ACCOUNTS of chemical research

Article

Cite This: Acc. Chem. Res. 2018, 51, 999−1013

pubs.acs.org/accounts

Nanosystems Based on Magnetic Nanoparticles and Thermo- or pH-Responsive Polymers: An Update and Future Perspectives

Published as part of the Accounts of Chemical Research special issue "The Interface of Biology with Nanoscience and Electronics".

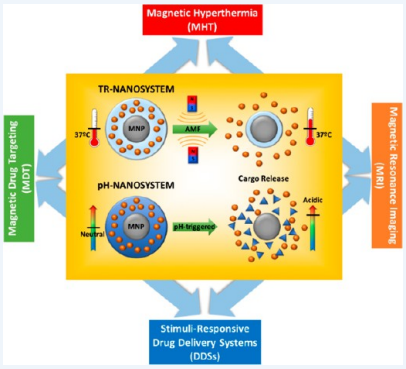
Binh T. Mai,[†] Soraia Fernandes,[†] Preethi B. Balakrishnan,[†] and Teresa Pellegrino*

Italian Institute of Technology, via Morego 30, 16163 Genoa, Italy

Supporting Information

CONSPECTUS: Combining hard matter, like inorganic nanocrystals, and soft materials, like polymers, can generate multipurpose materials with a broader range of applications with respect to the individual building blocks. Given their unique properties at the nanoscale, magnetic nanoparticles (MNPs) have drawn a great deal of interest due to their potential use in the biomedical field, targeting several applications such as heat hubs in magnetic hyperthermia (MHT, a heat-damage based therapy), contrast agents in magnetic resonance imaging (MRI), and nanocarriers for targeted drug delivery. At the same time, polymers, with their versatile macromolecular structure, can serve as flexible platforms with regard to constructing advanced functional materials. Advances in the development of novel polymerization techniques has enabled the preparation of a large portfolio of polymers that have intriguing physicochemical properties; in particular, those polymers that can undergo conformational and structural changes in response to their surrounding environmental stimuli. Therefore, merging the unique features of MNPs with polymer responsive properties, such as pH and thermal stimuli activation, enables smart control of polymer properties operated by the MNPs and *vice versa* at an unprecedented level of sophistication. These magnetic-stimuli-responsive nanosystems will impact the cancer field by combining magnetic hyperthermia with stimuli-dependent controlled drug delivery toward multimodal therapies. In this approach, a malignant tumor may be destroyed by a combination of the synergic effects of thermal energy generated by MNPs and the controlled release of antitumoral agents, activated by means of either heat or pH changes, finally leading to a much more effective cancer treatment than those available today. Also, taking advantage of such a triggered chemotherapy will overcome the notorious drawbacks of classic chemotherapy. Nevertheless, tracking the changes in the magnetic properties of such pH-responsive magnetic nanoparticles, which are provided by changes in relaxation signals of water molecules surrounding the nanoplatform, is a novel approach to the detection of pathological conditions (such as pH-changes at the ischemic and tumor sites). Despite great efforts by chemists to fabricate different featured materials, there have been few successful preclinical studies to date. A clinical translation of magnetic stimuli-responsive systems would require overcoming the actual nanosystem limitations and the joint efforts of an interdisciplinary scientific community.

In this Account, we have framed state of the art magnetic stimuli-responsive systems, focusing on thermo- and pH-responsive behavior, following an organization based on the response mechanisms of polymers. By evaluating the features of the most representative and advanced nanosystems that already exist in literature, we present the challenges to overcome, the future directions to undertake for the development of magnetic stimuli-responsive nanoplatforms that will work under clinical operating conditions and have biodegradable and biocompatible features, and a consideration of the technical aspects.



MAGNETIC THERMORESPONSIVE POLYMERIC NANOSYSTEMS (TR-NANOSYSTEMS)

Our immune system fights pathogens by recruiting multiple immune cells that release various inflammatory factors, consequently producing heat (fever) during their course of action.[1,2] Oncothermia mimics this natural fever, producing hyperthermia conditions in tumors. Over the last few decades, an increase in temperature specifically at disease sites has been achieved in the clinic by different external means (e.g., radiofrequency thermal ablation (RFA), microwave hyperthermia, high-intensity focused ultrasound, etc.). In thermal medicine, temperature elevation has been used as an adjuvant treatment to make surgery or standard chemotherapy more effective. In magnetic hyperthermia (MHT), producing heat using magnetic nanoparticles (MNPs) that are externally excited by an alternating magnetic field (AMF) has become popular due to the high spatial and temporal control of the generated heat.[2,3] Activating the MNPs that are located deep inside the tissues or organs by MHT can be accomplished at

Received: November 7, 2017
Published: May 7, 2018

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

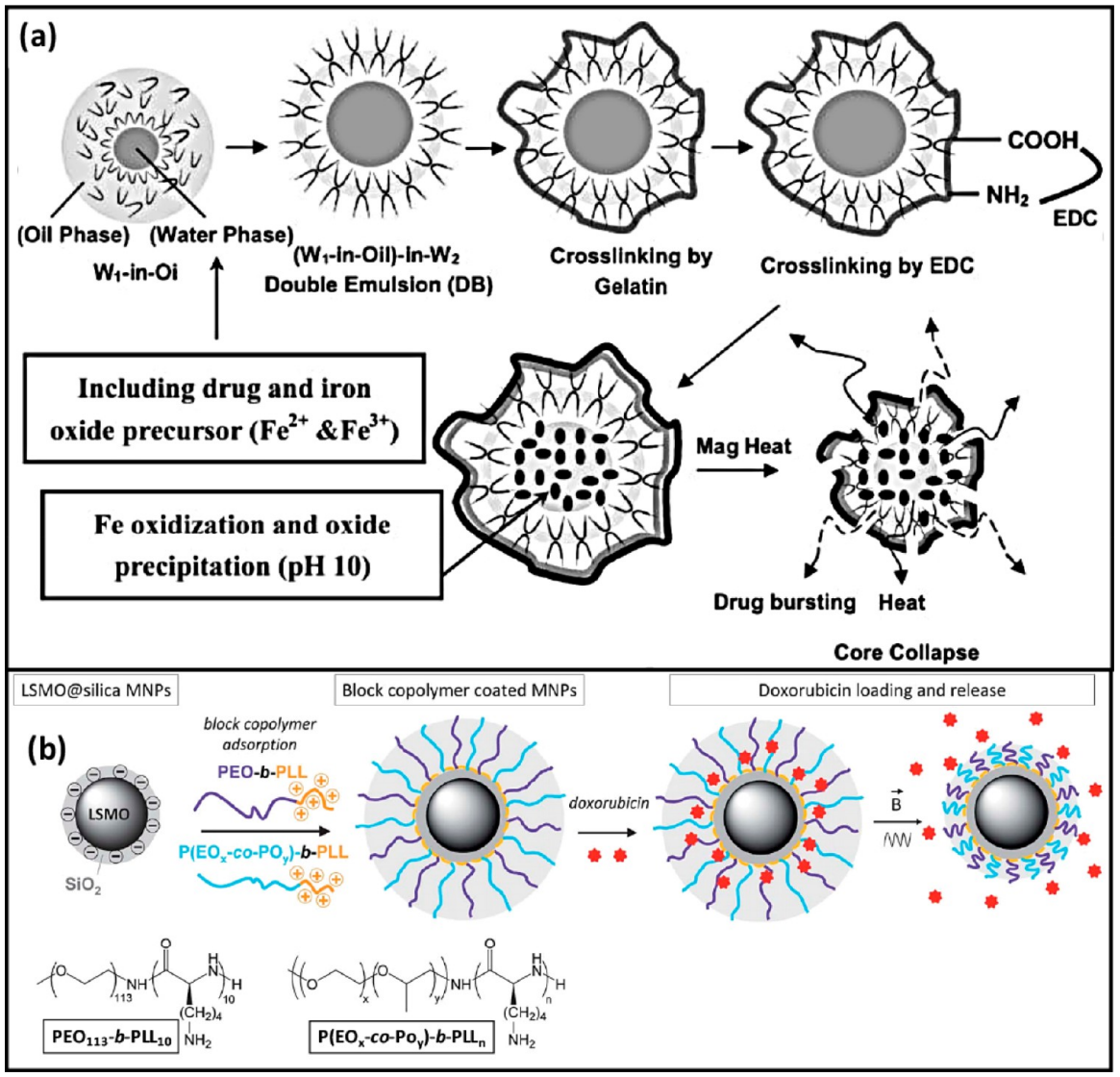


Figure 1. (a, b) Schematic representation of block copolymer-based TR-nanosystems. Reproduced with permission from refs 9 and 10. Copyright 2009 Wiley and 2012 RSC.

frequencies (f) and field ($\mathbf{H}$) conditions ($\mathbf{H}f \leq 5 \times 10^9$ A m^{-1} Hz) that do not harm the human body.[4] Iron oxide nanoparticles (IONPs) and MHT at 110 kHz and 24 kA/m are used on patients with glioblastoma multiforme.[5]

Raised temperatures, besides providing direct damage, can also trigger drug release. To date, heat-sensitive liposomes for doxorubicin (DOXO) delivery (ThermoDox,Celsion) are the most advanced thermo-activated formulations available, which, in combination with RFA, improved the overall survival of patients affected with hepatocellular carcinoma by 79 months.[6]

Using MNPs with thermosensitive materials can combine the advantage of MNP activation at a limitless penetration depth under AMF with a heat-mediated controlled drug release. In addition to heat-sensitive liposomes and thermolabile molecules, thermoresponsive polymers (TR-polymers) also possess heat-dependent activation properties.[2,7]

TR-polymers, which can undergo conformational and physical changes in response to changes in the solution temperature, are very popular among the magnetic materials community. Although TR-polymers have been extensively used alone, their practical applications as drug delivery systems (DDSs) are not completely accessible due to difficulties in producing local heat, specifically at pathologic areas, which is a requirement for selectively releasing the loaded cargo.[2] In this Account, we will focus on TR-polymers with different response mechanisms, which, when combined with MNPs, offer intriguing opportunities regarding the development of a novel class of nanomaterials for multicombinatorial therapies or trackable DDSs.

