Nanoparticle Activation in Cancer Treatment

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Activation, or release of a compound, at a tumour site can mitigate the side effects often experienced during cancer treatment by localizing the treatment. In addition, localized action can also permit the use of larger effective doses at the tumour site which would not be tolerated if administered systemically. However, controlling the release of a compound, or the activity of a molecule or nanoparticle, requires the design of smart systems. Such systems can be controlled either by differences between cancerous and normal cells, or by activation from a source outside of the cell.

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1. Introduction

Activation, or release of a compound, at a tumour site can mitigate the side effects often experienced during cancer treatment by localizing the treatment. In addition, localized action can also permit the use of larger effective doses at the tumour site which would not be tolerated if administered systemically. However, controlling the release of a compound, or the activity of a molecule or nanoparticle, requires the design of smart systems. Such systems can be controlled either by differences between cancerous and normal cells, or by activation from a source outside of the cell. This review first discusses the activation of nanoparticle systems due to altered cancer cell metabolism (Section 1), and discusses pH-, enzymatic-, and concentration-dependent activation. Subsequently, extrinsic activation (Section 2) is considered, which includes ultrasound, magnetic, and light and X-ray activation.

1.1. Intrinsic Activation Due to Altered Cancer Cell Metabolism

In healthy cells the intracellular pH is tightly regulated, and kept near neutral by virtue of ion transport proteins in the plasma membrane [1]. In contrast, cancer cells have an increased intracellular pH (~7.3–7.6 versus ~7.2) and a decreased extracellular pH (~6.8–7.0 versus 7.4). This acidic extracellular pH is considered a major feature of tumour tissue and is primarily due to the secretion of lactate from anaerobic glycolysis. The acidic extracellular pH activates lysosomal enzymes that have an optimal activity in this range, and also the expression of genes of pro-metastatic factors [2]. Therefore, proteins and enzymes will be differentially expressed in cancerous cells and tissues.

1.1.1. pH-Activated Nanoparticles for Cancer Treatments

Due to the differences in pH between healthy and cancerous cells, systems can be developed where changes in acidity trigger release. Release can also be triggered at a specific location in the body relating to physiological changes in pH.

– Organ Specific Release

The different organs of the body naturally differ in pH, for instance the stomach (pH 1.5–3.5) [3] or intestines (pH 5.1–7.8) [4][5]. However, oral administration is particularly challenging due to the extremes in acidity, and most compounds need protection. Without protection, or controlled release, the lifetime of the drug is likely to be low due to denaturation by the highly acidic environment in the stomach [6]. This can result in concentrations at the target site being lower than needed, leading to multi-drug resistance [7][8]. However, a specifically pH-triggered release system in the intestine could be beneficial. Indeed, a solid lipid nanoparticle has been developed to only release drug at intestinal pH in the presence of specific pepsin and pancreatic enzymes. Furthermore, several different polymeric materials, such as poly(lactic-co-glycolic-acid) (PLGA) [9] and poly(acrylic acid) (PAA) [10], have been shown to result in sufficient concentrations of anti-tumour substances via oral-delivery. Tian et al. [10] reported a specific example using a PAA coated mesoporous silica nanoparticle (MSNPs) system for the oral delivery of doxorubicin (DOX). pH-responsive PAA outer-layers were used to enfold the drug-loaded silica core and to protect the cargo from the strongly acidic environment in the stomach. Only when the nanosystem reached the higher pH of the colon, would the PAA coat degrade and release the chemotherapeutic from the core. The loading capacity of PAA-coated MSNPs could reach 785.7 mg DOX per 1g of PAA/MSNPs. Incubation of human mesenchymal stem cells (hMSCs) with 300 μg mL^{-1} of the loaded PAA/MSNPs showed cytotoxicity of over 30% after 24 h [10].

Oral systems have also been developed for the delivery of natural products, such as curcumin which has been known to have anti-cancer effects for many years. The insolubility of curcumin (which is at ng level) greatly restricts the bioavailability by oral administration [11]. Cui et al. developed a unique self-microemulsifying drug delivery system (SMEDDS) which could significantly increase the water solubility of curcumin and enhance the adsorption rate in gastrointestinal tract by pH-responsive release. The adsorption rate increased to over 90% within 12 h compared with only 20% for free curcumin [12].

2. Extrinsic Activation

2.1. Ultrasound Activation

Ultrasound has been used in medicine since the 1930s for both diagnostic and therapeutic purposes, due to its non-invasive, non-ionising and generally safe nature. Ultrasound irradiation works by an identical mechanism to soundwaves; positive and negative pressures produced by waves cause both thermal and non-thermal effects through mechanical friction [13].

2.1.1. Sonoporation

When ultrasound is applied to cells it causes an increase in their porosity; an effect known as sonoporation. This effect can be combined with microbubbles to enhance the effect further. Although hypotheses about the exact mechanism vary, it is believed that increased uptake is a result of stable or inertial cavitation of the microbubbles [14]. During stable cavitation a microbubble oscillates under the alternating pressure of the applied ultrasound and causes streaming of fluid around the bubble. This causes shearing and fracture of the cell membrane and hence increased porosity. In this mechanism the microbubble remains intact even after the interaction. Alternatively, inertial cavitation can be induced, in which the bubble collapses under the alternating pressure and produces microjets and shockwaves that lead to pore formation. These induced pores can be either transient or permanent; permanent porosity will eventually lead to cell death, but cell death in this manner is generally uncontrollable and undesired in remote activation of nanoparticles [15].

