changes in temperature, specifically when the temperature is above a certain threshold. In the case of cancer treatment, the tumor microenvironment (TME) has a slightly higher temperature than healthy tissue, which allows for targeted drug release. These systems can be based on various materials, including polymers, lipids, and inorganic materials, and can be designed to respond to different temperature ranges depending on the specific application. It is necessary to use safe polymers that are sensitive to even slight changes in temperature to make DDS that can respond to temperature. This can be a challenging task [128]. In various diseases such as cancer, inflammation, or infection, certain tissues are exposed to a temperature shift, and this temperature change can be exploited to trigger the destruction of the micelles and release the drug [101]. The temperature higher than the lowest critical solution temperature (LCST) of PNIPAAm poly(*N*-isopropylacrylamide) induces a transition in its coil structure, changes it into a spherical shape [117]. As a result of the destruction of the hydrophobic–hydrophilic balance caused by the ambient temperature being higher than the LCST, the polymer structure is destroyed, and the drug is released [28].

PEO–PPO block copolymers are known as Pluronic or poloxamers, and they are widely used for temperature-sensitive drug delivery. PEO–polyesters such as polylactic acid and PCL are also commonly used for drug delivery due to their biocompatibility and biodegradability. Block copolymers based on PNIPAAm poly(*N*-isopropylacrylamide) are also popular for temperature-sensitive drug delivery due to their LCST behavior [177]. Poly(*N*-vinylalkylamide), poly(*N*,*N*-diethylacrylamide), Pluronics, Tetronics,

Table 4: Selected redox-responsive micelles for cancer therapy

Polymer	Drug load	Results	Reference
PEO113-*b*-PCL35-*b*-PEO113 and PAA13-*b*-PCL35-*b*-PAA13	CAPE	Cargo release because of disulfide-group destruction	[155]
FHSV micelle	PTX	At high GSH levels, micelles were destructed	[156]
POEG-*co*-PVDSAHA	TAM	Cell poisoning elevated	[157]
DA-P-SS-T	PTX	At high-level GSH, fast PTX release was found	[136]
HA-ss-FA	DOX	20 mM GSH resulted in fast DOX release, the ligand was CD44	[158]
HA-ss HA-ss-TOS	MTX	Drug release in redox-sensitive micelles was higher than in non-sensitive micelles	[159]
HA-ss-TOS	PTX	Used for breast cancer and melanoma treatment	[160]
RGD-PEG-ss-PCL	DOC/ICG	(RGD acts as a ligand) efficiency of anticancer drugs was high in *in vivo* study	[161]
FA-ss-P/A	PTX/ADD	(FA use as a ligand) high uptake and efficient anti-tumor effect for MDR	[162]
Methoxy poly(ethylene oxide)-*b*-poly (aspartate-hydrazide)	DOX/SN-38	Hydrolysis of hydrazone bond and drug release	[163]
HA-ss-BF	DOX	Disassemble of micelles in redox condition	[164]
mPEG-SS-PzLL/TPGS	DOX	Disulfide bond can be destructed by reduced GHS	[165]
PEG-*b*-P(CPTM-*co*- ImOAMA)	Polymer prodrug micelles	Disintegration of redox-responsive disulfide bonds and drug release	[166]
HA-ss-PTX	PTX	Fast drug release in tumor cells in response to GSH	[167]
Gal-PEEP-*a*-PCL-ss-PDMAEMA	DOX	Redox-triggered drug	[168]
P(HEMA-*g*-PCL-SS-POEGMA)	DOX	Cargo release under redox condition	[169]

Abbreviation: PSSP: Star-shaped polymeric prodrug; RGD: Peptide (arginine-glycine-aspartic acid); PCL: Polycaprolactone; DOC: Docetaxel; ICG: Indocyanine green; FA; Folic acid; and ADD: Adjudin.

polysaccharide derivatives, phosphazene, and chitosan derivatives are examples of temperature-sensitive polymers that have been used as vehicles for drug or gene delivery [117]. Temperature-sensitive polymers have been extensively explored as DDS, primarily due to their capacity to undergo conformational changes in response to temperature variations. For instance, block copolymers like Pluronics and Tetronics exhibit the ability to self-assemble into micelles at lower temperatures, and disassemble at higher temperatures, thereby facilitating the release of encapsulated drugs.

