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# Responsive Nanostructure for Targeted Drug Delivery

**Vaishali Pawar [1], Priyanka Maske [1], Amreen Khan [1,2], Arnab Ghosh [1], Roshan Keshari [2], Mahek Bhatt [1] and Rohit Srivastava [1,*]**

[1] Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Mumbai 400076, India
[2] Center for Research in Nanotechnology and Science, Indian Institute of Technology Bombay, Mumbai 400076, India
* Correspondence: rsrivasta@iitb.ac.in

**Abstract:** Currently, intelligent, responsive biomaterials have been widely explored, considering the fact that responsive biomaterials provide controlled and predictable results in various biomedical systems. Responsive nanostructures undergo reversible or irreversible changes in the presence of a stimulus, and that stimuli can be temperature, a magnetic field, ultrasound, pH, humidity, pressure, light, electric field, etc. Different types of stimuli being used in drug delivery shall be explained here. Recent research progress in the design, development and applications of biomaterials comprising responsive nanostructures is also described here. More emphasis will be given on the various nanostructures explored for the smart stimuli responsive drug delivery at the target site such as wound healing, cancer therapy, inflammation, and pain management in order to achieve the improved efficacy and sustainability with the lowest side effects. However, it is still a big challenge to develop well-defined responsive nanostructures with ordered output; thus, challenges faced during the design and development of these nanostructures shall also be included in this article. Clinical perspectives and applicability of the responsive nanostructures in the targeted drug delivery shall be discussed here.

**Keywords:** responsive nanostructure; target site delivery; wound healing; pain management; cancer therapy; inflammatory disease treatment; clinical perspectives



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## 1. Introduction

The main research goal in drug design has been synthesizing and developing innovative therapeutic agents with enhanced biological activity. Even though this is still a core area of study, the methods for administering these medications are increasingly receiving more focus [1]. The use of biodegradable polymers is expanding as customers become more concerned about environmental protection and climate change. Comparing biopolymers to common plastics derived from fossil fuels, the environment is less negatively impacted by biopolymers [2]. Nanotechnology is the development, fabrication, characterization, and use of devices and materials to create new nano-sized material, ideally between one and one hundred nanometres (nm) in size [2]. Through temporally regulated medication delivery, nanostructure (NS)-based carriers have the potential to revolutionize disease therapy [3]. The sustained release of toxic drugs selectively at intended places leads to fewer side effects, lower doses, higher compliance, and ultimately better patient outcomes [4]. The application of nanostructures in the transdermal and topical administration of medications is rapidly becoming more widespread [4]. For systemic implementations of the drug-loaded carriers, how to permit the release of the drug in a regulated manner remains a crucial concern despite the improvements in a higher concentration of the drug just at the target site and greater cellular absorption. It is anticipated that the carrier will remain stable and prevent drug leakage while at the same time blood circulates, but that it will quickly release the encapsulated drug once it has accumulated in the target areas [5,6].

There is a significant demand for medications to be transported to subcellular compartments in an effective manner precise exact spatial and temporal controls [6]. In order to accomplish these objectives, stimuli-responsive carriers based on the pathological or physiological circumstances at the sick sub-cellular organelles have been developed [7,8]. Many dynamic supramolecular systems have been created and can change their topologies and characteristics in response to environmental factors such as temperatures, illumination, pH, and redox potential to successfully kill tumor cells, many nanostructured delivery systems have been created recently [9]. However, the majority of these systems are still unable to target tumors appropriately, and their release of drug process is poorly managed, resulting in substantial side effects [10,11]. In biomedical applications, lipid-based systems have proven to be highly valuable as drug delivery platforms. Such delivery methods might be as straightforward as oil solutions or as intricate as complicated mixtures of lipids, surfactants, and co-surfactants [12,13]. Stimulus-electro-spun nanofibers with a diameter less than one thousand nanometres are the intelligent smart polymer fibers created by the electrospinning method that can respond to external stimuli by altering their physicochemical properties. Near-infrared (NIR)-responsive nanofibers offer a platform for cancer therapy in which the drug release profile can be obtained by the on-demand delivery of medications at the desired dose [14]. Nanofibers can play a crucial role in wound treatment as wean excellent great drug carrier for the skin cancer treatment cancer, missing qualities such as curing, managing the microenvironment around the wound to maintain enough hydration, and shielding the wound from any further harm [15]. Hydrogels are a type of soft substance that is composed of tiny molecules and polymers. Hydrogel is a potential material for a wide range of biomedical applications because its network can soak a huge number of biological substances to give a similar environment to living tissues [16]. Hydrogels that undergo structural or mechanical modifications in response to environmental cues/triggers are among the essential modifying and combining various gelators and crosslinking agents allows stimuli-responsive hydrogels that could be designed with features such as controlled gelation, disintegration, and stiffness change [17]. Thermoresponsive hydrogels are hydrogels that undergo structural and mechanical changes in response to changes in temperature. These thermosensitive polymers have a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST). Polymers having LCST often exhibit separation once the temperatures reach LCST and revert to a single phase when the temperatures drop below LCST. Unlike polymers having LCST, UCST polymers typically exhibit dissociation below UCST and revert to a single phase above UCST [18].

Lipid-based nanostructures can interact easily with tissue and cells because they have qualities with natural biological components. They can be supplied orally and are non-toxic and biodegradable as well. Lipid-based nanostructures are now particularly attractive for the delivery of antimicrobials due to these properties [19]. Lipid-based nanostructures, such as liposomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) nanoemulsions, have been produced. Such nanostructures can increase the bioavailability of poorly water-soluble as well as the transport of bioactive substances [20]. Polymeric nanostructures are among the most innovative non-invasive drug delivery methods. Its primary purpose is to deliver the therapeutic molecule, be it drugs, proteins, or nucleic acids, directly to the organ or tissue of interest. Several biocompatible synthetic polymers, including chitosan, polycaprolacand tone, polylactic acid, (PLA) are among the most commonly used polymers in the synthesis process [21]. Recent advances in protein-based nanostructures have revolutionized the era of nanomedicine. Protein nanoparticles have enhanced biocompatibility biodegradability, as well as surface modification potential. Proteins such as albumin, gelatin, zein, and soy protein can be used to synthesize these nanostructures [22]. Chitosan-based have several non-parenteral drug delivery applications the cancer therapy, gastrointestinal illnesses, lung diseases, cerebral drug delivery, and eye infections. Chitosan demonstrates low toxicity in both in vivo and in vitro studies. Chitosan serves as a permeation enhancer by loosening the epithelium's tight connections. Chitosan has both paracellular and transcellular drug delivery and forms a compound

with mucus via ionic or hydrogen bonding [23]. Polymer nanoparticles (PNPs) consist of polymeric nanospheres and nanocapsules. Molecules can either be adsorbed onto the surface of the sphere or contained inside the particle matrix. Polycaprolactone (PCL)-based PNPs garner increased interest and are extensively explored [24,25].

Bovine serum albumin (BSA), the most abundant soluble protein in the vascular system with numerous physiological activities, has been increasingly employed in protein-based nanoparticles [25]. For the administration of Doxorubicin, a stimuli-responsive method for delivery of drugs and regulated release has been created by engineering the BSA. Doxorubicin-loaded BSA nanoparticles demonstrated a significant capacity for drug loading. Experiments on in vitro drug release demonstrated that drug release was enhanced by acidity, showing that pH plays a significant role in the controlled release of drugs [26]. Gelatin is among the most useful natural biopolymers because of its biocompatibility, degradability, low price, and abundance of active groups for binding targeted molecules [27]. Crosslinking of GNPs seems necessary to provide gelatin with stability, form, and an increased in vivo circulation time. Numerous studies demonstrated that glutaraldehyde (GA) is an excellent crosslinker. Hydrophilic compounds can be successfully integrated into GNPs incubating the molecule with an aqueous gelatin medium prior to nanoparticle synthesis for sufficient time to facilitate drug–protein binding. Most of GNPs produced by the aforementioned techniques have mean diameters between 200 and 400 nm. Particle size substantially influences emulsion stability, drug entrapment efficacy, drug loathe ding, release of drugs and cellular uptake profile, etc. [27]. Few metabolites or biomolecules or stimuli used for response generation are stated in Table 1.

**Table 1.** Differences in the concentrations of metabolites/biomolecules/stimuli that can be used for stimuli responsiveness.

| Biomolecule/Metabolite/Stimuli | Physiological Concentration | Pathological Concentration | Reference |
|---|---|---|---|
| pH | pH of ~7.4 | extracellular pH of tumor tissues is between 6.0 and 7.0 | [28] |
| Temperature | ~37 °C | ~40–42 °C | [29] |
| ROS | Low to moderate levels | Elevated levels in Inflammation and various cancer. | [30] |
| Glutathione | Lower level of expression with similar intracellular concentrations and extracellular concentrations | ~2–10 μM in extracellular environment, ~2–10 mM in intracellular space. | [29] |
| Human Neutrophil Elastase | Lower level of expression | High expression in chronic respiratory disease | [31] |
| Aldose Reductase | Only present in diabetes target tissues | Its catalytic activity is crucial in a variety of inflammatory processes. In human malignancies such as liver, cervical, and ovarian, its gene is overexpressed. | [32] |

To transport small molecule drugs and nucleic acid cargo for treating cancer, liposomes have now been widely used. They are preferred carrier systems because they may be created in high drug/lipid concentrations by remote loading and are simple to construct in the size-controlled way [33]. To accomplish selective loading of the therapeutic drug, hydrophilic and amphiphilic molecules can be confined in the core while hydrophobic compounds can be segregated into the bilayer membrane of lipids. Pharmacodynamics and pharmacokinetics can be improved by liposomal compositions [34]. Additionally, the Warburg effect causes solid tumors to frequently have higher acidic microenvironments than healthy tissue, which can be seen as an advantage for tumor-specific delivery via a number of techniques. First, by employing molecular moieties with pKa values close to the tumor interstitial pH, pH-sensitive nanocarriers have been created [35,36]. Another often-

used internal trigger for the targeted release of medicines or genes is body temperature. To create stimuli-responsive carriers, it is essential to choose the stimuli that will alter the material's physicochemical properties the most significantly [37]. Since a variety of diseases have also been linked to an overproduction of Reactive oxygen species (ROS), ROS-responsive carriers may make it easier for drugs to be released at disease sites where ROS levels are high [38]. Certain enzymes have a great deal of potential as an internal trigger for controlled drug release because of their excellent specificity and selectivity [39]. The stimuli responsive drug delivery is a step towards achieving precision medicine. In recent decades, drug delivery research has centered on regulating and/or sustaining drug delivery, cutting dose frequency, and enhancing medication efficacy compared to traditional distribution [36]. Managing and modulating the pharmacodynamics, pharmacokinetics, aspecific toxicity, and immunogenicity, is the objective of targeted drug delivery [37]. The final objective is to increase therapy efficacy while decreasing negative effects. Targeted drug delivery systems are different from standard or conventional drug delivery systems in that they achieve site-specific drug release from a dosage form, whereas conventional DDSs rely on drug absorption across biological membranes [38].