2.1.2. Gas Filled Microbubbles

Microbubbles for medical use typically comprise a perfluoro carbon gaseous interior and a polymer or protein biocompatible shell. Gas-filled microbubbles can be used for the delivery of nanoparticles by chemical attachment or encapsulation on or within the microbubble, followed by ultrasound irradiation [14][16]. Independent studies have shown a range of increased nanoparticle uptake of between 5–57 and 60–600 fold when administering the nanoparticles using microbubble attachment. In addition, the effective penetration depth of nanoparticles in tissue can be increased by hundreds of micrometres [17][18][19][20].

Successful delivery of nanoparticles bonded to the surface of microbubbles relies on the localized destruction of the microbubbles within the tumour blood vessel and subsequent distribution of the bound nanoparticles to the surrounding tumour tissue [18][20][21][22]. This technique has been used for the delivery of compounds such as doxorubicin. Polymer microbubbles have also been formulated which contain doxorubicin. In the latter, the drug is encapsulated using an emulsion method, and when the shell is ruptured by ultrasound irradiation the drugs are released into the tissue [23][24]. While it was successful, only a low loading capacity of doxorubicin in the bubbles was achieved and so the system was adapted to encapsulate the very potent microtubule stabilizing drug paclitaxel [25][24].

A drawback of adhering nanoparticles to microbubbles is the vast reduction of circulation time in vivo. In addition, the microbubbles often collapse upon ultrasound irradiation, and hence cavitation times are very short. Recently, however, nano-cones and nano-cups have been designed that increase and sustain cavitation times four-fold, and retain the long circulation times nanoparticles possess. Within the single cavity of the nano-cones and nano-cups, a nanobubble is formed and stabilised. Upon ultrasound irradiation the particles are propelled into surrounding tissue and uptake is again aided by cavitation and subsequent sonoporation. Gold particles of this nature have been used to deliver IgG mouse antibody in vivo, increasing delivery distances from blood vessels to hundreds of micrometres [17][19]. mRNA-lipoplex loaded microbubbles have also been shown to increase transfection of dendritic cells from negligible amounts to 50%, when ultrasound is used as an activating stimulus [16].

2.2. Magnetic Field Activation

Magnetic nanoparticles show potential in oncology for their use in induced magnetic hyperthermia, localized drug delivery by external magnetic fields, and also as contrast agents in magnetic resonance imaging (MRI). The most frequently used materials are magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3).

Magnetic nanoparticles are able to convert electromagnetic energy into heat. This is typically accomplished by the hysteresis loop mechanism in alternating magnetic fields (AMFs) due to either Néel relaxation, Brownian motion, or possibly particle-particle interaction in super-paramagnetic nanoparticles at frequencies between 100–300 kHz [26]. The efficiency of heat generation is dependent upon magnetic field strength and frequency, nanoparticle size, concentration, and solution viscosity [27]. Alternating magnetic fields have long been used to induce hyperthermia for a variety of medical treatments. The main advantage in using an alternating magnetic field as a stimulus lies in its non-ionising and specific nature.

2.2.1. Magnetically Induced Hyperthermia

Since the development of hyperthermia treatment in the 1970s this method has been the focus of intense research both as a sole therapeutic method, and in combination with other treatments. When used in combination with radiotherapy, hyperthermia treatment has shown excellent results in a variety of cell lines [28]. With the discovery of the very high specific absorption rate of iron oxide nanoparticles (IONs), subsequent hyperthermia research greatly increased in effectiveness and specificity, leading to the first clinical trials in 2009 [29]. The inductive heating effect of IONs is caused when an alternating magnetic field (AMF) constantly flips the magnetic orientation of the superparamagnetic magnetite particles. Superparamagnetism occurs when a ferro/ferrimagnetic material becomes suitably small, that is, ~10 nm, and behaves as a single spin system. Rapid alternation of the magnetic orientation may then generate heat after internalization, and cell death can occur when temperatures reach approximately 42 °C [29][30]. The inductive heating effect from magnetic field stimulation can be used in conjunction with a chemotherapy system in which release is triggered by a temperature change.

Magforce has developed the NanoTherm™ therapy for treating brain tumours. The iron oxide particles are 14 nm in diameter with an aminosilane coating, and the ferrofluid is used at a concentration of 17 quadrillion particles per millilitre. NanoTherm™ is inserted into the tumour and the coating causes the particles to remain in situ, permitting multiple treatment cycles. Their proprietary Nanoactivator™ creates an alternating magnetic field such that the magnetic field alternates around 100,000 times per second, and the rapid change in the nanoparticles magnetic orientation activates the particles resulting in heat. Using such an approach the tissue can reach temperatures of up to 80 °C, directly destroying cancer cells. The technology was tested in clinical trials for glioblastoma and used in conjunction with radiotherapy. Conventional treatment showed a median survival time of 6.2 months, compared to 13.4 months for the 59 patients using NanoTherm™; more than double. The technology is being trialled in prostate cancer patients; the first patients were enrolled in late 2018, and is expected to take 12–15 months to complete. There are however, two drawbacks to this technology, firstly all metal must be removed from within 40 cm (e.g., dental work) and secondly MRI can never be used again, including for diagnosis of tumour progression.

