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Chuanfeng Li
Western University

Zhengyu Deng
Western University

Elizabeth R. Gillies
Western University, egillie@uwo.ca

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Chuanfeng Li,[†] Zhengyu Deng,[†] and Elizabeth R. Gillies[†‡*]

[†]Department of Chemistry, The University of Western Ontario, London, Ontario, Canada, N6A 5B7.

[‡]Department of Chemical and Biochemical Engineering, The University of Western Ontario, London, Ontario, Canada, N6A 5B9.

[*]Author to whom correspondence should be addressed: egillie@uwo.ca

Abstract

Early biomedical applications of polymers were in areas such as joint replacements and often involved durable polymers. However, biodegradable polymers are increasingly being used to perform temporary functions such as drug delivery or supporting cells, after which they can breakdown and be eliminated from the body. Polymers that degrade specifically in response to stimuli offer additional opportunities to control when and where this degradation occurs, enabling enhanced functions such as site-specific drug release and the early detection of disease. In this article, we will discuss recent advancements in the design, preparation, and application of stimuli-responsive polymer degradation. In particular, we will highlight the introduction of new linkers, and advanced multifunctional systems. Recent approaches towards maximizing the responses to stimuli, including self-immolative and self-amplifying polymers, will also be highlighted. Finally, some of the challenges in applying these more complex, functional polymers will be discussed, along with important areas for future research.

Introduction

For the past several decades, polymers have played many important roles in medicine, ranging from personal protective equipment and packaging for sterile tools to materials and devices that are implanted or inserted into the body. In many of these applications, even *in vivo*, durable polymers have been used. For example, ultrahigh molar mass polyethylene is used for the articulating load-bearing surfaces of joint replacements due to its chemical inertness, abrasion resistance, impact resistance, and lubricity, while poly(methyl methacrylate) is used as a cementing material between bone and the implant surface [1]. A variety of durable polymers such as poly(styrene-*b*-isobutylene-*b*-styrene), poly(ethylene-*co*-vinyl acetate), and poly(*n*-butyl methacrylate) have been used in drug-eluting coronary stents [2] while polyurethane, silicone, and various other polymers have been used in ureteral stents [3]. Furthermore, poly(ethylene glycol) (PEG) has been used as a laxative [4] and pharmaceutical excipient [5] and has also been conjugated to a wide array of protein drugs and nanoparticles such as siRNA vaccines, to improve their solubility, stability, and pharmacokinetic properties [6].

While durability under physiological conditions is critical in certain applications such as orthopedic implants, in many other areas there has been significant progress towards the use of biodegradable polymers. For example, absorbable sutures made of poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers (PLGA) were developed to replace non-absorbable sutures composed of nylon or polypropylene, with the advantage of not requiring follow-up medical appointments to remove them [7]. In addition, concerns about long-term polymer-induced inflammation and delayed restenosis has prompted the replacement of durable polymers with biodegradable polymers such as PLA and PLGA in drug-eluting stents [2]. Biodegradable polymers are increasingly used in drug formulations to facilitate the slow release

of drugs, after which they can be metabolized and removed from the body. Examples of clinically-approved products include Eligard®, a subcutaneously injectable formulation of leuprolide acetate in PLGA for the treatment of prostate cancer and Genexol-PM®, an intravenously injectable formulation of paclitaxel encapsulated in micelles of PEG-PLA [8]. Furthermore, biodegradable polymers including PLA and various polyhydroxyalkanoates are of growing interesting for tissue engineering and regenerative medicine applications as they can be processed by techniques such as electrospinning or 3D printing to achieve scaffolds that support cell growth [9,10].

In many applications of biodegradable polymers, the materials undergo a gradual degradation over time via enzymatic or non-enzymatic hydrolysis, with the rate tunable through control of the polymer hydrophobicity, crystallinity, and other parameters such as surface to volume ratio [11]. However, for some applications, it would be ideal to stimulate the degradation to occur rapidly under specific conditions. For example, the selective release of drugs at the target site *in vivo* can lead to enhanced efficacy and reduced systemic side effects [12]. In addition, the spatially controlled degradation of hydrogels has enabled real-time manipulation of material properties and consequently the manipulation of cell migration and differentiation in tissue engineering scaffolds [13]. Consequently, there has been substantial interest in the development of polymers that undergo degradation in response to specific stimuli. In this article, recent exciting developments in the design of polymers that undergo degradation in response to stimuli will be presented. We will focus on polymeric systems where the stimuli lead to cleavage of the polymer backbone and not drugs or other pendent groups alone. Furthermore, we will discuss examples aimed at amplifying and propagating responses to these stimuli. Applications of these different approaches for intracellular drug release, tissue clearance, site-selective

chemotherapy and photodynamic therapy, controlled cell release, wound repair, and in vivo imaging and sensing will be presented. Some advantages and limitations of the different approaches will be discussed.