In this article, more emphasis will be given on the various nanostructures explored for the smart stimuli responsive delivery at the target site such as wound healing, cancer therapy, inflammation, and pain management in order to achieve the improved efficacy and sustainability with the lowest side effects. However, it is still a big challenge to develop well-defined responsive nanostructures with ordered output; thus, challenges faced during the design and development of these nanostructures are also included in this article.

## 2. Design and Development of Biomaterials Comprising of Responsive Nanostructures

Nanostructures, including nanosurfaces, cylindrical nanotubes, and nanospheres are composed of materials resulting in final structures in the range of 1 nm to 100 nm or beyond in one dimension. These nanostructures are lab synthesized and possess a wide range of properties and thus can be used in a number of applications. These nanostructures can be stimuli responsive or non-responsive. The stimuli-responsive nanostructures perform their function as a response to an external stimulus; this includes, pH, enzyme, light, temperature, redox or multistimuli responsive nanostructures. The stimuli responsive nanostructures can be synthetic or natural. The natural polymer includes chitosan, cellulose, gelatin, albumin and the synthetic polymer includes, Pluronic F127, Poly(*N*-isopropylacrylamide), Poly(ethylene glycol) (PEG), Polyacrylic acid (PAA), Poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA) and poly(*N*,*N*-diethylaminoethyl methacrylate) (PDEAEMA). Nanostructures can be categorized based on the material used to prepare and its application. Nanostructures can be liposomes, dendrimers, quantum dots, metallic nanoparticles and fullerene as represented in Figure 1. These nanostructures are characterized by using Ultraviolet Visible spectroscopy, Photoluminescence, Dynamic Light Scattering (DLS), Transmission electron microscopes (TEM), Energy Dispersive X-ray Analysis (EDX), Selected area electron diffraction (SAED), Field emission scanning electron microscopy (FE-SEM), Atomic force microscopy (AFM), Nuclear magnetic resonance (NMR), X-ray Powder Diffraction (XRD), Raman spectroscopy, Fourier transform infrared spectroscopy (FTIR). The nanomaterials based on its intrinsic property and surface functionalization can be used in vast biomedical applications, including active and passive targeting [40]. Similar to the conventional therapeutic agents, the therapeutic or non-therapeutic nanomaterials can be introduced into the body via the respiratory tract, gastrointestinal tract, skin, blood and placenta and fetus via maternal exposure. As described earlier, the size of these nanostructures plays a crucial role in absorption, translocation, metabolism and excretion; smaller particles (<50 nm) are internalized at a faster rate compared to larger particles (~250 nm) [41]. Similar to the conventional drugs, the nanomaterials can reach the site of action directly or via body fluids. The fundamental phenomenon for cellular uptake of the nanomaterials is endocytosis [42]

including clathrin- and caveolin-mediated pathways [43]. The nanomaterial can also be internalized by pinocytosis [44]. Once into the cell, the nanomaterials are internalized in an endosome, which then fuses with the lysosomes wherein the particles undergo hydrolysis by enzymes. The positively charged particles are more efficiently internalized compared to neutral or negatively charged particles [45]. The nanomaterials can pose systemic toxicity; thus, deciphering the therapeutic dose is highly crucial. The main objective of the stimuli-responsive nanostructure and its application in a drug delivery system is for creating the nanostructures with enhanced safety and efficacy. These nanostructures are constructed for optimum delivery of active drugs at the site of action and thus their sizes are very crucial. The liposomes are derived from phospholipids which are biological in origin and thus these are easily available for respective function in vivo; hence, liposomes are the favored choice in drug delivery for highly sensitive drugs such as anti-cancerous drugs. The content of phospholipids including cholesterol if varied does not significantly affect the tissue distribution, therapeutic properties of the drug or in vivo metabolism [46]. The metallic nanostructures have various sizes and shapes; thus, their function and characteristics can vary based on the size and surface functionalization. Thus, the in vivo and in vitro biocompatibility and toxicity data of metallic nano-composites suggest that these can be safely used in biological systems and are metabolically cleared from the system [47].

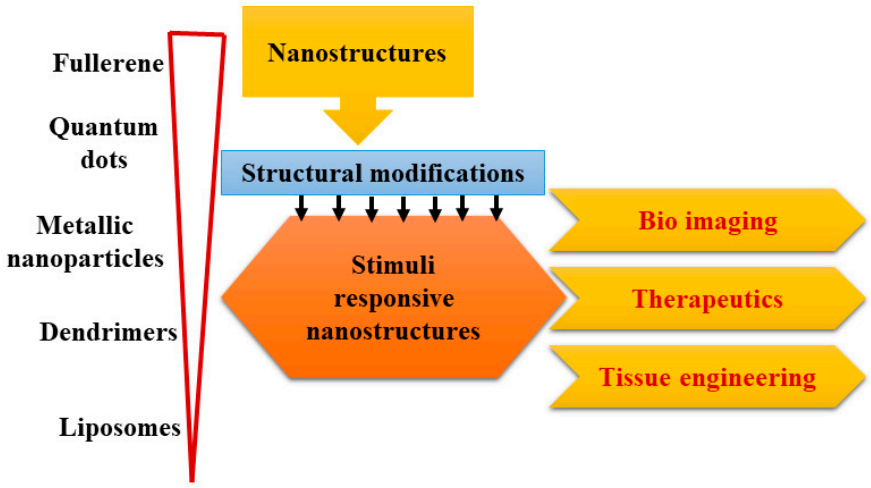


**Figure 1.** Different stimuli responsive nanostructures.

### *2.1. Liposomes*

Liposomes are vesicles mimicking the biological lipid bilayer, these synthesized from natural phospholipids. As liposomes mimic the biological membrane; thus, these are an ideal candidate as a nano-drug carrier [33]. Generally, liposomes are prepared by the solvent evaporation method. The lipids are then re-suspended in aqueous media and purified by filtration or sonication. The intended drugs are added to the liposomes via passive or active loading techniques, these include sonication, French pressure cell extrusion, freeze–thaw technique, handshaking, micro-emulsification, membrane extrusion, dried reconstituted vesicles [48,49]. The application of surface-modified gold nanoparticles with liposomes have been explored in doxycycline antibiotic delivery for treating *Helicobacter pylori* bacterial infection. The gold nanoparticle surface modified with chitosan has been used to augment the drug release from liposomes in the gastric environment. In the gastric pH of the stomach, the liposomes are constituted of lipid moieties which can be degraded in the acidic environment; hence, initially gold nanoparticles were surface modified with chitosan, which were then further adsorbed on the liposomes' surface. The pH-responsive liposomes were prepared using hydrogenated L-α-phosphatidylcholine (Egg PC) and 1,2-dioleoyl-*sn*-glycero-3-phosphate (sodium salt) (DOPA) which possess a more negative charge. Under the gastric pH of 1.2–7.4, the gold nanoparticle surface modified with chitosan initially protects the liposomes in the acidic pH; however, as the liposomes travels

in the lower parts of the stomach where the pH is more and where the *H. pylori* resides, the active liposomes then releases the drug doxycycline precisely at the site of action. Thus, the results demonstrate that at the acidic pH the gold nanoparticles modified with chitosan remains attached to the liposomes; however, at a neutral pH these modified gold nanoparticles detach from the liposome surface to facilitate the drug release directly where the *H. pylori* resides [50].

### *2.2. Dendrimers*

Branched polymeric synthetic macromolecules which are organized in a symmetrical manner [51]. Dendrimers are well-chosen candidates for pharmacokinetics and pharmacodynamics models due to its enhanced monodispersity and solubility [52]. Dendrimer synthesis involves molecular and polymer chemistry. Linear, cross-linked, and branched macromolecular architect are used in the synthesis of dendrimers [53]. Dendrimers are prepared by a cascade of divergent or a convergent method. In divergent method, initially a reaction between the core molecule and monomers leads to the synthesis of one reactive and two dormant groups; thus, generating a first-generation dendrimer. Further, the periphery of molecules is activated by the monomers. In the case of the convergent method, the dendrimers are synthesized from exterior, i.e., starting from a molecular assembly which becomes the outmost structure of the dendrimer, hence, keeping the final generation of the dendrimers as fixed [53,54]. Dendrimers also have a vast array of applications; these can be single stimuli or multi-stimuli dendrimer based on the surface modification. Photothermal therapy is a leading field in oncology, wherein the cancer cell death is induced by heat generation by exposing to near-infrared (NIR) light [55]. The application of dendrimers has also been explored in photothermogenic and thermosensitive dendrimer nanoplatforms. A thermosensitive polyamidoamine G4 dendrimer modified with acetylated valine-proline-glycine-valine-glycine repeats VPGVG and (VPGVG)2 thus forming elastin-like peptides (ELP1 and 2, respectively) at the periphery were constructed for dual stimuli responsive nanoparticles. Taken ahead, the gold nanoparticles modified by dendrimer-nanotemplated method for photothermogenic dendrimer were constructed. These gold nanoparticles were loaded with ELP1 and ELP2, which demonstrated a phase transition temperature between 55 °C and 35 °C. The research group demonstrated that, gold nanoparticles loaded with PEGylated dendrimer and gold nanoparticle loaded with ELP2 showed free association with cells and also induced efficient photocytotoxicity at 37 °C, suggesting that the modified dendrimers can be used in photothermal therapy [56]. Furthermore, dendrimers with dual stimuli such as pH and temperature for monitoring drug loading and release due to its photoluminescence property have also been researched. The Poly(β-aminoester) dendrimers which display pH and temperature response as the surface groups of the dendrimer are modified to possess dual response. The drug can be delivered at physiological pH and temperature; interestingly, these modified dendrimers can release drugs intracellularly as well, like in the lysosome. Taken together, the surface-modified dendrimers can be an excellent choice in drug delivery as they have pH sensitivity, slow and steady drug release at body temperature and its photoluminescence provides drug monitoring [57].