Therapies involving the inductive heating of gold nanoparticles have been a topic of hot debate for some time. Gold has been shown empirically to demonstrate inductive heating upon application of an AMF. Theoretically, however, gold does not possess an electronic configuration that would allow such a process, and it has been suggested that nano-surface and quantum electronic effects were the cause [31][32]. In 2017 it was concluded that the temperature change observed by investigators was a result of the movement of the ion layer surrounding gold particles in a colloid, and the conjugation of proteins in solution with the surface of the gold particles [33]. Despite the controversy over mechanism of heating, the activation of gold NPs by AMF has proven effective. Antibody-conjugated gold nanoparticles have been shown to actively accumulate in liver cancer cell lines (Panc-1, Hep3B, and SNU449) and cause hyperthermia and subsequent cell death under AMF [32]. A smart biosensor consisting of a gold nanoparticle core, a DNA 'melting stem' coded for the recognition of tyrosine hydroxylase and a one reporter fluorochrome allows fluorescence imaging under a 3 GHz AMF [31]. Although there is not the range and depth of research into gold nanoparticles activated by AMF compared to IONs, this is a promising area and retains potential for further development.

2.2.2. Magnetically Induced Localized Drug Release

Liposomes and micelles carrying IONs have been used as a means of encapsulating and delivering therapeutic drugs to tumour sites. The shells are commonly based on a thermosensitive polymer such as poly-N(isopropylacrylamide) or poly(vinylcaprolactame). The liposomes, while varying in construct and payload, are typically activated by two methods; the first involves the inductive heating of the internal IONs by an AMF and a subsequent structure change of the thermosensitive polymer making up the liposome. The structure change releases the entrapped drugs and can be reversible or irreversible depending on the polymers used. The second method involves the application of a permanent magnetic field, causing the IONs to drag and squeeze the liposomes to a point at which they burst and the payload is released [34][35][36][37][38]. Nanocapsules designed in this manner by an emulsion approach have enabled the simultaneous activated delivery of both hydrophobic and hydrophilic drug molecules contained within the same vesicle. Utilising block polystyrene acrylic acid copolymers, compounds such as FITC-DNA, fluorophores and pyrene are contained within their phases until activated [38]. When activated in this manner drug delivery can have a high specificity and payload efficiency. However, it is not a perfect system and the size and composition of the micelles or liposomes can vary hugely during synthesis and often result in unwanted effects on the penetration of treatment into tumour tissue, thus hindering the efficiency of delivery in vivo.

Improved tumour uptake and localization of compounds can be achieved using magnetite-based nanoparticles. Fe_3O_4 core nanoparticles with a poly(N-(1-1-butyric acid)) aniline shell have been shown to improve the delivery of carmustine from within the polymer, shown active targeting in directed magnetic fields, and can simultaneously serve as a contrasting agent for MRI imaging. In addition to this, the nanocarrier improved drug half-life from 18 to 62 h, and improved survival rates by 20% in mice models compared to administration of the drug alone [39][40]. Another combinational treatment method uses cationic, biocompatible peptide dendrimers loaded with doxorubicin and grafted onto the surface of ION's. An applied AMF induces hyperthermia in cells and promotes the release of

the chemotherapeutic drug giving a best of both worlds treatment. These particles showed high rates of cell death in HeLa, PC-3, MCF-7, and KB cell lines [41].

A proof-of-principle system for stimulating insulin release has been developed using a modified temperature sensitive TRPV1 channel in conjunction with antibody coated Iron Oxide Nanoparticles (IONs). The IONs were coated with anti-histidine (His) which bound to an extracellular His epitope tag on the modified TRPV1 channel. Application of the AMF inductively heated the IONs such that the temperature sensitive TRPV1 channel generated a calcium current. This in turn activated the Ca^{2+} sensitive promoter of the human insulin reporter gene [42]. Not only does this method utilise the stimulus responsive activation of nanoparticles, but it demonstrates the activation of cells using nanodevices. The system shows potential for use in stimulating tumour cells to self-destruct.

Advances in thermosensitive polymers and the optimisation of inductive heating methods has resulted in an increase in research into trapping drugs and IONs within a polymer matrix for delivery to tumour sites. A combination particle comprising a poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer matrix containing polyvinyl alcohol shell, ION and drugs such as ethosuximide has shown incredibly tuneable drug release upon stimulation. The reversible collapse of the copolymer and the swelling of the PVA core upon temperature rise provides an outstanding mechanism of drug release [43]. In contrast, nanocomposites of poly-N(isopropylacrylamide) matrices and ION showed the suppression of drug release upon inductive heating. Owing to the collapse of the polymer and the closure of pores in the matrix, this provides a means of turning off drug delivery once the desired therapeutic effect has been achieved, reducing the potential for off-target toxicity [44].

Core shell structured nanoparticles have been designed that provide an almost zero release profile of drugs unless activated by an AMF. A contemporary example consists of a PVA-ION-hydrophobic drug core surrounded by a thin layer of silica, which can help regulate the release pattern. A burst release occurs when the inductive heating effect of the AMF causes disintegration of the inner core [45]. In a mirrored manner to this, a core shell system with a drug containing silica core surrounded by an iron oxide crystal shell has been created. Again considerable release is only seen after an external field is applied [46]. Utilising functionalised mesoporous silica nanoparticles ca.100nm in diameter, methylene blue for fluorescence imaging and ION are entrapped within the pores of the silica particles and capped with a lipid bi-layer. Upon AMF stimulation and subsequent ION inductive heating the bi-layer is broken and the payload of the pores released [47]. This innovative design has the potential to have even greater effect if the payload is optimised to carry therapeutic drugs and the bilayer surface engineered with receptor targeting ligands.

