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Smart chemistry in polymeric nanomedicine

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This review provides an overview of smart chemistry developed and utilized in the last 5–10 years in polymer-based drug delivery nanomedicine. Smart chemistry not only facilitates the controlled drug loading in a highly specific manner, but also potentially controls the drug release kinetics at the targeted tissues. This review highlights the emergence of new chemistry or unique utilization of conventional chemistry in drug delivery, which is believed to play an important role in developing next generation nanomedicine.

1. Introduction

There are many existing challenges in drug delivery, among which include designing vehicles that can carry a sufficient amount of drugs, efficiently cross various physiological barriers to reach disease tissues, and cure diseases in a less toxic and sustained manner.[1,2] Integration of nanotechnology and drug delivery, termed nanomedicine, refers to multi-component drug or drug delivery systems in the size range of one to several hundred nanometers.[3,4] In parallel to the development of nanotechnology, the advances in modern synthetic chemistry have made it possible the preparation of a large variety of polymeric materials with structures tailored to accommodate the specific needs for systemic drug delivery in a highly controlled manner.[5–7] Most drug delivery systems developed and studied for clinical trials are either liposome- or polymer-based. Liposome-based drug delivery has been extensively reviewed elsewhere.[8–11] This review will only focus on smart chemistry utilized in various types of polymer-based nanomedicine, including polymer–drug conjugates,[12–14] polymeric micelles,[15–21] dendrimers,[22–25] polymeric vesicles,[26–31] and polymeric hydrogels and films[32–40] (all of which are integrated with therapeutics). The "smart chemistry" in this review refers to intriguing chemical reactions or synthetic strategies that can (1) accelerate or facilitate the development or preparation of polymeric delivery vehicles, (2) control drug release in response to external stimuli, such as pH, temperature, light, *etc.*, and (3) improve the *in vivo* performance of polymeric therapeutics. This smart chemistry is

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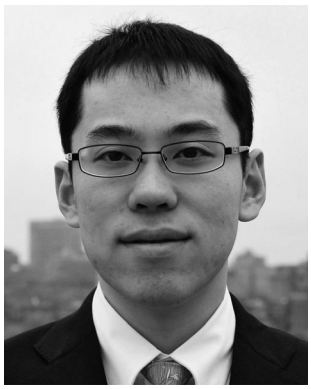

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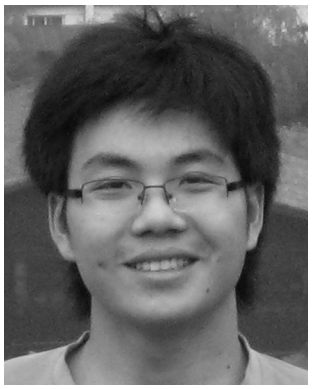
expected to provide sophisticated control over drug loading and release properties. When coupled with emerging technologies in both engineering and fabrication, it may eventually become possible to deliver chemotherapy in a time-, tissue-, and patient-specific manner with the use of smart chemistry in polymeric nanomedicine.

2. Highly-efficient chemistry for nanomedicine synthesis

The heterogeneity of polymeric materials by way of uncontrolled chemistry can affect tacticity, conjugation efficiency, and conjugation site selectivity. Variations in these properties can affect several aspects of nanomedicine, ranging from polydispersity to release profiles, which may become hindrances of clinical translation. Rapid, high-yield, bio-orthogonal (chemical reaction not interfering native biochemical process[41]), and chemo-selective (reactions with selective reactivity towards one functional group in the presence of others[42]) chemistry with simplified purification can provide desired materials with less heterogeneity compared to conventional techniques, which can lead to further control over the desired properties of nanomedicine. Here, we will discuss a few highly-efficient chemical reactions including click chemistry (*e.g.*, azide–alkyne chemistry), thiol–ene (or thiol–yne) chemistry, and regioselective polyester–drug conjugation chemistry.

2.1 Click chemistry

The concept of click chemistry was coined by Sharpless and coworkers in 2001 and received immediate recognition for its potential in site-specific biological conjugation.[43,44] The most popular form of click chemistry, the azide–alkyne [3+2] Huisgen cycloaddition, has been extensively studied[45,46] since it allows for site-specific cellular protein and glycan conjugations (Scheme 1a).[47–49] In such a reaction, a [3+2] cycloaddition between an azide and an alkyne gives a 1,2,3-triazole, which is catalyzed by copper (Cu-catalyzed azide–alkyne cycloaddition, CuAAC).[44]



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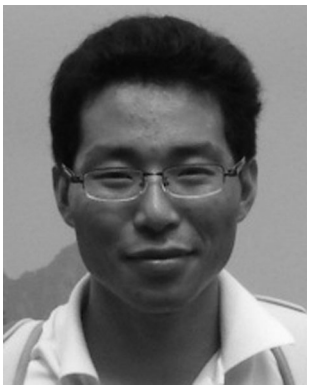

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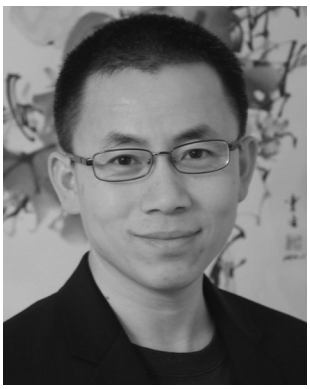

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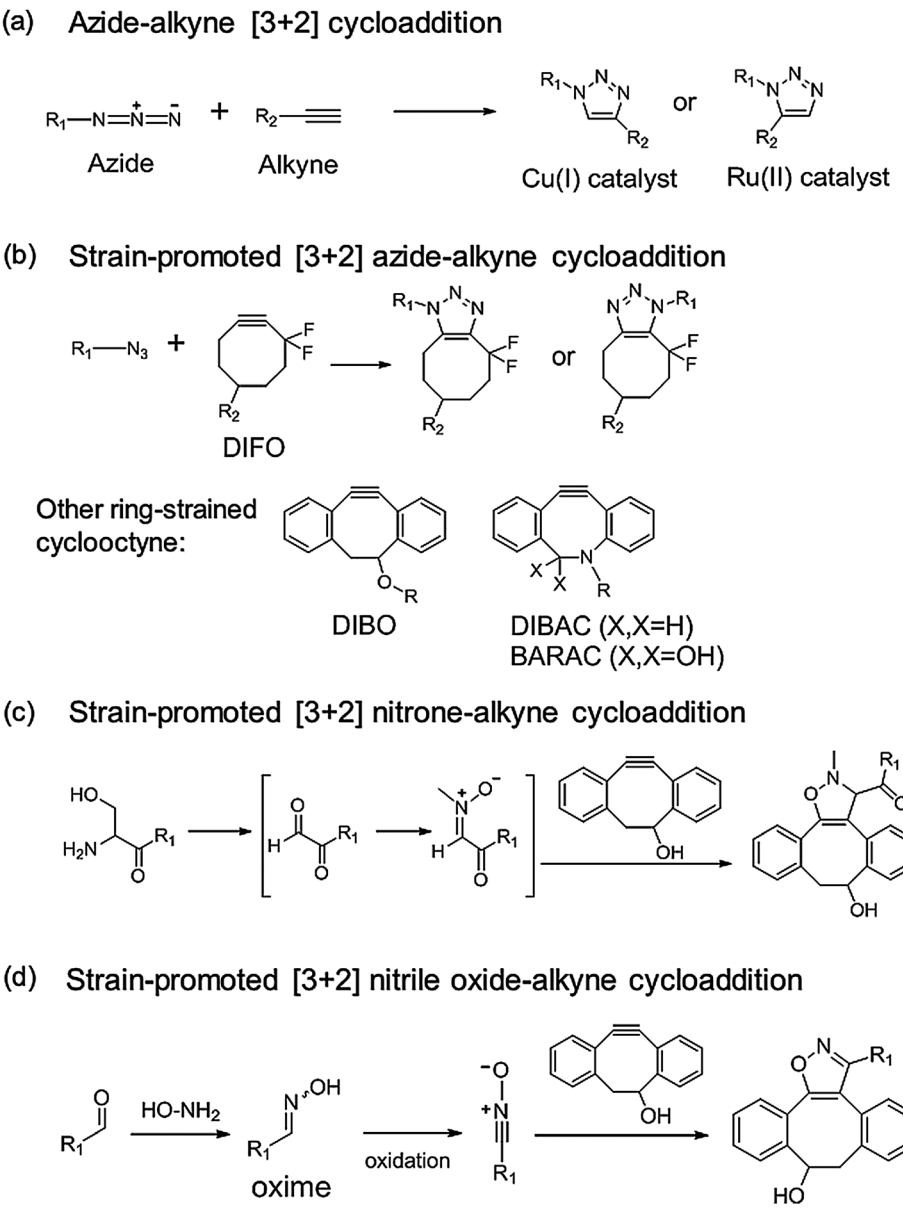


Scheme 1 (a) Azide–alkyne click chemistry; (b) strain-promoted azide–alkyne cycloaddition (SPAAC); (c) strain-promoted nitrone–alkyne cycloaddition (SPNAC); (d) strain promoted nitrile oxide–alkyne cycloaddition (SPNOAC).

Click chemistry gives conjugated products in high yields and proceeds under mild conditions for *in situ*[50] or *in vitro* applications,[51] including the modification or conjugation of glycans, proteins, DNA, RNA, and other biomolecules.[52–57] While copper can generate biologically detrimental reactive oxygen species when used with sodium ascorbate as an *in situ* reducing agent, recent advances have been made to reduce undesired reactions using other accelerating ligands.[52,58] These accelerating ligands not only increase the rate of reaction, leading to fewer side reactions, but can also act as sacrificial reductants that can eliminate reactive oxygen species. This has allowed for rapid CuAAC without cytotoxicity for noninvasive imaging of fucosylated glycans during zebrafish early embryogenesis.[52] Click chemistry can also be used as a tool to construct polymer backbones, or to crosslink polymers to achieve different polymer architectures. These uses of click chemistry have been comprehensively reviewed elsewhere.[7,59–62] Notably, in many click reactions water is the ideal reaction solvent, providing the best yields and highest rates. In many conjugation reactions or synthesis, the click reaction even requires no purification. Usually, reaction work-up and purification in click reactions uses benign solvents and avoids chromatography.[63–65]

One example using click chemistry in the synthesis of polymers for drug delivery applications is demonstrated by using polycationic β-cyclodextrin (β-CD) "click clusters" for gene delivery.[66] The Reineke group designed a series of multivalent polycationic β-CDs with discrete molecular weights by controlling the reaction between a series of alkyne terminated oligo-ethyleneamine

and acetylated-per-azido-β-CDs. The strategy was later adapted by other groups to construct β-CD derivatives or other cationic polymers for gene and siRNA delivery.[67–69] Such CuAAC polymerization has been proven to be a versatile approach not only to rapidly prepare linear cationic polymer libraries, but also to improve transfection efficiency through the introduction of interactions between the resulting triazole ring and the adjacent amide group in polymers with DNA.[70,71]

Click chemistry was also used to modify polymer side chains to incorporate functional groups or drugs into polymeric delivery vehicles. For instance, while aliphatic polyesters, such as poly(ε-caprolactone) (PCL), poly(lactide) (PLA) and poly(lactide-*co*-glycolide) (PLGA), are promising polymeric drug carriers for biomedical applications,[72] such polyesters are limited in broader scope due to their hydrophobic and semicrystalline properties and the absence of functionality in the polymer backbone for tailoring physical properties and introducing bioactive moieties. Pendent functionalization of polyesters was achieved by the Emrick group by ring-opening polymerization (ROP) of alkyne-functionalized lactone and other monomers.[73] The alkyne-containing polyesters were conjugated with azide-terminated camptothecin (CPT) or phosphorylcholine for preparation of polyester–drug conjugates.[72,74] The alkyne-functionalized lactone was also utilized by other groups for polyester modification.[75] Furthermore, Jérôme and co-workers functionalized PCL using an azide group containing CL analogues for polyester synthesis,[76] which allows for grafting moieties with alkyne groups.[77,78] Of note, other strategies have been reported to introduce a side chain for click reaction based PLA–prodrug conjugation; Cheng *et al.* showed that such brush PLA–drug conjugates have exceptional drug loading (up to 20–30 wt%) and well-dispersed sizes (10–30 nm).[79,80] In addition to polyester, recently, the Wooley group synthesized PEG-*b*-polyphosphester-based paclitaxel conjugates *via* the click reaction based conjugation of the paclitaxel–azide prodrug to the alkyene-containing polymer side chain; ultrahigh drug loading (up to 65 wt%) can be achieved in such conjugates.[81]

Click chemistry has also found use in surface decoration of polymeric drug delivery vehicles with cell-specific targeting (*e.g.*, antibodies, aptamers) or fluorescent groups. These moieties can improve therapeutic efficacy by active targeting or by introducing contrast agents into vehicles for imaging.[82,83] One example, reported by Caruso and co-workers,[83] was to use CuAAC for the conjugation of an azide-functionalized antibody with alkyne containing capsules to achieve highly specific binding to cancer cells expressing the targeted antigen.