Similarly, chitosan derivatives have been employed as temperature-sensitive carriers for drug delivery as they change solubility and viscosity in response to temperature fluctuations. Notably, PNIPAAm, with an LCST of approximately 32°C, closely resembles the natural temperature of the human body [178]. Therefore, it is widely used as a micellar polymer that can respond to temperature changes. PNIPAAm can be copolymerized with various monomers to enhance tissue targeting and drug release to optimize LCST [101].

3.2.2 External stimuli

3.2.2.1 Magnetic field-responsive PMs

Magnetic field-responsive PMs, a type of smart-responsive PM, exhibit responsiveness to magnetic fields. Magnetically responsive micellar structures can be formed by incorporating magnetic NPs such as iron oxide, magnetite, or cobalt ferrite into the core or shell of polymer micelles. These structures combine the advantages of polymer micelles and magnetic NPs [101,179]. Upon exposure to an external magnetic field, the magnetic NPs within the PMs generate a magnetic moment, causing the PMs to align with the direction of the magnetic field. The magnetic properties of these micelles can be harnessed to target specific tissues in the presence of an external magnetic field, allowing precise and non-invasive control over cargo distribution [101,179].

Incorporating magnetic NPs into the structural characteristics of the micelles allows for targeted delivery, which holds great promise for minimizing the side effects of conventional chemotherapies [180,181]. To create magnetic sensitivity, superparamagnetic iron oxide nanoparticles (SPIONs) such as magnetite (Fe_3O_4) and maghemite (Fe_2O_3) are used, which are typically smaller than 10 nm [182,183]. An exciting feature of SPIONs is that they exhibit magnetic properties in the presence of a magnetic field. Still, when the field is removed, it loses its magnetism and can be easily redispersed [181]. SPIONs have various biomedical applications, including magnetic resonance imaging, magnetic transfection, and magnetic hyperthermia (MH) [184]. The sensitivity difference between magnetically responsive

materials and cells or tissues in a magnetic field gradient is essential in drug release and NP aggregation. These magnetically responsive materials exhibit minimal interference with the biological environment and demonstrate good penetration because of the non-magnetic properties of cells and tissues.

The contactless activation of magnetic polymeric micelles is another advantage, which minimizes potential harmful effects such as reduced cell integrity and viability [101,185]. Magnetic stimulation can be applied in a constant or time-varying magnetic field. A fixed field is used in cases where a specific area is intended for drug accumulation, such as a tumor. Permanent magnets can apply a constant external field. It is also possible to generate an alternating field by moving the charge in solenoids or by using electromagnetism. Time-varying magnetic fields can be used to induce controlled payload release and thermal treatments, such as hyperthermia or thermal ablation. SPIONs can be classified as low- or high-frequency based on the speed at which the magnetic field changes over time [181]. Under alternating magnetic fields, they can induce direct destruction of tumor cells through local temperature increases or sensitize them to chemotherapy agents [101].

Due to the positive effect of hyperthermia on *in vivo* drug diffusion, Wang *et al.* designed a magnetothermally sensitive micelle (MTM) that integrates magnetic targeting (MT), MH, and magnetothermally responsive drug release to facilitate simultaneous drug accumulation and penetration in tumors. They synthesized a thermosensitive polymer modified with cyanine-7 to prepare MTMs loaded with drugs. The drugs were encapsulated with superparamagnetic $MnFe_2O_4$ NPs and DOX. The DOX–MTMs obtained had high DOX (9.1%) and $MnFe_2O_4$ (38.7%) contents and several advantages, such as superparamagnetism, high saturation magnetization, an excellent magnetocaloric effect, and magnetothermal-dependent drug release. The study's authors demonstrated that DOX–MTM enhances DOX endocytosis with the assistance of MH and increases DOX cytotoxicity. Furthermore, in the presence of DOX–MTM accumulation and penetration, MT and MH inhibited tumor growth by 84% *in vivo* while exhibiting excellent biosafety [186].