2.3. Light Activation and Photodynamic Therapy

Photodynamic therapy (PDT) has seen rapid progress since the first modern use in 1975 [48]. Unlike chemotherapy and radiotherapy the systematic toxicity is very low. Nanotechnology has found a place in PDT treatment to improve the efficiency, localisation and penetration depth of conventional PDT. Upconversion nanoparticles (UCN) have been a key contributor to advances in PDT. Photon upconversion involves the sequential absorption of two or

more photons which results in the emission of light at a shorter wavelength than the excitation wavelength. The UCNs are therefore commonly excited with visible light wavelength to generate ultraviolet light. Alternatively, near infrared light can be used as the excitation source due to its minimally damaging tissue effects, and high penetration depths. Typically, the upconversion material comprises crystals of $NaYF_4$ doped with either Yb/Er or Yb/Tm; the choice of activator dopant is influenced by comparative energy levels [49].

Using the principles of UCN and traditional PDT, many methods of visible or near infrared light stimulated chemotherapy have been developed. Using light as a stimulus mechanism has allowed localized release, reduced incident light effects and synergistic treatments to be developed. The illumination of photosensitisers within the patient generating ROS and subsequent tumour destruction, provides a means of effective, non-invasive treatment.

This section will also focus on light activated chemotherapy as well as advancements in PDT.

2.3.1. Near Infrared Light Activation

Near infrared radiation (NIR) specifically 700–1200 nm, has been used as a stimulus for PDT since the inception of upconverting nanomaterials [50]. Visible light can only penetrate <1 cm into body tissue and intense prolonged exposure will cause burns and lesions [48][51]. NIR light increases penetration depth by several fold and reduces the possibility of damage to healthy tissue [52][53][54][55]. Gold nano clusters have been designed that in response to NIR activation, can image, assist gene delivery, and enable PDT in HeLa cells. Gold nanoclusters conjugated to TAT-peptide were shown to actively accumulate in the nucleus and enable red fluorescence imaging in vitro and in vivo. In addition to imaging, the peptide catalyses singlet oxygen production and serves as a DNA delivery medium, giving ultrahigh uptake (90%) and transfection (80%) [55].

Imaging has also been performed with PLA-PEG-FA polymers encapsulating a NIR sensitive carbazole substituted boron-dipyrromethene photosensitiser. These small, biocompatible, organic nanoparticles were used with an ultralow power lamp (670–800 nm) and tumour volume reduction was on average around 80% in mice bearing subcutaneous 4T1 tumour xenograft [54]. The photosensitizer TiO_2 can also be adapted to respond to NIR light. The addition of an $NaYF_4$:Tm upconverting shell permits the activation by NIR light. After coating with PEG, particles were shown to be hydrophilic, biocompatible and result in >70% cell death of oral squamous cell carcinoma (OSCC) cells after NIR exposure [52].

Controlled drug release can also be achieved using NIR light. A unique approach using black phosphorous nano sheets and a low melting point agarose hydrogel matrix has shown fully controllable drug release. Black phosphorous nano sheets show a very high photothermal conversion under NIR, therefore after activation in vivo the hydrogel degrades and releases encapsulated therapeutic molecules. A key feature of this system is the control over the rate of drug release (light intensity and exposure time) and the biocompatibility of the breakdown products after degradation [56]. The NIR mediated release of doxorubicin has also been shown using gold nanorods coated with a mesoporous silica shell. Pores in the silica were capped with the phase changing molecule 1-tetradecanol, and upon NIR heating of the gold nanorods the chemical caps change phase and open the pores, releasing the

drug. In addition to doxorubicin release, under intense NIR, the nanorods were also able to induce hyperthermia in the tumours. The nanoparticles were tested in KB cells (a sub-line of the cervical cancer HeLa cell line) and showed massive cell death in response to NIR exposure [57]. A further example of a NIR responsive with a mesoporous silica shell incorporates a $NaYF_4$:$Yb_{0.4}$/$Tm_{0.02}$@NaGdF4:$Yb_{0.1}$@$NaNdF_4$:$Yb_{0.1}$ core. Doxorubicin is retained within the porous shell by photocleavable platinum (IV) complexes. Upon NIR exposure and upconversion by the core to UV light photons, the platinum (IV) complex breaks down into a chemotherapeutic platinum (II) complex and simultaneously opens the pores and releases doxorubicin [53]. Chemotherapy and PDT were also combined in a system using nanoparticles with a polymer core containing a payload of cisplatin surrounded by an ordered asymmetrical shell of cholesterol and PEG, as well as the photosensitizer pyrolipid. Upon 600 nm irradiation the lipid layer is ruptured and the therapeutic molecule released in addition to ROS generated by the photosensitizer [58]. However, PDT can sometimes result in hypoxia. To tackle this, a smart system was designed to incorporate ROS-generating and hypoxia-sensitive 2-nitroimidazole-grafted conjugated polymer (CP-NI), polyvinyl alcohol-based surface coatings, and encapsulated doxorubicin hydrochloride. When exposed to NIR the polymer shell will generate ROS, this will cause cell death or may induce hypoxia, and in turn this causes the rupture of the nanoparticle and releases the encapsulated doxorubicin [59]. Targeting has also been extensively incorporated into nanoparticle systems to improve selectivity. One such example uses a β-$NaGdF_4$:Yb,Tm@NaGdF core to produce ROS in conjunction with the photosensitizer PC70, and a PEG coating for biocompatibility, which were also chain capped with folic acid. The nanoparticles were tested in HeLa-luc cells both in vitro, and in vivo within female mice; in both cases tumours were completely destroyed and negligible side effects were observed [60].