Lower Critical Solution Temperature (LCST) Polymers

These polymers are soluble at temperatures lower than their transition temperature (T_c), forming hydrogen bonds with water or hydrophilic drug molecules. These interactions explain the encapsulation of the cargo molecules within the polymer matrix. At temperatures higher than the LCST, the hydrogen bond networks are disturbed, favoring hydrophobic polymer interactions, thus promoting mechanical polymer contractions and consequently releasing the hydrophilic cargo.[8]

Huge efforts were dedicated to fabricating most of these TR-nanosystems, where water bath heat treatments were used rather than AMF to verify their heat-responsiveness. This renders most of these works preliminary. Herein, we consider

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

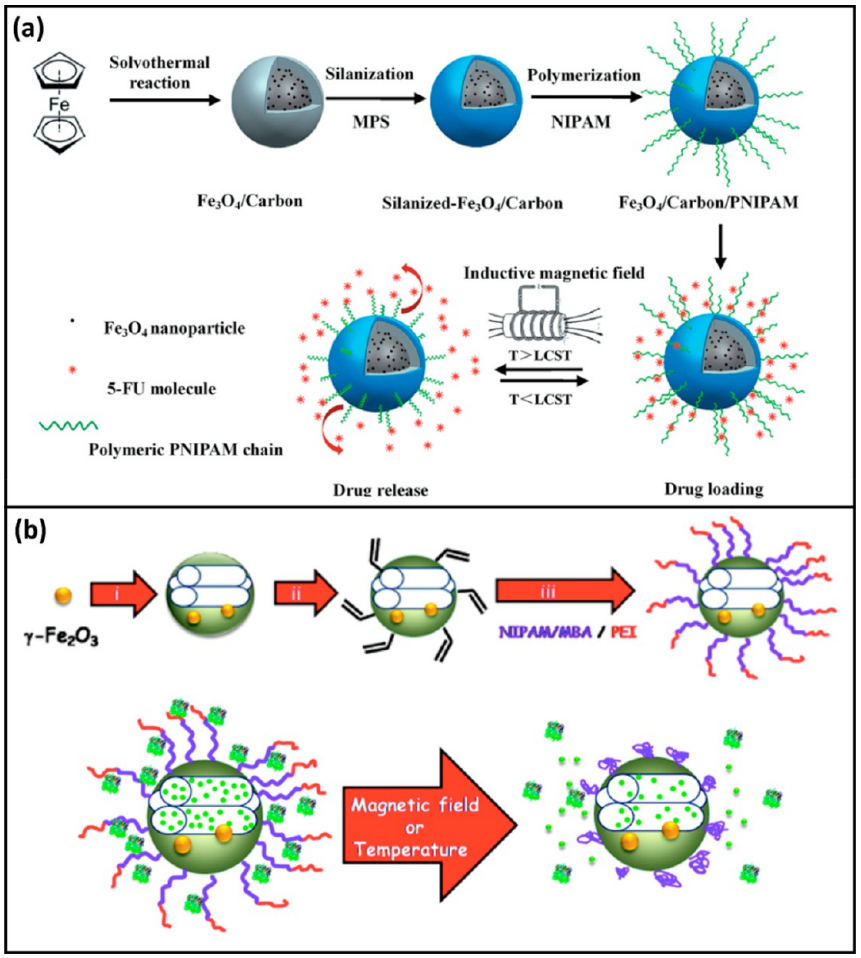


Figure 2. TR-nanosystem incorporated mesoporous silica matrices and the release profile of small molecules and proteins (dual release system, b). Reproduced with permission from refs 15 and 17. Copyright 2014 RSC and 2012 ACS.

TR-nanosystems that have been exploited for drug release experiments, in not only test tube or cellular studies but also *in vivo* proofs of concept using hyperthermia (Table S1−S5).

Pluronic Polymers Systems

Among the first examples exploiting this concept, Chen's group used water-in-oil thermosensitive PEO-*b*-PPO-*b*-PEO, Pluronic F127 (F127), nanospheres as templates to grow *in situ* MNPs. DOXO was loaded, and interestingly, the release by applying an external AMF (2.5 kA·m^{-1} and 50−100 kHz) was two times higher than that obtained in a thermal water bath (WB) at 62 °C. However, the LCST (35 °C) of this polymer, which is lower than body temperature, impaired its practical application. The same group prepared magneto-nanocapsules based on PEO-*b*-PPO-*b*-PEO triblock copolymers (Pluronic F127 and F68) that were cross-linked with gelatin, reaching a LCST of 40 °C (Figure 1a).[9] Less and slower vitamin B12 (model drug) release was observed from magneto-nanocapsules based on Pluronic F68 (LCST ≈ 40 °C) in WB at 4, 25, or 37 °C than under AMF (2.5 kA·m^{-1}and 50−100 kHz, T = 45 °C). A system with such characteristics is ideal for triggered drug delivery, as it ensures long-term storage and minimal drug leakage at body temperature. Although mild MHT conditions were used, a comparison with other works is difficult because the amount of MNPs is not reported. In a more recent work, Lecommandoux's group performed an electrostatic coabsorption of poly(ethylene oxide)-*b*-poly(L-lysine) (PEO-*b*-PLL) and thermoresponsive poly(ethylene oxide-*co*-propylene oxide)-*b*-poly(L-lysine) (P(EO$_x$-*co*-PO$_y$)-*b*-PLL) onto the surface of silica-coated magnetic lanthanum strontium manganite NPs (Figure 1b).[10] The release of DOXO from such carriers could be accelerated under AMF, even without reaching a temperature above the LCST (43 °C), thus allowing it to be delivered even with a very low dose of MNPs. Nevertheless, the AMF conditions (88 mT, 108 kHz) were above the biological limit.

Poly(*N*-isopropylacrylamide) (PNIPAm)

This polymer is considered a gold standard material for preparing TR-nanosystems.[8] Despite its low LCST (∼32 °C), the temperature can be easily tuned above 37 °C by simply copolymerizing NIPAm with more hydrophilic monomers.[11,12] The original systems were developed by Ramanujan's group, in which IONPs were encapsulated in a PNIPAm matrix, cross-linked with *N*,*N*-methylene(bis)acrylamide (MBAm) and used for an AMF-triggered delivery of DOXO *in vitro*.[13] Good *in vivo* magnetic targeting, MRI performance, heating capacity under AMF, and heat-triggered release of DOXO on hepatocellular carcinoma (HCC) were recorded in their studies.[14] To deliver 5-fluorouracil, Liu's group (Figure 2a) synthesized a similar structure, using IONPs in a carbon matrix, post-modified with 3-(trimethoxysilyl) propyl methacrylate then copolymerized with PNIPAm and MBAm via dispersion polymerization.[15] In another approach, Jaber's group first prepared mesoporous silica-modified IONPs, then filled the pores with PNIPAm.[16]

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

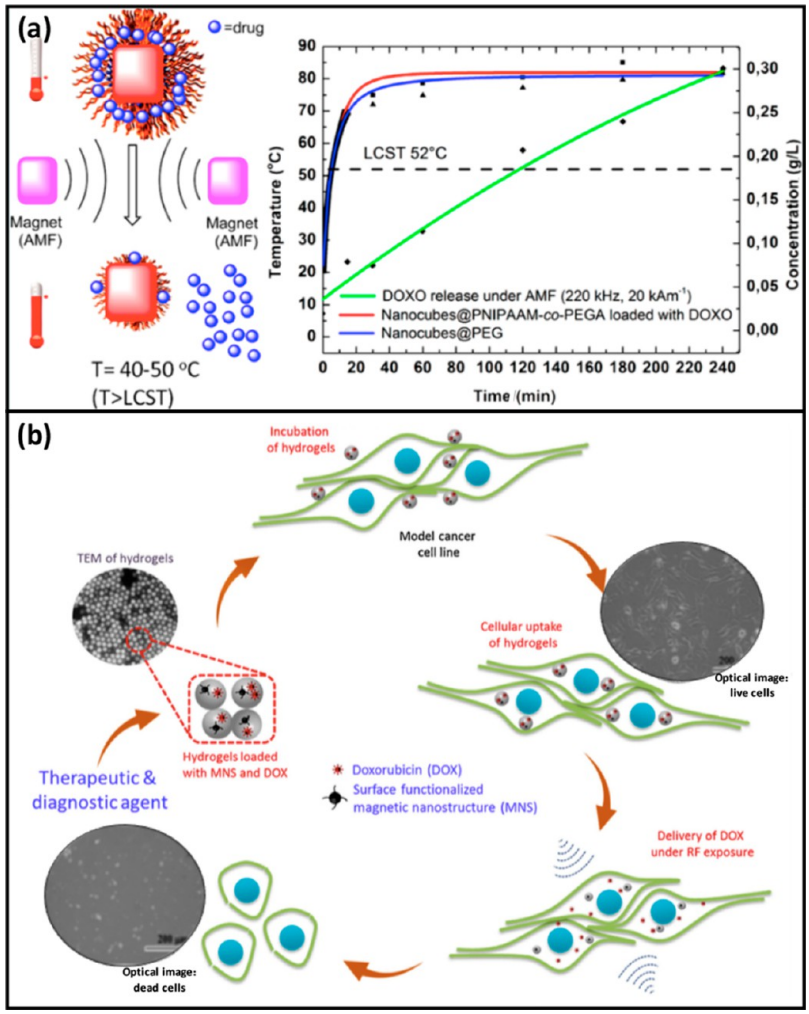


Figure 3. Examples of PMIPAM-based TR-nanosystems with LCST polymers. Reproduced with permission from refs 19 and 20. Copyright 2015 ACS and 2015 Elsevier.

The heat generated by MNPs under AMF induced the release of preloaded $H_3PMo_{12}O_{40}$, a heteropoly acidic agent showing antiviral and anticancer activity. Using IONPs@mSiO$_2$ as a building block, Vallet-Regí's group (Figure 2b) functionalized these nanostructures with PNIPAm-*b*-PEI.[17] The resulting materials delivered small molecules or proteins following a magnetically triggered mechanism without losing their bioactivities. In all PNIPAm based materials here described, a LCST of 34−35 °C was targeted, which was suitable for proof of concept but not for practical applications.[14−18]

Our group (Figure 3a) managed to grow a copolymer P(NIPAm-*co*-PEGA) from the surface of cubic-IONPs with a tunable LCST above 37 °C by varying the NIPAm/PEGA ratio.[19] DOXO release was demonstrated in a test tube under mild MHT, within the biological limit and with a significantly low material dose (2.5 g·L^{-1} of iron). In another configuration, PEGylated IONPs were embedded into nanogels made of PNIPAm cross-linked with MBAm (LCST 40 °C) (Figure 3b).[20] The DOXO-loaded nanogels showed more toxicity to bladder cancer cells upon exposure to AMF than cells without AMF exposure.

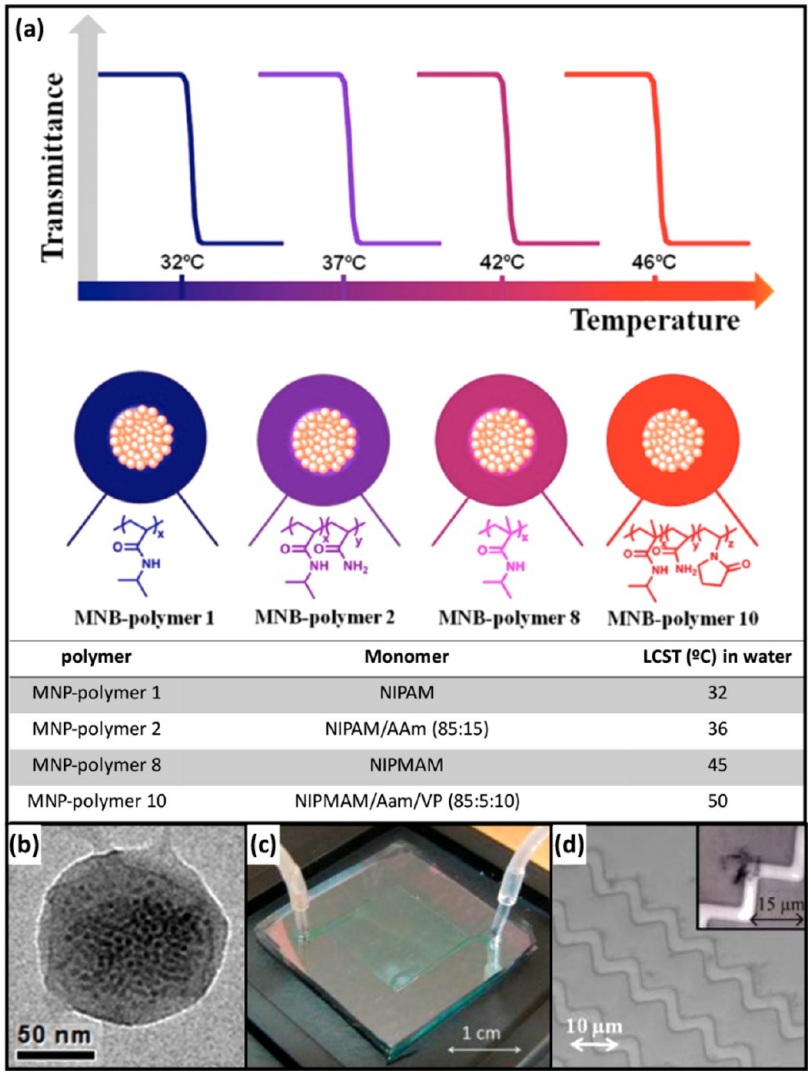
Few groups have used TR-nanosystems for magnetic drug targeting (MDT). Pellegrino's group exploited the heat-response of various TR-nanosystems to enhance accumulation at the magnetic corners (Figure 4).[12] The PNIPAm shell was grown on top of multiple MNPs (nanobeads). In a microfluidic chamber mimicking the capillary blood flow, nanobeads were trapped only at temperatures above the T_c. TR-nanosystems collapsed in larger aggregations with higher magnetic responses than single nanobeads. This heat-mediated aggregation facilitated the physical accumulation of the DOXO−TR-nanosystem at the targeted magnetic sites (permalloy tips) placed underneath the microchannels.