Stimuli-responsive degradation of polymers

Over the past couple of decades, a wide variety of endogenous stimuli associated with various disease states such as inflammation and cancer have been explored for biomedical applications such as imaging and drug delivery [14,15]. The commonly investigated stimuli include change in pH, reductive milieu, reactive oxygen species (ROS), and enzymes. External stimuli, particularly various forms of electromagnetic radiation including light, ultrasound, X-rays and γ-rays, have also been investigated with the aim of achieving enhanced spatiotemporal control. The degradable bonds (see Figure 1 for examples) can be incorporated directly into the backbone, into pendent groups that lead to backbone cleavage after their activation, or into polymer network structures (Figure 2). Key developments in the past few years have particularly focused on expanding the range of responsive functional groups that can be incorporated to mediate polymer degradation and combining degradable groups into functional and multifunctional systems to address challenging biomedical problems (Table 1).

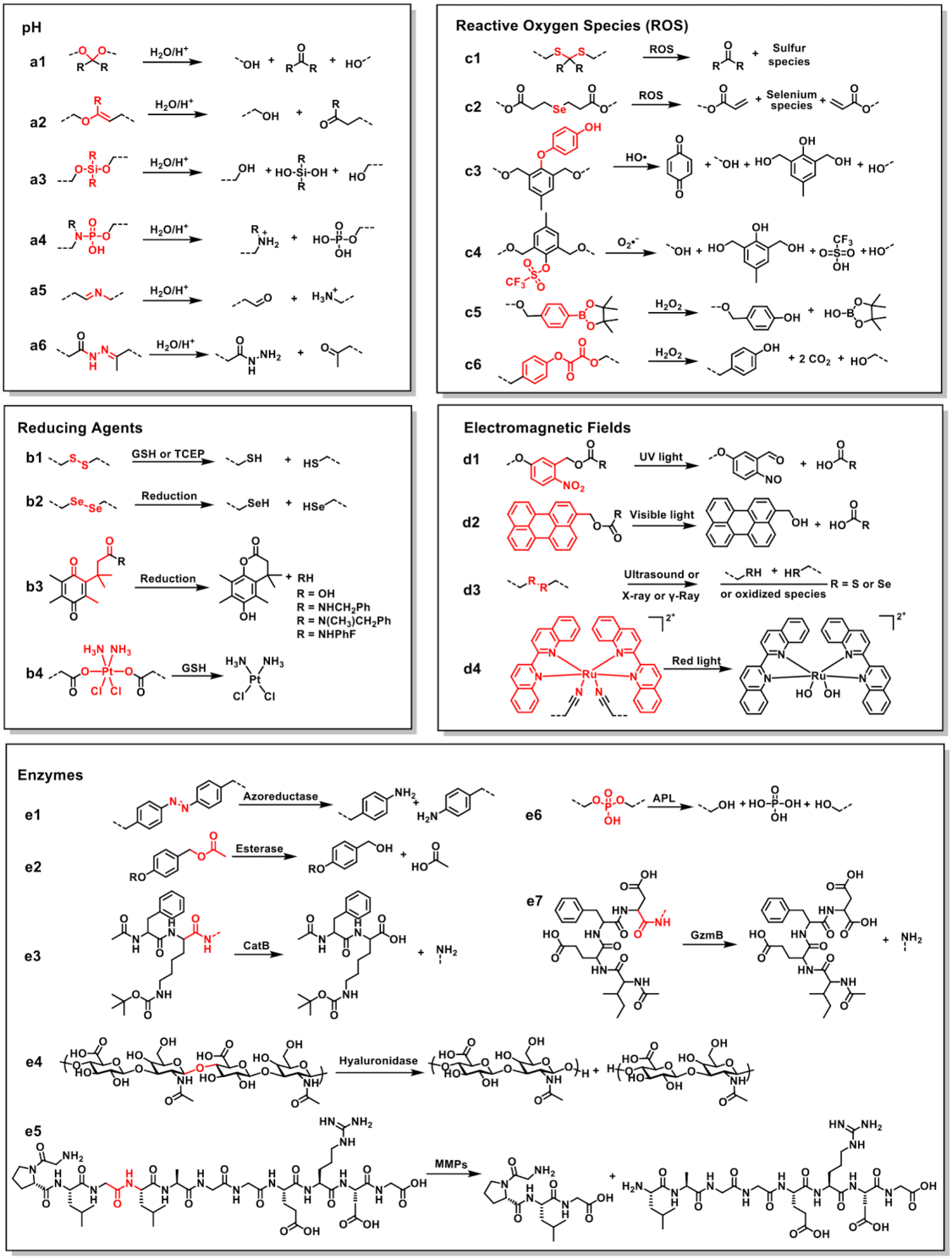

Figure 1. Examples of stimuli-responsive linkages (in sequence): a) pH (acetal, vinyl ether, silyl ether, phosphoramidate, imine, hydrazone); b) Reducing Agent (disulfide, diselenide, trimethyl-

locked benzoquinone, Pt(IV) complex); c) ROS (thioketals, β-selenylated carbonyl, trifluoromethanesulfonate, boronic ester, diselenide, aryl oxalate); d) Electromagnetic field (*o*-nitrobenzyl alcohol derivative, perylene-3-ylmethanol derivative, disulfide/diselenide, Ru complex) e) Enzyme (example linkers responsive to azoreductase, esterase, CatB, hyaluronidsase, MMPs, APL, GzmB);