3. Evaluation of Both Intrinsic and Extrinsic Activation Systems

Activatable systems have the potential to provide an even greater level of specificity to cancer treatments. The aim will be to provide treatment with fewer side-effects and to enable a greater dose at the target site. While exploitation of the intrinsic changes in the physiology of cancer cells is an attractive proposal, problems lie in the relative changes seen compared to healthy cells. Enzyme targets, for example, are often expressed to some level in normal cells and can therefore lead to non-specific release. However, despite this, there are concentration differences in enzymes, proteins, and other small molecules which may assist in altering the therapeutic index by selective activation. In a similar fashion, pH-targeting may be able to provide an improved degree of resolution, but is reliant on either being targeted to the tumour, or intracellular uptake specifically in cancer cells. This can be improved by the addition of targeting moieties or combination with other functionalities such as directed radiotherapy or ultrasound. Despite this, those systems carrying chemotherapeutics or nucleic acids which are only released at the site of action can prevent degradation of the cargo, ensuring that more of the active compound is available for therapy.

Applications which use extrinsic activation are increasingly used to target therapies. Ultrasound has been used for many years in medicine for imaging, and may now find a new role. Ultrasound has been shown to have negligible cytotoxicity. However, there are limitations due to the poor penetration of ultrasound through bone and air. This

means that activation in regions such as the lungs or ribs could be difficult. More critically, some ultrasound frequencies cannot be used to treat intracranial tumours due to the possibility of inertial cavitation causing petechial haemorrhage [18].

Sonoporation also has limitations due to the fact that increased poration allows accumulation of therapeutic molecules in undesired tissues and organs, especially when performed close to vascular tissue [14]. This would be especially damaging when administering highly cytotoxic drugs. Ultimately this contradicts the selective uptake advantage of using ultrasound but could be overcome by optimization of ultrasound equipment. However, one big advantage for ultrasound therapy is that the frequencies and amplitudes needed for activation are achievable through existing hospital equipment.

Activation using NIR light has provided a means of stimulus that is a cheap, safe and minimally adverse to healthy tissue. However, penetration depths are still sub 4 mm through skin [61], which limits the usefulness of this technique. This is even more of an issue for wavelengths of light in the visible range. New systems using X-ray energy to activate PDT may be able to address the issue of limited utility due to penetration depth. An alternative technique which is highly penetrating, but non-ionizing, involves the use of AMF. Its ability to access areas of the body where other stimuli often fail is a distinct advantage. Also, AMF can be focused in targeted areas of the body with minimal adverse effects to the surrounding tissue.

While many activatable therapies are in their infancy, and are yet to reach the clinic, it can be clearly seen that there are many advantages to such systems. The ability to release therapies specifically at the target site can only confer advantages for cancer patients.

References

1. Boron, W.F. Regulation of intracellular pH. Adv. Physiol. Educ. 2004, 28, 160–179.
2. Kato, Y.; Ozawa, S.; Miyamoto, C.; Maehata, Y.; Suzuki, A.; Maeda, T.; Baba, Y. Acidic extracellular microenvironment and cancer. Cancer Cell Int. 2013, 13, 89.
3. Lin, W.-C.; Yu, D.-G.; Yang, M.-C. pH-sensitive polyelectrolyte complex gel microspheres composed of chitosan/sodium tripolyphosphate/dextran sulfate: Swelling kinetics and drug delivery properties. Colloids Surf. B Biointerfaces 2005, 44, 143–151.
4. Mura, S.; Nicolas, J.; Couvreur, P. Stimuli-responsive nanocarriers for drug delivery. Nat. Mater. 2013, 12, 991–1003.
5. Yang, Y.Q.; Zheng, L.S.; Guo, X.D.; Qian, Y.; Zhang, L.J. pH-Sensitive Micelles Self-Assembled from Amphiphilic Copolymer Brush for Delivery of Poorly Water-Soluble Drugs. Biomacromolecules 2011, 12, 116–122.