### *2.3. Quantum Dots*

Quantum dots (QDs) are semiconductor materials of 2–10 nm diameters in range. The QDs possess unique electronic properties and have high surface-to-volume ratios. The QDs produce unique colors based on the size of the particles [58,59]. The QDs can be prepared by a top-down method by narrowing down the bulk material to smaller parts and thus reducing their size. Hydrothermal cutting involving oxidation followed by exposure to high temperature and pressure is conducted for QDs synthesis. Other techniques such as oxidative cleavage, solvothermal cutting, microwave-assisted irradiation, and an electrochemical cleavage of precursors, laser ablation with laser irradiation, arc discharge and electron-beam lithography can also be used. QDs can be prepared by a bottom-up method wherein self-assembled particles are formed by the deposition of a smaller particle.

The bottom-up approach involves precursor pyrolysis, hydrothermal aggregation, reverse micelle synthesis, microwave-assisted methods, hydrothermal and solvothermal routes for the preparation of the QDs [60]. Cancer biology is a daunting field of research as the conventional means of therapies possess high risk and adverse side effects. The idea of QDs can be applied in drug delivery in cancer treatment by exploring the modification using stimuli responsive nature. ZnO with a biodegradable polymer polyacrylamide loaded with doxorubicin hydrochloride (DOX) were used to construct 3 nm sized ZnO@polymer–DOX nanocomposite. The nanocomposite showed a pH responsive behavior for drug release in the cancer cells [61].

### *2.4. Fullerene*

Fullerenes are the allotrope of carbon where molecules of carbon are connected by single and double bonds resulting in fully or partially closed cage-like structure. These structures can form a hollow sphere, be an ellipsoid, tube, cylindrical such as carbon nanotubes, or any other different shape or size [62]. In the medical field these fullerenes are used as light-activated antimicrobial agents, MRI contrast agents, X-ray imaging contrast agents, photodynamic therapy and drug and gene delivery [63]. Fullerene can be prepared by the pulse arc discharge method; the process involves a high temperature along with carbon electrodes at a high voltage of 1.1 kV, 22 A and 50–300 s duration. Further, the annealing is carried out by a buffer gas passed via a quartz tube to form fullerenes. The tube temperature is maintained between 25–1000 °C and the buffer gas is maintained at 300 $cm^3/s$ with 500 Torr pressure. The fullerenes can be characterized and detected by high performance liquid chromatography (HPLC) [64].

### *2.5. Metallic Nanoparticles*

Metal nanoparticles as stimuli responsive nanostructures provides a wide range of applications in controlled drugs or biomolecule release. The metal nanoparticles provide a greater number of applications such as biocompatibility, reduced toxicity, and improved efficiency in permeation. There can be a number of triggers such as pH change, ion or ATP concentration, miRNA, redox reaction or physical stimuli such as light or heat for release from nanoparticles [65]. These nanoparticles can be surface modified for release by certain triggers or by another approach these nanoparticles can be prepared with structural information for stimuli responsive distortion resulting in release of the drug/biomolecule. The metallic nanoparticles can be synthesized by a top down or bottom-up method. The top-down method includes mechanical milling, laser ablation, and thermal. In the case of the bottom-up method, the nanoparticles are synthesized from smaller molecules, the nanostructured building blocks are initially produced and further assembled as the final nanoparticle. The bottom-up approach includes solid state method and liquid state synthesis method [65–67]. Mesoporous silica nanoparticles (MSNs) for controlled drug delivery functionalizing it with polylactic acid (PLA) has been used as an anti-microbial agent. Levofloxacin, which is an anti-fungal drug was encapsulated on the MSNs, functionalized with PLA. The conjugation of drug with PLA functionalized MSN showed significant zone of inhibition in *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans* and *Aspergillus niger*. The rapid release of the drug for achieving the anti-fungal and anti-bacterial activity is due to the pH as a stimuli response. Thus, the documented results show functionalized nanocarriers with surface modification can be used directly on a targeted cell with improved anti-microbial potency and decreased side effects. The application of metallic nanoparticle modified for stimuli responsive nanostructure is also explored for drug release using temperature stimuli. The zirconium (Zr)-based metal–organic frameworks containing linear 2-amino-1,4-benzenedicarboxylate (BDC-$NH_2$) ligands and $Zr_6O_4(OH)_4$ clusters had been constructed for drug release in the presence of Zn ion [68].

## 3. Applications of Responsive Nanostructures in Various Clinical Applications

### *3.1. Cancer Therapy*

#### 3.1.1. External Stimuli

The development of theranostics has been more efficiently explored with stimuli-responsive nanocarrier systems. One category of such response system falls under external stimuli, which has significantly opened the scope for advancements such as an era of personalized medicine with its unique characteristics. For better control, feasibility and assurance of cancer-targeted delivery, manual control is preferred. The suitability of external stimuli henceforth becomes important [69].

Photo Responsive

In cancer therapy, photothermal and photodynamic light-responsive stimulation is mostly employed by using polymeric nanocarriers either individually or in combination with other therapies. Indeed, various light-responsive therapies have been strategized for anticancer activity. Infrared light-responsive polymeric nanoparticles having selenium-inserted copolymer have showed rapid dissociation upon interaction with reactive oxygen species (ROS). The drug release as a result of selenium oxidation upon irradiation caused synergistic effects by tumor ablation through efficient cytoplasmic delivery [70]. In a study done by Li and group, chitosan-coated gold/gold sulfide nanoparticles were used to treat cancer. The results suggested the ablation of cancer cells upon near-infrared irradiation of accommodated gold nanoparticles [71]. A similar stimulus was used by another research group with an organic and inorganic hybrid system of titanium carbide nanoparticles coated on pluronic F127 hydrogel. During the study, laser irradiation caused nanoparticles to produce sufficient heat for tumor ablation by increasing local temperature [72]. Another response to light can be approached by designing organic molecules undergoing photoactivation. Photocages are one-time activators with cleavage groups that breaks under light irradiation whereas photoswitches can convert reversibly with their ability to be activated multiple times. However, different factors determine the efficiency of photoswitching as side reactions, dimerization and extent of isomerization of the molecule may regulate their thermodynamic stability. Photoisomerization quantum yield is also an indicator of photoswitchability with photoisomerization process [73].

In a work, quinazoline derivatives were developed to explore their photochemical properties against human epidermoid carcinoma cells-A431. The antiproliferative action of these compounds was found as a result of light-induced isomerization exhibiting response as an effective anticancer compound and scaffold development [74].

Photopharmacology is a dynamic field to assist in revealing the role and application of ligands involving light. The approach used deals with the deactivation of ligand through photocages for a short time. Upon light irradiation, the chemical bonds are broken between the biologically active molecules and protecting group of the photocage breaks. This uncaging event leads to spatiotemporal structural changes, supporting to review protein response. One such study on knowing the structural basis of light-induced inhibitors affecting biological activity that can help to tune the potency was performed by Valentina and group [75]. The crystal analysis on two pharmacologically active agents, p-OMe-azo-TBOA (photoswitch) and ONB-hydroxyaspartate was carried out to evaluate their binding affinity with glutamate membrane transporter analogue [75]. Many other approaches are being researched to facilitate the clinical use of photocages and photoswitches [76].

Thermal Responsive

Approach for thermal responsive nanocarrier design causes thermosensitive drug carrier agents to generate heat for burst release of payload such as polypyrrole-based polymer [77]. A high temperature of nearly 44 °C helps to get rid of cancer cells by inducing localized hyperthermia. The enlarging blood vessels create holes in tumor cell membrane facilitating the anti-tumor drug delivery property of nanocarrier [78]. Li and group studied the release of doxorubicin encapsulated in pegylated liposome. The thermosensitive liposome produced mild hyperthermia, enough to show anticancer activity under thermal response with a 42 °C temperature [79]. In another study, the PNIPAM temperature-responsive polymer in conjugation with poly(fluorene-*co*-vinylene) was used to deliver doxorubicin with a controlled release profile showing a thermal response. The scheme has been presented in Figure 2. The nanocarrier system also generated ROS upon white light irradiation making the nanocarrier multifunctional and effective for anticancer treatment [80].