To expand the scope of TR-nanosystems, Aoyagi's group electrospun nanofibers made of MNPs and poly(NIPAm-*co*-HMAm) loaded with DOXO (Figure 5).[21] A temperature response at 45 °C was reached under AMF, and this direct heat damage in combination with released DOXO was capable of killing skin cancer cells. However, this proof of concept was provided under AMF conditions above the safe limit. In another approach, poly(ε-lysine) dendrons tethered with carboxybetaine were used to functionalize superparamagnetic IONPs to deliver a vascular endothelial growth factor (VEGF). However, the release of VEGF mediated by mild MHT was demonstrated only in test tube.[22]

Upper Critical Solution Temperature (UCST) Polymers

These polymers exhibit the opposite behavior to LCST. Hydrophobic polymer interactions are strong below the UCST (collapsed state), while above UCST, they are reduced

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013



polymer	Monomer	LCST (ºC) in water
MNP-polymer 1	NIPAM	32
MNP-polymer 2	NIPAM/AAm (85:15)	36
MNP-polymer 8	NIPMAM	45
MNP-polymer 10	NIPMAM/Aam/VP (85:5:10)	50

Figure 4. TR-nanosystems for MDT application. (a) Various PNIPAm-based systems studied; (b) TEM image of a nanobead; (c) microfluidic device; (d) nanobeads trapped at the magnetic corners. Reproduced with permission from ref 12. Copyright 2012 ACS.

and the polymer becomes water-soluble. Only one example of TR-nanosystem based on UCST-type polymers (Figure 6) has been reported.[23] Non-protonated DOXO and hydrophobic MNPs were encapsulated in poly(ethylene glycol)-*g*-poly(acrylamide-*co*-acrylonitrile) micelles surface-modified with A54, a targeting peptide for hepatic tumor cells. Stable micelles dissociated and burst-released DOXO above 43 °C, achieved by means of a microwave. AMF has not been tested yet with this system.

Injection Induced-Gelation Polymers

Poly(organophosphazene)s (PPZs) are interesting biocompatible, biodegradable, thermosensitive polymers. PPZs first undergo a gelation transition then decomposition upon a gradual temperature increase. Hydrophobic MNPs were encapsulated in PEGylated PPZs (Figure 7). In a pioneer *in vivo* study on a glioblastoma mouse model, the gelation process under AMF, retained MNPs at the tumor site.[24] As materials for the gelation, other groups have used polysaccharides and alginates, which are sensitive to Ca^{2+} and Mg^{2+} cations,[25] and hydroxypropyl methyl cellulose, which is sensitive to the switch of media.[26] Such gelation processes, which occur at 37 °C, are useful for local injections but might be problematic for intravenous injections.

Glass Transition (T_g) Polymer

Hayashi's group prepared clustered Fe_3O_4–poly(pyrrole carboxylic acid) loaded with DOXO.[27] In this case, poly(pyrrole) allowed drugs to be loaded via $\pi-\pi$ stacking between DOXO and pyrrole, and a temperature response at T_g of 44 °C. This material, when intratumorally injected, was able to efficiently subside tumor induced by human multiple myeloma cells. These three preclinical studies used mild MHT conditions, under the biological limit. In preliminary studies, T_g polymers based on FDA-approved poly(lactide-*co*-glycolide) (PLGA) were also employed in combination with MNPs for MHT and drug delivery.[28] These studies were conducted under nonoptimized conditions (commercially available IONPs of unknown performance, only test tubes), and further improvements for clinical translation are certainly possible.

MAGNETIC pH-RESPONSIVE POLYMERIC NANOSYSTEM (pH-NANOSYSTEMS)

Local changes in pH occur naturally in our body at different organs, tissues, and cellular levels, for example, the stomach

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

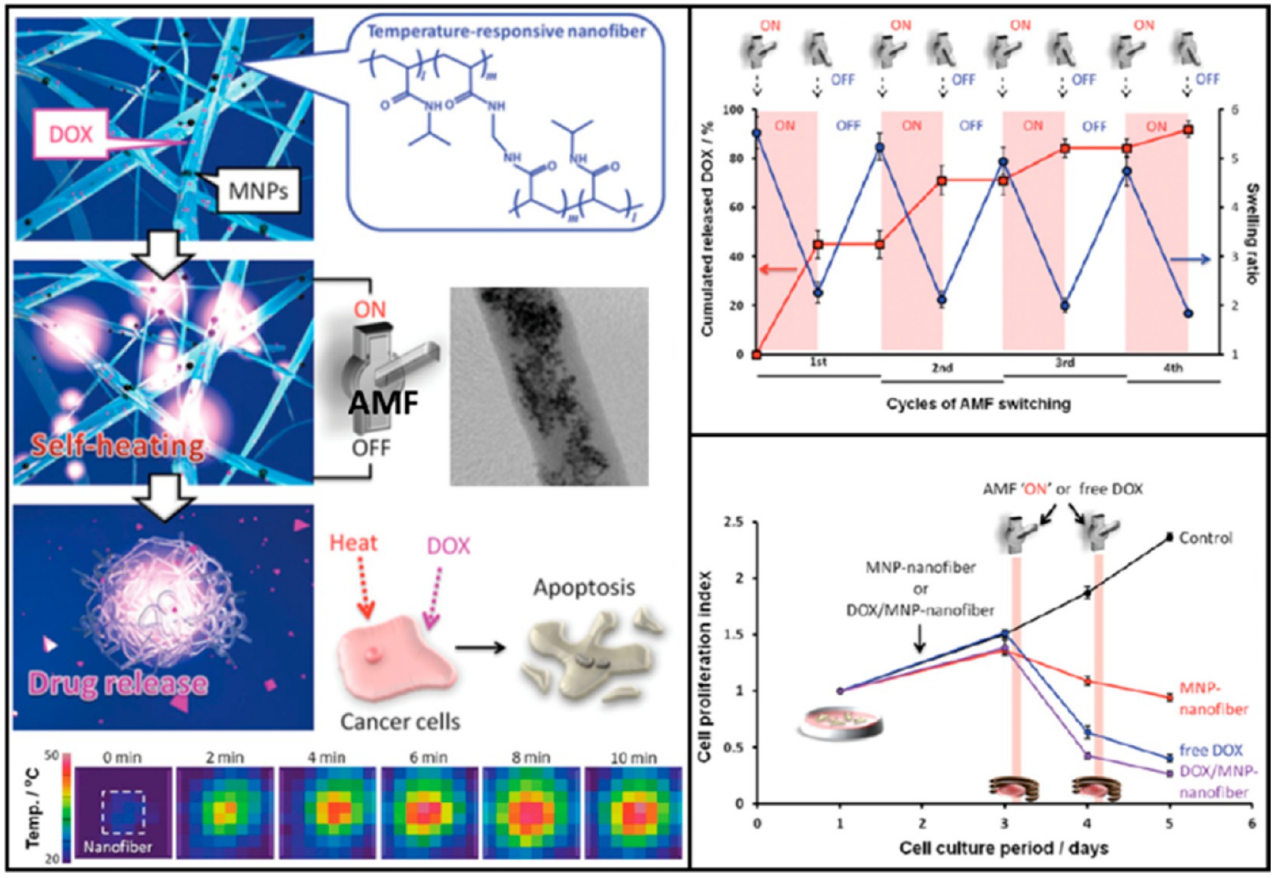


Figure 5. Electrospun nanofibers as TR-nanosystem for MHT and drug release. Reproduced with permission from ref 21. Copyright 2013 Wiley.

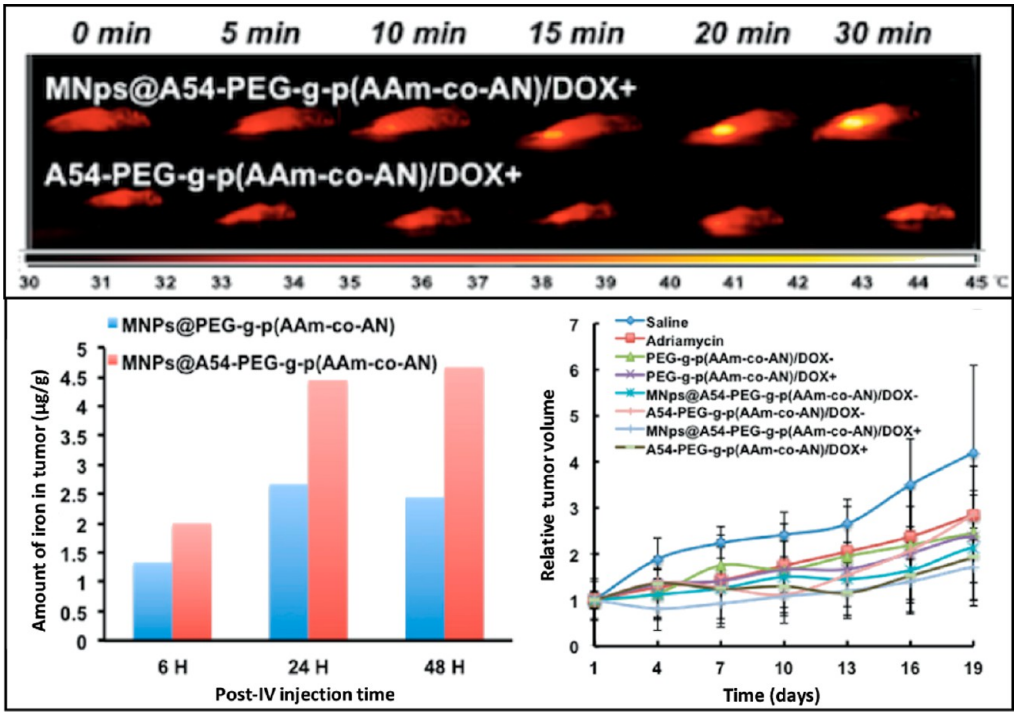


Figure 6. An UCST TR-nanosystem. Reproduced with permission from ref 23. Copyright 2017 Elsevier.