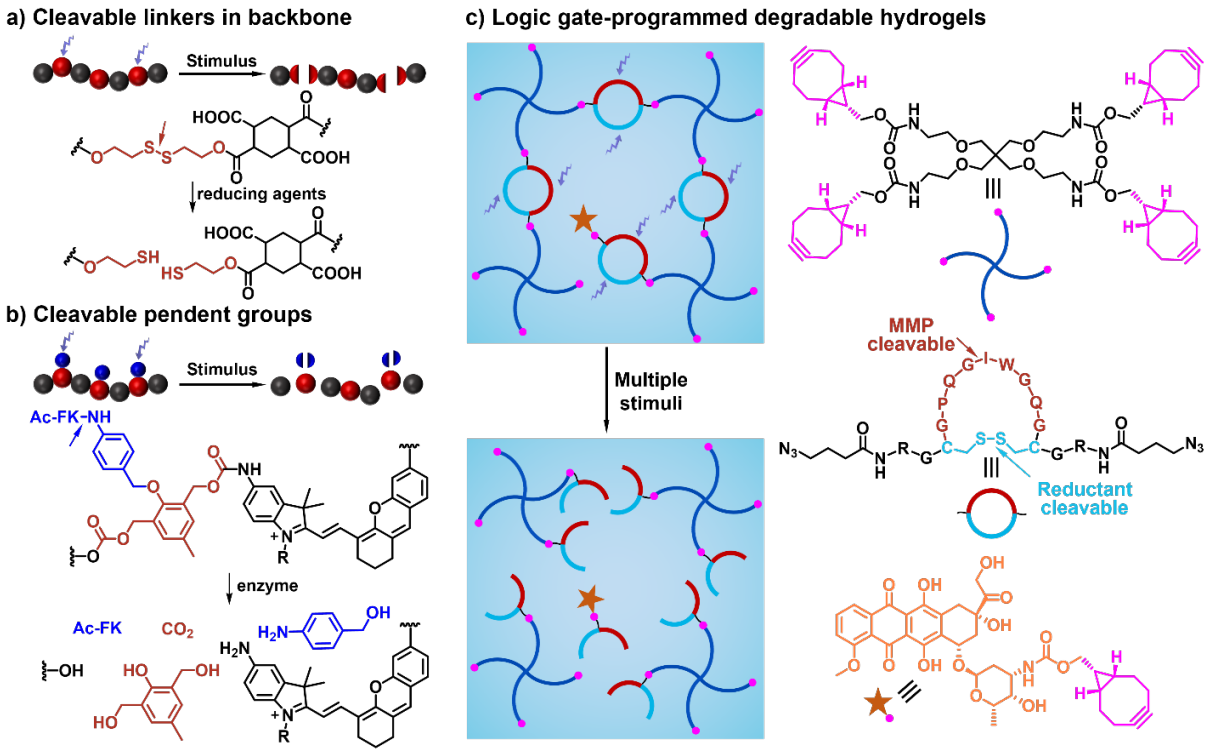

Figure 2. Schematic illustration of representative polymer or network degradation mechanisms and examples of each. a) Degradable polymers with stimuli-responsive linkers in the backbone [16]; b) Backbone degradable polymers with responsive pendent groups [17]; c) Degradable hydrogel networks containing logic gate-programmed cleavable crosslinkers [18].

Table 1. Summary of recent examples of stimuli-responsive degradable polymers and their biomedical applications

Stimulus		Linkage	Application	Reference	Corresponding to Figure 1
pH		Acetal	Self-reassembly into sheets to rupture endosomal membrane for drug release	[19]	a1
		Vinyl ether	Degradable PEGylation of proteins	[20]	a2
		Silyl ether	Long term tissue clearance	[21]	a3
	GSH	Disulfide	Treating temozolomide resistant glioblastoma	[16]	b1
	GSH	Disulfide	Laser-enhanced cellular uptake for tumor accumulation; drug release monitoring	[22]	b1
	GSH	Disulfide	GSH induced mitoxantrone and curcumin release to address multidrug resistance in chemotherapy	[23]	b1
ROS	H_2O_2	Thioketal	Wound repair	[24]	c1
	H_2O_2	Beta-selenylated carbonyl	General biomedical application	[25]	c2
	•OH	Hydroquinone	Sensing low abundance biomarkers	[26]	
	$O_2•^-$	Trifluoromethanesulfonate	In vivo imaging and urinalysis of hepatic ischemia-reperfusion injury	[27]	c3
enzyme	CatB, GzmB	Peptide via self-immolative spacer	Non-invasive near-infrared fluorescence	[17]	e3, e7
	CatB	GFLG peptide	Site specific release of Pt(II) in cencer cells	[28]	e3
	ALP	phosphoesters	Site specific release of doxorubicin in tumor	[29]	e6
	NQO1	Trimethyl-locked quinone proionic acid	Site specific release of anti-cancer drug	[30]	e3
	Azoreductase	Azo group	Accommodate photodynamic therapy	[31]	e1
	MMP	GCGPLG-LWARCG peptide	Osteocyte differentiation and bone extracellular matrix deposition	[32]	e5