Gao *et al.* developed a rod-like magnetic micelle that provides good nanoplatforms for the precise and highly efficient delivery of therapeutic agents to the tumor site for effective cancer treatment. The self-assembly of a copolymer forms the micelle functionalized with phenylboronic acid (PBA) and simultaneously loaded with the anticancer drug DOX and magnetic NPs Fe_3O_4. The presence of magnetic NPs in the micelles enhances their accumulation at the tumor site by applying an external magnetic field. Additionally, it improves the contrast difference between the polymer micelles and cell compartments, allowing for the evaluation of the distribution of the nanocarriers. The presence of PBA targeting ligands allows the DOX-loaded NPs to be selectively recognized by sialic acid-positive tumor cells, which endocytose the NPs. This, combined with the magnetic responsiveness of the micelles, resulted in an 83% inhibition of tumor growth in an H22 hepatocarcinoma model [187].

3.2.2.2 US-responsive PMs

US waves are mechanical waves with a frequency greater than 20 kHz. Due to their non-ionizing and non-invasive characteristics, they have found many uses in imaging, focused US surgery, and tumor ablation [188,189]. Since the report on the application of US in drug delivery in 1989 [190], its use has expanded as an effective technique to stimulate drug delivery at targeted sites by adjusting the power density, frequency, exposure time, and position of the targeted acoustic transducer [191,192]. US-responsive PMs represent an up-and-coming category of DDS capable of responding to external US stimuli for controlled drug release. These systems generally consist of a polymer matrix that encapsulates the drug and incorporates gas-filled microbubbles or NPs capable of expanding and contracting in response to US waves [193,194]. US can be used to trigger drug release and enhance it by utilizing either the thermal properties (hyperthermia) or the mechanical properties (cavitation and microflow) [195].

One of the mechanisms that can induce the release of drugs in a specific area is local hyperthermia, which involves stimulating temperature-sensitive NPs in smart drug delivery. US waves can absorb energy in the target tissue, causing a local increase in temperature without causing significant thermal damage to surrounding natural tissues. Additionally, hyperthermia induced by US can increase the permeability of tissues and vessels in the tumor, leading to drug accumulation in these areas [196–198]. The use of thermoresponsive poly(*N*-alkylacrylamide) blocks in the micellar structure or the polymerization of hydrogels inside the micellar cores with a low critical solution temperature are some of the design solutions for these DDS [189,199].

Another method for drug release by US is cavitation, in which the interaction of sound waves causes the perturbation of materials, which leads to the displacement of less dense materials and the formation of bubbles. The cellular delivery of molecules by US has been widely reported through processes called transient cavitation and sonoporation. These processes increase the cell membrane's transient permeability by forming transient pores or defects in the lipid bilayer. This is accomplished through

the growth and collapse of gas bubbles, which ultimately release molecules such as drugs from certain structures [190,200]. Liu *et al.* examined US's impact on ROS-responsive micelles loaded with hypocrellin (HC). By tracking the fluorescence intensity of the HC-encapsulated micelles, they discovered that the exposure of PEG-PPS-HC micelles to US significantly increased fluorescence intensity. Consequently, US can considerably expedite the release of HC by disassembling the micelles [201].

The study conducted by Wu *et al.* investigated drug release by US from P123/F127 Pluronic (M) polymer micelles loaded with Cur. For *in vivo* experiments, a focused US transducer with a frequency of 1.90 MHz was used, and the load power (LP) was adopted as 1 (US1), 2 (US2), and 3 W (US3). The study found that local US radiation did not cause adverse effects in xenograft mice. The results demonstrated that using US at a LP of 3 W (US3) significantly increased the release of Cur from P123/F127 Pluronic (M) polymer micelles. This was indicated by an increase in the intensity of the fluorescence markers for Cur, suggesting that the micelles were disrupted by US irradiation, and the drug was released. They found that the intensity of US is a crucial factor in initiating drug release from P123/F123 mixed micelles, and this release may be related to US-induced cavitation. The drug release percentage was found to be 19.78, 28.34, and 38.64% at LPs 1 (US1), 2 (US2), and 3 W (US3) in 30 min, respectively, indicating that higher US intensity leads to a greater drug release. The drug release in response to US was completed rapidly within approximately 5 min, thereby making this method superior to pH-responsive and light-sensitive systems that are constrained in the TME. The stimulation of local drug release with US significantly inhibited tumor growth, and the reduction in tumor weight was approximately 6.5-fold higher than when NPs were not exposed to US radiation [202].