versus the intestine, the intracellular endosomal−lysosomal compartments versus the cellular cytoplasm. This pH difference also occurs in some pathological conditions, such as inflammatory or tumor microenvironment. pH-responsive polymers from either natural or synthetic origins, showing changes in solubility, volume, chain conformations, or hydro-

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

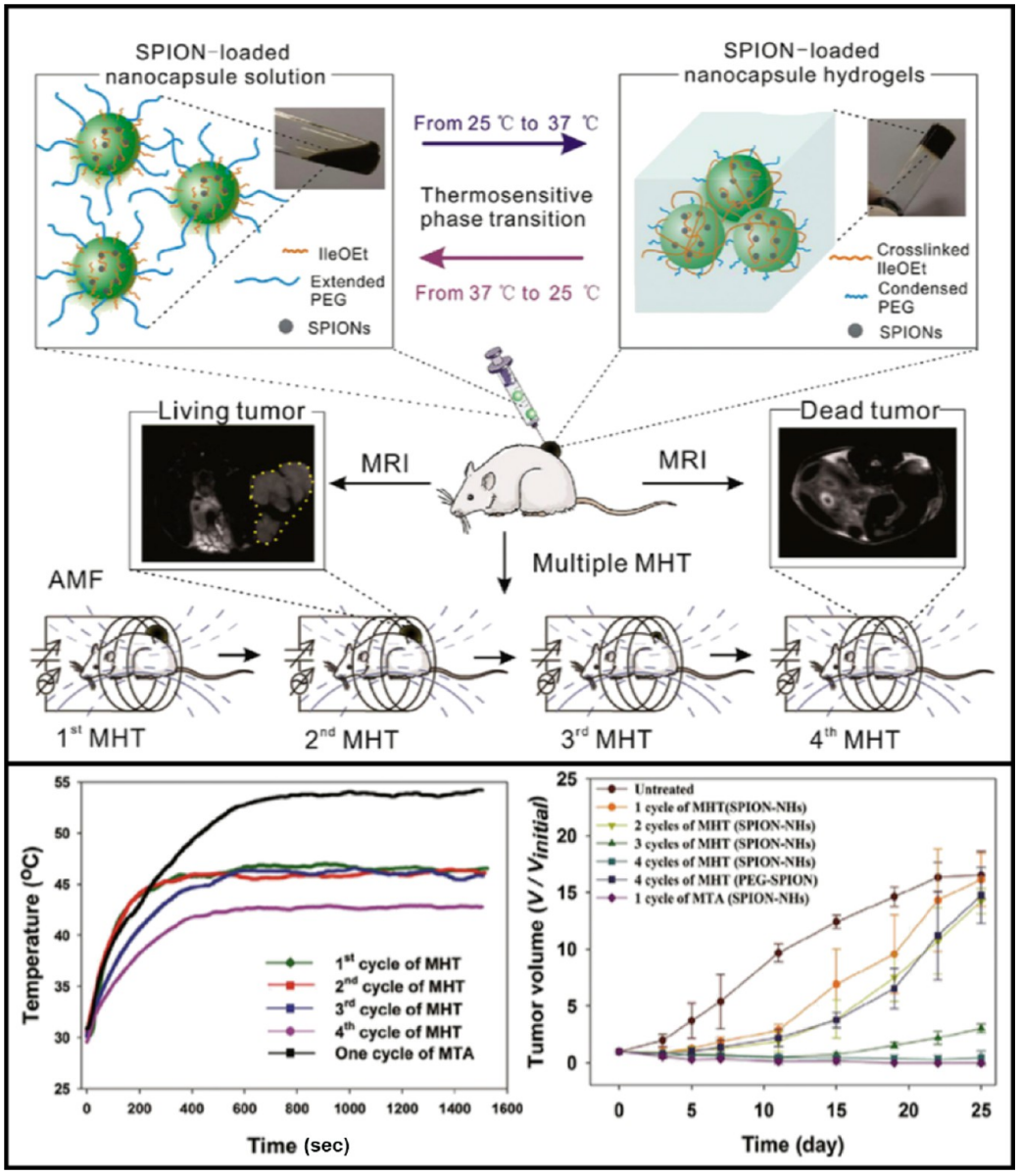


Figure 7. An *in vivo* study with PPZ-based TR-nanosystem. Reproduced with permission from ref 24. Copyright 2016 Elsevier.

lytic stability in response to environmental pH, have been combined with MNPs to produce new probes for drug delivery systems, tracking, and imaging.[2]

Tables S6–S9 summarize selected pH-nanosystems developed over the last few decades.

pH-Cleavable Linkage

For drug delivery applications, pH-nanosystems originally focused on structures in which the drugs were covalently linked to the polymeric matrix via pH-labile bonds such as imines, hydrazones, boronate monoesters, and coordination amine–cation complexes (Figure 8a).[29−32]

Such linkages are sustainably stable under physiological conditions (pH ≈ 7.4), while they are readily hydrolyzed in acidic environments (pH ≈ 4.5–6.5). As a result, the drugs can be selectively delivered to the acidic pathologic sites, minimizing nonspecific releases and their corresponding side effects. In an early study, Sun's group demonstrated that chromone, a potential anticancer drug, can be linked to IONP–catechol–PEG-NH_2 by an imine bond, which was later hydrolyzed at acidic endosomal/lysosomal pH (4–6) to achieve sustainable release in HeLa cells (Figure 8b).[29] Later, Gong's group developed a biodegradable, self-assembling amphiphilic triblock copolymer (Figure 8d) loaded with water-soluble IONPs in the hydrophilic core and DOXO bound to the hydrazide groups on the polymer walls.[30] Given its biodegradability, a higher MRI contrasting efficiency than Feridex was recorded together with pH-induced DOXO release, providing the first *in vitro* example of theranostic agents. Among the materials studied *in vivo,* Kim's group used IONPs functionalized with poly(2-hydroxyethyl methacrylate-*co*-dopamine methacrylamide) (MNPs-HEDO) (Figure 9a).[31] The dopamine catechol moieties anchored IONPs and bound boronic acid of bortezomib (BTZ) via reversible boronate linkages. An *in vivo* study on subcutaneously injected murine squamous carcinoma cells showed clear evidence of the synergistic effects of magnetic hyperthermia and pH-mediated chemotherapy, though complete tumor regression was not achieved.

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999–1013

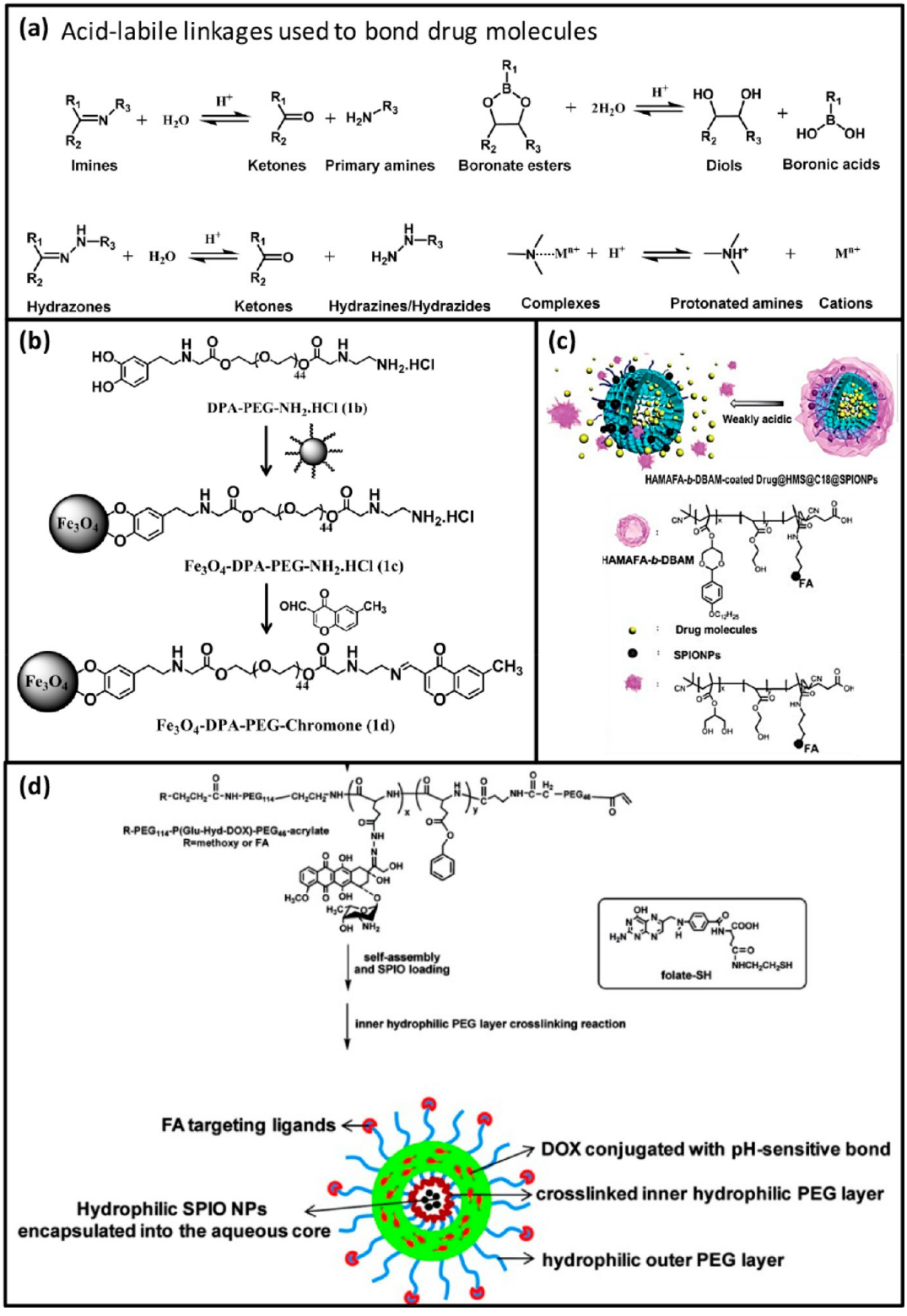


Figure 8. "(a) Examples of acid-labile linkages; (b) pH-nanosystems based on imine-bonds and (c, d) co-assembly of MNPs and doxorubicin. Reproduced with permission from refs 29, 32, and 30. Copyright 2008 ACS, 2012 RSC and 2010 ACS.

Recently, Wu's group developed a yolk-like Fe_3O_4−PEI@Gd_2O_3 nanoplatform further functionalized with poly(ethylene glycol) (PEG) and folic acid (FA, for tumor targeting) for T1−T2 dual-mode MRI and cisplatin delivery activated at pH 4.5 (Figure 9b).[33] The drug-loaded nanoplatform showed better performance on tumor regression than that of free cisplatin.