Despite the many merits of CuAAC, its use in living systems has been hampered by the concern of copper ions which are potentially toxic for living organisms. Copper-free click chemistry was developed in order to perform benign bio-orthogonal reaction *in vivo* without Cu catalysts.[84–88] Bertozzi and coworkers designed ring-strained cyclooctyne derivatives (Scheme 1b) that can mediate efficient [3+2] cycloaddition with an azide with no need for using a copper catalyst (strain-promoted [3+2] azide–alkyne cycloaddition, SPAAC).[86,89,90] Several strain-promoted systems, such as cyclooctynes,[91–93] dibenzocyclooctynes[94] and azacyclooctynes,[95] have been developed for the fast and selective reaction with azide-containing biomolecules and have found widespread applications, *e.g.*, biomolecule labeling,[96–98] surface modification,[99,100] PEGylation of proteins,[95] and *in vivo* imaging.[101,102] SPAAC chemistry was adapted by the Anseth group to incorporate metalloproteinase in click-functionalized macromolecular precursors containing the difluorinated cyclooctyne moiety (DIFO, Scheme 1b). The macromolecular precursors reacted with four-arm PEG–azide for direct encapsulation of cells within hydrogels which can be degraded by metalloproteinase enzyme.[103]

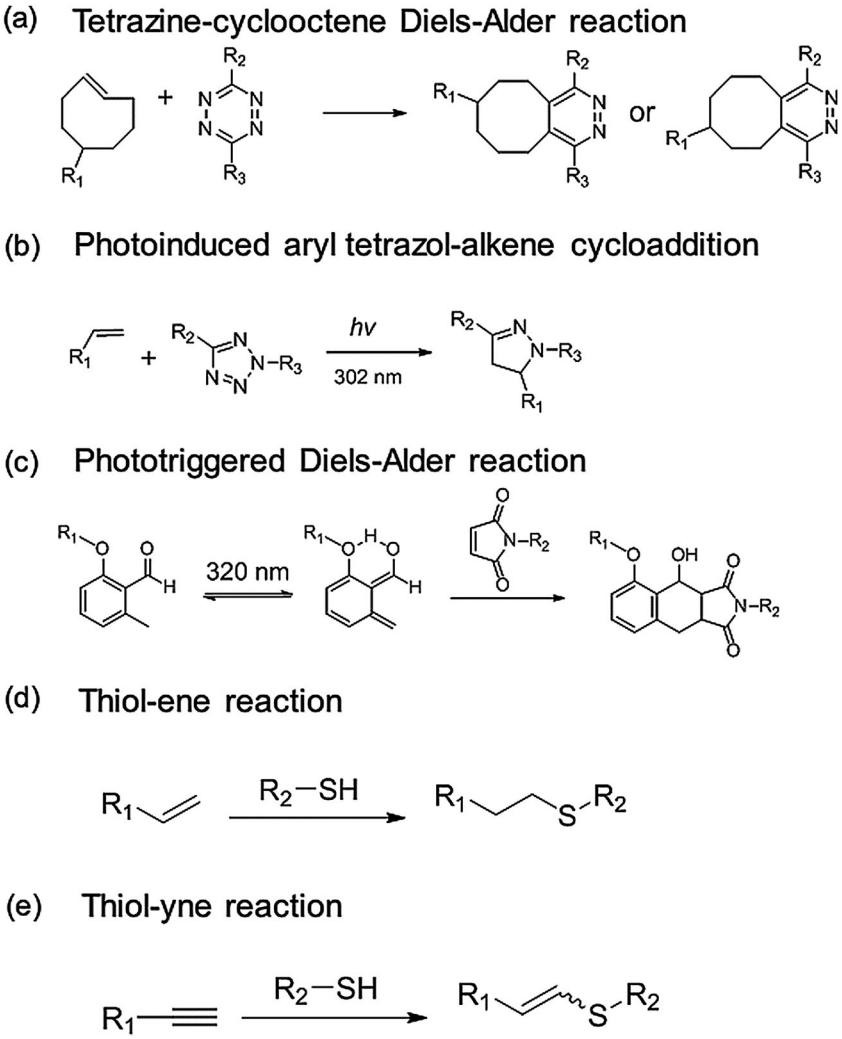
Other strain-promoted cycloaddition reactions (Scheme 1c) have been developed with much faster kinetics than alkyne–azide reactions for protein modification, including strain-promoted alkyne–nitrone cycloaddition (SPANC, Scheme 1c),[94] and alkyene–nitrile oxide cycloaddition (SPANOC, Scheme 1d).[104]

Besides the aforementioned click chemistry, many other types of bio-orthogonal click chemistry have been developed.[105] Among them, a Diels–Alder reaction between a tetrazine and a cyclooctene recently emerged as an alternative catalyst-free bio-orthogonal reaction (Scheme 2a). This reaction is rapid, highly selective, efficient, and can also proceed in aqueous media.[106,107] The utility of this reaction is demonstrated by the specific labeling of Her2/neu receptors on breast cancer cells, and for ^{18}F *in vivo* whole animal imaging.[108] A novel technique known as ''bio-orthogonal nanoparticle detection'' based on this click reaction was further developed by Weissleder and co-workers to target live cells.[109] A similar strategy was also reported by Robillard and co-workers for pre-targeted tumor imaging in the live mice.[110] Additionally, an interesting photo-induced aryl tetrazole–alkene click reaction was reported by Lin and coworkers. A genetically encoded alkene-containing protein could be selectively functionalized with a tetrazole *via* photo-initiated 1,3-dipolar cycloaddition (Scheme 2b).[111–113] Similarly, Barner-Kowollik and coworkers reported a Diels–Alder [4+2] cycloaddition reaction between photo-induced isomerization of a 2-formyl-3-methylphenoxy derivative and a dienophile (*e.g.*, a maleimide derivative),[114] which enables spatial control for the photolithographic and polymer–protein conjugates (Scheme 2c).

Click chemistry provides a unique method of making a polymer scaffold for drug delivery. More importantly, it allows for unprecedented control of drug or targeting ligand conjugation to polymeric nanomedicine as well as *in vivo* labeling and biomedical imaging.[55,115] There is little question that the future development of materials for nanomedicine will benefit greatly from click chemistry.

2.2 Thiol–ene (thiol–yne) reaction

Another highly efficient chemistry that is becoming increasingly popular is the century-old addition of thiols to alkenes (Scheme 2d), which is currently called thiol–ene click or called thiol–ene coupling.[116] Similarly, the reaction between thiol and alkyne (thiol–yne reaction, Scheme 2e) is also highlighted. These reactions were not in the scope of ''click chemistry'' according to the definition by Sharpless, since thiols exist in many biological systems and are thus not bio-orthogonal. These particular reactions have caught attention due to their high activity within seconds



Scheme 2 (a) Tetrazine–cyclooctyne Diels–Alder reaction; (b) phototriggered aryl tetrazol–alkene cycloaddition; (c) phototriggered Diels–Alder reaction; (d) thiol–ene reaction; (e) thiol–yne reaction.

(more rapid than many other click chemistries) achieving high conversions with simplified purification steps under mild conditions, even in the presence of water and oxygen. The biologically friendly nature and stability of the formed thioether linkage in extreme environments are very attractive for its biological application.[117] Both thiol–ene (thiol–yne) reactions can take place through either the radical or Michael addition mechanism:[118] *via* the radical mechanism, both UV- and thermal-induced reaction conditions can be utilized in a controllable and simple manner; *via* the Michael addition mechanism, thiol–maleimide coupling is important and particularly suitable for bio-functionalization.[119] This approach has been successfully applied in the formation of various drug delivery vehicles including dendrimers,[120,121] hydrogels,[122] nanocapsules,[123] nanoparticles (NPs),[119,124–126] vesicles[127] and micelles.[128,129] The acid-labile thiolester linkage obtained *via* thiol–ene reaction can facilitate drug release under acidic conditions (*e.g.* acidic environment in tumor). Recently the Wooley group reported the thiol–ene synthesis of PEG-*b*-polyphosphester-based paclitaxel conjugates with ultrahigh drug loadings for acid-triggered drug release.[130] Thiol–ene chemistry also shows advantages in the highly efficient preparation of well-defined polymeric scaffolds for nanomedicine, which have not been obtained by other chemistries. For instance, UV-induced thiol–ene cross-linking in transparent mini-emulsions can readily produce well-defined nanoparticles and nanocapsules;[131] specifically, as reported by Cheng *et al.*, PLA-based cationic biodegradable nanocapsules prepared by this strategy can evade multidrug resistance of cancer cells and have applicability in the co-delivery of both the drug and therapeutic gene.[132] Other reviews discussing the application of thiol–ene chemistry can be found elsewhere.[116,133–136] Several systems combining alkyne–azide and thiol–ene chemistries have found extraordinary application in biological and biochemical fields.[103,137–139] However, the application of UV light might limit the use of the chemistry *in vivo*.

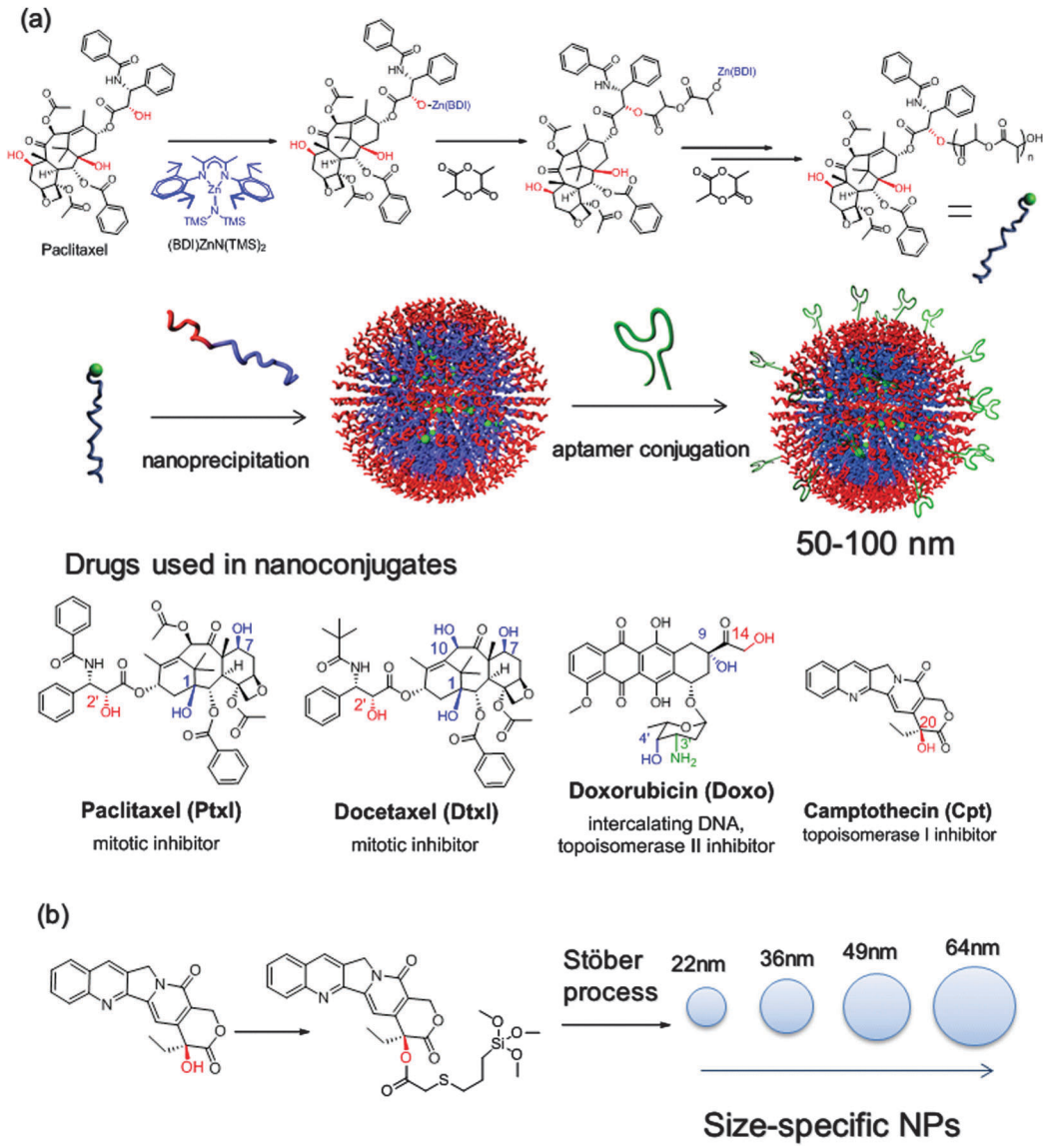
2.3 Metal catalysts mediated controlled drug conjugation

Nanoprecipitation is a simple well-known method for many hydrophobic polymer based nanoparticles (NPs) containing therapeutics: the polymer and drug in water-miscible organic solvent is added dropwise into water; NPs containing drugs

assemble rapidly upon addition.[140] This process is easy to control and allows convenient access to large-scale nanoparticulate delivery vehicles.[141] However, the nanoprecipitation formulation often leads to NPs with low drug loading and burst drug release kinetics.[140,142–145] It is also extremely difficult to prepare NPs with narrow polydispersities at sizes below 100 nm by such conventional technologies. Accumulated evidence indicates that NPs below this size range may enhance NP accumulation and penetration in tumor tissues.[146–148]

On the other hand, the preparation of polymer–drug conjugates with cleavable linkers was regarded as an alternative approach in drug delivery. The realization of such a task, however, can be difficult. Therapeutic molecules usually have very complex structures and multiple functional groups, which create heterogeneous structures of conjugates (conjugation happens on either different sites of polymer chains or different functional groups on drugs).[149] The heterogeneous structures of polymer–drug conjugates may present as bottlenecks for clinical translation.

To address these challenges, a unique drug incorporation strategy by using a drug to initiate the ring-opening polymerization of lactide was recently reported (Scheme 3a).[149] Using a metal catalyst containing a bulky ligand, paclitaxel initiated polymerization of L-lactide (LA) can be specifically controlled at the least sterically hindered hydroxyl group of the drug molecule. When bulky chelating ligands are used, the Zn-catalyst can only interact with the least sterically hindered 2′-hydroxyl group of paclitaxel and thus regulates the initiation and polymerization at this hydroxyl position. This resulted in paclitaxel–PLA conjugates with precisely controlled composition and molecular weights, having low polydispersities (as low as 1.02).[150] Of note, the Zn



Scheme 3 Synthesis of nanoconjugates. (a) Preparation of polylactide nanoconjugates with regioselective activation of a specific hydroxyl group of drugs (hydroxyl group in red color); (b) preparation of camptothecin-loaded silica nanoconjugates with distinctive nanoparticle (NP) sizes from ~20 nm to 70 nm.

catalyst is non-toxic and can be readily removed from the conjugates after polymerization by simple washing. At a low monomer/initiator (LA/paclitaxel) ratio, the nanoparticle derived from the paclitaxel–PLA conjugates had extremely high loadings (close to 40 wt%) and displayed controlled-release kinetics with negligible "burst" drug release. This technique has been extended to the formulation of PLA conjugates of drugs with a more complex structure, such as doxorubicin (Doxo).[151] Doxo can be incorporated into the terminus of PLA *via* the 14-hydroxyl group, with no need to protect the intrinsic nucleophilic 3′-amine group. This strategy can also be adapted to the delivery of CPT and fluorescent dyes for targeted cancer therapy.[152–154] Additionally, it has been shown that CPT can be used to initiate the ring-opening polymerization of phenyl-*O*-carboxyanhydride (Phe-OCA).[155] This polymer shows greater hydrophobic characteristics and thus, once formulated into polymeric micelles, gives greater stability than that of PLA, as well as slower blood clearance. The regioselective activation of drugs for controlled polymerization can also be broadly developed for regioselective *O*-acylation reaction of therapeutic drugs with anhydride or carboxylic acid functionalities. This can allow for sharp control over prodrug structure while easing the synthesis of complex drug derivatives, including paclitaxel and rapamycin.[156]

2.4 Other drug-conjugated nanomedicine

Another facile and scalable drug conjugation chemistry was recently reported to prepare monodisperse NPs with precise size control from 20 nm to 100 nm.[157] A bifunctional trimethoxylsilane-carboxylic linker was first conjugated to hydroxyl-containing therapeutic agents (*e.g.* CPT) *via* hydrolysable ester linkage; the pendant trimethoxylsiliane group would subsequently incorporate *via* tetraethyl orthosilicate polycondensation reaction (Stöber process) in a quantitative manner, resulting in monodisperse NPs (Scheme 3b). The precise NP sizes can be achieved by tuning the concentrations of components in the Stöber process, offering 22 nm NPs with distinct size differences from 36 nm NPs. The size-specific drug–silica conjugates can be potentially used to investigate the optimized NP sizes for therapeutic effects.