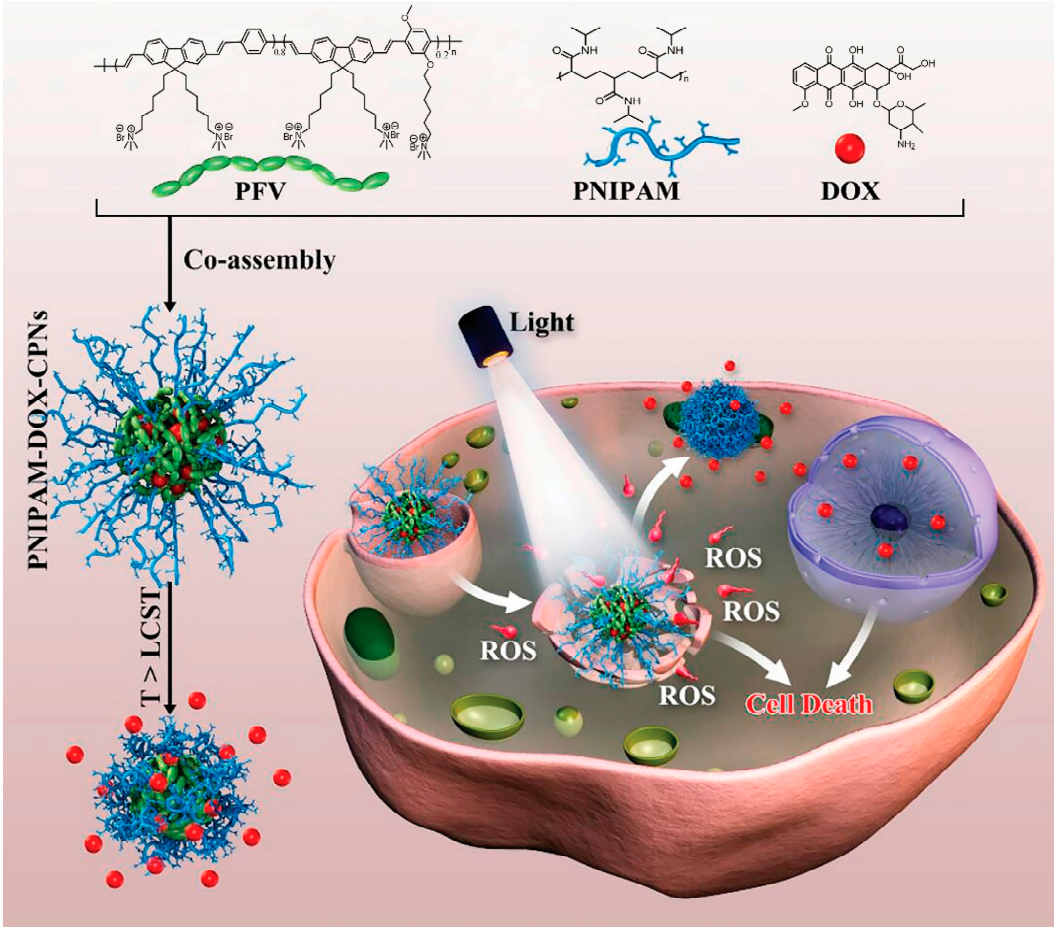


**Figure 2.** Stimuli responsive nanoparticle drug release upon thermal stimulation of thermosensitive polymer. Reprinted (adapted) with permission from ref. [80]. Copyright 2019, American Chemical Society.

Magnetic Field Responsive

The applied magnetic field helps the anticancer drug to accumulate in the tumor site retaining prolonged circulation time. Ha and group synthesized and studied multifunctional iron oxide nanoparticles for the release of doxorubicin. A generation of sufficient heat was reported with an effective drug release under magnetic field from the alginate shell with folate attaching group [81]. Iron oxide magnetic nanoparticles functionalized with polyethylene glycol 600 diacid indicated hyperthermia due to their magnetic prop-

erties. In a similar experiment, the radiolabeled form also turned out to have sufficient agglomeration and theranostic properties under an external magnetic field [82].

Ultrasound Responsive

The ultrasound-responsive thermal effect causes the transition of acoustic to thermal energy. Similar to thermoresponsive cancer therapy behavior, hyperthermia contributes to abnormal permeabilization of the blood vessels of the tumor [83]. In a study, pegylated liposome modified with transferrin and loaded with calcein was synthesized and designed to respond to ultrasound. A low frequency of 20 kHz was employed and calcein release was studied. The therapeutic encapsulation was found to be an effective drug delivery system with triggered release of calcein [84]. A similar anticancer agent doxorubicin release was evaluated with estrone synthesized liposome-encapsulated drug with cyanuric chloride as a linker acting against estrogen receptor. The nanocarrier showed a good response under the trigger by ultrasound frequency with better uptake and activity on human breast adenocarcinoma Metastatic Breast 231 (MDA-MB-231) cells than on human metastatic breast adenocarcinoma epithelial Michigan Cancer Foundation-7 (MFC-7) cells [85].

3.1.2. Internal Responsive

Internal stimuli have been known for their safe and effective drug delivery for cancer treatment. The difference in pH, temperature, reactive oxygen species, etc., in tumor microenvironment occur naturally and are being extensively used for better nanocarrier outcomes to avoid no external stimuli requirement and cost-effective reach [86].

pH Responsive

Nanomedicine design with pH-responsive carriers deals majorly with two phenomena for drug release in cancer cells. The extracellular environment of the tumor and lysosomes or endosomal having a quite acidic pH [87]. Yao et al. reported pH-responsive nanocarrier with poly(2-(diisopropylamino)ethylmethacrylate) polymer, lipid-poly(ethylene glycol) and nanocarrier surface with RGD peptide. The triggered response for anticancer activity was observed in endosomal pH to inhibit the tumor [88]. In another study, polylactic-*co*-glycolic acid (PLGA) was covalently surfaced by crosslinked serum protein to form a shell and was loaded with the drug. Acidity triggered rational membrane peptide to internalize the nanocarrier and released drug under intracellular conditions producing anticancer effect [89]. Another pH-responsive nanocarrier was designed with carboxymethylated hydroxypropyl chitosan for effective delivery of doxorubicin. The amphiphilic micelles could self-assemble to show a sustained and pH-dependent drug release profile [90]. One research group designed a triblock copolymer mPEG-*b*-PGCA-*b*-PGTA to deliver nucleotide and drug through pH-responsive linkage leading to synergistic anticancer effect. The dynamic covalent conjugation gave a stable platform for the delivery of both the active moieties to show regulated release [91]. A dual pH-responsive targeted drug delivery nanoparticle-based system was synthesized to promote its nuclei internalization. Lysine residue was amidated to β carboxylic amide providing micelle negative charge with affinity to endo/lysosomes acidic environment. The peptide used for nuclei targeting was further conjugated on polypeptide for complete antitumor effect [92].

Redox Responsive

Inhibition of ROS utilizing antioxidants can stimulate apoptosis resulting in potential therapeutic activity. In particular, with major redox-responsive cancer therapies, the reducing agent GSH breaks the disulfide bonds of nanocarriers causing controlled drug release [93]. To study redox potential responsive nanocarrier, one research group synthesized mesoporous silica nanoparticles and decorated it with collagen on the nanoparticle surface. Further lactobionic acid was attached for targeting of nanoparticles. The redox stimuli helped to break the disulfide bond and release the drug from nanoparticles [94]. Another study on anti-carbonic anhydrase IX antibody (A-CAIX Ab) conjugated on mesoporous

silica nanoparticles (MSNs) by disulfide linkage was conducted and exhibited cleavage of glutathione as a result of response to redox stimuli. Internalization of nanoparticle and presence of glutathione assisted in bond cleavage [95]. Peptides are also being incorporated for designing targeted redox responsive nanostructures effectively. Cyclic RGD (Arginine-Glycine-Aspartic acid) peptide ligand decorated core-crosslinked polyplex micelle loading therapeutic plasmid DNA showed efficient tumor growth regression with the aid of ligand for $\alpha$ v$\beta$ 3 and $\alpha$ v$\beta$ 5 integrin-mediated uptake and intracellular glutathione-responsive disulfide crosslinks for the smooth release of cargo [96,97].

### Enzyme Responsive

Enzyme-responsive release includes modification of nanocarriers that are sensitive towards biocatalytic reactions such that overexpressing enzymes can assist to release drug in cancer cells [98]. A research group studied the effect of enzymatic cleavage by designing and characterizing MSNs with CD44 and mitochondrial targeting properties. The nanocarrier system had doxorubicin encapsulation and a hyaluronic acid molecule to ensure targeted drug delivery. The hyaluronidase overexpression helped to cleave the hyaluronic acid and showed effective anticancer drug release from the degrading nanocarrier system [99]. A drug delivery system with doxorubicin drug was conjugated on dendrimer by a peptide to respond to the enzymatic stimuli. The peptide bond cleavage turned to be important for drug delivery of doxorubicin from the conjugated nanocarrier for effective anticancer activity [100]. A few peptide dendrimers conjugated with drug have also been studied for an enzymatic response. A nanoparticle system consisting of a doxorubicin drug was conjugated to mPEGylated peptidedendron through a linker which gets cleaved by the GFLG enzyme and was synthesized and characterized. The therapeutic nanoparticle has potential applications for targeting breast cancer [101].

### Hypoxia Responsive

Angiogenic signals lead to disorganized and rapidly growing blood vessels by a vascular endothelial growth factor explaining the importance of hypoxia in cancer progression and solid tumor metastasis [102,103] Reduced partial pressure in cancer vicinity helps to trigger targeted drug delivery. Many novel approaches have been strategies to treat hypoxic tumors by raising the oxygen level or by interfering with the hypoxia-induced pathways. A polymer synthesized with the hydrophobic small molecule attached to the side chain of methoxy poly(ethylene glycol)-*b*-poly($\gamma$-propargyl-L-glutamate) copolymer was used to assess the delivery of doxorubicin from its nanocarrier system. The doxorubicin was easily internalized and released in the hypoxic environment showing good anticancer treatment regime for a hypoxia tumor [104]. In a study, diblock polymer with polyethylene glycol and poly[glutamic acid (3-(2-nitro-imidazolyl)-propyl)] self-assembled to form hypoxia-responsive micelles. The controlled release of doxorubicin was studied under hypoxic conditions as a potential anticancer nanocarrier [105].