The covalent linkage of the drug molecules to the carriers might introduce some drawbacks: the polymers and drugs have to carry proper functionalities introduced either by polymer post-functionalization or drug molecule modification. The pre-modification of drug molecules might change the pharmacological properties; therefore few drugs can be delivered using

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

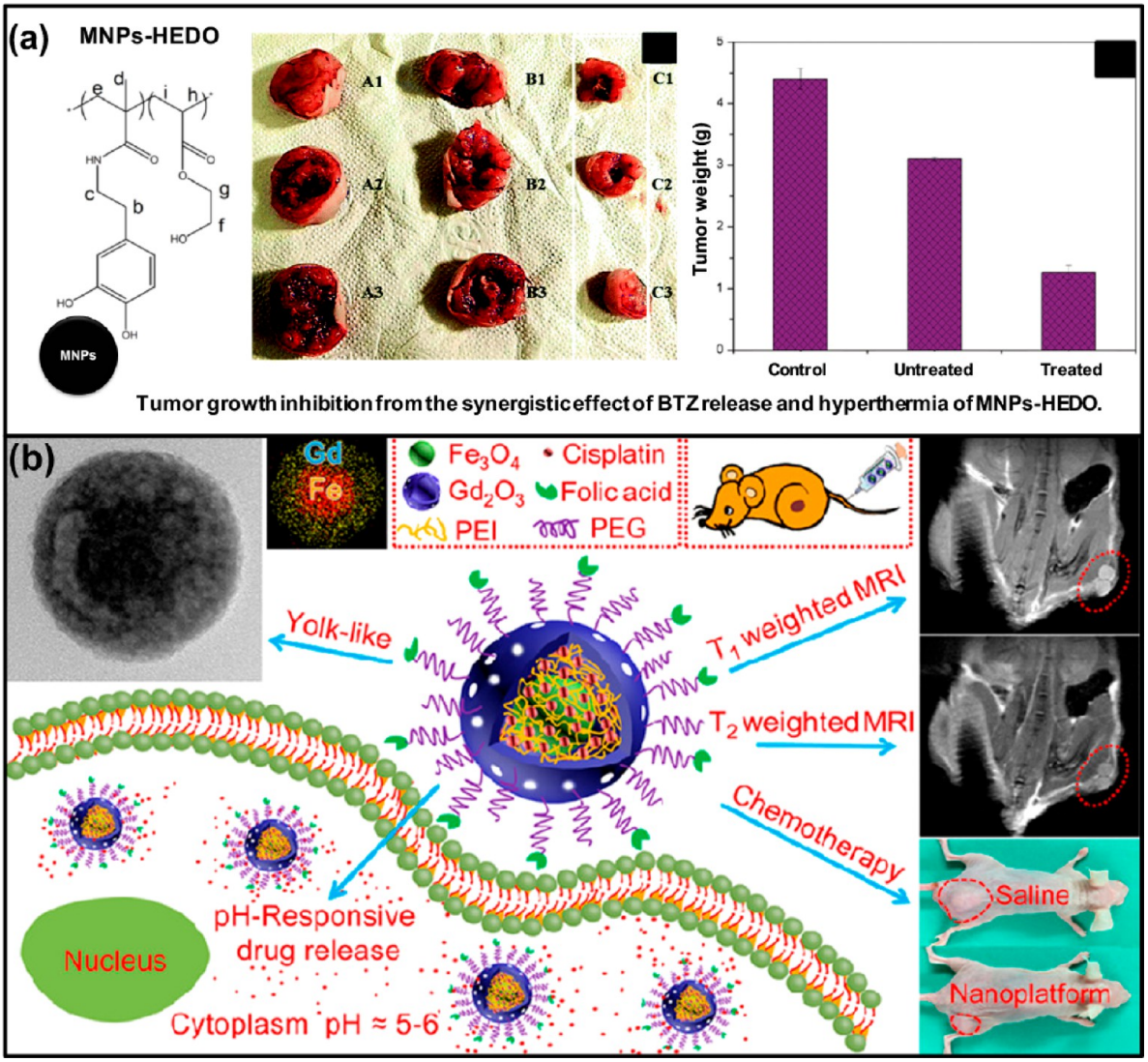


Figure 9. pH-nanosystems for (a) anticancer effect of bortezomib and MHT and (b) drug delivery and T1-contrast agent. Reproduced with permission from refs 31 and 33. Copyright 2015 RSC and 2017 ACS.

this approach.[30−33] Moreover, the loading capacity strongly depends on the number of anchoring moieties in the polymer matrix: when the drug molecules per polymer chain significantly increase, the physiochemical properties of the polymers' post-functionalization might be altered with respect to the nanocarrier properties of the drug-free polymer.

Amphiphilic pH-Responsive Polymers

As a different approach, hydrolyzable groups can be exploited to disrupt the hydrophobic and hydrophilic balance of the polymeric matrix, consequently affecting the mutual interaction and dissociation between the drug molecules, MNPs, and the polymer. Exploiting this mechanism, Lu's group synthesized amphiphilic diblock copolymers that could simultaneously co-encapsulate hydrophobic oleic acid-capped IONPs and hydrophilic DOXO (Figure 8c).[32]

Ionizable Polymers

Alternatively, polymers that have ionizable functionalities (i.e., $-NH_2$, $-COOH$, $-SO_3H$, $-PO_3H_2$, $-B(OH)_2$) within their backbone can be converted into charged groups depending on the pH. Carboxyl-based polymers including poly(acrylic acid) (PAA, pK_a = 4.2), PMAA (pK_a = 6−7), and their derivatives were exploited to construct pH-nanosystems for DDSs. Indeed, having a pH lower than their pK_a results in a gradually weaker electrostatic interaction between the cargo and polymer due to polymer protonation, thus favoring drug release. An example of a pH-nanosystem made of MNPs grafted with methoxy poly(ethylene glycol)-*b*-poly(methacrylic acid)-*b*-poly(glycerol monomethacrylate) (MPEG-*b*-PMAA-*b*-PGMA) was prepared by Yue's group (Figure 10a).[34]

An example of amino-containing polymers was instead provided by Shen's group, which prepared IONPs grafted with poly(dimethyl amino ethyl methacrylate) (PDMAEMA, pK_a 7.0−7.3) and proved that the release of phenolphthalein, as a drug model, was two times higher at pH 3 than at pH 7.0.[35]

Majewski's group has provided an example of pDNA encoding enhanced green fluorescent protein (EGFP) delivery using PDMAEMA-grafted-MNPs. Here, the transfected cells expressing EGFP could be magnetically collected.[36]

Peptide-mimicking dendrimeric polymers have been developed due to their enhanced cargo loading into their branched structure. Hassan's group reported the synthesis of a pH-responsive dendrimer. This peptide mimic shell cross-linked magnetic nanocarrier (PMNC) showed an *in vitro* pH-

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

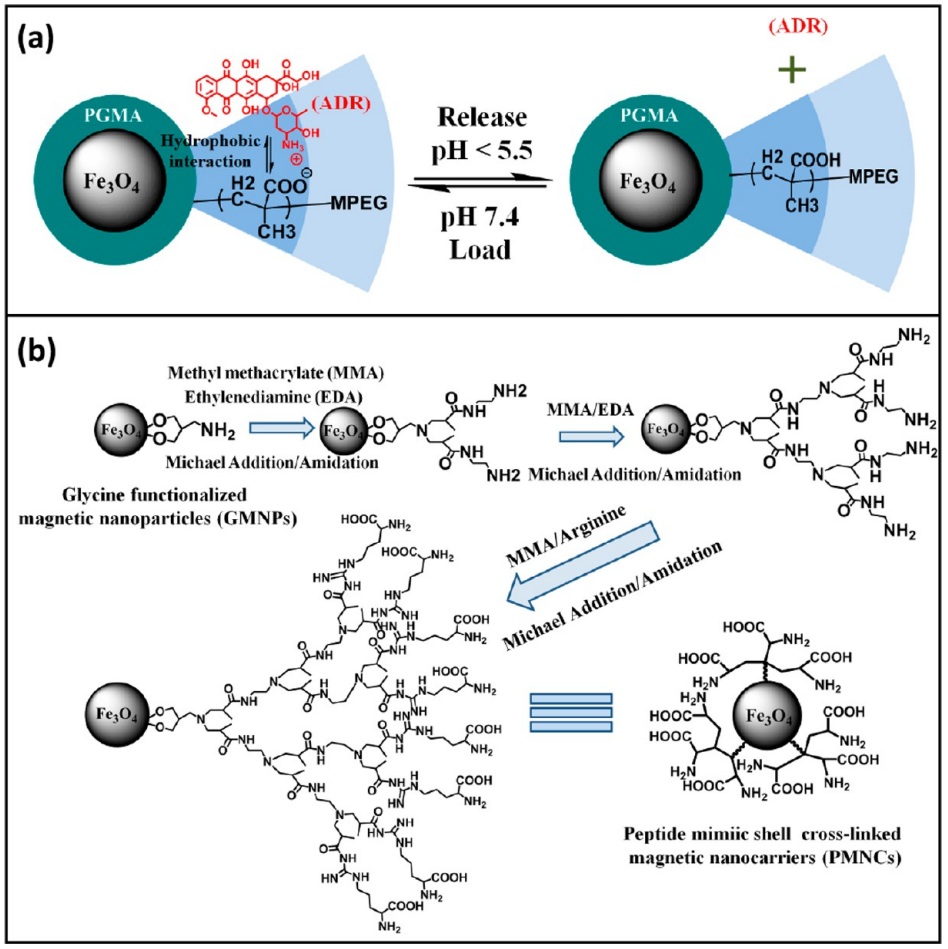


Figure 10. (a) Polymers equipped with ionizable functionalities (−COOH) and (b) peptide-mimicking dendrimeric-based pH-nanosystem ($-NH_2$) for drug delivery. Adapted with permission from refs 34 and 37. Copyright 2008 RSC and 2012 Wiley.

dependent DOXO release, which was enhanced under AMF (Figure 10b).[37]

Linear biodegradable polymers are another class of materials that were exploited to develop pH-nanosystems. For instance, Shuai's group first synthesized poly(ethylene glycol)-*b*-poly(*β*-benzyl L-aspartate-*co*-2-diisopropylethyl L-aspartate), showing pH-responsiveness at pH 5.0 and having peptide-degradable units (Figure 11a).[38] This diblock copolymer could undergo self-assembly in an aqueous solution to form a vesicular nanostructure with a hydrophilic interior for accommodating DOXO and IONPs. The system showed a 5-times enhancement of T2 relaxivity in comparison to the IONP-free vesicles, while DOXO could be rapidly released, limiting cancer cell growth. Recently, Kim's group encapsulated cubic-IONPs, exploiting a lipid tail functionalized poly(imidazole ethyl aspartamide) (pH-DENs) polymer, carrying sorafenib by means of a hydrophobic interaction (Figure 11b).[39] At the tumor site (pH 6.5), the imidazole pendants were protonated and soluble, which induced the local release of sorafenib and IONPs, thus inhibiting HCC tumor growth (upon administration via selective trans-catheter hepatic intra-arteria). In another attempt to treat advanced gastric cancer, Xing's group synthesized novel amphiphilic poly(*β*-aminoester) micelles made of pentaerythritol diacrylate monostearate, 4,4′-trimethylenedipiperidine, and poly(ethylene glycol) methyl ether acrylate (F-P-DOX) (Figure 11c).[40] The micelles could load oleic capped-IONPs and DOXO and could effectively deliver DOXO *in vivo* in a stomach tumor. The IONPs were tracked using MRI. Tumor growth was heavily delayed for the animal group treated with F-P-DOX but full retraction was not reached at the end-point of the study.