Another interesting polymer–drug conjugate developed by the Uhrich group is the chemical incorporation of salicylate drugs (non-steroidal anti-inflammatory drugs) into the polymer backbone of poly(anhydride esters). The polymer can degrade into biocompatible compounds, salicylic acid and sebacic acid,[158–162] whose drug release is directly dependent on the hydrolytic cleavage of the anhydride and ester bonds. Recently, the same strategy has been used to incorporate naproxen and ibuprofen into a degradable polyester through their respective propionic acid functionalities.[163] This strategy allows for elevated as well as controlled drug loadings of 65–67 wt%, significantly higher than typical polymer–drug conjugates. Additionally, this methodology allows for prolonged and controlled release through ester bond hydrolysis and avoids burst release kinetics typically associated with encapsulation based nanomedicine.

3. Stimuli sensitive chemistry

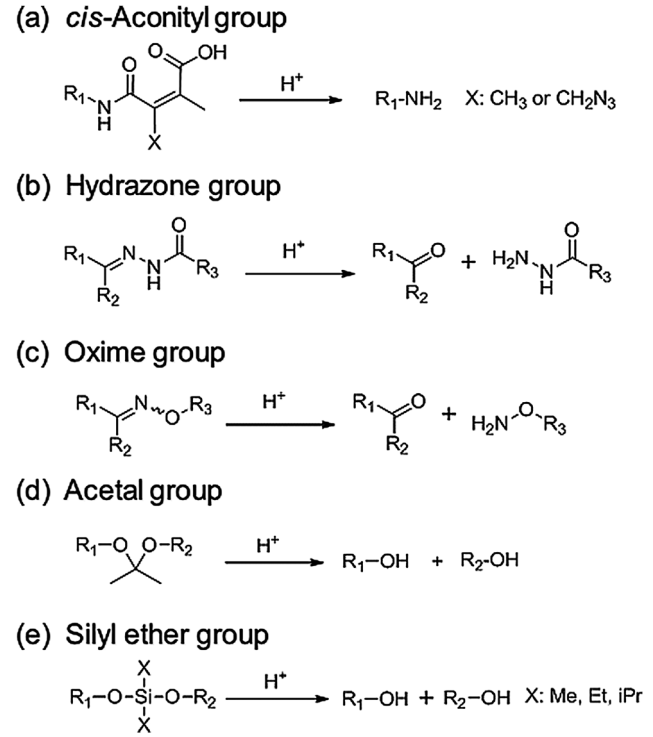
Despite recent advances in drug delivery technologies, one significant drawback of marketed drug delivery NPs is that drugs are released at a predetermined rate irrespective of patient needs or changing physiological circumstances.[164] They were "controlled" only in the sense that the encapsulating matrices are affected, or that the chemical conjugation linker is degraded. More recently, there has been increasing interest in developing "smart chemistry" where drug release can be controlled directly, triggered by either an interaction between the "smart" material and changes in its environment, or by an external stimulus.[164] Ideal chemistry designs are expected to achieve control of the timing, duration, dosage, and even location of drug release, and thus allow remote, noninvasive, repeatable, and reliable delivery of therapeutic agents. We will discuss a few interesting and facile trigger sensitive groups used in drug delivery technology, including: pH, redox, enzyme, and light. Many stimuli-responsive systems may have difficulty translating into clinical practice, which should be known at the beginning of the system design. For example, endogenous triggers are somewhat difficult to control because they may vary from one patient to another (*e.g.*, the pH of a tumor or the presence of reducing agents in the blood circulation). For systems responsive to external stimuli, major improvements would be needed to increase tissue-penetration depth and avoid damage to healthy tissues.[165]

3.1 pH sensitive groups

The mildly acidic pH in tumor tissues (pH $\sim$ 6.5–7.2)[166] and inflammatory tissues[167] as well as in the endosomal intracellular compartments (pH $\sim$ 4.5–6.5) may trigger drug release from pH sensitive delivery vehicles upon their arrival at the targeted disease sites. Many pH-sensitive drug delivery systems have been developed including *cis*-aconityl amide linkages, hydrazone, oxime, acetal/ketal, or other groups like trityl, *N*-ethoxybenzylimidazoles and imino groups (Scheme 4).[168,169]

3.1.1 *cis*-Aconityl linker and analogues (Scheme 4a). Hydrolysis of the link between the polymer and drug in polymer–drug conjugates can be stimulated by a change in pH to release bioactive reagents into targeted areas. In the early 1980s Shen and Ryser first utilized the concept of pH-controlled drug release *via* modified aminoethyl polyacrylamide beads and poly(D-lysine) conjugated with daunomycin *via* *cis*-aconityl linkages.[170] The *cis*-aconityl linkage between the drug and the polymer is pH-sensitive with a hydrolysis half-life of 3 h at pH 4. The configuration of the intermediate isomers (*cis*- and *trans*-) had an influence on the kinetic release profile. Kakinoki and coworkers conjugated Doxo to poly(vinyl alcohol) (PVA) *via* a *cis*-aconityl spacer.[171] At pH 5 the half-life for the release of Doxo was 3 h for PVA-*cis*-aconityl-Doxo whereas it was 14 h for PVA-*trans*-aconityl-Doxo. Other groups have developed *cis*-aconityl linkers for use in polymer–drug conjugates which have been evaluated both *in vitro* and *in vivo*.[172,173]

Analogues of *cis*-aconityl amide groups can also be used to mask molecules for specific biological applications. Wagner and coworkers recently reported a shielding strategy to incorporate a pH-responsive endosomolytic peptide in gene delivery vehicles.[174]



Scheme 4 Structures of acid sensitive linkers.

They modified the Melittin (Mel) peptide with dimethylmaleic anhydride (DMMAn) which decreased the lytic activity and cytotoxicity at neutral pH. After intracellular transport into endosomal compartments, the activity of Mel is restored after the DMMAn protecting groups are cleaved. pDNA transfer activity of the resultant poly(L-lysine)-PEG-DMMAn-Mel was similar to that of the PEI analogue and even better in the case of siRNA transfer, and considerably lowered the acute cytotoxicity of the polycation poly(L-lysine).[175] DMMAn was also applied by Wang and co-workers to modify amine terminated poly(2-aminoethyl methacrylate) (PAMA), forming acid sensitive, negatively charged terminal carboxylate functionalities. Interactions of these charges with positively charged Doxo and encapsulation into nanogels or conjugation to polymeric NPs can promote tumor cell uptake. Furthermore, pH triggered drug release can be triggered upon charge conversion of the polymer backbone to a positively charged amine. This charge conversion greatly enhanced the cellular uptake of the nanogel and improved cargo release, which resulted in remarkably enhanced efficiency in killing cancer cells[176,177] or for delivering siRNA.[178]

The *cis*-aconityl amide group can be cleaved in a traceless manner leaving an unmodified molecule of interest. This traceless *cis*-aconityl amide linker was recently modified by the Wagner group to adapt an azide group (azidomethyl-methylmaleic anhydride) as a hetero-bifunctional linker for protein modification and delivery.[179] Proteins with amines were first activated by azidomethyl-methylmaleic anhydride to form *cis*-aconityl amide linkage with an azide group, which can then be utilized to introduce functional agents *via* click chemistry. Under acidic conditions the protein molecule will be released intact for disease treatment.

3.1.2 Hydrazone (Scheme 4b). Chemotherapy agents containing carbonyl units (*e.g.*, ketone in Doxo) are of special interest for conjugation since the amine/carbonyl reaction into an imine type linkage takes place under mild conditions at physiological pH, and the resultant linkers undergo disassociation at acidic pH.[180–182] The application of hydrazone and related oxime functionalities involved in tissue engineering and surface patterning has been extensively investigated[183–187] and is thus not covered in this review. Conjugates of Doxo with polymers *via* a hydrazone linker have been developed as anticancer drug delivery systems.[188–190] Ulbrich and co-workers have reported acid-sensitive *N*-(2-hydroxypropyl)methacrylamide (HPMA)–Doxo copolymer conjugates containing hydrazone linkers.[191] The rate of Doxo release from these different conjugate systems was pH-dependent with the highest release rate obtained at pH $\sim$ 5, while only a very small amount of Doxo release was observed at physiological pH. The cytotoxicity of the hydrazone-based conjugates was the highest and comparable to that of the free Doxo. Another interesting pH-sensitive drug conjugate delivery system was reported by Kataoka and co-workers using an acid-labile hydrazone linker to conjugate Doxo to poly(L-aspartic acid).[192] A kinetic study demonstrated the pH-dependent release of Doxo, in a manner resembling what was observed in HPMA pH-sensitive drug conjugates. The *in vivo* antitumor activity of the hydrazone-based conjugates was notably better compared to the free drug or the clinically tested, enzymatically degradable conjugate PK1.[168] These studies suggest a reliable rationale for the design of pH-sensitive polymer–drug conjugates. To date, several polymer drug carriers including polymeric nanoparticles,[193,194] dendrimers,[195,196] micelles,[197–200] and star-comb polymers[201] with acid cleavable hydrazone linkers have been explored for controlled delivery of Doxo, cisplatin, and other agents.

Lehn and co-workers recently synthesized a nanostructured poly(acylhydrazone) which undergoes reversible polycondensation between di(aldehyde) and di(acylhydrazine) under acidic conditions. The polymer system showed control of the assembly state by two orthogonal agents, heat and protons (pH). As the temperature increases, the polymer molecular weight will significantly increase, whereas under neutral and alkaline conditions the polymer molecular weight is not affected. Under acidic conditions however, reversible polymerization occurs. The dynamic materials displaying multiple controlled adaptive behavior might be potentially useful for triggered drug delivery systems.[202]

Of note, imine (Schiff base) itself can be stably synthesized *via* the reaction between aromatic amine and aldehyde. The pH sensitive imine linkage has been employed in biodegradable polymeric nanomedicine to enable acid-triggered drug release.[203]

3.1.3 Oxime (Scheme 4c). Oximes possess greater intrinsic hydrolytic stability than other imines and are cleavable under acidic conditions, making these drug–polymer conjugations ideal for biological applications.[204,205] Zhu and coworkers synthesized a triblock copolymer comprising hydrophilic PEG and hydrophobic oxime-tethered PCL. The drug release rate was significantly accelerated under mildly acidic conditions compared to the physiological environment. The *in vitro* cell assay also showed that Doxo-loaded micelles had a high

anticancer efficacy.[206] Recently, Müller *et al.* applied the oxime conjugation reaction to prepare diblock PEG–polysaccharide copolymers.[207] The success of this approach enables end-modification of polysaccharides. Moreover, this reaction has been applied to the preparation of polymer–protein conjugates,[208] and the coupling of large peptide blocks.[209]

3.1.4 Acetal and ketal linkers, and polyacetals and polyketals (Scheme 4d). Among the pH sensitive linkers, the acetal linker has been extensively studied and applied in the preparation of delivery vehicles. Heller and co-workers have developed a series of polyketal and poly(ortho ester) polymer–drug conjugates containing acetal groups for drug delivery and controlled release since the 1970s.[210] Later, Fréchet and co-workers developed a pH-dependent micelle that can release encapsulated cargos significantly faster at pH 5 than at pH = 7.4.[211–213] The amphiphilic copolymer with an acid-labile hydrophobic block can form micelles at physiological pH and when exposed to mildly acidic pH, the accelerated hydrolysis of the micelle acetal bonds results in the formation of hydroxyl groups in the hydrophobic core triggering disruption of the micellar assembly, and release of the encapsulated cargos. The strategy of incorporating a pH sensitive acetal linker was broadly extended through the preparation of various delivery vehicles, including hydrogels and microgels for protein delivery,[214,215] nonviral gene carriers,[216,217] microparticles to deliver antigens to dendritic cells,[218] polymersomes for both hydrophilic and hydrophobic anticancer drugs,[219] and aliphatic polyester dendrimers with an acetal linker periphery to encapsulate a near infrared dye.[220,221] Murthy *et al.* synthesized acid-sensitive polyketal polymers *via* acetal exchange reaction; the polyketals can be used to formulate NPs or microparticles for drug or gene delivery for the treatment of inflammatory diseases, *etc.*[222–227] The acid sensitive polysaccharide-based particles prepared from acetal-modified dextran[228] have found applications in gene delivery[229] and immunotherapy,[230,231] and can be regarded as the substituent of well-known PLGA particles. Dual responsive dextran nanoparticles with one pH solubility switch (amine) and one acidic labile group (acetal) were also developed by the Fréchet group. The particles exhibited rapid hydrolysis only after the hydrophobic backbone became hydrophilic at mildly acidic pH = 5.0–6.5.[232] Grinstaff and co-workers have also engineered cross-linked NPs with hydroxyl groups masked by an acetal protecting group.[233] The decrease in pH cleaves the protecting group and causes the transformation of polymers from hydrophobic to hydrophilic. Nanoparticle loaded paclitaxel, a poorly water-soluble anticancer drug, can then be released to prevent the onset of lung cancer *in vivo* better than the conventional drug delivery method for paclitaxel using Cremophor EL/ethanol. A similar strategy to prepare acid labile core-cross-linked micelles and polycarbonate micelles for drug delivery was also reported.[234,235] Acetal groups can also be incorporated into polymer side chains, *e.g.*, polyserine–PEG; the hydrophilicity of the polymer will change in response to the acid environment.[236] Drugs can be conjugated to polymer backbones through acetal linkage.[237] In addition, acetal groups were used to link ~5 nm gold NPs to cap pores of mesoporous silica NPs, acting as a nanovalve, which could release gold NPs and entrapped drugs in an acidic pH environment.[238]