The rapid drug release and targeted localization enabled by US-responsive PMs hold significant promise for cancer treatment, potentially mitigating the systemic toxicity associated with conventional chemotherapy. However, several challenges must be overcome before US-responsive PMs can effectively translate into clinical applications. One major challenge pertains to the non-uniform distribution of the ultrasound field, which can result in inconsistent drug release. Moreover, the mechanical stress induced by US may cause premature damage to the micelles, leading to suboptimal therapeutic outcomes [193,194,198,203]. Another challenge that needs to be addressed is the limited penetration depth of US in biological tissues, which may hinder the application of US-responsive PMs in treating deep-seated tumors. In addition, it is crucial to thoroughly evaluate the safety of US exposure in humans to ensure that the potential benefits of this technology outweigh any associated risks. Comprehensive studies are necessary to assess the depth of US penetration and to determine appropriate strategies for delivering US energy to target tissues safely and effectively [193,194,198]. Therefore, extensive research is required to optimize US parameters, such as frequency, intensity, and exposure duration, to ensure uniform drug release and minimize micellar damage.

3.2.2.3 Light-responsive PMs

Light-responsive polymer micelles in their polymer structures contain chromophores, such as azobenzene, pyrene, cinnamoyl, spirobenzopyran, or nitrobenzyl groups. These chromophores can control the spatiotemporal drug release in response to various light sources, including ultraviolet (UV), visible, and near-infrared (NIR) light. Furthermore, these micelles can be created by incorporating these chromophores into their structures [204,205]. Various parameters, including light intensity, emission wavelength, pulse duration, and exposure time, can modulate light-induced reactions [206]. The use of light as an external stimulus in biomedicine is ideal due to its remote control capability, high spatial and temporal resolution, and non-invasive nature [101]. The wavelength of the emitted light is pivotal in its ability to penetrate the human body. NIR wavelengths, which fall within the range of 650–900 nm, are widely used due to their capability to penetrate up to 10 cm deep into the tissue. Conversely, radiation with a wavelength of fewer than 650 nm can only penetrate up to a depth of 1 cm due to absorption and scattering by hemoglobin, water, and tissues [207–209].

Light stimulation can trigger drug release through various mechanisms. The rigidity of *trans*-oriented isomers is greater than that of *cis*-oriented isomers, and the *cis* structure increases polarity. Therefore, one approach for destabilizing and disrupting the integrity of micelles is to induce a structural transition from *trans* to *cis* through UV light exposure, known as photoisomerization. Retinoyl, spiropyran, azobenzene, and stilbene are examples of photoswitchable chemicals that can undergo a *trans*-to-*cis* transformation upon light irradiation [209]. Another mechanism by which light can induce drug release involves a photosensitizer material that becomes excited by absorbing photons and produces ROS, which can be either radicals (such as hydroxyl and superoxide) or non-radicals (such as singlet oxygen). If the photosensitizer is located close to an oxidizable lipid, it can trigger local instability in the lipid. In photo-cleavage, incorporating light-sensitive materials and oxidizable lipids into the composition of nanocarriers enables drug release upon exposure to light radiation [210,211].

Modifying the hydrophobicity of amphiphilic polymers is another approach that involves converting them into more hydrophilic forms. This can be achieved through light-sensitive materials, such as organic chromophores, which undergo a radiation-induced transformation into hydrophilic forms, leading to an increase in CMC and, ultimately, micelle instability. This photochemical reaction to alter the hydrophobicity of molecules results in the thermodynamic instability of micelles and subsequent drug release [208]. The use of crosslinks to enhance the stability of micelles and preserve the drug payload has been extensively investigated in numerous studies. In the process of de-crosslinking, nanocarriers that incorporate photosensitive crosslinks can release drugs spatiotemporally upon light stimulation [207].