One peculiar application of the pH-nanosystems is their use as MRI contrast agents to selectively visualize pathologic sites exhibiting an alteration of the local acidic environment. Lee's group demonstrated the effectiveness of imaging the cerebral ischemic area by using amphiphilic block copolymer-based pH-nanosystems.[41,42] At a neutral pH, hydrophobic IONPs were loaded into the hydrophobic polymer core. Once these nanostructures reached the ischemic pathologic sites at the acidic local environment, the polymer underwent protonation, consequently swelling and exposing the inner contents to water molecules. The IONPs were kept in the ischemic areas due their insolubility in aqueous media. As a result, the concentration of contrast agents in the pathologic areas increased with a significant change in the MRI signal over time.[41,42] Recently, a change in the nanostructure has also been proposed (Figure 12).[43] The IONPs were covalently anchored to the methyloxy-poly(ethylene glycol)-*b*-poly(dopamine L-glutamate-*co*-2-(dibutylamino)ethylamine L-glutamate) polymer, and upon demicellization, the tertiary groups of the polymer were then in close contact with the water molecules. The covalent linkage of the IONPs to the polymer matrix ensured that the MNPs persisted longer at the pathological ischemic area, while a better distribution of IONPs within the

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

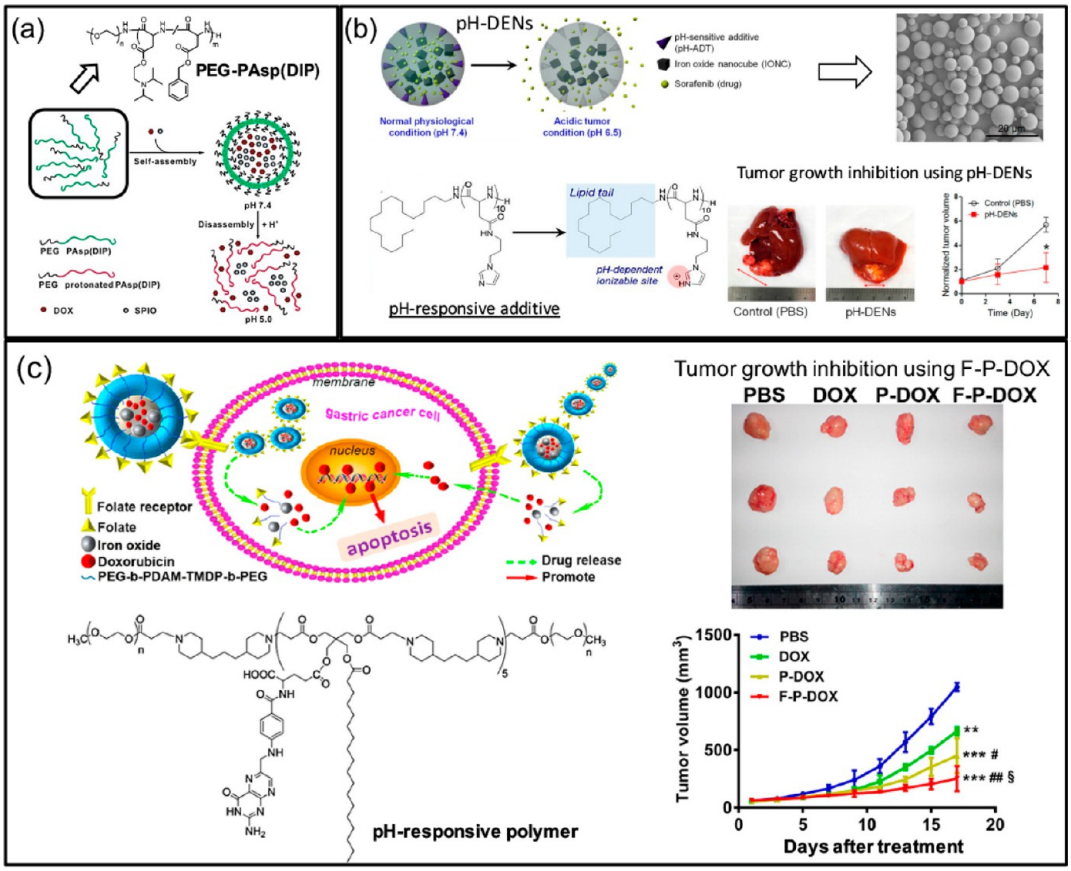


Figure 11. Linear amphiphilic biodegradable polymer-based pH-nanosystems for DDSs. Reproduced with permission from refs 38, 39, and 40. Copyright 2011 RSC, 2016 ACS, and 2015 ACS.

polymer matrix likely provided the higher contrast efficiency than that of previous configurations.

FUTURE DIRECTIONS

TR-Nanosystems

To date, the most advanced preclinical studies on TR-nanosystems are mainly two. The first one is an injectable hydrogel that undergoes a gelation process at 37 °C, keeping the MNPs at the tumor site and causing a heat mediated release of encapsulated necrotic factors.[44] The second one is a DOXO-loaded T_g-based magnetic cluster system, injected intratumorally, causing complete tumor suppression due to the dual MHT heat (44 °C) and chemotherapeutic effect.[27] Despite the large portfolio of TR-nanosystems tested *in vitro*, only two preclinical studies have demonstrated the efficacy of the synergic effects of MHT and heat-mediated chemotherapy under safe AMF parameters for patients.[2,5,27,44]

Glioblastoma, prostate cancer, and bone cancer patients have been treated with MHT, using MagForce MHT 300F or a coiled-AMF generator from Yamamoto VINITA medical systems.[5,45] A single low-field MRI system for imaging coupled with MHT therapy was patented in 2010 (US 20100292564A1). In the future, a more precise diagnosis of the tumor and better spatial heat control will lead to improved patient care.

For heat-performances, whenever it is not possible to test the material intratumorally, studies can be conducted under clinical AFM conditions heat response of TR-nanosystems in a matrix (such as matrigel) or viscous media (glycerol solution), both of which can mimic an *in vivo* viscous environment.[46] The polymer shrinkage and MNP performances could be significantly different if particles were to be blocked in a subcellular compartment or tumor stroma.

Moreover, pharmacokinetic and *in vivo* degradation of TR-nanosystems must be studied. The goal of having intravenously circulating TR-nanosystems that can be accumulated at the tumor site at a sufficient dosage for MHT and heat-triggered drug release is even more ambitious. To face these challenges, two directions of development have been foreseen: improving the heat performances of MNPs and developing advanced polymers.

The recently renewed interest in stimuli-responsive nanosystems has coincided with the parallel boost in a new generation of MNPs.[3,19] Moving from aqueous coprecipitation methods to nonhydrolytic thermal decomposition methods, which allow better control over MNP parameters, has drastically affected the heat efficiency of MHT.[3,47] For instance, reshaping IONPs from spheres to cubes using these new methods has established new record values of MHT heat performance for IONPs.[19] Synthetic cubic-shaped or rod-like IONPs could be further exploited for TR-nanosystems with advanced performances.[3,19] It is known that chain-like assemblies of IONPs can improve the heat performance of MNPs, while centrosymmetric clusters can degrade MNP heat performance.[48] In the future, stimuli-responsive polymers could be grown to promote chain assemblies, thus improving MHT heat performance and magnetic accumulation by physical means. Changing the already FDA-approved IONP composition (Fe_xO_y, see Table S11) to that of mixed ferrites (such as

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

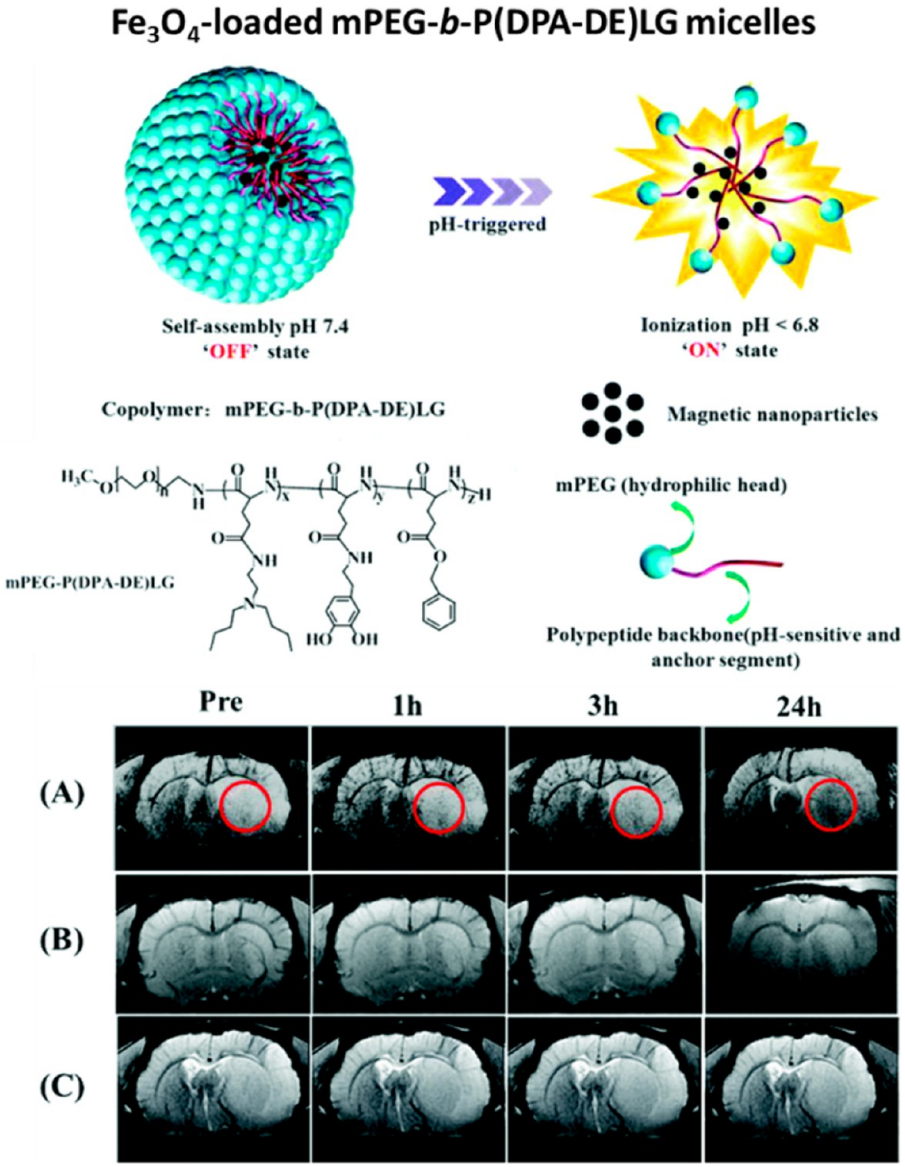


Figure 12. pH-nanosystems as T2-contrast agents to track acidic areas of ischemic brain. Reproduced with permission from ref 43. Copyright 2016 RSC.