Electromegnetic field	UV	Ortho-nitrobenzyl	Interfacing with implantable devices (e.g. bariatric balloons, esophageal stents)	[33]	d1
	Ultrasound	Disulfide	drug activation and release of camptothecin	[34]	d3
	X-ray or γ-Ray	Disulfide	Fluorescence-reported drug release	[35]	d3
	γ-Ray	Diselenide	Antitumor effect through enhancing natural killer cell's function; release of doxorubicin	[36]	d3
Multi-stimuli	UV or Reducing Agents	Photocaged thioether/ disulfide	Site-specific ultrasensitive delivery of theranostic agents	[37]	d1, b1
	Red light or Reducing Agents	Pt(IV) and Ru(II) complex	Anti-cancer dual prodrug delivery	[38]	b4, d4
	TCEP, MMP-8, UV	Disulfide, GPQGIWGQ, *o*NB	Cytocompatible hydrogels with user-specified programmable degradation for drug release or cell-based therapeutics	[18]	b1, e5, d1
	UV/vis, ROS, GSH, acidic pH, esterase, and ALP	Various	Anti-tumor therapies	[39]	a6, b1, c4, e2, e6, d1, d2
	UV and acid	*o*-Nitrophenyl ethanol locked acetal	Sequential trigger for temporospatial drug release control	[40]	d1⇒a1
Self-immolative	Fluoride ions	Silyl ether	Anti-bacterial activity with low hemolytic toxicity	[41]	
	ROS or pH	Boc, boronate, 4-nitrobenzylideneamino	In situ covalent trapping for $^{19}F/^{1}H$ dual-modality MRI	[42]	
	Reducing agent, UV light, H_2O_2	Disulfide, *o*NB, boronate	Selective drug release	[43]	
	Reducing agent, UV light	Disulfide, *o*NB	Controlled drug release	[44]	
	pH	Trityl derivatives	forming cationic nanoparticles with plasmid DNA	[45]	
	H_2O_2	Boronate, Ketal	Potential drug delivery system	[46]	
Self-amplifying	Light, ROS	Thioketal	Light-activated release of anti-cancer drug	[47]	
	H_2S	Aryl azide	Biological signalling gas depolymerizable material	[48]	
	pH	3-iodopropyl acetal	Accelerated drug release	[49]	
	pH	Fmoc derivative	Base triggered drug release	[50]	