### Combinational Stimuli-Responsive

The response of a nanocarrier towards multiresponsive stimuli allows enhanced anticancer treatment with high drug payload and better control over the drug release profile [106]. Table 2 suggests combinational stimuli-responsive nanocarrier drug delivery systems used in cancer therapy.

**Table 2.** Combinational stimuli-responsive nanocarriers with their effective outcomes.

| S. No. | Stimuli | Nanocarrier System | Mechanism/Response | Reference |
|---|---|---|---|---|
| 1. | pH, temperature | PNIPAM-Nile red-oil soluble fluorescent green | Independent release of molecules with selectivity, multicompartment microcapsules with programmed release | [107] |
| 2. | Near-infrared, nitric oxide | PpRE@PEG-PpIX nanoparticles | Increase in temperature and intracellular internalization to inhibit cancer cells. | [108] |
| 3. | pH, near-infrared | g-$C_3N_4$ and doxorubicin encapsulated $MnO_2$ nanodots | Release of encapsulated drug in acidic environment, elevated oxygen level for effective anticancer activity | [109] |
| 4. | Infrared, radiofrequency | TR-NDA Porous silicon nanoparticles | Trigger the release of encapsulated drug by collapsing the polymeric chain | [110] |
| 5. | pH, enzyme | TLR7/8 agonist conjugated nanovaccine | Receptor signaling activation, dendritic cell maturation, enhance cellular immunity | [67] |

### *3.2. Pain Management*

Drug release from nanostructures is the most well-known studied triggered behavior based on stimuli-responsive nanomaterials for biomedical applications. Some nanoparticle used for pain relief are shown in Figure 3. Transdermal drug delivery system (TDDS) is a prominent topic for controlled drug delivery systems [111]. Poly *N*-vinyl caprolactum (PNVCL) on-demand TDDS patch has been used for the pain management of osteoarthritis and rheumatoid arthritis [112]. Chitosan-*g*-PNVCL (CP gel) is used transdermally in a pH and temperature-dependent manner to release drugs acetamidophenol and etoricoxib [113]. Ultrasound-responsive theranostics nanomaterials have been developed to control pain management. Sonodynamic therapy has been used to treat canine cancers chondrosarcoma, osteosarcoma, hepatocellular cancer, and prostate cancer using NC-6300 micelles filled with epirubicin. The dog showed reduced tumor size within two weeks of the therapy and significantly lower pain [114]. The ultrasound-induced vaporization of Nanoemulsion also increases the delivery of drug cargo into the skin to decrease pain [115]. For instance, Paulina D et al. have designed pH-responsive polymeric nanoparticles for pain management via inhibiting the endosomal signaling events. The nanoparticle was designed so that the chronic pain substance P and neurokinin receptor redistribute from the plasma membrane and reach acidified endosomes where it signals to maintain pain. Therefore, the neurokinin receptor provides a significant target for pain relief. So, pH-responsive nanoparticles were designed to enter the cells via clathrin and dynamin-dependent pathway endocytosis and accumulate in neurokinin receptors to encounter pain relief. An in vivo assay was carried out in rodents via encapsulating FDA-approved neurokinin receptor antagonist, i.e., aprepitant, which showed that it inhibits the substance P-induced activation of spinal neurons and thus prevents transmission [116]. Some recent examples of stimuli-responsive drug delivery systems are light-activated drug delivery systems such as arthritis, chronic wounds and joint dysfunction. Light responsive stimuli for pain management are stated in Table 3. pH-sensitive niosomes loaded with Ibuprofen have shown antinociceptive effects on acute and chronic mouse models for pain. This promising result shows that with further development of the nanocarrier formulation, it can be further used in humans for pain management [117]. Glucose responsive Microneedles (MNs) are suitable for delivering anti-diabetic drugs. Microneedles have drawn a lot of attention because of many advantages including pain free drug delivery, least invasive, self-administered, etc. Therefore, glucose-responsive MN patches are developed which contains glucose-responsive vesicles. The study shows that these MN patches regulates glucose levels in a simple, safe and pain-free manner. Although Microneedle patches have great advantages, but it has certain drawbacks too such as trypanophobia. Interstitial fluid (ISF) has many biomarkers and its concentration in blood can be used to correlate

several levels of molecules in the blood [118]. In view of this, novel MN is encapsulated with specific photonic system (PhC) barcodes that detects biomarkers from ISF. These MNs can detect macromolecules that can detect cancers and other diseases [118,119]. PH and temperature-dependent responsive bionanomaterial consisting of Chitosan with Lidocaine (anesthetic drug) and nano-ferrite to form drug-delivery system for pain relief is efficient [120].

**Table 3.** Light-activated drug delivery system for pain management.

| Drug | Photosensitizer | Trigger | Nanometer | Effect | Reference |
|---|---|---|---|---|---|
| Bupivacaine | Copolymer oligo (ethylene glycol) methyl ether methacrylate (OEGMA) and di (ethylene glycol) methyl ether methacrylate coupled to copper sulfide NPs | NIR light | 808 nm | Controlled Release | [121] |
| Lidocaine | PCL MN loading lanthanum hexaboride nanoparticles | NIR light | 808 nm | Lidocaine blood levels (15–20 ng/mL) after each irradiation | [122] |
| Tetrodotoxin | Liposome loading the photosensitizer | NIR light | 730 nm | Sciatic nerve blockade | [123] |
| Tetrodotoxin +Dexmedetomidine | Liposome tethered with gold nanorods | NIR light | 808 nm | Sciatic nerve blockade | [124] |
| Tetrodotoxin | Liposome tethered with gold nanorods and loading the photosensitizer | NIR light | 730 nm | Sciatic nerve blockade | [125] |

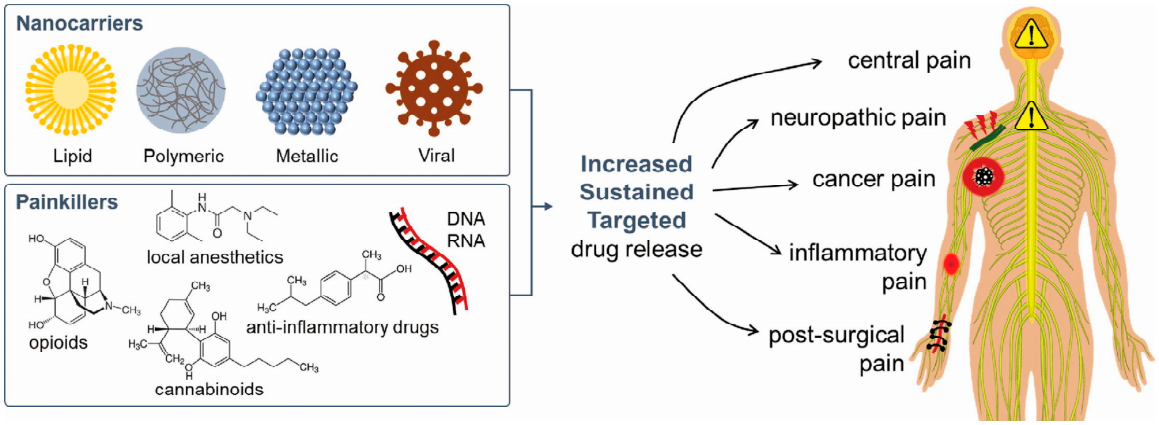


**Figure 3.** Nanoparticles for pain relief. Design considerations for analgesic nanoparticulate drug delivery systems include the type and location of pain (**right**), types of nanocarriers composition (**top left**), types of painkillers (**lower left**). Adapted with permission from ref. [126]. Copyright 2022, Elsevier.

### *3.3. Inflammatory Disease*

The management of inflammatory disease has been complex via pharmaceutical therapeutics due to low bioavailability, low efficacy of anti-arthritic agents viz. low cell permeability, water solubility, random distribution in vivo to the target site and unregulated drug degradation before reaching the target sites. In this context, stimuli-responsive drug delivery systems are considered very specific and impart targeted delivery. Few multifunctional nanomaterials are presented in Table 4. Stimuli-responsive nanocarriers are specially designed so that the core area contains therapeutic agents and a hydrophobic drug-loaded shell containing stimulus-responsive polymer, which is very sensitive to various endogenous and exogenous stimuli [127]. The TG-18 hydrogel has enzymes

such as MMPs, protease, etc., that tunes in the enzyme-responsive drug delivery material for targeted drug release at the site for inflammatory arthritis [128]. Some natural product based nanomedicines for inflammatory disease have been described in Figure 4. For inflammatory disorder, stimuli-responsive drug delivery carriers are initiated by multiple internal and external factors via different mechanisms such as specific protonation, hydrolytic cleavage, molecular or supramolecular conformational changes, etc. [129]. It can be designed in various architectures and applied for sustained or controlled release, offering excellent materials flexibility via stimuli-responsive to inflammation. For example, Zimeng Li et al. synthesized engineered hydrogel derived from nanoparticles, which produces a response under an acidic environment both physiologically and pathologically. These nanoparticles were prepared from the hydrophobic pH-responsive cyclodextrin and hydrophilic guest macromolecule. This nanoparticle-derived hydrogel was intended for oral delivery, which can coat the stomach by generating a hydrogel barrier on the mucosa, which can function as a responsive and transformable nano vehicle for various therapeutic agents for sustained and triggered release, thereby can be used for the treatment of different inflammatory disorder [130]. Stimuli responsive fluorogenic prodrug for the delivery of NSAID Diclofenac was developed which turns on in NRI fluorescence. This strategy enables DCl-ROS in cancer cells to inhibit COX-2 in the inflamed macrophage cells that slowly releases drug in the cellular medium. In the future, this may help to target more inflammatory diseases and it will be feasible and non-invasive [131]. Anionic liposomes containing phosphatidylethanolamine have antisense oligonucleotides which is released at lower pH in the body to treat viral infections, cancer and many inflammatory diseases [132]. Batrakova et al. developed an exosome-based delivery system to treat Parkinson's disease. These exosomes were reformed with saponin which formed molecules with sustained release and had catalase preservation against proteases degradation which is used to treat inflammatory and neurodegenerative diseases [133]. A polymeric prodrug of polyvanillin oxalate (PVO) having vanillin was designed. This PVO was molecularly modified to release vanillin in acidic pH and presence of $H_2O_2$ to treat ROS-related inflammatory diseases [134]. Vancomycin is used as an inflammatory therapeutic drug which is responsive to dual stimuli of temperature and pH [135]. Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease which can affect the entire GI tract. Therefore, Li and his co-workers developed oxidatively sensitive dextran (OxiDEX) that has Chitosan in the exterior and is additionally encapsulated by pH sensitive hydroxypropyl methylcellulose acetate succinate (HPMCAS). Rifampicin was further used because it is stable in the upper GI tract and HPMCAS is cleaved in the intestine to release nanodrug. When ROS levels are triggered, Rifampicin is released [136].