$Mn_xFe_{3-x}O_4$, $Zn_xFe_{3-x}O_4$) could also improve MHT heat performances.[24,49] As a future material, in order to avoid overheating, Cr^{3+} substituted Co−Zn ferrites might enable self-regulating MHT if they are employed in TR-nanosystems.[50] Other groups have exploited $MnFe_2O_4$ and $La_{0.73}Sr_{0.27}MnO_3$ instead of IONPs when synthesizing PNIPAm-based TR-nanosystems.[49,51] Although they showed outstanding hyperthermia performances, concerns about the ion toxicity (Mn, La, Sr, and Cr^{3+}) need to be addressed. In particular, for MNPs that are different from IONPs, the study of biodistributions and the clearance of non-iron ions must correlate to the type of TR-polymer, as the controlled degradation of the material can determine its safety. With regards to polymer development, a PEO−PPO−PEO TR-polymer, although commercially available, is rather inert and gives rise to limited post-synthesis modifications.[9,10] NIPAm-based polymers raise concerns about the non-biodegradability and toxicity of PNIPAm due to accumulation,[8] but it has recently been safely used as an injectable intravitreal tissue adhesive for some retinal diseases using a rabbit model.[52] However, no profound *in vivo* studies have been investigated using PNIPAm. In the future, replacing PNIPAm with poly(oligo(ethylene glycol) methyl ether methacrylate) shows great promise. As demonstrated, the LCST can be finely tuned by simply changing the length of the PEG pendants as well as the ratio between the long and short PEG-methacrylates.[53] These polymers might be degradable *in vivo* to PEG and poly(methacrylic acid) (PMAA) with a low molar mass, and they might be cleared via renal excretion.[53] Most efforts so far have focused on the development of LCST-featured TR-nanosystems, but research on UCST-based systems is still limited. A UCST polymer could be used to deliver more hydrophobic drugs.[23] However, controlling the UCST behavior in a physiological solution would require further polymer research development.[54]

There are few reports that show an AMF-mediated release at temperatures lower than the LCST of the TR-nanosystems.[10,55] This approach, being independent of the macroscopic heat, might require a low dose of MNPs for drug delivery. Further studies are needed to better understand the mechanism by which these TR-nanosystems release the drug when no

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

measurable temperature changes occur, as shown in other MNP-thermolabile systems.[7] It is not yet clear if the polymer can still shrink and release the drug without a macroscopic temperature that is lower than the polymer transition temperature. Some works have shown that the release occurred under a local heat increase,[10,55] but in another work, the TR-nanosystems did not release the drug when using a low dose of MNPs that did not provide a macroscopic heat under MHT.[19] These controversial results might be related to the different polymer compositions, to the materials' arrangement, and to the heat dissipation mechanisms. Nevertheless, for TR-nanosystems that exhibit such a behavior, controlled-drug deliveries (perhaps of multiple drugs in a combinatorial drug therapy) will be accessible, but direct MHT heat damage will not occur.

pH-Nanosystems

The most advanced preclinical demonstrations are in the field of detections that exploit MRI signals. T1 (Gd-based) or T2 (IONPs) contrasts were exploited for tracking the delivery of a pH-nanosystem, and this application could be further pursued to detect different types of solid tumors.[33,41−43]

The application based on a pH-nanosystem that is proposed for detecting an ischemic area, is unique.[41−43] The pH-responsiveness of the polymer that reacted to the change in the acidic pH of the pathological site provides a change in the T2 contrast. Similar systems could be applied to detect other acidic pathological areas (i.e., tumor) or to better plan combined therapies. Indeed, pH-nanosystems that change pH and T2-contrast configurations could help the release of drugs from the cargo to be followed and could more accurately predict when MHT should be applied to enhance the synergic effects.

Only one preclinical study on combined MHT and pH-mediated drug deliveries has provided clear synergic effects, so there is still room for improvement.[31] More block copolymers exhibiting a dual pH- and thermoresponsiveness were merged with MNPs, and despite the broad variety of pH-nanosystems already available (Table S10), the advantages of such systems are not yet clear since no preclinical study has been undertaken.

Thanks to their hydrolytic stability, biodegradability, and biocompatibility, synthetic polypeptides such as poly(L-aspartic acid) and poly(L-glutamic acid) seem promising for the construction of magnetic pH-nanosystems.[38,43] Other systems based on the non-biodegradability and cytotoxicity of polycation-based pH-nanosystems might impair further applications.[56] In some cases, using an additional layer of biocompatible silica has reduced cytotoxicity.[36]

The issue for drug delivery application is that these systems release the drugs at lysosomal pH ≈ 4.5−5.5, which might degrade the drugs before reaching the cytosol.[30−33] Engineering a pH-responsiveness close to a physiological or early endosomal pH might be crucial for a high *in vivo* efficacy. In this regard, polymers with a peptide backbone comprising hindered tertiary amine pendants are the most promising candidates to pursue.[38,43]

Finally, clinical translation will require the mass production of such sophisticated materials. Methods for the continuous preparation of MNPs, in flow synthesis or in automated robot synthesis might help to scale the production of magnetic MNPs. Also, the so-called living/controlled polymerization will enable the mass production of the majority of the functional polymers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.accounts.7b00549.

Summary descriptions of various studies discussed in this manuscript (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: teresa.pellegrino@iit.it.

ORCID

Preethi B. Balakrishnan: 0000-0001-5576-7530
Teresa Pellegrino: 0000-0001-5518-1134

Author Contributions

†B.T.M., S.F., and P.B.B. have contributed equally to this work.

Notes

The authors declare no competing financial interest.

Biographies

Binh T. Mai completed his Ph.D. in Nanochemistry (2017) and is currently working as a Postdoctoral researcher in NABM, IIT.

Soraia Fernandes completed her Ph.D. in Natural Sciences and Chemistry and Materials Science Technology (2016) and is currently working as a Postdoctoral researcher in NABM, IIT.

Preethi B. Balakrishnan completed her Ph.D. in Nanochemistry (2017) and is currently working as a Postdoctoral researcher in NABM, IIT.

Teresa Pellegrino completed her Ph.D. in Chemistry at University of Bari (2005). She worked as permanent Staff Scientist at National Nanotechnology Lab in Lecce (2004−2010). Currently she is Senior Team Leader of the Nanomaterials for Biomedical Applications (NABM) Lab at IIT (Genoa, Italy).

■ ACKNOWLEDGMENTS

This Account is partially funded by the European Research Council (starting grant ICARO, Contract No. 678109).

■ REFERENCES

(1) Rivera, A.; Siracusa, M. C.; Yap, G. S.; Gause, W. C. Innate cell communication kick-starts pathogen-specific immunity. *Nat. Immunol.* **2016**, *17*, 356−363.
(2) Mura, S.; Nicolas, J.; Couvreur, P. Stimuli-responsive nanocarriers for drug delivery. *Nat. Mater.* **2013**, *12*, 991−1003.
(3) Lee, N.; Yoo, D.; Ling, D.; Cho, M. H.; Hyeon, T.; Cheon, J. Iron Oxide Based Nanoparticles for Multimodal Imaging and Magneto-responsive Therapy. *Chem. Rev.* **2015**, *115*, 10637−10689.
(4) Hergt, R.; Dutz, S.; Müller, R.; Zeisberger, M. Magnetic particle hyperthermia: nanoparticle magnetism and materials development for cancer therapy. *J. Phys.: Condens. Matter* **2006**, *18*, S2919.
(5) Maier-Hauff, K.; Ulrich, F.; Nestler, D.; Niehoff, H.; Wust, P.; Thiesen, B.; Orawa, H.; Budach, V.; Jordan, A. Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. *J. Neuro-Oncol.* **2011**, *103*, 317−324.
(6) http://celsion.com/thermodox/.
(7) Riedinger, A.; Guardia, P.; Curcio, A.; Garcia, M. A.; Cingolani, R.; Manna, L.; Pellegrino, T. Subnanometer Local Temperature Probing and Remotely Controlled Drug Release Based on Azo-