reducing agents, light, esterase	Disulfide, *o*NB, ester	Selective drug release to cancer cells	[51]

pH

It is well established that a range of pH values exist in human body. For example, the gastrointestinal tract ranges from pH 1.5 – 3.5 in stomach to pH 8 in small intestine. Healthy tissues typically have a pH of 7.4, but inflamed tissues or solid tumors can have slightly acidic extracellular environments in the range of pH 6.5 to 7.2 [52]. Furthermore, compared to a cytoplasmic pH of about 7, the pH of the endosomal and lysosomal lumen ranges from 6.5 – 4.5 [53]. These pH variations have made pH-responsive polymer systems a widely explored target over the past few decades as polymers can be designed to chemically degrade at acidic pH to facilitate the release of drugs in inflamed or cancerous tissues or upon uptake of a delivery system into cells [54,55]. To achieve this breakdown, a variety of pH-sensitive linkages including hydrazones, acetals, ortho esters, imines, vinyl ethers, silyl ethers, and phosphoramidates have been incorporated into polymer backbones (Figure 2). In recent years, researchers have been using pH to mediate increasingly elegant architectural changes, new cargo, and new polymer backbones.

Gong et al. developed a proton-driven nanotransformer-based vaccine (NTV) for cancer immunotherapy to address the challenge that antigens often become trapped in endosomes [19]. Spherical nanoparticles loaded with antigenic peptides were prepared from a polymer-peptide conjugate and had diameters of about 100 nm at pH of 7.4. Upon internalization by cells, the mildly acidic endosomal environment accelerated cleavage of the acetal that linked the peptide to the polymer. Release of the peptide from the polymer allowed it to reassemble into large micrometer-sized sheets, which mechanically ruptured the endosomal membrane, allowing for

cytosolic release of the antigenic peptide. The peptide sheets also activated inflammasome pathways, further boosting the antitumor immunity.

One of the important applications of PEG has been to enhance the *in vivo* circulation half life and stability of protein therapeutics [6]. However, there are drawbacks to PEGylation, as it can impair bioactivity, and since it is not biodegradable, high molar mass PEG can accumulate in tissues. To address these challenges, Steiert et al. developed a degradable copolymer containing PEG and vinyl ether units, as well as an activated terminus for protein conjugation [20]. Upon conjugation to cytochrome *c*, the protein became soluble in organic solvents, allowing for particle preparation by emulsion methods, while preserving its structure and activity. The particles were stable at physiological pH but degraded at pH 4-5, releasing the protein, due to hydrolysis of the backbone vinyl ethers.

Building on earlier research incorporating silyl ethers as pH-sensitive linkers in biomaterials [56], Shieh et al. incorporated bifunctional silyl ether-containing cyclic olefins into polynorborenes to make their backbones degradable [21]. Their silyl ether monomer could be copolymerized with various norbornene monomers including norbornene-terminated PEG macromonomers (3.2 kg/mol), leading to a variety of polymer architectures. Furthermore, the incorporation of different substituents on the silicon atom allowed the degradation rate to be tuned. Minimal cytotoxicity was observed when water-soluble versions of the polymers were incubated with OVCAR8 and Jurkat cells for 36 h. Combined, the low toxicity and potential for clearance from the body via polymer degradation suggest that this approach may enable otherwise non-degradable carbon-carbon backbone polymers to be employed in biomedical applications.