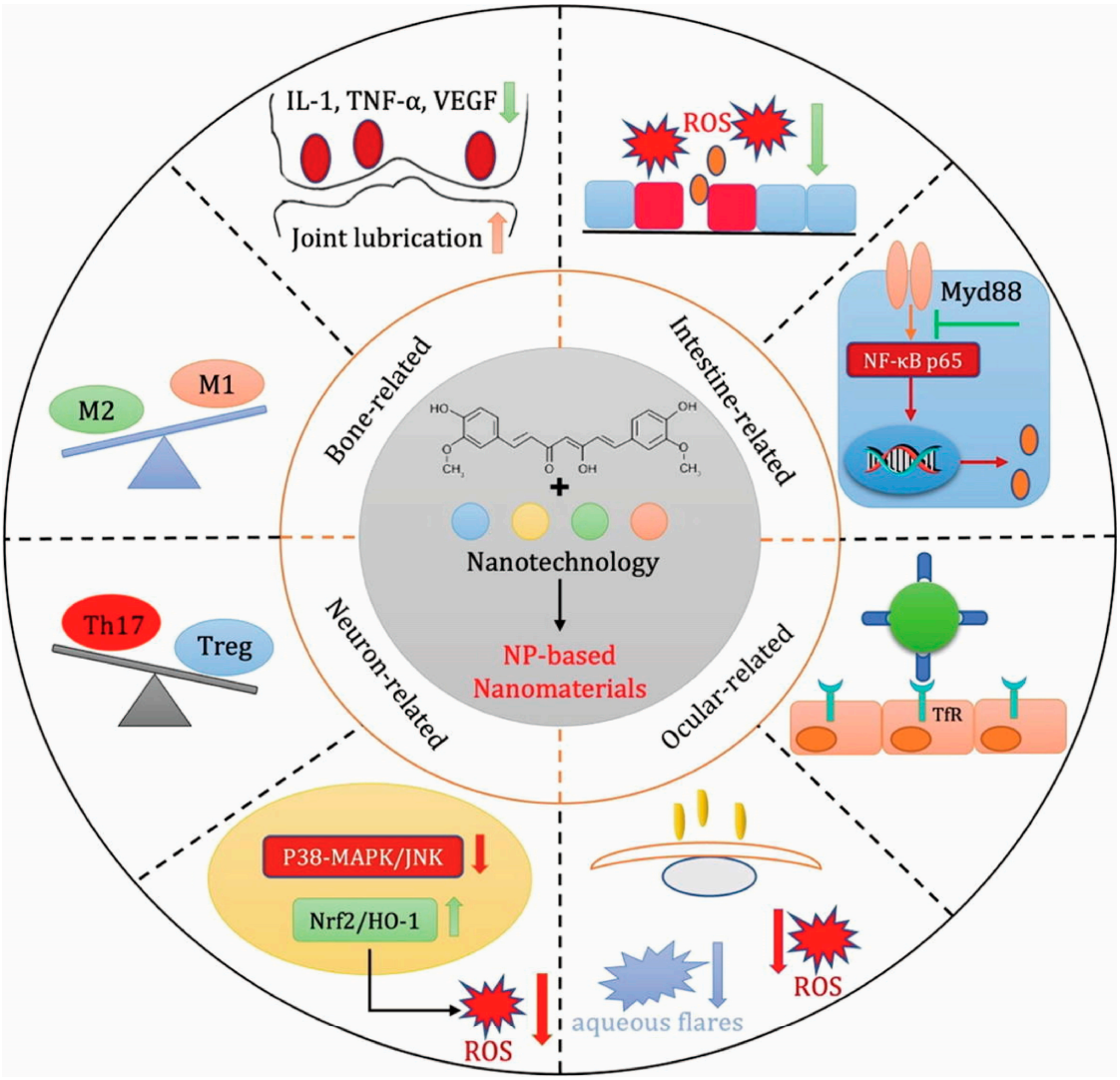


**Figure 4.** Natural product-based nanomedicine resulting from the combination of NPs with nanotechnology has been extensively investigated to improve the therapeutic index and safety profile of NPs in massive inflammatory diseases, including bone-, intestine-, neuron-, and ocular-related conditions. Adapted with permission from ref. [137], Copyright 2022, Elsevier.

**Table 4.** Multifunctional stimuli-responsive nano-drug delivery systems for the treatment of inflammatory disorders.

| Materials Used | Therapeutic Agent | Disorder | References |
|---|---|---|---|
| Hyaluronic acid-coated Poly (cyclohexane1,4diylacetone dimethylene ketal) | Dexamethasone | Rheumatoid arthritis | [138] |
| Polyketal | Superoxide dismutase | Lung fibrosis | [139] |
| Folic acid targeted Poly(cyclohexane-1,4-diylacetone dimethylene ketal)/Poly(lactide-*co*-glycolic acid) blend | Methotrexate | Arthritis | [140] |
| Poly(lactide-*co*-glycolic acid -Poly ethylene glycol-c(RGDfC) | Rapamycin | Atherosclerosis | [141] |
| mung bean-derived nanoparticles | Mung bean | Psoriasis | [142] |
| Gold nanoparticles | Rosa rugosa | Skin Inflammation | [143] |

### 3.4. Wound Healing

Wound healing is a multifactorial immunological phenomenon involving complex processes of angiogenesis and vascularization. Additionally, wound healing in a natural phenomenon includes change in pH, temperature and other responses [144]. Hence, to contemplate the same a chitosan based thermosensitive hydrogel consisting of lysolipid based thermosensitive liposomes (LTSL) with the therapeutic drugs and growth factors has been established. The liposomes loaded hydrogel can release different drugs as well growth factors to facilitate the wound healing [145]. Wound healing involves change in pH, the same has been explored by change in pH to monitor the wound healing process. A pH responsive hydrogel based wearable immunosensor in wound healing is customized in biomedical application [146]. Hydrogel of poly(*N*-isopropylacrylamide) with cellulose nanocrystals has a thermos-responsive effect on wound healing in the body temperature range of 36–39 °C. These hydrogels loaded with drugs for skin infection treatment has been reported to show temperature responsive property in wound healing and slow and sustained drug release [147]. Further, chitosan along with poly(*N*-vinyl-2-pyrrolidone) in poly acrylic acid has been shown a promising effect in wound healing as response to changes in pH [148]. $Fe_3O_4$ magnetic nanoparticles conditioned with exosomes derived from bone mesenchymal stem cells (BMSCs) and a static magnetic field were constructed for enhanced wound healing. The $Fe_3O_4$ magnetic nanoparticles combined with static magnetic field (SMF) resulted in increased expression of miR-21-5p suggesting improved wound healing [149]. Wound healing in diabetic patients is vital if there is risk involved, thus the electric-stimuli-based Chitosan-Vaseline® gauze (CVG) has also been developed for faster wound healing in sensitive populations [150]. Furthermore, graphene quantum dots-decorated luminescent porous silicon (GQDs@PSi) based peptide such as epidermal growth factor and insulin along with embedded in chitosan loaded films have been prepared for wound healing in diabetic patients. Due to the tissue damage in the wounding process, there is an increased level of $H_2O_2$ which serves as a stimulus for peptide release [151].

## 4. Challenges Faced during Design and Development of Responsive Nanostructures

Although responsive nanomaterials benefit in being sensitive towards external and/or internal stimuli with the possibility of design with high drug loading, biodegradability, drug release and surface chemistry modifications; certain limitation persist [143]. Uniformity in size of nanostructure, precision of nanoparticle architecture, optimization to get specific morphology and controlled drug release remain highly demanding. Compatible nanomaterial with reduced cytotoxicity and implementing the correct strategy to develop the proper combination of biodegradable materials is important. Biodegradation directly affects the stability of the carrier system in a biological environment and likewise the behavior analysis on the interaction of blood circulating components to stimuli responsiveness of the nanocarrier [152]. From the application prospect, some treatments which involve material injection and then activation by stimuli such as advanced light sources, ultrasonic waves and strong magnetic field could hinder cost-effectiveness of therapy, lacking a practical approach. Another problem exists in fine-tuning the drug release from the nanocarrier in accordance with the depth of penetration of light with a particular wavelength specially in the case of near-infrared light-based exogenous stimuli [152,153]. Apart from these, the basic challenge that is encountered in designing an effective drug nanocarrier for preventing early leakage, not allowing the active pharmaceutical to aggregate in the tumor site and demonstration of good degradability have also to be taken into consideration [143]. During designing the nanocarrier, over-engineering due to surface functionalization may complicate the clinical trial hence both the structural and functional aspects need to be reviewed well. From the beginning of the advent of nanomedicines, simple and cost-effective operation has guided the deployment in market. As material properties changes with time, a faster action of nanocarriers is an important aspect of developing a rapidly acting stimuli-responsive nanomaterial and requires more attention [154]. Response to biochemical signals even in minute concentration, turns to be the main challenge in achiev-

ing maximum activity. Another aspect is ensuring long-term stability under working conditions like an effect of temperature, pH, light and solvent. Change in mechanical strength often determines the success of drug release which also pave obstacle if remain underdetermined throughout the activity profile. The incorporation of thorough study during preclinical trials is another aspect that needs to be looked upon since the response system performs well in vitro but often the efficacy is less prompt in vivo [155]. A valuation of scalability and choice of correct material is also necessary as encapsulation or loading of drug itself is a challenging task to avoid unintended off-target accumulation. In case of single responsive nanocarrier, the system depends upon bond breakage by one stimulus and any difficulty in recognizing linkage can lead to failure of nanocarrier. Intracellular trafficking and escaping the endosomal system are another risk related to engineering coordinated nanocarriers [156]. At the characterization stage, the main issue arises to avoid one into multiple fits. A precaution needs to be taken with the main goal of categorizing the nanocarrier properly. Many stimuli can give rise to single bond breakage or single stimuli can initiate the cleavage of multiple bonds of the nanocarrier system. This can limit the active ingredient potency and activity [156]. One major problem in the nonspecific targeting of drug/nanoparticles comes with their clearance from liver. Nonspecific capture of nanocarriers by the reticuloendothelial system organs, particularly the liver, is one of the critical issues for systemic administrations, causing not only a substantial decrease in the delivery efficiency of nanocarriers into the target tissues but also toxicity [157,158].