3.1.5 Poly(histidine) and the imidazole group. L-Histidine is a major amino acid responsible for the buffering capacity of biological systems and its side chain imidazole group, in the base form, has a pK_b of 6.5.[239] Poly(histidine) (polyHis) has been utilized as a smart extracellular tumor pH trigger for various responses of the delivery vehicle, acting as an extracellular pH-sensitive actuator for ligand exposure, a pH induced endosomal micelle destabilizer, as well as a membrane disruptor.[240,241] The Bae group specifically engineered a core–shell type micelle constituted from two block copolymer components, polyHis-PEG and PLLA-*b*-PEG-*b*-polyHis-biotin. The micelles exhibit four functionalities with the decrease of the pH value: ligand exposure at pH 7.0, micelle destabilization below pH 6.8, followed by enhanced Doxo release, and endosomal membrane disruption.[242] Later, similar chemistry was incorporated into a pH-sensitive nanogel composed of poly(His-*co*-Phe)-PEG for Doxo delivery.[243] The imidazole analogues, such as *N*-ethyoxybenzylimidazole, are also utilized as pH-sensitive linkers for drug delivery with tunable hydrolysis rates from minutes to months.[244,245]

The pH sensitivity of the imidazole group can be adapted for use in host–guest chemistry, where its interaction with cyclodextrin allows the complex to act as a 'nanovalve' for controlled release.[246–248] In such cases,[247] mesoporous silica NPs with cylindrical channels and physically entrapped drugs were modified with benzyl-imidazole derivatives at pore openings. β-Cyclodextrin was used as a cap for the benzyl-imidazole at physiological pH and blocked the pores to prevent drug leakage. Under acidic conditions (pH $<$ 6) the protonated imidazole derivatives would repel β-cyclodextrin and open the porous channels in silica NPs to release the drugs that are pre-loaded inside NP channels.

3.1.6 Silyl ether group (Scheme 4e). Silyl ethers are one of the most widely used protecting groups in organic chemistry, which can be cleaved by acid catalysis. DeSimone and co-workers recently investigated bifunctional silyl ether groups as acid-labile linkers for drug delivery of PRINT fabricated nanoparticles.[249,250] The increase in the size of the substituents on silicon atoms significantly reduces the linker hydrolysis rate under acidic conditions. The bifunctional silyl linkage can introduce therapeutic agents containing hydroxyl groups into surfaces of nanoparticles having well-defined sizes and shapes, allowing tunable drug release under acidic conditions from days to months.

3.1.7 Other pH-sensitive groups. Some other pH-sensitive moieties have also been applied in drug delivery, including β-thiopropionates,[251] vinyl ethers,[252] anhydrides[253] and trityls.[254] One interesting example is amidine, which is a type of CO_2-switchable molecule that was pioneered by the Jessop group.[255] A switchable transformation exists between amidine and amidinium triggered by CO_2.[256] Yuan and co-workers reported a specific amidine-containing block copolymer to fabricate CO_2-responsive polymeric vesicles.[257] The vesicles can expand or contract to mimic breathing as CO_2 or argon flows through; these vesicles can tune release time and speed.

Protonation of the amino group has been applied in NPs to release encapsulated drugs. For example, chitosan swelling

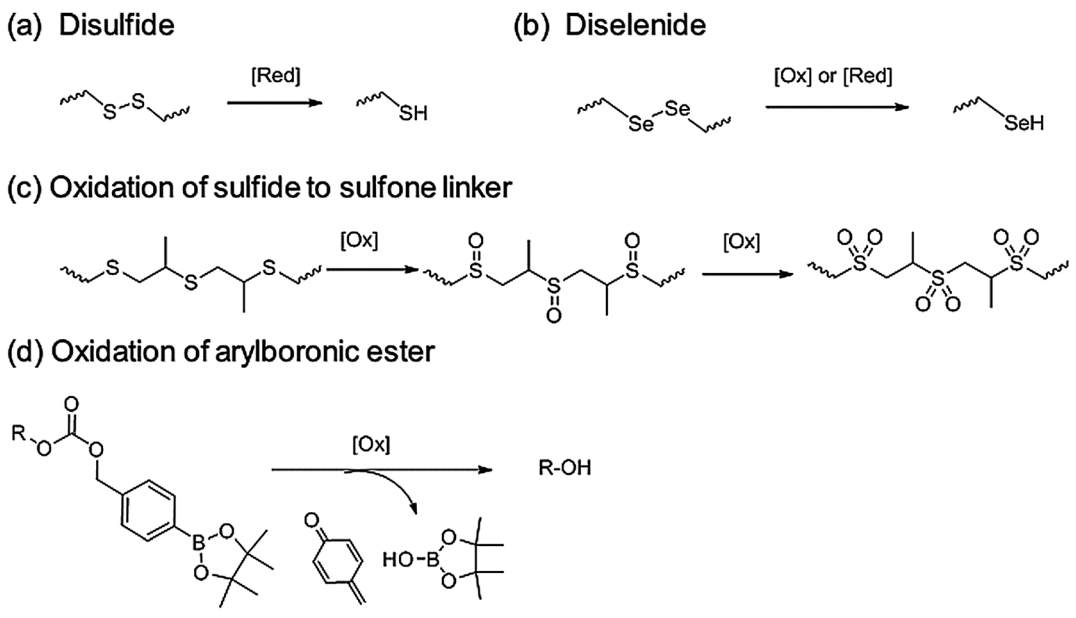
induced upon amino-group protonation ($pK_a \sim 6.3$) could release the encapsulated tumor necrosis factor alpha (TNFα) in the acidic tumor tissues.[258] The disassembly of CPT encapsulated micelles composed of PEG-poly(β-amino ester) can also be triggered at pH 6.4–6.8, releasing entrapped CPT.[259] The PEG-poly(β-amino ester) can be further modified with piperidine and imidazole groups to modify the pK_a, thus tuning the disassembly of the NPs.[260] Similarly, the Gao group utilized different tertiary amino groups that have different pK_a values to formulate pH responsive micelles and probes comprising PEG-*b*-poly(methyl methacrylate) with various tertiary amino groups; these polymeric NPs can be used to image tumor tissues or target specific cell organelles, *etc.*[261–264] The protonation of the amino group can also be utilized to prepare pH-sensitive particles or liposomes.[265,266] The liposome containing 1,2-dioleoyl-*sn-glycero*-3-phoshoethanolamine (DOPE) or 1,2-dipalmitoyl-*sn-glycero*-3-phosphoethanolamine can undergo a phase transition from a lamellar phase to a fusogenic hexagonal phase at acidic pH to release drugs.[267,268] Furthermore, the conjugation of DOPE to low-molecular-weight PEI improved gene and siRNA delivery through a combination of fusogenicity and buffering properties.[269]

Of note, pH-sensitive drug delivery systems can be used in oral-drug delivery, with the design to protect drugs from harsh conditions in gastric cavity (acidic) and enhance the absorption in intestine (pH increase from 6 to 7.4).[270] For instance, poly(methacrylic acid)-based copolymers were used as pH-sensitive coatings at the surface of porous silica NPs, as well in the preparation of copolymer micelles which are stable at acidic pH, yet disassemble at neutral pH.[271,272]

3.2 Redox sensitive groups

There exists a large difference in the redox potential between the mildly oxidizing extracellular milieu and the reducing environment of the intracellular fluids, such as the cytoplasm and the cell nucleus.[273] This renders reduction-sensitive polymers particularly appealing for use in triggered release and other biomedical applications. The disulfide bond has been extensively used to formulate many different polymeric particles (Scheme 5a). For example, reduction-sensitive polymer–DNA complexes,[274–276] polyion complex micelles,[277] polymersomes,[278,279] and degradable nanogels[280,281] have been reported to achieve fast intracellular release of their cargo. Zhong and co-workers reported one type of particle prepared from dextran–lipoic acid derivatives and readily cross-linked them using a catalytic amount of dithiothreitol (DTT).[282] The *in vitro* release studies of encapsulated Doxo showed that the leakage was minimal, while in the presence of 10 mM DTT (which mimics the intracellular reductive environment), over 90% of the Doxo was released in 11 h. *In vitro* cell studies further confirm the application based use of this redox sensitive delivery vehicle which shows good uptake and cytotoxicity towards cancer cells. Similar approaches to convert thiols to disulfide bonds using DTT have been applied by Thayumanavan and co-workers to develop crosslinked polymer nanogels for redox responsive drug delivery.[283,284] Similar to pH sensitive linkers, polymers with disulfide groups have also been used as protective layers for gene delivery.[285]

Cheng *et al.* have recently used the redox responsive nature of the disulfide bond to trigger disulfide cleavage of core-crosslinked micelles containing polymer-conjugated CPT.[286] To realize this strategy, CPT was modified with a disulfide linker that contains the hydroxyl group to initiate polymerization; free CPT could be released upon reductive cleavage. This modified CPT prodrug can initiate ring opening polymerization of alkyne functionalized tyrosine based *O*-carboxyanhydride (Tyr-OCA). The resulting polymer was co-nanoprecipitated with mPEG-*b*-Tyr-OCA and the inner hydrophobic core was further crosslinked with the di-azide linker, which yielded the redox responsive core-crosslinked micelles. Such micelles showed enhanced stability upon dilution



Scheme 5 Structures of redox sensitive linkers. [Red]: reductive agents; [Ox]: oxidative agents.

and no drug leakage in PBS. Upon incubation with DTT, however, slow release of CPT over the course of 5 days was observed. A more rapid release of the CPT within 24–48 hours can be achieved by incorporating disulfide crosslinkers in the hydrophobic core.

In addition to disulfide bonds, diselenide bonds have also shown promise as an oxidation and reduction responsive trigger due to their good activity in the presence of either type of environments (Scheme 5b). Selenium-containing compounds have been widely used in pharmacochemistry as antioxidants.[287,288] To achieve dual redox responsiveness, a tri-block copolymer with one hydrophobic diselenide-containing block and two hydrophilic PEG blocks was synthesized and self-assembled into micelles in water.[289] Diselenide bonds would undergo structural dissociation in the presence of oxidants (H_2O_2) or reductants (glutathione), and released drugs inside micelles. Additionally, a pH and dual redox responsive nanogel could be formulated based on PEG-*b*-poly(L-glutamic acid) and diselenide bond crosslinking. In the presence of glutathione, an initial burst release of the encapsulated Doxo was followed by prolonged zero-order release over 48 hours, freeing 57% of the encapsulated drug.[290]

Another interesting type of oxidation-sensitive polymeric vesicle was developed by the Hubbell group, using an A–B–A type triblock copolymer (Scheme 5c).[291] The hydrophilic A blocks consisted of PEG and the hydrophobic B block was made of poly(propylene sulfide) which can be oxidatively converted to poly(propylene sulfoxide) and ultimately hydrophilic poly(propylene sulfone). This new class of block polymers may find applications as nanocontainers in drug delivery, biosensing and biodetection. Such chemistry was recently adapted to change glycopolypeptide conformation. A thioether linker was incorporated into peptide side chains and subsequently oxidized to sulfone groups, resulting in the disruption of α-helical conformation to random coil, without the loss of water solubility.[292]

In another interesting application of controlled oxidation triggered chemistry, Fréchet and coworkers reported an oxidation triggered delivery method based on the dextran. The use of an oxidation trigger is rationalized because of the heavy production of reactive oxygen species within the phagosomes of antigen-presenting cells as critical initiators of the adaptive immune response. The method involved masking hydroxyl groups on dextran with oxidation sensitive arylboronic esters (Scheme 5d), which partially converted hydrophilic dextran to hydrophobic one for the formation of micelles. In pH neutral aqueous solution with the same H_2O_2 concentration as in phagosomes of antigen-presenting cells, the arylboronic esters were oxidized to phenols and then rearranged to a quinone methide to unveil the hydroxyl groups, which disrupted the hydrophobic cores in particles and released the payload.[293]

The Murthy group developed poly(thioketal) particles with ROS sensitive thioketal linkages. The polymer can be synthesized *via* the reactions similar to polyketal; the thioketal linkage, however, is stable under acidic and basic conditions and only decomposes in the environment with the high level of ROS (*e.g.*, inflammatory tissues).[294] The poly(thioketal) particles can orally deliver siRNA through a harsh environment such as the gastrointestinal tract to inflamed intestinal tissue.

Besides incorporating redox sensitive functional groups, the introduction of inorganic NPs inside polymeric NPs may potentially bestow new properties (*e.g.*, directional movement) to NPs. The newly developed bowl-shaped deformed polymer vesicles entrapped platinum NPs within vesicle cavities.[295,296] The platinum NPs inside vesicles rapidly decompose with addition of catalytic hydrogen peroxide, and generated a rapid discharge of oxygen, which induced thrust and directional movement of vesicles. Such vesicles may have potential applications for use in a redox-sensitive environment to prompt particles *in vivo* diffusion.