Chen *et al.* developed a light-responsive doxorubicin-conjugated polymer (Poly-Dox) tethered to PEG. Upon radiation exposure, the amide bond linking Dox with PEG is cleaved, leading to enhanced cellular uptake of Dox. In their investigation, using UV radiation with varying exposure times, they determined that the optimal illumination duration for Poly-Dox to exert its maximal lethal effect should be around 5 min [212]. Feng *et al.* synthesized amphiphilic biopolymers by incorporating hydrophobic methyl succinate (7-diethylaminocoumarin-4-yl) onto the hydrophilic carboxymethyl chitosan (CMCS) backbone. These biopolymers were then used to fabricate CMCS-DEACMS micelles, which were subsequently loaded with 2,4-dichlorophenoxyacetic acid (2,4-D) as a model pesticide. Under simulated sunlight, the coumarin moieties in the CMCS-DEACMS micelles were cleaved from the CMCS backbone, thereby altering the hydrophilic–hydrophobic balance of the micelles and inducing their destabilization. Consequently, the 2,4-D pesticide payload was released [213]. Zhang *et al.* employed the self-assembly of the amphipathic polymer P-DASA to fabricate NIR light-responsive nanocarriers. The micelles were loaded with upconversion nanoparticles and DOX. The micelles were fully disassembled after NIR exposure, leading to a marked increase in the DOX release rate. The drug release reached 83.7% within 30 min after 5 min of NIR irradiation. It has been demonstrated that exposure to 5 min of NIR results in the efficient production of NO, which inhibits the expression of P-gp and prevents the release of the drug from the target cells through P-glycoprotein [214].

Despite the considerable potential of light-responsive PMs in drug delivery, several obstacles exist. Concerns regarding biocompatibility arise because light-responsive PMs may induce adverse immune responses or exhibit toxicity. Before clinical applications can be pursued, exhaustive biocompatibility studies must be conducted. In addition, the limited depth of light penetration into biological tissues limits the application of light-responsive PMs in deep tissues [215–217]. The lack of established protocols for synthesizing and characterizing light-responsive particles hinder comparing results across studies. Consequently, developing and certifying light-responsive photonic microparticles as medical devices or drugs require extensive safety and efficacy data and the ability to navigate a complex and time-consuming regulatory process. Successfully translating light-responsive PMs into clinical practice necessitates additional research and collaboration. Efforts should focus on enhancing biocompatibility, improving light penetration, establishing standardized protocols, and meeting regulatory requirements [216,217].

3.3 Multi-responsive PMs

PMs can respond to various environmental stimuli, such as temperature, pH, light, enzymes, and redox potential, allowing for the controlled and triggered release of therapeutic agents. By leveraging these responsive mechanisms, drug delivery can be optimized to improve efficacy, specificity, and safety, resulting in improved therapeutic outcomes. The main goals of nanocarriers responsive to multiple stimuli are the same as those of nanocarriers responsive to a single stimulus [218–220]. These goals include achieving long circulation times, high accumulation in the target tissue, penetration into the target tissue, and controlled drug release. However, they release their cargo more precisely and efficiently. Incorporating multiple stimuli-responsive substances into a single NPs enables the release mechanism to be triggered by more than one stimulus, either simultaneously or sequentially [218,220]. This feature facilitates multi-stage drug delivery (as shown in Figure 5), allowing for greater control over the timing and location of drug release [222,223]. Multimodal carriers have shown great potential for drug delivery and targeted cancer therapy by integrating different stimulation strategies (Table 2).

Photothermal and photodynamic therapies represent two light-responsive approaches displaying potential in multimodal systems for treating cancer. These strategies leverage light to precisely target and eliminate cancer cells over specific spaces and time intervals. Photothermal therapy works by transforming light energy into thermal energy, which is capable of facilitating drug release and prompting alterations in the chemical structure of nanomaterials. In contrast, photodynamic therapy employs photosensitive agents to produce ROS when exposed to light, facilitating drug release and enhancing the effectiveness of cell-killing mechanisms. Yan *et al.* synthesized dual photo/thermo-responsive micelles by hydrolyzing poly(methacrylamido-