This minimizes the efficiency of the nanoparticle at the site of action decreasing its potency. The problem has been tried to be controlled by a research group by designing polyethylene glycol (linear or two-armed) conjugated with oligo-L-lysine. The in situ stealth coating of nanomedicine helps to stay for longer in circulation sufficiently enough to inhibit the clearance mechanism of liver [157]. The future brings new challenges in developing biomarker-based nanocarriers effective even at small concentrations and responding promptly to activating factors [33].

## 5. Clinical Perspective and Applicability of Responsive Nanostructures

A large number of functional nanoparticles can be synthesized by controlling the dimension and surface of nanoparticles. It has been possible to create nano-platforms with an array of various novel nanocarriers, which impart improved therapeutic efficacy, more target specificity, controlled and efficient drug release, lower therapeutic doses, and minimal tissue interference. Moreover, the use of nanostructured systems which can be controlled by stimuli-responsive (assembly/disassembly) mechanisms combined with 'ligand–receptor' recognition processes can offer theranostic possibilities for various biomedical applications, for instance, controlled drug release, precise imaging, and multipurpose and multi-component therapeutic modalities. The development of integrated medical nano systems enables the early diagnosis and global profiling of a patient's health or disease, thereby providing new methods for personalized health monitoring and preventative medicine. However, despite the fact that these nanoplatforms demonstrate good performance against a large number of specific diseases, a number of inherent disadvantages and critical issues limit their clinical applications. This section highlights the clinical applications, trials, and regulatory aspects of responsive nanoparticles.

### *5.1. Clinical Response in Varied Patient Profiles*

Internal stimuli are very hard to control because of the complexity of the biological microenvironment and variations in clinical settings unique to each patient. Although it is relatively easier to control the systems using external stimuli or exogenous triggers, there are chances of more damage to the normal tissues and also of going beyond the depth of desired tissue-penetration. Exposure to electromagnetic fields may have a weak effect on parts of the cell membrane. For example, even very low exposure to electromagnetic fields can change the secondary structures of $\alpha$-helix and $\beta$ pleated sheet and modify the

way peptide linkages vibrate. This can further initiate an unfolding process in the cell membrane proteins [159].

#### 5.1.1. Endogenously Activated Particles in Variable Clinical Scenarios

In systems with pH-responsive nanocarriers, the presence of ionizable moieties such as sulfonic and/or carboxylic acids (acidic) or imidazole, amines, and pyridine (basic) can become proton donors upon a change in the environment, resulting in a change in electrostatic charges within the system [70,160]. This in turn can disrupt the nanocarrier structure in pH-responsive SRNP-systems [103]. The process can be exploited for drug delivery in an intrinsically low pH system (∼5.0) like in cancer cells.

#### 5.1.2. Exogenously Activated Particles in Variable Clinical Scenarios

The exogenous stimuli (such as light, magnetic field, temperature, ultrasound, electric pulse/radiation field), can trigger or enhance targeted drug release [161,162]. The photochromic moieties, upon photon (light) exposure can undergo photochemical changes (e.g., photo-dimerization, photo-isomerization, or photo-cleavage). It can induce structural disaggregation or alterations of the nanocarrier followed by drug-release in the SRNP system [161]. Intense optimization and improvement experiments are required for the translation of each stimulus from pre-clinical experimental models into clinical practice [163].

#### 5.1.3. Personalized Medicine and System Biology

Pharmaceutical therapies in personalized medicine are tailored to each individual patient based on their unique presentations and profiles. For achieving such customized or optimized therapy goals, an interdisciplinary approach should be applied to understand the functioning of individual living systems and also the pathophysiological pathways. The study of complex interactions between biological systems and smart and highly sensitive integrated SRNPs is facilitating new biosensor developments, early diagnosis of diseases and in global profiling of health. These new approaches for personalized health monitoring and preventative medicine (called "system biology") are based on the collection of a large number of data ("in parallel") using "-omics" technologies. They serve as a precursor to the development of personalized medicine, which uses genomics and proteomics to treat a wide range of diseases. Although its primary focus is on preventative medicine, a genomic approach will enable earlier disease detection (by using specific disease biomarkers). Despite its primary focus on prevention, a genomic approach will allow for earlier disease detection (by using specific disease biomarkers). Interdisciplinary and cross-disciplinary collaboration between the fields of molecular nanomedicine, biochemistry, bioengineering, and biotechnology is required for this program [164].

However, one of the major obstacles to clinical application of the above is the complex human genomic variations. There may be numerous genes involved in the metabolism of a substance which is used in determining the etiopathogenesis of a disease or assessment of drug responses. Furthermore, a significant number of genetic variations may exist, making it difficult and costly to fully identify them within the intricate genetic map. Although significant questions about biocompatibility, toxicology, and ethical considerations remain, the personalized medicine approach may play a larger role in the future of clinical medicine [165].

#### 5.1.4. Integrated Nanoplatforms for Personalized Medicine

It is possible to incorporate a number of different components into a single nanoplatform in order to achieve the goal of designing diagnostic and therapeutic modalities that can be used for personalized applications. By combining nanodiagnostics and drug formulation on the same nanocarrier system, it is possible to achieve proper pharmacokinetic/pharmacodynamic behavior of an agent. It can also increase the bioavailability of a drug, achieve more targeted/effective treatment response at lower doses, decrease systemic toxicity and reduce the adverse drug reactions. In order to create lab-on-chip methods,

a variety of miniature tools and nanostructure platforms can now be developed. For the fabrication of the nanocarriers, several steps are necessary, including initial chemical synthesis, formulation, and purification of the finished nanostructures. Large consortiums must be established, with many institutes cooperating and working closely with regulatory agencies, in order to plan and complete these scientific tasks in research and clinics. The commercialization of novel nano-formulations will be aided by this as it will encourage the translation of research findings to the pharmaceutical sector.

#### 5.1.5. Critical Issues with Smart Nanocarriers

The most effective drug delivery systems are those that confine drug administration to diseased tissue while sparing unaffected areas. Different options exist for integrating any desirable set of functions into a single scaffold thanks to the novel design concepts and versatile control ability offered by smart nanostructures [165,166]. These nanostructured systems are predicated on a wide variety of (non-covalent) supramolecular interactions, which in turn permit the formation of materials and devices with extraordinary functionality. To be more specific, amphiphilic compounds can self-assemble into a wide variety of nanomaterials with complex new properties and structures through a process called supramolecular self-assembly. Target specificity, controlled drug release, reduced therapeutic doses, and minimal exposure to normal tissues are all areas where these methods show great promise for improving therapeutic efficacy [167]. However, it can be very difficult to study, describe, and predict the dynamic cellular-level changes and biological events that occur in response to drug delivery processes. The effectiveness of the drug delivered to tumor targets has been found to be less than 5% in actual clinical experience, despite recent advances in our understanding of a wide range of diseases and pathologies, suggesting that targeted therapy still holds great promise [159].

The enhanced permeability and retention (EPR) effect and the complexity of diffusional barriers in solid tumors contribute to these crucial problems. In fact, there may be subtle shifts in the surface expression of tumor-targeting receptors over time. It is also common for the receptors to be present (albeit at lower concentrations) in the tissues of healthy cells, even though they are overexpressed in a particular disease or pathology state. In addition, receptor overexpression is frequently heterogeneous both between individual tumor cells and between patients with the same disease type. There are significant obstacles to overcome in order to detect such complex phenomena due to all of these factors. Therefore, the achievement of effective active targeting is not guaranteed simply by the presence of a ligand-receptor combination on nanocarrier systems. If we want to increase the success of targeted therapies, we need to conduct more predictive studies and develop better drug delivery methods [159,168].

Given the complexities mentioned above, research into multiple factors, such as tumor dynamics (including spatial and temporal heterogeneity) and controlled distribution in the blood, is required for the development of advanced targeted drug delivery systems. Studies of model bio-membranes and their interactions with nanoparticles have made significant contributions to our understanding of the complex processes driven by the interactions that a nanostructured material can develop toward biological systems, emphasizing the importance of interaction (electrostatic, hydrogen bond, ion coordination sites, etc.) in the development of increasingly intricate morphologies, architectures, and dynamic structural transitions.

### *5.2. Clinical Trial Status of SRNPs*

Translation of SRNPs have seen various real-world challenges. Despite the promises it projects, SRNPs is not widely being explored in clinical practices due to many challenges. The number of clinical trials, as shown in Table 5, related to SRNPs (chiefly thermosresponsive) are not plenty and few have been completed.