3.3 Enzyme sensitive groups

Another powerful method for targeted drug release exploits the enzymatic cleavage of linkers in polymer–drug conjugates or NPs.[3,297,298] In an attempt to increase the rate and maximum extent of side-chain hydrolysis by lysosomal enzymes, Duncan and co-workers developed polymer–drug conjugates using HPMA copolymers and *p*-nitroaniline drug analogues, bearing oligopeptidyl-*p*-nitroanilide side chains, which are specific to certain lysosomal proteinases, yielding an enzyme-sensitive delivery system. This enzyme-sensitive strategy was also explored by Langer and co-workers, with drug molecules linked to polymeric carriers *via* a peptide linker (Pro-Val-Gly-Leu-Ile-Gly), which can be cleaved by tumor associated matrix metalloproteinases (MMP).[299] A new enzyme-responsive polymeric assembly was introduced by Zhang and co-workers utilizing the electrostatic interactions between a cationic block polymer and enzyme-responsive multi-negative charged adenosine 5′-triphosphate (ATP). The polymeric assemblies disassociated in the presence of the phosphatase which converted ATP to neutral adenine.[300] Although enzymatic triggered release of drugs has been extensively reviewed,[301] it is noted that the enzymatic sensitive linker should be specifically degraded by its corresponding enzymes existing at disease sites, in order to eliminate systemic toxicity. The concentration of enzymes at the disease site should also be sufficient for the disruption of polymeric assemblies.

3.4 Photo-sensitive polymers and groups

3.4.1 Photo-luminescent polymers. There are few biodegradable polymers that can function as both implant materials and fluorescent imaging probes. The Yang group developed aliphatic biodegradable photoluminescent polymers (BPLPs) and associated crosslinked variants for biomedical applications.[302] BPLPs are degradable oligomers synthesized from biocompatible monomers including citric acid, aliphatic diols, and various amino acids *via* a convenient polycondensation reaction (Scheme 6). Crosslinked BPLPs with cysteine and serine (BPLP-Cys and BPLP-Ser) offer advantages over the traditional fluorescent inorganic quantum dots and small-molecule dyes because of their biocompatibility with minimal chronic inflammatory responses *in vivo*. They also possess controlled degradability, high quantum yields (up to 62%), tunable fluorescence emission (up to 725 nm), and photostability. The crosslinked BPLP-Cys has excellent mechanical properties and possesses great processability for micro/nanofabrication such as particles, scaffolds and films.

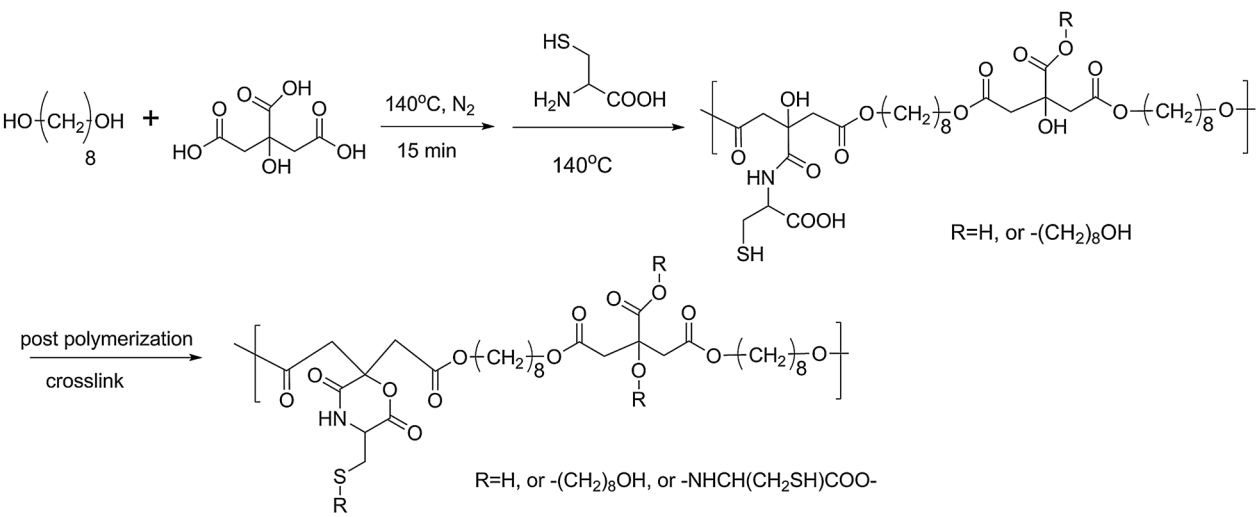
BPLP-Ser nanoparticles can be used for *in vitro* cellular labeling and noninvasive *in vivo* imaging of tissue engineering scaffolds. The development of BPLPs represents a new direction in developing fluorescent biomaterials and could impact tissue engineering, drug delivery, and bioimaging. It is noted that a similar condensation strategy to prepare crosslinked polyester scaffolds has great potential for *in vivo* tissue engineering application,[303–305] which is beyond the discussion of this review.

3.4.2 Photo-responsive groups. There has recently been growing interest in light-responsive block polymeric assemblies whose aggregation state in solution can be disrupted by illumination.[306–310] The use of an optical stimulus is appealing because it could provide a greater selectivity in terms of control over the moment and the location of drug release.[164] In order to make light-sensitive assemblies, the polymer should contain photochromic groups whose photoreaction upon illumination shifts the hydrophilic–hydrophobic balance toward the disruption of assemblies. Both reversible photo-isomerization and irreversible photo-cleavage reactions of various chromophores have been exploited to design light-responsive materials.[311–313] Several classes of photocaging groups[314] have been reported including the *o*-nitrobenzyl, coumarin-4-yl-methyl, *p*-hydroxyphenacyl, and 7-nitroindoline derivatives[315] with ester, amide, carbonate, carbamate, and phosphate linkages for photolysis. The photocaging 4,5-dimethoxy-2-nitrobenzyl group in a cationic, α-helical, cell-penetrating polypeptide (PVBGL-8)[316] for gene delivery was recently reported.[317] The photocaging nitrobenzyl group capped a negatively charged carboxylate; upon UV light-irradiation, the DNA/PVBGL-8 complex disassociated due to the uncaging of anionic carboxylate, which enhanced intracellular DNA release and outperformed commercial Lipofectamine™ 2000 in transfection efficiency by nearly 20-fold.

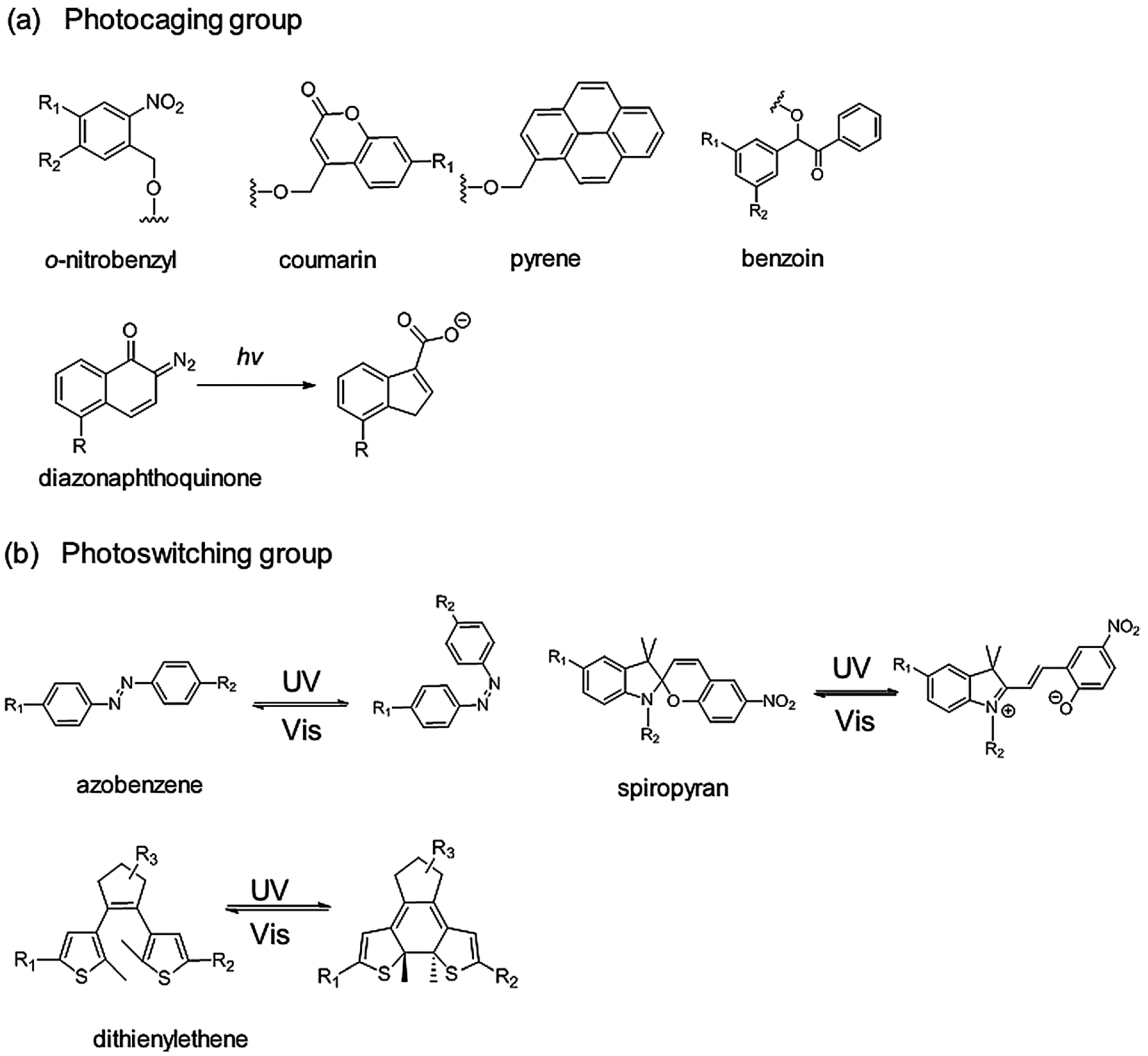
Photo-sensitive groups have also been incorporated into polymer–drug conjugates to impart controlled and triggerable release characteristics to achieve spatio-temporal *in vivo* drug release.[318,319] While these systems are successful in achieving cell killing, their drawbacks stem from inconsistent and uncontrolled site conjugation along the polymer backbone. To overcome this shortcoming and maintain high drug loading as well as a controlled triggered release profile, Cheng *et al.* succeeded in developing a chain shattering polymer therapeutic (CSPT): the polymer backbone consists of a regularly spaced trigger-responsive domain,[320] and the drug, 10-hydroxycamptothecin (HCPT) is directly incorporated into the polymer backbone[321] *via* *o*-nitrobenzyl caged self-immolative 2,6-bis(hydroxymethyl)anilines. The CSPTs showed rapid light-responsive drug release with complete degradation of the polymer and HCPT release within 20 minutes.

Other commonly used reversible photo-triggers often induce conformational changes rather than covalent bond cleavage. The most widely used groups consist of azobenzenes, spiropyrans, dithienylethenes, and stilbenes. (Scheme 7) Their illumination can lead to macroscopic shape deformation (contraction,[322] bending,[323,324] rotation,[325] swimming,[326] ciliary motion[327]), or physical property changes[328] (such as hydrophilicity, viscosity and permeability *etc.*). Numerous photo-responsive reactions and functional groups (*e.g.*, nitrobenzyl) can only be achieved with light in the ultraviolet (UV) or visible range. The use of UV or visible light suffers from a number of drawbacks, the most notable one being that they cannot be used for deep-tissue triggering due to the absorbance by skin and tissues. Moreover, it will damage tissue at lower powers than light of a longer wavelength (*e.g.*, near-infrared light). Nevertheless, organs and tissues such as the skin, ear, or the back of the eye are excellent candidates for treatment as long as the irradiation power is safe.

3.4.3 Photo-responsive materials using a near-infrared light source. Although a surfactant-like amphiphile and a linear-dendritic copolymer sensitive to near-infrared light (NIR) have been reported, the large majority of light-responsive micelles that have been reported to date are activated by UV and visible light.[329] NIR light, with wavelengths in the range of about 700–1000 nm, is more suitable for biomedical applications than UV or visible light. At these longer wavelengths, the irradiation is less detrimental to healthy cells, and the absorption and



Scheme 6 Preparation of photo-luminescent polyester from amino acid, diol and citric acid.



Scheme 7 Structures of (a) photocaging groups and (b) photoswitching groups.

scattering by water and biological substances are reduced, which results in a greater tissue penetration depth for NIR light (on the order of millimeters to centimeters).[330]

Two-photon excitation with NIR light may provide a promising solution to the short excitation light wavelength issues for many photocaging groups.[331,332] However, many photocaging groups do not have large enough two-photon cross-sections to be efficiently activated by NIR light; two-photon excitation usually requires high-intensity pulsed laser.[333] Some successful examples using two-photon excitation technology are reviewed here. Fréchet and co-workers reported an intriguing release triggering mechanism through the use of two-photon NIR light.[310] The amphiphilic structure has a 2-diazo-1,2-naphthoquinone at the terminal of the hydrophobic end and an oligo(ethylene glycol) as the hydrophilic block. When the micelles were exposed to NIR light, 2-diazo-1,2-naphthoquinone undergoes a *Wolff* rearrangement and forms a hydrophilic 3-indenecarboxylate, which destabilizes the micelle and causes drug release (Scheme 7a). Another example reported by the Zhao group showed that the photo-reaction of a 2-nitrobenzyl-containing polymer occurs upon two-photon absorption at 700 nm, but the sensitivity was low because of inefficient two-photon absorption.[334] They also reported a novel block copolymer micelle whose disruption can effectively be triggered by two-photon NIR absorption at 794 nm.[335] To achieve this NIR sensitivity, a coumarin chromophore, namely, [7-(diethylamino)coumarin-4-yl]methyl (DEACM) with a large two-photon absorption cross section was incorporated. The disruption of micelles under irradiation (one-photon UV or two-photon NIR) leads to the release of both preloaded Nile red and photo-cleaved coumarin molecules from the hydrophobic micelle core into aqueous solution (Scheme 7a).