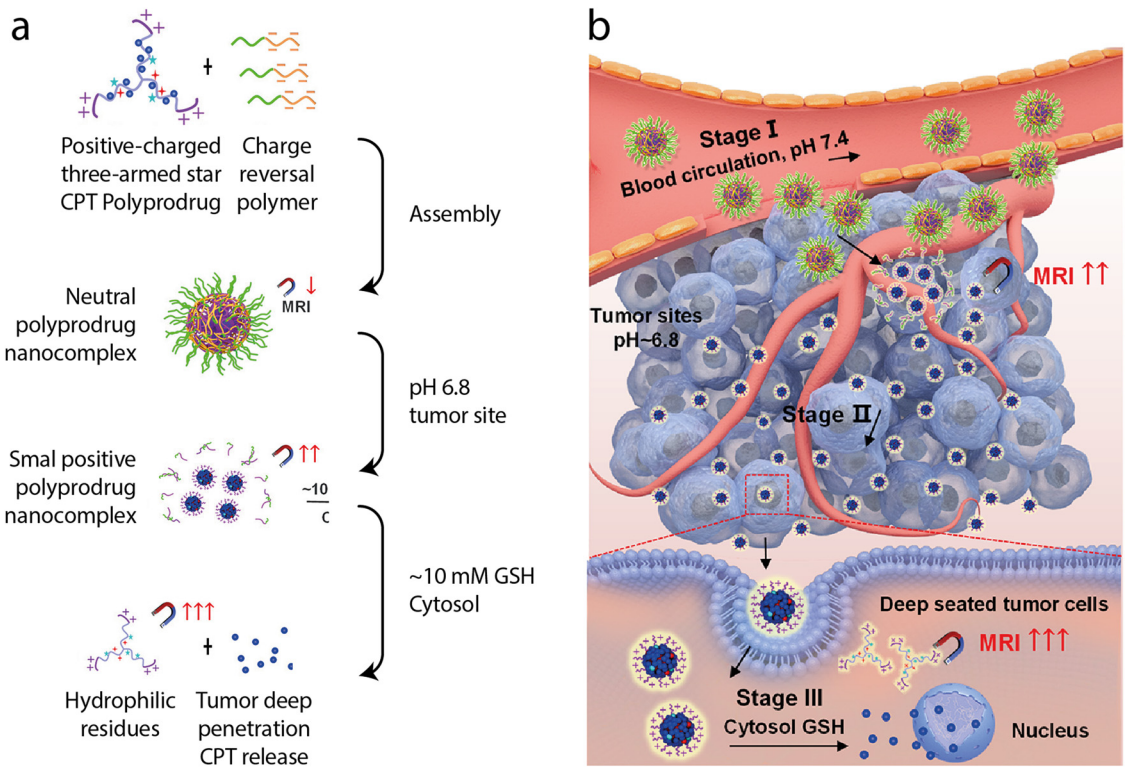

Figure 5: An example of a multi-responsive PM. (a) Different parts of nanocomplexes self-assemble in the aqueous environment. Low pH degrades the outer layer, and high levels of GSH could destroy the core and release the drug. Moreover, these nanocomplexes are labeled with a magnetic resonance imaging contrast agent that gives them theranostic properties. (b) The nanocomplex is stable in the normal pH of the circulatory system (stage I). In tumor tissue, low pH causes the degradation of the outer layer and the release of small positive NPs (stage II). Next NPs enter cancer cells, and high levels of GSH in cytosol promote NP degradation and release of loaded cargo (stage III). Adapted with permission from [221] (copyright 2020 American Chemical Society).

azobenzene) to obtain a random amphiphilic polymer (methacrylamido-azobenzene)ran-poly(2-hydroxyethyl acrylate) (PMAAAB-ran-PHEA), which comprises thermo-responsive PHEA hydrophilic moieties and photo-responsive hydrophobic PMAAAB moieties. The hydrophobicity of the micelle core changes upon UV and visible light irradiation, and with an increase in external temperature, there is a noticeable decrease in the hydrodynamic radius. Moreover, the temperature can regulate the size and dissolution capacity of the micelles [243].

Liu *et al.* synthesized a biodegradable anionic copolymer with side carboxylic groups named methoxy-poly (ethylene glycol)-*block*-poly(α-carboxyl-ɛcaprolactone). The synthesized samples demonstrated superparamagnetic behavior with an appropriate magnetic saturation value, proving their efficacy as a magnetically guided drug delivery system. Upon comparing the release of PTX/mPEG45-*b*-PCCL15@Fe_3O_4 and PTX/mPEG45-*b*-PCCL15, it was found that PTX/mPEG45-*b*-PCCL15@Fe_3O_4 exhibited reduced burst release due to enhanced hydrophobic interactions. They also found that increasing the molecular weight of the PEG fragment could further reduce the burst release and result in a sustained release. The release of PTX from the nanocomposites is faster at pH 6.5 than at pH 7.4, which is attributed to the protonation of carboxylic groups and PEG segments on the surface of the nanocomposites. Therefore, these nanocomposites exhibit a pH-responsive release pattern [244].