6. Gao, W.; Chan, J.; Farokhzad, O.C. pH-Responsive Nanoparticles for Drug Delivery. Mol. Pharm. 2010, 7, 1913–1920.
7. Bradley, G.; Juranka, P.F.; Ling, V. Mechanism of multidrug resistance. Biochim. Biophys. Acta - Rev. Cancer 1988, 948, 87–128.
8. Wang, Z.; Deng, X.; Ding, J.; Zhou, W.; Zheng, X.; Tang, G. Mechanisms of drug release in pH-sensitive micelles for tumour targeted drug delivery system: A review. Int. J. Pharm. 2018, 535, 253–260.
9. El-Sherbiny, I.M.; Abdel-Mogib, M.; Dawidar, A.-A.M.; Elsayed, A.; Smyth, H.D.C. Biodegradable pH-responsive alginate-poly (lactic-co-glycolic acid) nano/micro hydrogel matrices for oral delivery of silymarin. Carbohydr. Polym. 2011, 83, 1345–1354.
10. Tian, B.; Liu, S.; Wu, S.; Lu, W.; Wang, D.; Jin, L.; Hu, B.; Li, K.; Wang, Z.; Quan, Z. pH-responsive poly (acrylic acid)-gated mesoporous silica and its application in oral colon targeted drug delivery for doxorubicin. Colloids Surf. B Biointerfaces 2017, 154, 287–296.
11. Hsu, C.-H.; Cheng, A.-L. Clinical studies with Curcumin. In The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease; Springer: Boston, MA, USA, 2007; pp. 471–480.
12. Cui, J.; Yu, B.; Zhao, Y.; Zhu, W.; Li, H.; Lou, H.; Zhai, G. Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. Int. J. Pharm. 2009, 371, 148–155.
13. Robinson, R.K.; Batt, C.A.; Patel, P.D. Encyclopedia of Food Microbiology; Academic Press: San Diego, CA, USA, 2000; ISBN 0122270703.
14. Mullin, L.B.; Phillips, L.C.; Dayton, P.A. Nanoparticle delivery enhancement with acoustically activated microbubbles. IEEE Trans. Ultrason. Ferroelectr. Freq. Control 2013, 60, 65–77.
15. Deng, C.X.; Sieling, F.; Pan, H.; Cui, J. Ultrasound-induced cell membrane porosity. Ultrasound Med. Biol. 2004, 30, 519–526.
16. De Temmerman, M.-L.; Dewitte, H.; Vandenbroucke, R.E.; Lucas, B.; Libert, C.; Demeester, J.; De Smedt, S.C.; Lentacker, I.; Rejman, J. mRNA-Lipoplex loaded microbubble contrast agents for ultrasound-assisted transfection of dendritic cells. Biomaterials 2011, 32, 9128–9135.
17. Mannaris, C.; Teo, B.M.; Seth, A.; Bau, L.; Coussios, C.; Stride, E. Gas-Stabilizing Gold Nanocones for Acoustically Mediated Drug Delivery. Adv. Healthc. Mater. 2018, 7, 1800184.
18. Burke, C.W.; Alexander, E.; Timbie, K.; Kilbanov, A.L.; Price, R.J.; Price, R.J. Ultrasound-activated agents comprised of 5FU-bearing nanoparticles bonded to microbubbles inhibit solid tumor growth and improve survival. Mol. Ther. 2014, 22, 321–328.
19. Kwan, J.J.; Myers, R.; Coviello, C.M.; Graham, S.M.; Shah, A.R.; Stride, E.; Carlisle, R.C.; Coussios, C.C. Ultrasound-Propelled Nanocups for Drug Delivery. Small 2015, 11, 5305–5314.

20. Burke, C.W.; Hsiang, Y.-H.J.; Alexander, E.; Kilbanov, A.L.; Price, R.J.; Price, R.J. Covalently linking poly(lactic-co-glycolic acid) nanoparticles to microbubbles before intravenous injection improves their ultrasound-targeted delivery to skeletal muscle. Small 2011, 7, 1227–1235.
21. Chappell, J.C.; Song, J.; Burke, C.W.; Klibanov, A.L.; Price, R.J. Targeted delivery of nanoparticles bearing fibroblast growth factor-2 by ultrasonic microbubble destruction for therapeutic arteriogenesis. Small 2008, 4, 1769–1777.
22. Price, R.J.; Skyba, D.M.; Kaul, S.; Skalak, T.C. Delivery of colloidal particles and red blood cells to tissue through microvessel ruptures created by targeted microbubble destruction with ultrasound. Circulation 1998, 98, 1264–1267.
23. Shi, H.; Gao, T.; Shi, L.; Chen, T.; Xiang, Y.; Li, Y.; Li, G. Molecular imaging of telomerase and the enzyme activity-triggered drug release by using a conformation-switchable nanoprobe in cancerous cells. Sci. Rep. 2018, 8, 16341.
24. Cochran, M.C.; Eisenbrey, J.; Ouma, R.O.; Soulen, M.; Wheatley, M.A. Doxorubicin and paclitaxel loaded microbubbles for ultrasound triggered drug delivery. Int. J. Pharm. 2011, 414, 161–170.
25. Villar-Alvarez, E.; Cambón, A.; Pardo, A.; Mosquera, V.X.; Bouzas-Mosquera, A.; Topete, A.; Barbosa, S.; Taboada, P.; Mosquera, V. Gold Nanorod-Based Nanohybrids for Combinatorial Therapeutics. ACS Omega 2018, 3, 12633–12647.
26. Pearce, J.; Giustini, A.; Stigliano, R.; Jack Hoopes, P. Magnetic Heating of Nanoparticles: The Importance of Particle Clustering to Achieve Therapeutic Temperatures. J. Nanotechnol. Eng. Med. 2013, 4, 011005.
27. Shah, R.R.; Davis, T.P.; Glover, A.L.; Nikles, D.E.; Brazel, C.S. Impact of magnetic field parameters and iron oxide nanoparticle properties on heat generation for use in magnetic hyperthermia. J. Magn. Magn. Mater. 2015, 387, 96–106.
28. Noto, V.; Taper, H.S.; Yi-Hua, J.; Janssens, J.; Bonte, J.; De Loecker, W. Effects of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K3) treatment on human tumor cell growth in vitro. I. Synergism of combined vitamin C and K3 action. Cancer 1989, 63, 901–906.
29. Johannsen, M.; Gneveckow, U.; Eckelt, L.; Feussner, A.; WaldÖFner, N.; Scholz, R.; Deger, S.; Wust, P.; Loening, S.A.; Jordan, A. Clinical hyperthermia of prostate cancer using magnetic nanoparticles: Presentation of a new interstitial technique. Int. J. Hyperth. 2005, 21, 637–647.
30. Bañobre-López, M.; Teijeiro, A.; Rivas, J. Magnetic nanoparticle-based hyperthermia for cancer treatment. Rep. Pract. Oncol. Radiother. 2013, 18, 397–400.
31. Vedova, P.D.; Ilieva, M.; Zhurbenko, V.; Mateiu, R.; Faralli, A.; Dufva, M.; Hansen, O. Gold Nanoparticle-Based Sensors Activated by External Radio Frequency Fields. Small 2015, 11, 248–256.