Another solution is to employ NIR-absorbing particles that can emit UV light which has sufficient energy to activate the photocaging groups. Upconverting NPs are good candidates for converting NIR laser light into different shorter wavelengths of UV and visible light and therefore induce the liberation of photocaging groups in NPs.[336–338] Upconverting NPs are usually $NaYF_4$ NPs containing rare-earth ions (Yb^{3+}, Tm^{3+}, Er^{3+}, *etc.*) and can be excited by 980 nm NIR continuous-wave light. Such upconverting NPs have been applied in bioimaging applications

due to their large anti-Stokes shifts (>400 nm), sharp emission bandwidths, high resistance to photobleaching, stable emission, deep penetration within tissue (using NIR light), and ability to undergo surface modification with biomolecules.[339,340] Less photic energy is required when using upconverting NPs compared to two-photon excitation imaging ($\sim 10^6$–10^9 W cm^{-2}).[341] The biocompatibility of these inorganic NPs is still under investigation for future *in vivo* applications.[342] Recently, organic upconverting NPs have been prepared: the albumin–dextran NPs contain photo-sensitizers that can absorb long-wavelength light to emit short-wavelength light *via* triplet–triplet annihilation, while keeping reasonable quantum efficiency for *in vivo* imaging. The application of such upconverting organic NPs may open the avenues for remote light triggered drug delivery.

Some other inorganic NPs, including gold NPs with various shapes and sizes, are also promising for disease treatments using hyperthermal therapy which can be efficiently induced by light. The detailed discussion and the combination of polymeric NPs with inorganic NPs are beyond the scope of this review.[343–346]

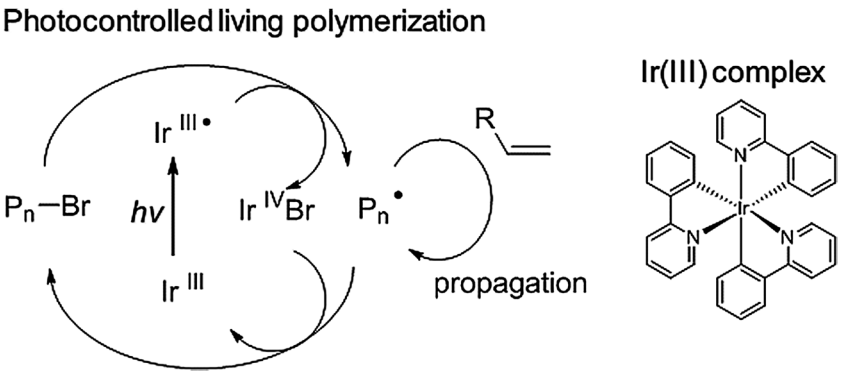
3.4.4 Controlled photo-polymerization. Photo-polymerization is a widely used form for radical polymerization in both academia and industry. Early attempts to control living radical polymerization with UV light used dithiocarbamate as an iniferter (*ini*tiator, trans*fer* agent and *ter*minator) for radical polymerization, which offered polymers with limited control and broad molecular weight distribution.[347] Photoinitiation in living radical polymerization has been developed later with only photo-control in the initiation process;[348–350] however, the subsequent chain growth lacks regulation. The Hawker group recently adapted a photoredox iridium catalyst in organic reactions[351,352] using visible light with classical atom-transfer radical polymerization (ATRP):[353] the Ir(III) complex was activated by visible light to form an oxidizing Ir(IV) complex which subsequently reduced bromide initiation to give the desired alkyl radical and regenerating the starting Ir(III) complex, which acts similar to the Cu(I)/Cu(II) catalysts used in ATRP (Scheme 8). Such a new mechanism can control both initiation and the chain propagation process by light, resulting in controlled molecular weight and narrow molecular weight distribution. The new photo-controlled chemistry may be useful for surface patterning and preparation of functional materials for tissue engineering.

3.5 Thermo-sensitive polymers

In the 1980s, Hoffman and co-workers conjugated temperature-responsive polymers such as pNIPAAm to proteins.[354,355] Poly(*N*-isopropylacrylamide) (PNIPAM)-based polymers have been widely investigated for drug delivery applications owing to their thermo-responsive behavior. These polymers have high aqueous solubility below their lower critical solution temperature (LCST) and precipitate above their LCST (Scheme 9a).[356,357] However, *in vivo* application of PNIPAM is limited due to the non-biodegradability of the polymer unless significant chemical modification is performed. The nerve toxicity of residual acrylamide-like monomers and the lack of sufficient *in vivo* evidence of the bioabsorbance of high molecular weight PNIPAM also limit the use of this thermo-sensitive polymer.[358]

Other synthetic copolymers exhibit an inverse sol–gel transition in which spontaneous physical gelation occurs upon heating instead of cooling. Various therapeutic agents or cells can be entrapped in the aqueous polymer solution and injected *via* syringe at target sites with minimal invasiveness and pain. If the transition in water takes place below the body temperature and the chemicals are biocompatible and biodegradable, such gelling behavior makes the associated physical gels become injectable biomaterials with unique applications in drug delivery and tissue engineering. Polymers that exhibit such a transition include: methyl- or hydroxypropyl methyl-cellulose,[357] chitosan derivatives,[357] PEG–PPG–PEG (Pluronic or Poloxamer),[356] PLA/PLGA-PEG copolymers of various architectures;[359–361] poly(organophosphazene);[362] hyperbranched polyether;[363] hyperbranched poly(amine-ester);[364] and elastin-like polypeptides (ELP).[365,366] Many of these polymers have been extensively reviewed elsewhere.[367]

An advantage to the application of ELPs for the delivery of protein based drugs is that the two can be conjugated at the genetic level *via* recombinant DNA methods (Scheme 9b). ELP drug delivery systems have been designed to aggregate upon intra-articular injection at 37 °C which slowly degrade and clear from the joints over time, which can treat localized joint disease of a variety of etiologies.[368] *In vivo* studies in a rat model were conducted to compare the half-life of soluble and insoluble (aggregates) ELPs with different transition temperature *via* intra-articular injection. The soluble polypeptide had a half-life of less than 4 h while the aggregated ELPs had a half-life of more



Scheme 8 Mechanism of photocontrolled living free radical polymerization.

than 85 h, suggesting that aggregating ELPs concentrate in the joint upon injection and slowly disaggregate to release protein drugs.[369] Chilkoti and coworkers have extended the use of ELP to develop artificial chimeric ELPs that spontaneously self-assembled into ~100 nm, mono-dispersed NPs, with subsequent conjugation of drugs and imaging agents.[370] They also reported a new methodology to involve ELPs for use in hyperthermia targeted nanomedicine since the temperature sensitive ELPs aggregate and adhere to the tumor vasculature once the temperature of tumors is higher than 41.5 °C.[371,372]

It is well-known that a polymer end group with an opposite lipophilicity to that of the main chain can lead to the formation of NPs through self-assembly.[373] Nevertheless, the alkyl end-group effect leading to macroscopic gelation reported herein is rather unique. Ding and coworkers reported the modification of PLGA–PEG–PLGA with different alkyl termini (acetate or propionate groups) that can induce a thermal-reversible physical gelation in an otherwise sol-like suspension (Scheme 9c).[374] They studied in detail the effects different alkyl groups had on the gelation behavior and concluded that the gelation is driven by entropy resulting from the hydrophobic interaction. By adjusting the end groups, the LCST of PLGA–PEG–PLGA can be tailored and therefore used as an injectable hydrogel. These thermogelling polymers were further applied for use as a slow release delivery system for mPEG-CPT. The sustained *in vitro* release of the PEGylated CPT *via* the thermogelling PLGA–PEG–PLGA copolymers resulted in slow drug release over 30 days. The release profile was thought to be diffusion-controlled at the first stage, and controlled by both drug diffusion and hydrogel erosion at the late stage. *In vivo* anti-tumor tests in mice further demonstrated the feasibility of this combinatory technique.[142]

A thermo-responsive polymer can also be used under conditions of a brief temperature decrease (*e.g.*, cold shock or cryotherapy). In such a case, the thermo-sensitive NPs can release encapsulated drugs due to the increase of porosity, in response to the temperature decrease. For example, poloxamer – polyethyleneimine (PEI) NPs have been used for siRNA delivery *via* cold shock.[375]

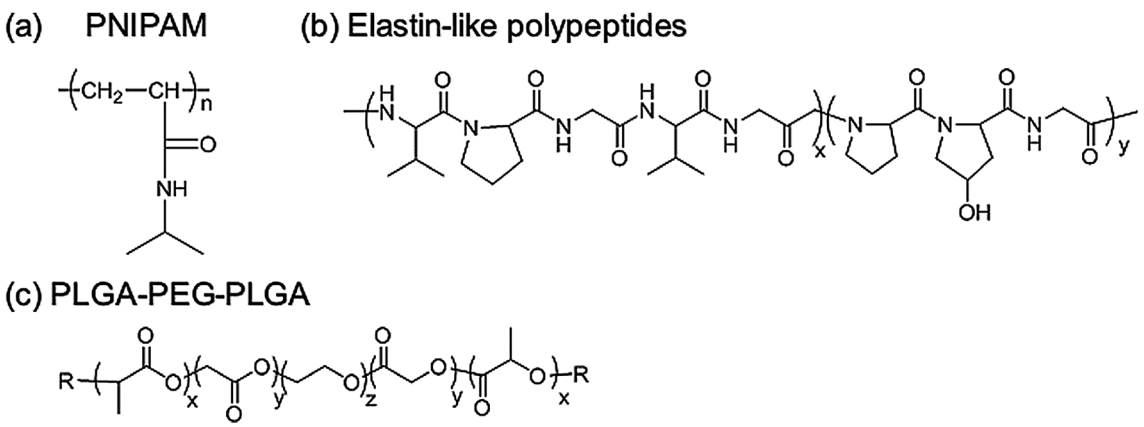
It is noted that temperature-sensitive liposomes have been used for drug delivery since 1990s[376,377] and one formulation, ThermoDox®, has entered the clinical trials to deliver Doxo for the treatment of breast cancer (phase II) and hepatocellular carcinoma (phase III). Although clinical trials for ThermoDox have been recently suspended since the life span increase has not reached the threshold of 33%, these trials have demonstrated the well-tolerated safety profile of such thermo-sensitive NPs in patients.

3.6 Glucose sensitive groups

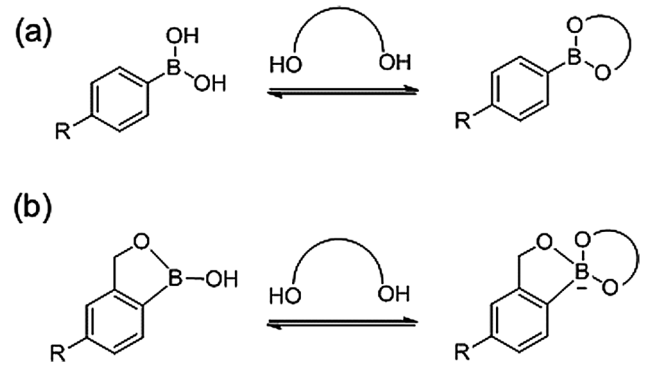
One of the most challenging problems in the controlled drug delivery area is the development of self-regulated (modulated) insulin delivery systems, as insulin has to be delivered in an exact amount at the exact time of need.[378,379] Self-regulated insulin delivery systems require the glucose sensing ability and an automatic shut-off mechanism.

Glucose oxidase is probably the most widely used enzyme in glucose sensing. It oxidizes glucose to gluconic acid, resulting in a pH change of the environment. The chemistry has been adapted for many pH sensitive hydrogels (usually with carboxylic groups to change pK_a); the decrease of pH will result in the shrinkage of the hydrogel matrix, thereby squeezing out encapsulated insulin.[380–382]

Arylboronic acids are widely used in this field as they bind preferentially to sugars and other vicinal diols, forming a tight complex between a 1, 2- or 1, 3-diol (Scheme 10a).[383,384] Over the past few decades, several fluorescent probes functionalized with arylboronic acid have been developed for glucose sensing.[385–388] Hydrogels containing a complex between arylboronic acids and polyols were prepared as insulin release systems. Glucose competes with polyols for borate cross linkages, which induces the decrease of polymer crosslinking density, leading to insulin release.[389,390] Such a competitive interaction was also used in a silica NP system for insulin delivery.[391] Mesoporous silica NPs functionalized with arylboronic acid were complexed with gluconic-acid insulin; the increase of glucose concentration triggered the release of insulin and other drugs capped inside mesoporous silica NPs. In another case, polymersomes comprised of amphiphilic polymers with styreneboroxol disassembled once glucose was introduced in the environment,



Scheme 9 Structures of some thermo-sensitive polymers.