Dual targeting polymer micelles were generated through the self-assembly of camptothecin (CPT), which was chemically conjugated to monomethyl poly(ethylene glycol) (mPEG) *via* a redox-responsive linker and an enzyme-responsive copolymer. An enzyme-responsive copolymer was obtained by connecting hydrophobic PCL segments and hydrophilic PEG segments with azo bonds. It was observed that the amount of CPT release increased by 30% when the concentration of GSH was increased from 10 μM to 10 mM. As a result of the breaking of azo bonds and dissociation of micelles in the presence of 10 mM GSH and azoreductase, approximately 80% of CPT was released within 48 h. Zhang *et al.* demonstrated that PBA-PEG-Azo-PCL/mPEG-ss-CPT could achieve rapid intracellular release and active targeting for cancer therapy [245].

Although multi-responsive particles (PMs) hold significant promise for targeted drug delivery, there are several

obstacles to overcome in advancing their development. Formulating and synthesizing PMs that can effectively respond to multiple stimuli while maintaining stability, controlled release properties, and biocompatibility poses a substantial challenge. Achieving the optimal response to each stimulus is crucial for ensuring the precise and punctual release of the drug at the desired site. In addition, the clinical translation of multi-responsive PMs necessitates a thorough examination of their pharmacokinetics, toxicity, immunogenicity, scalability, and reproducibility. In addition, regulatory approval is a challenge, as there is no established framework or regulations for DDS with multi-responsive properties. A rigorous evaluation of the safety and efficacy of these PMs will be required to meet regulatory requirements and ensure their clinical viability. Furthermore, *in vivo* studies assessing the sensitivity of nanomicelles to pH/ROS have demonstrated that this model can be utilized for cancer treatment [246].

4 Conclusion

Given cancer's substantial effect on mortality rates, developing and applying new therapeutic approaches is essential in cancer treatment. DDS are crucial among established treatment modalities such as chemotherapy and radiotherapy. These systems facilitate the precise and regulated delivery of chemotherapy drugs to cancer cells. Smart PMs have emerged as a promising platform for drug delivery, responding to various internal and external stimuli. The utilization of smart PMs not only enhances drug efficacy but also mitigates toxicity. These systems regulate drug release by incorporating stimulus-responsive elements into NP structures. The targeted release mechanism of stimuli-responsive PMs allows them to accumulate in malignant tissues while minimizing their exposure to healthy tissues, thereby reducing adverse effects on healthy tissues and improving the efficacy of cancer treatment. Continuing research and development are essential for optimizing stimuli-responsive PMs, gaining a more profound comprehension of their behavior *in vivo*, and ensuring their safety and efficacy for clinical applications.

5 Future perspectives

Recent studies delve into the design of micelles responsive to specific biological stimuli in the TME. These stimuli-responsive micelles aim to enhance the efficacy of cancer therapies, particularly immunotherapies, by facilitating precise drug delivery to the target site. The TME's unique characteristics, such as acidity, high GSH concentration, hypoxia, overexpressed enzymes, and excessive ROS, can be leveraged by intelligent DDS to release drugs specifically into tumor tissues. For instance, stimuli-responsive nanoparticles can maintain stability under physiological conditions but can be triggered to release drugs rapidly in response to these unique TME characteristics. PMs show promise in cancer immunotherapy by effectively addressing challenges associated with conventional cancer immunotherapies. These micelles can respond to and remodel the TME, modulate immunosuppressive cells within the TME, enhance immune checkpoint inhibitors, utilize cancer vaccine platforms, modulate antigen presentation, manipulate engineered T cells, and target other components of the TME. Moreover, micelles have been employed to deliver specific drugs, like DOX, to tumor cells. For example, a mixed-micelle system composed of polyHis-*co*-phenylalanine-*b*-poly(PEG) and poly(L-lactic acid)-*b*-PEG-folate was used to reverse MDR in cancer. Additionally, the emergence of targeted PMs for siRNA treatment marks a significant advancement in pursuing safe and effective cancer therapy. These micelles, designed for gene silencing, show promise in inhibiting tumor growth in experimental cancer models, opening new avenues for personalized medicine. A recent study discusses using PMs self-assembled from amphiphilic block copolymers as promising carriers for cancer targeting. PMs have been reported for tumor-specific delivery of drugs and siRNA in response to overexpressed MMPs.