**Table 5.** List of chemical trials on responsive nanostructures (from www.clinicaltrials.gov website. Accessed on 5 December 2022).

| Title of the Study | Drug and Clinical Condition/Use | Status | Stimuli | Clinical Trial No | Phases Covered | Purpose | Reference Citation |
|---|---|---|---|---|---|---|---|
| Phase 2 Study of Thermodox as Adjuvant Therapy with Thermal Ablation (RFA) in Treatment of Metastatic Colorectal Cancer(mCRC) (ABLATE) | ThermoDox in combination with Microwave Hyperthermia (heat). For recurrent regional breast cancer | Completed First Posted: 21 January 2009 Last Update Posted: 30 January 2017 | Thermo-responsive | NCT00826085 | I and II | To evaluate the effects of ThermoDox in combination with therapeutic heating of the chest wall in the treatment of recurrent regional breast cancer. | https://www.clinicaltrials.gov/ct2/show/NCT00826085 |
| ThermoDox™ in Combination with Radiofrequency Ablation (RFA) in Primary and Metastatic Tumors of the Liver | ThermoDox Hepatocellular Carcinoma Liver Neoplasms | Recruitment Status: Completed First Posted: 28 February 2007 Last Update Posted: 7 February 2019 | Thermo-responsive | NCT00441376 | I | To determine the maximum tolerated dose (MTD) of ThermoDox when used in combination with radiofrequency ablation (RFA) in the treatment of primary and metastatic tumors of the liver. | https://clinicaltrials.gov/ct2/show/NCT00441376 |
| Study of Thermodox as Adjuvant Therapy with Thermal Ablation (RFA) in Treatment of Metastatic Colorectal Cancer(mCRC) | Colon Cancer Liver Metastasis Drug: Lyso-Thermosensitive Liposomal Doxorubicin Other: 5% Dextrose Solution Drug: ThermoDox | Recruitment Status: Terminated (trial design contingent on RFA optimization) First Posted: 3 November 2011 Results First Posted: 13 October 2022 Last Update Posted: 13 October 2022 | Thermo-responsive | NCT01464593 | II | To determine the safety and efficacy of Thermodox, a thermally sensitive liposomal doxorubicin, in combination with thermal ablation in the treatment of hepatic colorectal liver metastases (CRLM). | https://clinicaltrials.gov/ct2/show/NCT01464593 |

**Table 5.** *Cont.*

| Title of the Study | Drug and Clinical Condition/Use | Status | Stimuli | Clinical Trial No | Phases Covered | Purpose | Reference Citation |
|---|---|---|---|---|---|---|---|
| ThermoDox with Standardized Radiofrequency Ablation (RFA) for Treatment of Hepatocellular Carcinoma (HCC) (OPTIMA) | Drug: ThermoDox Drug: Dummy infusion/Hepatocellular Carcinoma | Recruitment Status: CompletedFirst Posted: 14 April 2014 Last Update Posted: 24 October 2018 | Thermo-responsive | NCT02112656 | III | To determine whether ThermoDox, a thermally sensitive liposomal doxorubicin, is effective in the treatment of non-resectable hepatocellular carcinoma when used in conjunction with standardized radiofrequency ablation (sRFA). | https://clinicaltrials.gov/ct2/show/NCT02112656 |
| MRI Guided High Intensity Focused Ultrasound (HIFU) and ThermoDox for Palliation of Painful Bone Metastases | Painful Bone Metastases Breast Carcinoma Non-small Cell Lung Cancer, Small Cell Lung Cancer Adenocarcinoma Drug: High Intensity Focused Ultrasound (HIFU) in combination with ThermoDox | Recruitment Status: Withdrawn First Posted: 16 July 2012 Last Update Posted: 7 February 2017 | Thermo-responsive | NCT01640847 | II | To evaluate treatment with High Intensity Focused Ultrasound (HIFU)in combination with ThermoDox (liposomal doxorubicin) is safe and effective in reducing pain for patients with painful bone metastases. | MRI Guided High Intensity Focused Ultrasound (HIFU) and ThermoDox for Palliation of Painful Bone Metastases-Full Text View-ClinicalTrials.gov |

**Table 5.** *Cont.*

| Title of the Study | Drug and Clinical Condition/Use | Status | Stimuli | Clinical Trial No | Phases Covered | Purpose | Reference Citation |
|---|---|---|---|---|---|---|---|
| Phase 3 study of ThermoDox with radiofrequency ablation (RFA) in treatment of hepatocellularcarcinoma (HCC) | Hepatocellular Carcinoma Drug: ThermoDoxDrug: 5% Dextrose Solution | Recruitment Status: Completed First Posted: 18 February 2008 Results First Posted: 24 March 2017 Last Update Posted: 25 April 2017 | Thermo-responsive | NCT00617981 | III | To determine whether ThermoDox, a thermally sensitive liposomal doxorubicin, is effective in the treatment of non-resectable hepatocellular carcinoma when used in conjunction with radiofrequency ablation (RFA). | https://clinicaltrials.gov/ct2/show/NCT00617981 |
| A Phase I/II Single Dose Trial to Determine the Safety, Tolerance, Pharmacokinetic Profile, and Preliminary Activity of Intrahepatic Delivery (Via Hepatic Artery Catheterization) of Doxorubicin Hydrochloride Adsorbed to Magnetic Targeted Carriers (MTC-DOX) in Patients with Metastatic Cancer to the Liver. | Metastases, Neoplasm Colorectal Neoplasms Esophageal Neoplasms Stomach Neoplasms Pancreatic Neoplasms Breast Neoplasms Melanoma Sarcoma Gastrointestinal Neoplasms Lung Neoplasms Liver Neoplasms Cholangiocarcinoma Drug: MTC-DOX for Injection Procedure: Chemotherapy/ | Recruitment Status: Completed First Posted: 19 July 2002 Last Update Posted: 24 June 2005 | Iron and carbon magnetic beads (magneto-responsive) | NCT00041808 | I and II | Therapeutic | https://clinicaltrials.gov/ct2/show/NCT00041808 |

**Table 5.** *Cont.*

| Title of the Study | Drug and Clinical Condition/Use | Status | Stimuli | Clinical Trial No | Phases Covered | Purpose | Reference Citation |
|---|---|---|---|---|---|---|---|
| Preoperative staging of pancreatic cancer using superparamagnetic iron oxide magnetic resonance imaging (SPIO MRI) | Pancreatic Cancer | Recruitment Status: Completed<br>First Posted: 12 June 2009<br>Results First Posted: 25 July 2017<br>Last Update Posted: 25 July 2017 | Feraheme Iron oxide nanoparticle | NCT00920023 | IV | Diagnostic | https://clinicaltrials.gov/ct2/show/NCT00920023 |
| NanoTherm | Prostate Cancer/ Device: NanoTherm Ablation | Recruitment Status: Recruiting<br>First Posted: 18 August 2021<br>Last Update Posted: 24 August 2022 | Magnetic field | NCT05010759 | Not Applicable | Stage 2B: NanoTherm ablation of focal prostate cancer in small lesions in Gleason 3 + 4 disease. The outcome of this ablation is validated by a transperineal biopsy at 4 months after ablation. | https://clinicaltrials.gov/ct2/show/NCT05010759 |
| A study of Trastuzumab Emtansine (T-DM1) in combination with Docetaxel, and potentially Pertuzumab, in participants with advanced breast cancer | Breast Cancer/ Drug: Docetaxel Drug: Pertuzumab Drug: Trastuzumab emtansine | Recruitment Status: Completed<br>First Posted: 8 July 2009<br>Results First Posted: 6 April 2017<br>Last Update Posted: 6 April 2017 | Targeted antibody drug conjugate | NCT00934856 | I and II | Therapeutic | https://clinicaltrials.gov/ct2/show/NCT00934856 |

## 6. Future Outlook

The main traits of stimuli-responsive nanostructure employed in biomedical applications, notably drug delivery, have drawn the attention of many researchers due to their high loading capacity, cytocompatibility, and stimuli-responsive release of pharmacological qualities. Nanoparticles are suitable delivery systems for medical applications due to their biocompatibility, wide range of functionalization possibilities, and efficient cell absorption. Stimulation-responsive NPs that target cancer metabolism could enhance not only the properties of already existing drugs but also the curative effect by targeting the release of the drug to tumor locations. Nanoformulations provide superior antitumor treatment efficacy as compared to conventional drug delivery systems because they locally stimulate tumor cells and the microenvironment to govern medication uptake and release. To ensure manageable costs, batch-to-batch reproducibility, and maintaining stability, it is important to develop new, straightforward fabrication techniques for nanostructures. This will make it easier to standardize large-scale production and quality assurance of nanostructures for clinical translation. Dual- and multi-stimuli-responsive nanomaterials may eventually open the door to novel nanosystems that are useful in biomedical applications.

## 7. Summary and Conclusions

The biological system is maintained by the homeostatic mechanism, which involves interaction of pathways involving various internal and external milieu. These milieus are the triggers for the hoist of responsive nanostructures and thus, the nanostructures can be functionalized for different purposes including nanotheranostics, targeted drug delivery, and bioimaging. The stimuli responsive nanostructures in targeted drug delivery covers a multitude of biomaterials, these structures possess certain advantages or disadvantages based on their origin and intended use. Hence, nanostructures have been used in number of applications, including cancer therapy, inflammatory diseases etc. The in vitro and in vivo lab-based data supports the use of nanostructures in number of diseases; however, there are limitations to translate these to clinical set ups. At a cellular level, the nanostructures can behave in different ways as the cells possess a variety of functions based on the cellular internal and external environment. The nanostructure comes in a variety of sizes and shapes; however, they can possess toxicity at a cellular level in clinical settings as the metabolism and biotransformation participates actively. Hence, the dose and other optimization have great challenges. The major hurdle comes during scaling up of these nanostructures from lab scale to the industrial scale, as maintaining the uniformity in size, shape, the drug release in the biological system can be a challenge. Moreover, the functionalization of the nanostructures with the target cell specific modification requires uttermost precision, which can be a major challenge.

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