Scheme 10 Scheme of (a) aryl boronic acid and (b) styrene boroxol forming complexes with diols.

due to the hydrophobic to hydrophilic shift of styreneboroxol once complexed with glucose (Scheme 10b).[392,393] The chemistry has also been recently adapted in protein modification. One strategy utilizes the ε-amino group on lysine to form stable iminoboronates with an acrylboronic acid containing pendant functional group. These bonds will be cleaved upon the addition of fructose, dopamine or glutathione to release protein.[394] In addition, proteins with pendant boronic acid could bind with the cell surface with polysaccharides (glycocalyx), enhancing the cytosolic delivery of such proteins.[395]

4. Other smart chemistry in polymeric drug delivery

4.1 Injectable delivery systems using macromer reactions

Besides thermally-induced sol–gel systems, another injectable delivery system used chemistry based upon the macromer reactions, which use a relatively high molecular weight polymerizable monomer for the *in situ* hydrogel formation upon injection. The Michael addition between thiols and associated electrophilic unsaturated agents offers another novel approach to obtain *in situ* forming hydrogels.[396–398] For instance, Hubbell and coworkers synthesized PEG hydrogels through the Michael addition between multi-thiol compounds and either multi-acrylate or multi-vinyl sulfone PEG chains.[396,399,400] A rapid reaction was achieved at physiological temperature and pH. Although the reaction seems unfeasible for protein encapsulation considering the reaction of thiol moieties in proteins' cysteine residues with the Michael acceptor in macromer, surprisingly, the reaction somehow offers selectivity towards the macromers, leaving proteins containing thiols covalently unincorporated into the gel network. The incorporated human growth hormone was shown to undergo sustained release for up to a few months while preserving the integrity of the protein quite well. In addition, Mikos and coworkers exploited the use of *in situ* crosslinked oligo(poly(ethylene glycol)fumarate) hydrogels.[401,402] The hydrogel was formed by free-radical polymerization under physiological conditions with good biocompatibility and biodegradability. To overcome the challenges associated with clinical translation of injectable *in situ* gelling biomaterials, Pritchard and co-workers developed a novel PEG-based hydrogel which could crosslink in aqueous media *via* Michael addition reaction between thiols and acrylate groups, leading to nearly complete conversion to gel and minimal sol fraction. This new system also exhibited sustained release of methylprednisolone sodium succinate, a hydrophilic small molecule drug. The rational design of the physical, chemical and biological properties of the hydrogel makes it a potentially promising candidate for future injectable applications.[403]

Another interesting system utilizing hyaluronic acid (HA) to form a hydrogel *in situ* was realized through chemical crosslinking between one HA derivative with hydrazide moieties and another HA derivative with aldehydes.[404–406] The crosslinked matrix showed good biocompatibility *in vitro* and *in vivo*, and has been used in the prevention of peritoneal adhesions in rabbit experiments.[404] In another example applying HA, the Ossipov group selected two orthogonal reactive and chemoselective groups, hydrazide and thiol, to prepare an HA derivative bearing both cross-linkable groups and a bioactive bisphosphonate ligand.[407] Acrylate modified bisphosphonates were first covalently linked to the thiol functionalities on the modified HA as targeting ligands through Michael addition. The resulting polymer was then mixed with oxidized HA bearing aldehyde functional groups which formed hydrazone crosslinks to prepare an injectable HA hydrogel. The potency of the bisphosphonate prodrug is triggered by the ubiquitous enzyme, hyaluronidase, which degrades the HA hydrogel and facilitates the internalization by CD44 positive HCT-116 colorectal carcinoma cells. Additionally, Wang and coworkers introduced another interesting strategy for convenient synthesis of *in situ* crosslinked HA hydrogels *via* a rapid thiol–disulfide exchange reaction under mild conditions in minutes. The disulfide formed induced the degradation of hydrogels in the presence of external stimuli (glutathione) to release their cargos.[408] *In situ* cross-linking dextran hydrogels conjugated with antifungal agents have also been developed.[186]

Wang and co-workers described an *in situ* injectable hydrogel model to control the release of proteins by using nucleic acid aptamers as affinity sites for the proteins in the hydrogel. The release tests demonstrated that aptamer-functionalized hydrogels greatly prolonged the release of proteins and the release rates could be controlled by adjusting the affinity of the aptamer to the protein.[409]

Existing methods of controlling the gelation rate are limited to varying the gel precursor and/or cross-linker concentration, which inevitably change the stiffness of the hydrogel and lead to limitations on drug release from hydrogel. To overcome these limitations, the Kurisawa group proposed enzymatically cross-linked HA hydrogels which were formed by the oxidative coupling of tyramine moieties catalyzed by hydrogen peroxide (H_2O_2) and horseradish peroxidase. It was noticed that the mechanical strength of the hydrogel could be controlled by simply varying the H_2O_2 concentration, while the gelation rate could be tuned by changing the concentration of horseradish peroxidase without worrying about the change in mechanical strength. This unique characteristic provides a hydrogel with

high protein encapsulation efficiency while minimizing the uncontrolled diffusion of protein drugs after injection.[410–412]

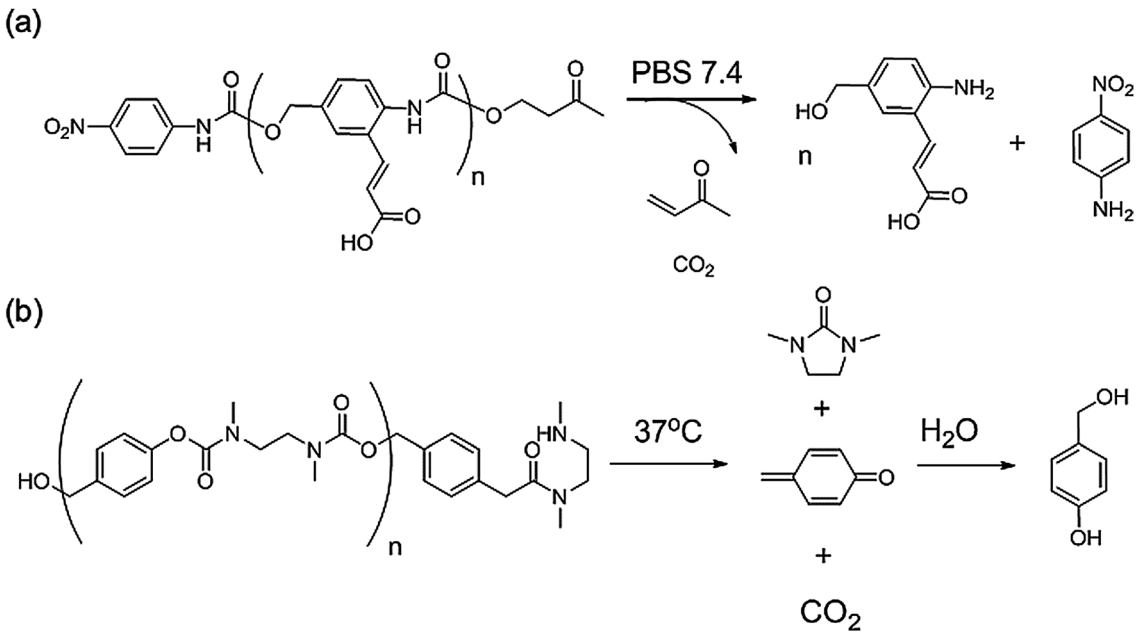
4.2 Self-immolative polymer

Self-immolative polymers are a type of new and attractive materials that can self-degrade upon stimulus.[413] Such polymers comprise a backbone that is stable when the end-cap is intact; upon the removal of the end-cap *via* a single bond cleavage, a functional group that is revealed at the polymer terminus subsequently initiates a cascade of intramolecular reactions leading to complete depolymerization from one end to the other. The chemistry was initially introduced in dendrimer systems in which the removal of a focal point group initiated an intramolecular degradation cascade, releasing multiple molecules from the dendrimer periphery.[414–416] Such systems were then further developed to provide for the simultaneous release of multiple different drug molecules and for the incorporation of tumor targeting groups or focal point groups that are sensitive to reducing conditions or enzymes.[417–420] Only few cascade degradable linear polymer backbones have been reported to date. One such polymer backbone was a polycarbamate based on 4-aminobenzyl alcohol derivatives, which degrades entirely through intramolecular 1,6-elimination reactions *via* iminoquinone methide intermediates (Scheme 11a).[421,422] Another linear cascade degradable polymer that degrades by alternating elimination and cyclization reactions was reported by the Gillies group (Scheme 11b).[423] By conjugating PEG to the terminus of the cascade degradable polymer as an end-cap, an amphiphilic block copolymer was obtained, which assembled into nanoparticles in aqueous solution. Hydrolysis of the ester linkage between the blocks initiated the cascade degradation process under physiological conditions. These nanoparticles were found to encapsulate a hydrophobic dye and release it upon depolymerization, thus demonstrating for the first time the utility of this class of molecules in the development of functional polymer assemblies potentially for nanomedicine. Moore and co-workers also formulated programmable microcapsules from the similar self-immolative polymers.[424] The Gillies group has also succeeded in producing a new reduction sensitive cascade degradable linear polymer that degraded entirely by cyclization reactions. They realized this through a disulfide end cap that was incorporated into the polymers so that the de-polymerization can be induced under reducing conditions such as glutathione.[425]

Besides the typical self-immolative polymers end-capped with different triggers, some polymers are conjugated with triggers on the backbone. The Almutairi group described a new NIR sensitive NP based on self-immolative polymers.[426] Upon the irradiation with light, the polymer backbone decomposed and the encapsulated Nile red was released. This system is designed to be versatile where the triggering group can be sensitive to a number of wavelengths.[426,427]

4.3 Topology of polymer and polymeric materials (cyclic polymers and cylindrical micelles)

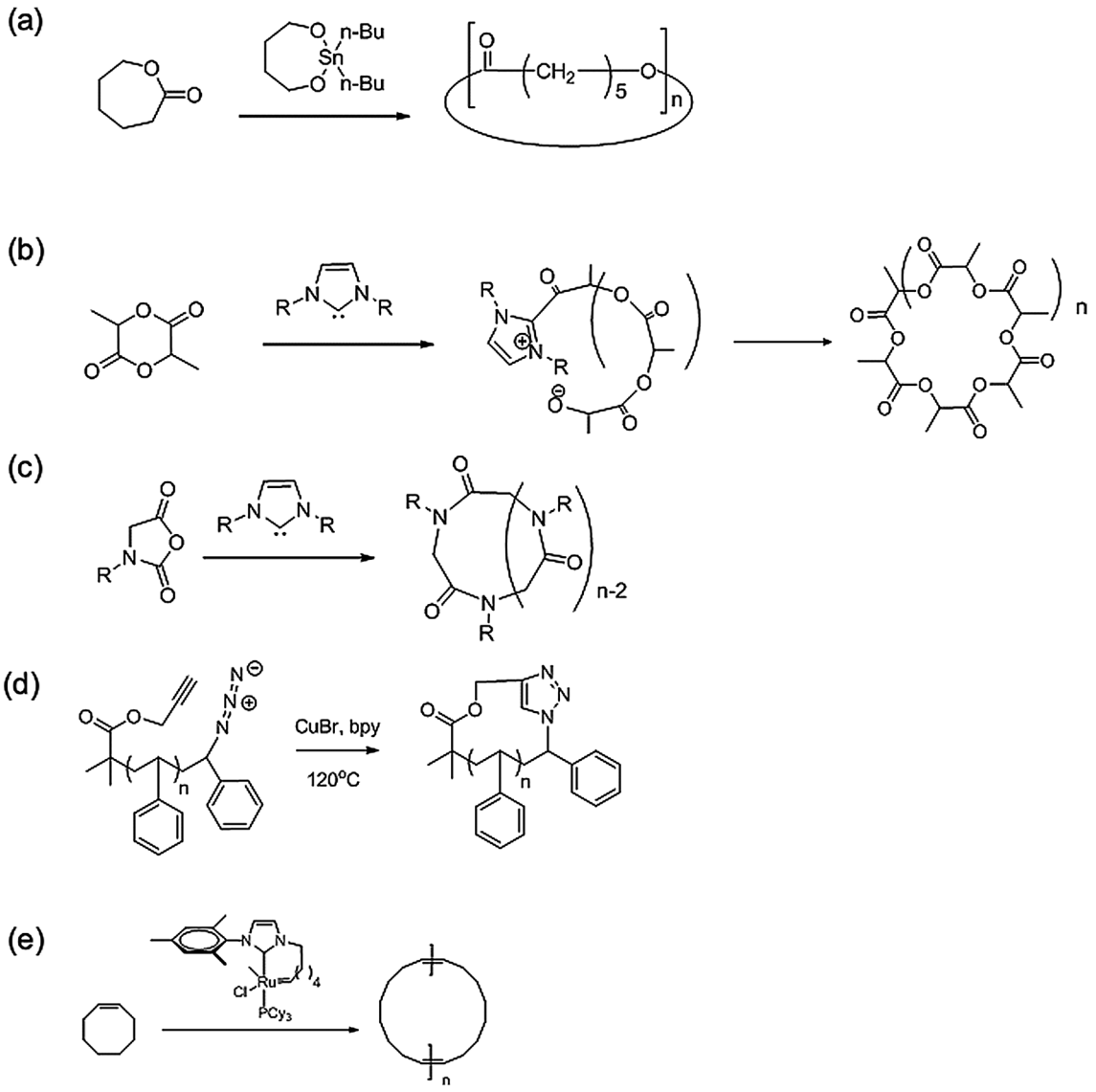
Long circulation times of water-soluble polymers are essential for the successful delivery of drugs to solid tumors. The circulation time of such a polymer depends upon molecular weight and polymer architecture. This is because physiological barriers in the kidneys have a nanoporous structure that retards the permeation of soluble polymers but allows the passage and elimination of low-molecular weight substances from the body. Since only one polymer segment needs to enter the pore for a linear polymer to traverse it, linear polymers cross nanopores more easily than star polymers. Cyclic polymers lack chain ends, two chain segments would need to enter the pore for the cyclic



Scheme 11 Degradation of self-immolative polymers.

polymer to transit. Fréchet *et al.* found that cyclic polymers behave differently *in vivo* with longer circulation time than linear polymers of the same molecular weight, which may provide a window of opportunity for cyclic polymers as drug carriers or imaging agents.[428,429] It was also found that the cyclic or branched polymer architecture increases the tumor uptake of polymers in comparison with the linear polymer of the same molecular weight.

The development of a cyclic polymer synthetic strategy is just emerging these years. The cyclic random copolymer of ε-caprolactone (ε-CL) and β-D,L-butyrolactone was polymerized using the cyclic tin-based catalyst 2,2-dibutyl-2-stanna-1,3-dioxepane (Scheme 12a).[430,431] Bismuth catalysts developed by the Kricheldorf group are also capable of synthesizing various cyclic polyesters.[432] Another synthetic pathway towards the formation of cyclic polyester was reported by Hedrick, Waymouth and coworkers, applying a N-heterocyclic carbene (NHC) based catalyst to mediate the cyclization step (Scheme 12b).[433,434] The NHC was also found to be useful in the cyclic poly(α-peptoid) polymerization (Scheme 12c).[435] Grayson and coworkers developed a high efficiency "click" reaction that enables the cyclization of styrenic polymers prepared by ATRP (Scheme 12d).[436] Both the end-group modification and the cyclization of linear poly(styrene) appear to be nearly quantitative, thus further purification to obtain reasonably pure macrocycle is unnecessary. In addition, the Grubbs group devised a sophisticated NHC-Rh catalyst for ring expansion metathesis polymerization (REMP, Scheme 12e).[437,438] The collaboration among Fréchet and Grubbs groups showed that this catalyst formed well-shaped cyclic norbornene, whose cyclic topology was confirmed by the AFM study.[437] Parker and Sampson modified the conditions of the alternating ring-opening metathesis polymerization (AROMP) and used the commercially available Hoveyda–Grubbs catalyst to provide an entirely cyclic alternating polymer.[439] It is anticipated



Scheme 12 Synthetic strategy to prepare cyclic polymers.

that more cyclic polymers can be extensively used in the drug delivery field to enhance the circulation and biodistribution performance of delivery vehicles (especially polymer–drug conjugates).