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

Functionalized Iron Oxide Nanoparticles. *Nano Lett.* **2013**, *13*, 2399−2406.
(8) Hoffman, A. S. Stimuli-responsive polymers: Biomedical applications and challenges for clinical translation. *Adv. Drug Delivery Rev.* **2013**, *65*, 10−16.
(9) Liu, T.-Y.; Liu, K.-H.; Liu, D.-M.; Chen, S.-Y.; Chen, I. W. Temperature-Sensitive Nanocapsules for Controlled Drug Release Caused by Magnetically Triggered Structural Disruption. *Adv. Funct. Mater.* **2009**, *19*, 616−623.
(10) Louguet, S.; Rousseau, B.; Epherre, R.; Guidolin, N.; Goglio, G.; Mornet, S.; Duguet, E.; Lecommandoux, S.; Schatz, C. Thermoresponsive polymer brush-functionalized magnetic Manganite nanoparticles for remotely triggered drug release. *Polym. Chem.* **2012**, *3*, 1408−1417.
(11) Roy, D.; Brooks, W. L.; Sumerlin, B. S. New directions in thermoresponsive polymers. *Chem. Soc. Rev.* **2013**, *42*, 7214−7243.
(12) Pernia Leal, M.; Torti, A.; Riedinger, A.; La Fleur, R.; Petti, D.; Cingolani, R.; Bertacco, R.; Pellegrino, T. Controlled Release of Doxorubicin Loaded within Magnetic Thermo-responsive Nanocarriers under Magnetic and Thermal Actuation in a Microfluidic Channel. *ACS Nano* **2012**, *6*, 10535−10545.
(13) Purushotham, S.; Ramanujan, R. Thermoresponsive magnetic composite nanomaterials for multimodal cancer therapy. *Acta Biomater.* **2010**, *6*, 502−510.
(14) Ungureanu, B. S.; Teodorescu, C.-M.; Săftoiu, A. Magnetic Nanoparticles for Hepatocellular Carcinoma Diagnosis and Therapy. *J. Gastrointest. Liver Dis.* **2016**, *25*, 375.
(15) Chen, L.; Li, L.; Zhang, H.; Liu, W.; Yang, Y.; Liu, X.; Xu, B. Magnetic thermosensitive core/shell microspheres: synthesis, characterization and performance in hyperthermia and drug delivery. *RSC Adv.* **2014**, *4*, 46806−46812.
(16) Jaber, J.; Mohsen, E. Synthesis of Fe3O4@silica/poly(N-isopropylacrylamide) as a novel thermo-responsive system for controlled release of H3PMo12O40 nano drug in AC magnetic field. *Colloids Surf., B* **2013**, *102*, 265−272.
(17) Baeza, A.; Guisasola, E.; Ruiz-Hernández, E.; Vallet-Regí, M. Magnetically triggered multidrug release by hybrid mesoporous silica nanoparticles. *Chem. Mater.* **2012**, *24*, 517−524.
(18) Purushotham, S.; Chang, P.; Rumpel, H.; Kee, I.; Ng, R.; Chow, P.; Tan, C.; Ramanujan, R. Thermoresponsive core−shell magnetic nanoparticles for combined modalities of cancer therapy. *Nanotechnology* **2009**, *20*, 305101.
(19) Kakwere, H.; Leal, M. P.; Materia, M.-E.; Curcio, A.; Guardia, P.; Niculaes, D.; Marotta, R.; Falqui, A.; Pellegrino, T. Functionalization of strongly interacting magnetic nanocubes with (thermo) responsive coating and their application in hyperthermia and heat-triggered drug delivery. *ACS Appl. Mater. Interfaces* **2015**, *7*, 10132.
(20) Jaiswal, M. K.; Pradhan, L.; Vasavada, S.; De, M.; Sarma, H.; Prakash, A.; Bahadur, D.; Dravid, V. P. Magneto-thermally responsive hydrogels for bladder cancer treatment: Therapeutic efficacy and in vivo biodistribution. *Colloids Surf., B* **2015**, *136*, 625−633.
(21) Kim, Y. J.; Ebara, M.; Aoyagi, T. A smart hyperthermia nanofiber with switchable drug release for inducing cancer apoptosis. *Adv. Funct. Mater.* **2013**, *23*, 5753−5761.
(22) Meikle, S.; Piñeiro, Y.; Bañobre López, M.; Rivas, J.; Santin, M. Surface functionalization superparamagnetic nanoparticles conjugated with thermoresponsive poly (epsilon-lysine) dendrons tethered with carboxybetaine for the mild hyperthermia-controlled delivery of VEGF. *Acta Biomater.* **2016**, *40*, 235−242.
(23) Li, W.-S.; Wang, X.-J.; Zhang, S.; Hu, J.-B.; Du, Y.-L.; Kang, X.-Q.; Xu, X.-L.; Ying, X.-Y.; You, J.; Du, Y.-Z. Mild microwave activated, chemo-thermal combinational tumor therapy based on a targeted, thermal-sensitive and magnetic micelle. *Biomaterials* **2017**, *131*, 36−46.
(24) Zhang, Z.-Q.; Song, S.-C. Thermosensitive/superparamagnetic iron oxide nanoparticle-loaded nanocapsule hydrogels for multiple cancer hyperthermia. *Biomaterials* **2016**, *106*, 13−23.
(25) Hayashi, K.; Sakamoto, W.; Yogo, T. Smart Ferrofluid with Quick Gel Transformation in Tumors for MRI-Guided Local Magnetic Thermochemotherapy. *Adv. Funct. Mater.* **2016**, *26*, 1708−1718.
(26) Wang, F.; Yang, Y.; Ling, Y.; Liu, J.; Cai, X.; Zhou, X.; Tang, X.; Liang, B.; Chen, Y.; Chen, H.; et al. Injectable and thermally contractible hydroxypropyl methyl cellulose/Fe 3 O 4 for magnetic hyperthermia ablation of tumors. *Biomaterials* **2017**, *128*, 84−93.
(27) Hayashi, K.; Nakamura, M.; Miki, H.; Ozaki, S.; Abe, M.; Matsumoto, T.; Sakamoto, W.; Yogo, T.; Ishimura, K. Magnetically responsive smart nanoparticles for cancer treatment with a combination of magnetic hyperthermia and remote-control drug release. *Theranostics* **2014**, *4*, 834.
(28) Ruggiero, M. R.; Crich, S. G.; Sieni, E.; Sgarbossa, P.; Forzan, M.; Cavallari, E.; Stefania, R.; Dughiero, F.; Aime, S. Magnetic hyperthermia efficiency and 1H-NMR relaxation properties of iron oxide/paclitaxel-loaded PLGA nanoparticles. *Nanotechnology* **2016**, *27*, 285104.
(29) Wang, B.; Xu, C.; Xie, J.; Yang, Z.; Sun, S. pH Controlled Release of Chromone from Chromone-Fe3O4 Nanoparticles. *J. Am. Chem. Soc.* **2008**, *130*, 14436−14437.
(30) Yang, X.; Grailer, J. J.; Rowland, I. J.; Javadi, A.; Hurley, S. A.; Matson, V. Z.; Steeber, D. A.; Gong, S. Multifunctional Stable and pH-Responsive Polymer Vesicles Formed by Heterofunctional Triblock Copolymer for Targeted Anticancer Drug Delivery and Ultrasensitive MR Imaging. *ACS Nano* **2010**, *4*, 6805−6817.
(31) Sasikala, A. R. K.; GhavamiNejad, A.; Unnithan, A. R.; Thomas, R. G.; Moon, M.; Jeong, Y. Y.; Park, C. H.; Kim, C. S. A smart magnetic nanoplatform for synergistic anticancer therapy: manoeuvring mussel-inspired functional magnetic nanoparticles for pH responsive anticancer drug delivery and hyperthermia. *Nanoscale* **2015**, *7*, 18119−18128.
(32) Yang, S.; Chen, D.; Li, N.; Mei, X.; Qi, X.; Li, H.; Xu, Q.; Lu, J. A facile preparation of targetable pH-sensitive polymeric nanocarriers with encapsulated magnetic nanoparticles for controlled drug release. *J. Mater. Chem.* **2012**, *22*, 25354−25361.
(33) Sun, X.; Du, R.; Zhang, L.; Zhang, G.; Zheng, X.; Qian, J.; Tian, X.; Zhou, J.; He, J.; Wang, Y.; Wu, Y.; Zhong, K.; Cai, D.; Zou, D.; Wu, Z. A pH-Responsive Yolk-Like Nanoplatform for Tumor Targeted Dual-Mode Magnetic Resonance Imaging and Chemotherapy. *ACS Nano* **2017**, *11*, 7049−7059.
(34) Guo, M.; Yan, Y.; Zhang, H.; Yan, H.; Cao, Y.; Liu, K.; Wan, S.; Huang, J.; Yue, W. Magnetic and pH-responsive nanocarriers with multilayer core-shell architecture for anticancer drug delivery. *J. Mater. Chem.* **2008**, *18*, 5104−5112.
(35) Zhou, L.; Yuan, J.; Yuan, W.; Sui, X.; Wu, S.; Li, Z.; Shen, D. Synthesis, characterization, and controllable drug release of pH-sensitive hybrid magnetic nanoparticles. *J. Magn. Magn. Mater.* **2009**, *321*, 2799−2804.
(36) Majewski, A. P.; Stahlschmidt, U.; Jérôme, V.; Freitag, R.; Müller, A. H. E.; Schmalz, H. PDMAEMA-Grafted Core−Shell−Corona Particles for Nonviral Gene Delivery and Magnetic Cell Separation. *Biomacromolecules* **2013**, *14*, 3081−3090.
(37) Barick, K. C.; Singh, S.; Jadhav, N. V.; Bahadur, D.; Pandey, B. N.; Hassan, P. A. pH-Responsive Peptide Mimic Shell Cross-Linked Magnetic Nanocarriers for Combination Therapy. *Adv. Funct. Mater.* **2012**, *22*, 4975−4984.
(38) Sun, Q.; Cheng, D.; Yu, X.; Zhang, Z.; Dai, J.; Li, H.; Liang, B.; Shuai, X. A pH-sensitive polymeric nanovesicle based on biodegradable poly(ethylene glycol)-b-poly(2-(diisopropylamino)ethyl aspartate) as a MRI-visible drug delivery system. *J. Mater. Chem.* **2011**, *21*, 15316−15326.
(39) Park, W.; Chen, J.; Cho, S.; Park, S.-j.; Larson, A. C.; Na, K.; Kim, D.-H. Acidic pH-Triggered Drug-Eluting Nanocomposites for Magnetic Resonance Imaging-Monitored Intra-arterial Drug Delivery to Hepatocellular Carcinoma. *ACS Appl. Mater. Interfaces* **2016**, *8*, 12711−12719.
(40) Ma, H.; Liu, Y.; Shi, M.; Shao, X.; Zhong, W.; Liao, W.; Xing, M. M. Q. Theranostic, pH-Responsive, Doxorubicin-Loaded Nanoparticles Inducing Active Targeting and Apoptosis for Advanced Gastric Cancer. *Biomacromolecules* **2015**, *16*, 4022−4031.
(41) Gao, G. H.; Im, G. H.; Kim, M. S.; Lee, J. W.; Yang, J.; Jeon, H.; Lee, J. H.; Lee, D. S. Magnetite-Nanoparticle-Encapsulated pH-

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013

Responsive Polymeric Micelle as an MRI Probe for Detecting Acidic Pathologic Areas. *Small* **2010**, *6*, 1201−1204.
(42) Gao, G. H.; Lee, J. W.; Nguyen, M. K.; Im, G. H.; Yang, J.; Heo, H.; Jeon, P.; Park, T. G.; Lee, J. H.; Lee, D. S. pH-responsive polymeric micelle based on PEG-poly(β-amino ester)/(amido amine) as intelligent vehicle for magnetic resonance imaging in detection of cerebral ischemic area. *J. Controlled Release* **2011**, *155*, 11−17.
(43) Yang, H. Y.; Jang, M.-S.; Gao, G. H.; Lee, J. H.; Lee, D. S. pH-Responsive biodegradable polymeric micelles with anchors to interface magnetic nanoparticles for MR imaging in detection of cerebral ischemic area. *Nanoscale* **2016**, *8*, 12588−12598.
(44) Zhang, Z.-Q.; Song, S.-C. Multiple hyperthermia-mediated release of TRAIL/SPION nanocomplex from thermosensitive polymeric hydrogels for combination cancer therapy. *Biomaterials* **2017**, *132*, 16−27.
(45) Luo, S.; Wang, L.; Ding, W.; Wang, H.; Zhou, J.; Jin, H.; Su, S.; Ouyang, W. Clinical trials of magnetic induction hyperthermia for treatment of tumours. *OA Cancer* **2014**, *2*, 2.
(46) Cabrera, D.; Lak, A.; Yoshida, T.; Materia, M. E.; Ortega, D.; Ludwig, F.; Guardia, P.; Sathya, A.; Pellegrino, T.; Teran, F. J. Unraveling viscosity effects on the hysteresis losses of magnetic nanocubes. *Nanoscale* **2017**, *9*, 5094−5101.
(47) Bauer, L. M.; Situ, S. F.; Griswold, M. A.; Samia, A. C. S. High-performance iron oxide nanoparticles for magnetic particle imaging - guided hyperthermia (hMPI). *Nanoscale* **2016**, *8*, 12162−12169.
(48) Abenojar, E. C.; Wickramasinghe, S.; Bas-Concepcion, J.; Samia, A. C. S. Structural effects on the magnetic hyperthermia properties of iron oxide nanoparticles. *Prog. Nat. Sci.* **2016**, *26*, 440−448.
(49) Shah, S. A.; Majeed, A.; Shafique, M.; Rashid, K.; Awan, S.-U. Cell viability study of thermo-responsive core−shell superparamagnetic nanoparticles for multimodal cancer therapy. *Appl. Nanosci.* **2014**, *4*, 227−232.
(50) Zhang, W.; Zuo, X.; Niu, Y.; Wu, C.; Wang, S.; Guan, S.; Silva, S. R. P. Novel nanoparticles with Cr3+ substituted ferrite for self-regulating temperature hyperthermia. *Nanoscale* **2017**, *9*, 13929−13937.
(51) Soleymani, M.; Edrissi, M.; Alizadeh, A. M. Thermosensitive polymer-coated La0. 73Sr0. 27MnO3 nanoparticles: potential applications in cancer hyperthermia therapy and magnetically activated drug delivery systems. *Polym. J.* **2015**, *47*, 797−801.
(52) Lima, L. H.; Morales, Y.; Cabral, T. Ocular Biocompatibility of Poly-N-Isopropylacrylamide (pNIPAM). *J. Ophthalmol.* **2016**, *2016*, 5356371.
(53) Lutz, J.-F.; Weichenhan, K.; Akdemir, Ö.; Hoth, A. About the phase transitions in aqueous solutions of thermoresponsive copolymers and hydrogels based on 2-(2-methoxyethoxy) ethyl methacrylate and oligo (ethylene glycol) methacrylate. *Macromolecules* **2007**, *40*, 2503−2508.
(54) Niskanen, J.; Tenhu, H. How to manipulate the upper critical solution temperature (UCST)? *Polym. Chem.* **2017**, *8*, 220−232.
(55) Cazares-Cortes, E.; Espinosa, A.; Guigner, J.-M.; Michel, A.; Griffete, N.; Wilhelm, C.; Ménager, C. Doxorubicin Intracellular Remote Release from Biocompatible Oligo(ethylene glycol) Methyl Ether Methacrylate-Based Magnetic Nanogels Triggered by Magnetic Hyperthermia. *ACS Appl. Mater. Interfaces* **2017**, *9*, 25775−25788.
(56) Mintzer, M. A.; Simanek, E. E. Nonviral Vectors for Gene Delivery. *Chem. Rev.* **2009**, *109*, 259−302.

DOI: 10.1021/acs.accounts.7b00549
Acc. Chem. Res. 2018, 51, 999−1013