32. Raoof, M.; Corr, S.J.; Kaluarachchi, W.D.; Massey, K.L.; Briggs, K.; Zhu, C.; Cheney, M.A.; Wilson, L.J.; Curley, S.A. Stability of antibody-conjugated gold nanoparticles in the endolysosomal nanoenvironment: implications for noninvasive radiofrequency-based cancer therapy. Nanomed. Nanotechnol. Biol. Med. 2012, 8, 1096–1105.
33. Mironava, T.; Arachchilage, V.T.; Myers, K.J.; Suchalkin, S. Gold Nanoparticles and Radio Frequency Field Interactions: Effects of Nanoparticle Size, Charge, Aggregation, Radio Frequency, and Ionic Background. Langmuir 2017, 33, 13114–13124.
34. Yildiz, T.; Gu, R.; Zauscher, S.; Betancourt, T. Doxorubicin-loaded protease-activated near-infrared fluorescent polymeric nanoparticles for imaging and therapy of cancer. Int. J. Nanomed. 2018, 13, 6961–6986.
35. Katagiri, K.; Imai, Y.; Koumoto, K.; Kaiden, T.; Kono, K.; Aoshima, S. Magnetoresponsive On-Demand Release of Hybrid Liposomes Formed from Fe3O4 Nanoparticles and Thermosensitive Block Copolymers. Small 2011, 7, 1683–1689.
36. Pradhan, P.; Giri, J.; Rieken, F.; Koch, C.; Mykhaylyk, O.; Döblinger, M.; Banerjee, R.; Bahadur, D.; Plank, C. Targeted temperature sensitive magnetic liposomes for thermo-chemotherapy. J. Control. Release 2010, 142, 108–121.
37. Plassat, V.; Wilhelm, C.; Marsaud, V.; Ménager, C.; Gazeau, F.; Renoir, J.-M.; Lesieur, S. Anti-Estrogen-Loaded Superparamagnetic Liposomes for Intracellular Magnetic Targeting and Treatment of Breast Cancer Tumors. Adv. Funct. Mater. 2011, 21, 83–92.
38. Hu, S.-H.; Chen, S.-Y.; Gao, X. Multifunctional Nanocapsules for Simultaneous Encapsulation of Hydrophilic and Hydrophobic Compounds and On-Demand Release. ACS Nano 2012, 6, 2558–2565.
39. Hua, M.-Y.; Liu, H.-L.; Yang, H.-W.; Chen, P.-Y.; Tsai, R.-Y.; Huang, C.-Y.; Tseng, I.-C.; Lyu, L.-A.; Ma, C.-C.; Tang, H.-J.; et al. The effectiveness of a magnetic nanoparticle-based delivery system for BCNU in the treatment of gliomas. Biomaterials 2011, 32, 516–527.
40. Yang, H.-W.; Hua, M.-Y.; Liu, H.-L.; Huang, C.-Y.; Tsai, R.-Y.; Lu, Y.-J.; Chen, J.-Y.; Tang, H.-J.; Hsien, H.-Y.; Chang, Y.-S.; et al. Self-protecting core-shell magnetic nanoparticles for targeted, traceable, long half-life delivery of BCNU to gliomas. Biomaterials 2011, 32, 6523–6532.
41. Nigam, S.; Bahadur, D. Dendrimer-conjugated iron oxide nanoparticles as stimuli-responsive drug carriers for thermally-activated chemotherapy of cancer. Colloids Surf. B Biointerfaces 2017, 155, 182–192.
42. Stanley, S.A.; Gagner, J.E.; Damanpour, S.; Yoshida, M.; Dordick, J.S.; Friedman, J.M. Radio-Wave Heating of Iron Oxide Nanoparticles Can Regulate Plasma Glucose in Mice. Science 2012, 336, 604–608.