Other smart chemistries to extend blood circulation times have also emerged in recent years. The Discher group found that nanocarriers with high aspect ratio can have greatly enhanced *in vivo* circulation time by ten fold compared to their spherical counterparts.[440] This interesting finding may shed light on the design of a new generation of drug delivery vehicles, such as cylindrical polymer micelles, for enhanced circulation time and improved *in vivo* performance. Interestingly, the aspect ratio of nanostructures also affects their cellular uptake behavior. Cylindrical nanostructures with an aspect ratio (height/width) of 3, for example, can be internalized into cells four times faster than those with an aspect ratio of 2. It has yet to be determined whether these uniquely designed nanostructures could outperform the traditional, spherical nanoparticles in terms of biodistribution and antitumor efficacy in translational studies. Of note, the Discher group recently designed a NP surface decorated with a peptide bound to CD47, which could escape phagocytosis *in vivo* with prolonged circulation time.[441]

4.4 Zwitterionic polymers

While PEGylation can increase NP circulation time and enhance NP stability, recently the zwitterionic polymer (neutral-charged polymer containing both cations and anions) has attracted significant attention because of its excellent antifouling properties and remarkable ability to prolong circulation time.[442–445] The Jiang group has developed super-hydrophilic zwitterionic poly(carboxybetaine) that can achieve stronger hydration compared with PEG.[446] NPs surface modified with poly(carboxybetaine) can remain stable in blood plasma and serum for a few days while PEGylated NPs eventually aggregate.[447] A recent study also indicated that such zwitterionic materials are biocompatible and resist foreign-body interaction for 3 months, potentially as alternatives to PEG.[448] Whether these zwitterionic materials are immunogenic as shown in repetitive administration of PEG[449–451] is still unknown.

4.5 Layer by layer assembly

In 1990s Decher and co-workers developed a new technique for constructing ultrathin organic films, creating multilayer assemblies by consecutive, layer-by-layer (LbL) adsorption of anionic and cationic polyelectrolytes.[452,453] A glass slide with a positively charged surface is immersed in a solution containing an anionic polyelectrolyte, and a layer of polyanion is adsorbed. After rinsing in pure water, the substrate is immersed in a solution containing the cationic polyelectrolyte. By repeating these steps in a cyclic fashion, alternating multilayer assemblies are obtained.[454] This technique can be applied to flat surfaces as well as to spherical particles. As recently reviewed, LbL capsules can be used in a variety of biomedical settings.[455,456] For example, polyelectrolyte capsules as potential drug delivery or cargo systems have been reported by the groups of Sukhorukov and Moehwald, De Smedt, and many others.[457–463] The release of nucleic acid-based therapeutics from polyelectrolyte assemblies has recently been reviewed by Jewell and Lynn.[464] Moreover, the drug delivery based on LbL formed systems can be controlled in response to environmental stimuli such as pH,[465] enzymes, and external voltage.[466]

The Hammond group recently described LbL films composed of poly(β-amino esters) (PBAE) as degradable polycations and a poly(carboxyl methyl-*b*-cyclodextrin) complex with small molecule drugs as an anionic supramolecular complex.[467] The release behavior of encapsulated small molecules can be tuned by the choice of PBAE which reveals slow release profiles over several days. This nanoscale coating approach is expected to regulate administration of various small molecules through programmable release kinetics. Tabrizian *et al.* realized this concept using a prodrug method to prepare a polyelectrolyte membrane.[468] Paclitaxel was conjugated onto HA as the polyanion with polycationic chitosan. The resultant multilayers could release paclitaxel gradually and induce the toxicity to macrophages.

Combinational therapies are extremely favorable for medical applications. Patients can benefit greatly from the synergistic release of different drugs. Hammond and co-workers presented a new bifunctional LbL platform made by combining a permanent microbicidal polyelectrolyte multilayered (PEM) base film with a hydrolytically degradable PEM top film that offers controlled and localized delivery of therapeutics. The initial infection was prevented by the release of an antibiotic, while diclofenac, an anti-inflammatory, was released to cope with further inflammation.[469] The Shastri group recently introduced another exciting "smart" technique. They developed an innovative method to modify a material surface using the LbL assembly of functionalized polymeric NPs.[470] Using this strategy one can incorporate different drugs into the system and manipulate them to release with a controlled rate. This novel approach may pave the way for the development of next generation medical devices.

A LbL assembly can also be formed through hydrogen bonding interactions. Hydrogen bonded (HB) LbL systems have received a great deal of attention in the last decade. These HB LbL materials possess several unique merits, for example, HB LbL films responsive to pH- and/or temperature at mild pH values can be easily fabricated. This is an important feature for the use of LbL materials under physiological conditions. Recent work indicated that HB LbL films could provide sustained release of protein under physiological conditions for more than one month. Extensive work on HB LbL for drug delivery has been done by Hammond and Caruso.[471–473] Some reviews can be seen elsewhere.[474]

A layer-by-layer technique not based on supramolecular interactions was presented by the group of Hennink.[475] Degradable polymeric microcapsules were fabricated using "click" chemistry utilizing two dextrans, modified with either azide or alkyne moieties.[475,476] The alternating layers of the two dextrans were covalently bonded by virtue of the 1,3-dipolar Huisgen cycloaddition reaction. Patil and co-workers fabricated a single-component multilayer on the flat and colloidal substrates *via* LbL covalent bonding using glutaraldehyde.[477]

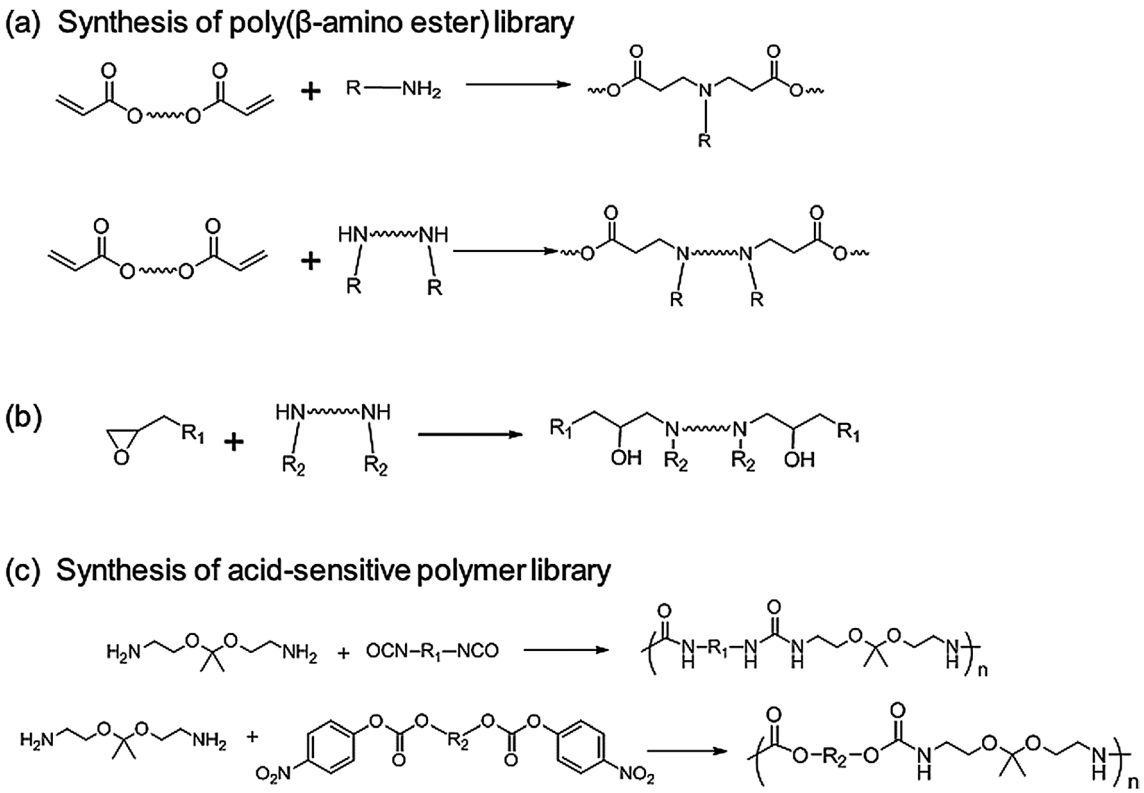
4.6 High throughput screening of polymeric nanomaterials

The high throughput discovery of new biomaterials can be achieved by rapidly screening many different materials synthesized by a combinatorial approach to identify the optimal

composition for specific biomedical application.[478,479] The process can be achieved in a microarray format, which enables thousands of cell-material interactions to be monitored on a single chip using modern high throughput surface analysis techniques (*e.g.* time-of-flight secondary ion mass spectrometry (ToF-SIMS), X-ray photoelectron spectroscopy (XPS) and water contact angle (WCA)) or cell based biological assays. Many high-throughput analysis techniques and assays have been reviewed elsewhere.[478] In 2010, it was reported that an *in vivo* selection technique was established to screen out specific candidate RNA for targeting hepatic colon cancer metastases in tumor-bearing mice.[480] The development of polymerization techniques to facilitate the preparation of screen libraries is highlighted, including some new design strategy for potential *in vivo* application of nanomedicine.

Since 2000, the Langer group has created libraries of over 2000 structurally unique poly(β-amino esters) (PBAEs),[481–483] through the Michael addition of amines to diacrylates (Scheme 13a). These biomaterials are promising for nonviral gene (DNA) delivery due to their ability to condense plasmid DNA into small and stable nanoparticles and their ability to promote cellular uptake and endosomal escape. The gene delivery efficacy could be regulated by the modification of the end groups of PBAEs.[484,485] The lead candidate from the initial study was demonstrated to facilitate sequence-specific knockdown in a variety of cellular targets and animal species, including mice, rats, and non-human primates.[486–492] The same Michael addition chemistry was also utilized to create a structurally diverse library of amino-alkyl-acrylate and -acrylamide agents termed 'lipidoids', which were then analyzed for their ability to transfect cells for siRNA delivery. A series of poly(β-aminosulfonamides) was also synthesized and demonstrated to be efficient *in vitro* transfection reagents.[493] Such lipidoid NPs for siRNA delivery are undergoing industrial development; results from clinical studies using lipidoid NPs/RNAi therapeutics demonstrate potent, rapid, and durable target gene silencing with general safe and well tolerance profiles in clinics.[494]

Another library created in the Langer lab is composed of non-degradable amino alcohols consisting of polar amine-containing head groups and nonpolar hydrocarbon tails.[495] The synthesis of the compounds was achieved through the efficient ring-opening reaction of epoxides by amine substrates (Scheme 13b). This synthetic strategy is particularly well suited to parallel synthesis and high-throughput screening. Reactions can be carried out without solvent, finishing within 3 days and do not require protection–deprotection steps; the obtained materials can be used in cell-based screens without purification. The Cheng group also developed a library of cationic α-helical polypeptides for gene delivery, which mimic cell penetration peptides entering cells.[316] 31 different amines were conjugated to the side chain of poly(γ-(4-vinylbenzyl)-L-glutamate), an ionic-stable helical polypeptide. The hits of the screened compounds exhibited high gene delivery efficiency by membrane-disruption with low cytotoxicity. More detailed synthetic delivery materials for siRNA therapeutics have been extensively reviewed elsewhere.[496]



Scheme 13 Strategies for preparing polymer libraries for high-throughput screening.

The high-throughput strategy was also extended to other purposes besides gene or siRNA delivery. The Fréchet group prepared an acid-sensitive polymer library for drug delivery (Scheme 13c).[497] Besides, Weissleder and co-workers described a rapid screen strategy to discover a series of NPs with high specificity for endothelial cells, activated human macrophages, and pancreatic cancer cells.[498] They formulated fluorescent magnetic nanoparticles, and different synthetic small molecules were conjugated onto particle surfaces using a robotic system in an array format. Small molecules with primary amines, hydroxyls, carboxylic acids, sulfhydryls and anhydrides were chosen for conjugation and compounds known to bind to proteins were excluded from their screening. Interestingly, hits for pancreatic cancer cells *in vitro* test also show the targeting capability for pancreatic cancer *in vivo*.

In addition, Schreiber, Weissleder, and co-workers also reported a rapid screening strategy to profile the nanomaterials biological activity, potentially providing guidance for *in vivo* nanomaterials study.[499] Quantitative nanostructure-activity relationship (QNAR) models were further proposed based on the above two cases. It is believed that QNAR models can be employed for predicting biological activity profiles of novel nanomaterials and for designing better and safer nanomaterials.[500]

The combinatorial strategy leads to rapid generation of a large number of new materials for a specific application; however, identifying a marketable lead compound for clinical applications using this approach remains a challenging problem. So far, only one *de novo* combinatorial chemistry-synthesized chemical has been approved for clinical use by FDA (Sorafenib, or Nexavar™). The dedicated resources, startup costs, as well as equipment sophistication severely limit the spread of this strategy.

5. Perspective

Nanomedicine is one of the most rapidly growing fields of translational medicine,[501] and has made marked impacts in terms of alleviation of toxicity and enhancement of efficacy for therapies. The convergence of chemistry and nanomedicine may allow the development of patient-individualized treatments (*e.g.* on-demand drug delivery and self-regulated drug delivery) and provide new therapeutic modalities (*e.g.* new therapeutic formulations and imaging modalities). Progress in this field will depend on the fundamental understanding of organic and polymer chemistry, materials engineering, biology and clinical practice to allow for rational design and creation of new smart chemistry. Incorporation of this chemistry will eventually impact the outcome of developed therapies in many aspects, including efficacy,[153,502] targeting,[503] biodistribution (pharmacokinetics)[504] and NP penetration into diseased tissues.[157,505] Biocompatibility and toxicity will remain important issues when designing smart chemistry for medical application.[506] For chemists, it is also important to leverage the sophistication of chemistry to treat disease in a facile and simple manner with a clinical translational formulation. Nontrivial optimization and engineering are often required for the translation of NP-based systems from preclinical experimental models to daily clinical practice. The design focus for chemists should shift towards more clinical acceptable systems with potentially simpler development routes.

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