It should be highlighted that PMs have made significant strides in drug delivery applications, boasting a robust core–shell structure, kinetic stability, and the ability to solubilize hydrophobic drugs. They have been utilized in various DDS, including oral, parenteral, transdermal, and intranasal, as well as for tumor-targeted delivery. However, challenges remain, such as the instability of micelles in the physiological environment, limiting their effectiveness as drug carriers. Micelles tend to disassociate and prematurely release encapsulated drugs, reducing delivery efficacy and raising toxicity concerns. Efforts to enhance micelle stability have primarily focused on reducing the critical micelle-forming concentration and improving blood circulation. Despite increased targeted delivery methods for cancer therapeutics, only a small percentage of nanocarriers accumulate in high-EPR xenografted tumors, possibly due to physiological barriers and randomness in nanocarrier extravasation through the tumor vasculature.

One key area of focus for future studies involves the development of new compounds for use in micelles to improve their safety. This entails utilizing biocompatible and biodegradable materials in micelle construction to

minimize the chances of adverse reactions and long-term toxicity. Researchers are exploring materials like polymers, lipids, and peptides to enhance the safety of micelle-based DDS. For instance, PMs containing cisplatin have been created by forming a polymer–metal complex between cisplatin and poly(ethylene glycol)-poly(glutamic acid) block copolymers, which were then tested as a targeted drug delivery system for tumors. A novel PM system for PTX-loaded micelles has also been developed, demonstrating excellent biocompatibility and superior antitumor activity in mice with tumors. These promising results suggest the potential of PTX-loaded micelles as a safe and effective method for cancer therapy, providing a glimpse into the future of oncological treatment.

Moreover, ongoing research emphasizes the refinement of micelle formulations to achieve better distribution to targeted tumors, aiming to adjust the size, surface charge, and stability of micelles to prolong their circulation time in the bloodstream and improve their accumulation in tumor tissues through the EPR effect. Additionally, efforts are being made to incorporate targeting ligands onto the micelle surface, enabling precise identification and binding to cancer cells, thereby enhancing the accuracy of therapeutic payload delivery.

Even though promising findings are presented, the clinical implementation of NPs as a drug delivery platform encounters numerous obstacles. One of the primary challenges is the necessity of developing stable and reproducible PMs to ensure consistent drug release and therapeutic efficacy. Precise formulation and manufacturing of NPs are crucial for guaranteeing their uniformity and reliability. Incorporating new compounds into the structure of PMs can enhance their properties, including drug solubility, bioavailability, and circulation time. However, conducting systemic toxicology studies is essential to assess biocompatibility and safety, aiming to prevent potential toxicity and immunogenic reactions. Furthermore, comprehensive research is necessary to assess the long-term effects of these NPs and their potential accumulation in vital organs. Achieving optimal drug release kinetics entails selecting appropriate stimuli and fine-tuning their response rates. Additionally, consideration must be given to the potential development of drug resistance and the emergence of adaptive responses to PM interventions in order to achieve long-term efficacy.

Improving the efficiency of smart NPs in the future is conceivable. Designing multi-responsive and targeted NPs appears to be a promising approach, as they exhibit greater efficacy than single-stimulus and targeted NPs. Combining therapies can further enhance treatment efficacy by reducing the likelihood of drug resistance. The growing field of personalized medicine holds substantial potential for the future. Designing smart PMs based on the disease stage, as well as the genetic and physiological characteristics of the patient, is a promising avenue. Moreover, artificial intelligence (AI) is one of the fastest-growing fields, applicable to virtually any domain. AI approaches can be employed by researchers to design and optimize smart PMs and predict their responses to different environments. On the other hand, advancements in nanotechnology and materials science have enabled the design and synthesis of compounds with tailored properties for micelle formation. These advancements address current challenges in drug delivery, such as off-target effects and limited therapeutic efficacy. As our understanding of tumor biology and the tumor microenvironment deepens, the customization of micelles for specific cancer types and patient populations is expected to advance.

Finally, the field of stimuli-sensitive micelles is advancing, focusing on micelles responsive to specific biological stimuli in the TME. This responsive behavior could potentially customize drug release and distribution, offering a refined and targeted approach to cancer treatment. Progress in this area addresses the need for enhanced safety and precision in DDS. Therefore, despite promising results, multiple challenges should be addressed in facilitating the translation from bench to bedside.

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