43. Huang, H.-Y.; Hu, S.-H.; Chian, C.-S.; Chen, S.-Y.; Lai, H.-Y.; Chen, Y.-Y. Self-assembling PVA-F127 thermosensitive nanocarriers with highly sensitive magnetically-triggered drug release for epilepsy therapy in vivo. J. Mater. Chem. 2012, 22, 8566.
44. Satarkar, N.S.; Zach Hilt, J. Hydrogel nanocomposites as remote-controlled biomaterials. Acta Biomater. 2008, 4, 11–16.
45. Hu, S.-H.; Liu, D.-M.; Tung, W.-L.; Liao, C.-F.; Chen, S.-Y. Surfactant-Free, Self-Assembled PVA-Iron Oxide/Silica Core-Shell Nanocarriers for Highly Sensitive, Magnetically Controlled Drug Release and Ultrahigh Cancer Cell Uptake Efficiency. Adv. Funct. Mater. 2008, 18, 2946–2955.
46. Hu, S.-H.; Chen, S.-Y.; Liu, D.-M.; Hsiao, C.-S. Core/Single-Crystal-Shell Nanospheres for Controlled Drug Release via a Magnetically Triggered Rupturing Mechanism. Adv. Mater. 2008, 20, 2690–2695.
47. Bringas, E.; Köysüren, Ö.; Quach, D.V.; Mahmoudi, M.; Aznar, E.; Roehling, J.D.; Marcos, M.D.; Martínez-Máñez, R.; Stroeve, P. Triggered release in lipid bilayer-capped mesoporous silica nanoparticles containing SPION using an alternating magnetic field. Chem. Commun. 2012, 48, 5647.
48. Allison, R.R.; Sibata, C.H. Oncologic photodynamic therapy photosensitizers: A clinical review. Photodiagn. Photodyn. Ther. 2010, 7, 61–75.
49. Wang, M.; Abbineni, G.; Clevenger, A.; Mao, C.; Xu, S. Upconversion nanoparticles: Synthesis, surface modification and biological applications. Nanomedicine 2011, 7, 710–729.
50. Haynes, W.M. CRC Handbook of Chemistry and Physics: A Ready-Reference Book of Chemical and Physical Data; CRC Press: Boca Raton, FL, USA, 2009.
51. Meng, Q.; Meng, J.; Ran, W.; Wang, J.; Zhai, Y.; Zhang, P.; Li, Y. Light-Activated Core–Shell Nanoparticles for Spatiotemporally Specific Treatment of Metastatic Triple-Negative Breast Cancer. ACS Nano 2018, 12, 2789–2802.
52. Lucky, S.S.; Muhammad Idris, N.; Li, Z.; Huang, K.; Soo, K.C.; Zhang, Y. Titania Coated Upconversion Nanoparticles for Near-Infrared Light Triggered Photodynamic Therapy. ACS Nano 2015, 9, 191–205.
53. Dai, Y.; Bi, H.; Deng, X.; Li, C.; He, F.; Ma, P.; Yang, P.; Lin, J. 808 nm near-infrared light controlled dual-drug release and cancer therapy in vivo by upconversion mesoporous silica nanostructures. J. Mater. Chem. B 2017, 5, 2086–2095.
54. Huang, L.; Li, Z.; Zhao, Y.; Zhang, Y.; Wu, S.; Zhao, J.; Han, G. Ultralow-Power Near Infrared Lamp Light Operable Targeted Organic Nanoparticle Photodynamic Therapy. J. Am. Chem. Soc. 2016, 138, 14586–14591.

55. Vankayala, R.; Kuo, C.-L.; Nuthalapati, K.; Chiang, C.-S.; Hwang, K.C. Nucleus-Targeting Gold Nanoclusters for Simultaneous In Vivo Fluorescence Imaging, Gene Delivery, and NIR-Light Activated Photodynamic Therapy. Adv. Funct. Mater. 2015, 25, 5934–5945.
56. Qiu, M.; Wang, D.; Liang, W.; Liu, L.; Zhang, Y.; Chen, X.; Sang, D.K.; Xing, C.; Li, Z.; Dong, B.; et al. Novel concept of the smart NIR-light-controlled drug release of black phosphorus nanostructure for cancer therapy. Proc. Natl. Acad. Sci. USA 2018, 115, 501–506.
57. Liu, J.; Detrembleur, C.; De Pauw-Gillet, M.-C.; Mornet, S.; Jérôme, C.; Duguet, E. Gold Nanorods Coated with Mesoporous Silica Shell as Drug Delivery System for Remote Near Infrared Light-Activated Release and Potential Phototherapy. Small 2015, 11, 2323–2332.
58. He, C.; Liu, D.; Lin, W. Self-Assembled Core–Shell Nanoparticles for Combined Chemotherapy and Photodynamic Therapy of Resistant Head and Neck Cancers. ACS Nano 2015, 9, 991–1003.
59. Qian, C.; Yu, J.; Chen, Y.; Hu, Q.; Xiao, X.; Sun, W.; Wang, C.; Feng, P.; Shen, Q.-D.; Gu, Z. Light-Activated Hypoxia-Responsive Nanocarriers for Enhanced Anticancer Therapy. Adv. Mater. 2016, 28, 3313–3320.
60. Guan, M.; Dong, H.; Ge, J.; Chen, D.; Sun, L.; Li, S.; Wang, C.; Yan, C.; Wang, P.; Shu, C. Multifunctional upconversion–nanoparticles–trismethylpyridylporphyrin–fullerene nanocomposite: A near-infrared light-triggered theranostic platform for imaging-guided photodynamic therapy. NPG Asia Mater. 2015, 7, e205.
61. Stolik, S.; Delgado, J.; Pérez, A.; Anasagasti, L. Measurement of the penetration depths of red and near infrared light in human “ex vivo” tissues. J. Photochem. Photobiol. B Biol. 2000, 57, 90–93.

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