Reducing agents

Reduction-responsive polymers have also been extensively investigated for biomedical applications. γ-L-Glutamyl-L-cysteinyl-glycine, commonly known as glutathione (GSH), is an antioxidant mainly found in the cytosol to prevent cell damage arising from ROS. It is estimated that the intracellular concentration of GSH is up to 10 mM, compared to an extracellular concentration as low as 100 μM [57]. In addition, due to their hypoxic environment, solid tumors also exhibit increased concentrations of GSH. By far, the most widely investigated reduction-sensitive linker is the disulfide bond, although other linkages including diselenides, metal-ligand complexes, and trimethyl-locked benzoquinones have also been reported [34,58]. Key recent advancements have involved combination therapies and new approaches to more effectively deliver the polymeric systems to the target tissues.

Wang et al. developed reduction-responsive nanoparticles to overcome temozolomide resistance in the treatment of glioblastoma [16]. The particles were prepared by nanoprecipitation of a polyester containing disulfide linkages in the backbone as well as pendent carboxylic acid groups. They were loaded with an oxaliplatin prodrug and a cationic DNA intercalating agent, then were used in combination with convection-enhanced delivery to bypass the blood-brain barrier. *In vivo*, this combination of approaches significantly enhanced the survival of mice having temozolomide-resistant tumors, without notable systemic toxicity.

Cheng et al. developed nanoparticles composed of amphiphilic polymeric prodrugs of the anticancer agent mitoxantrone (MTO) [22]. PEG was linked to both sides of the hydrophobic MTO by disulfide-containing self-immolative spacers, which were cleaved by GSH, and subsequently underwent cyclization to release a thiolactone and free MTO. The polymers self-assembled into 33 nm particles. Selective tumor accumulation and cellular uptake of the nanoparticles were enhanced by mild hyperthermia in the tumor, induced by laser irradiation of the MTO chromophore. Furthermore, it was possible to monitor the drug release with ratiometric

photoacoustic imaging. Overall, treatment with the nanoparticles and hyperthermia led to decreased tumor growth compared to controls. The polymeric prodrug approach using MTO was also extended by Yu et al. to tackle the multidrug resistance [23]. Their hydrophobic polycarbonate block consisted of both MTO and curcumin with self-immolative disulfide linkers in between, such that disulfide cleavage released the free drugs. Hydrophilic PEG blocks were conjugated on each end of the polycarbonate to enable self-assembly of the resulting amphiphilic copolymers into ~150 nm particles. The dual prodrug system more effectively inhibited the growth of MCF-7/ADR tumors, compared to traditionally encapsulated MTO/curcumin or the use of only one drug in polymeric prodrug form. The system is quite versatile in that the drug content and ratios can be easily adjusted to optimize the treatment of different cancers, although the prodrug approach may limit the choice of drugs to those having two suitable functional groups for polymer incorporation.

Reactive oxygen species (ROS)

ROS, including hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($HO^{\bullet}$), and hypochlorous acid (HOCl), are involved in the essential cellular redox landscape occurring inside living organisms and play vital roles in physiological and pathological functions, such as signaling, metabolism, and immune responses [59,60]. However, the overproduction and accumulation of ROS can lead to oxidative stress, which is associated with the onset and progression of multiple health conditions including cancer, acute and chronic inflammation, and neurodegenerative diseases. By leveraging higher levels of ROS at pathological sites, an increasing number of studies have demonstrated the potential to sense and modulate oxidative stress for imaging and treatment. The established ROS-responsive linkages include thioethers, thioketals, boronic acids/esters, selenides, diselenides, aryl oxalates, and vinyldithioethers [60].

Exciting recent efforts have focused on tuning the backbone linkers and incorporating functional molecules such as chromophores into the backbones of ROS-degradable polymers for biomedical applications.

Owing to its excellent stability against acid, base, and enzyme-mediated decomposition, the thioketal moiety has been increasingly exploited for ROS-sensitive drug delivery and tissue engineering [60]. Very recently, Patil et al. presented ROS-cleavable polythioketal urethane resorbable foam dressings with varied hydrophilicity to promote skin wound healing [24]. A small library of ROS-responsive urethane foams incorporating various polythioketal diols with different lengths of oligo(ethylene glycol)s (OEGs) between the thioketals was prepared. Increased hydrophilicity of the polythioketal diol enhanced the reactivity between the thioketal and water-soluble ROS, thus improving the polyurethane scaffold ROS scavenging capability and promoting more rapid material resorption *in vivo*. The most hydrophilic polythioketal urethane was more effective than a benchmark commercial wound repair foam in an established porcine skin wound repair model, showing the promise of this stimuli-responsive biomaterial for wound healing applications.

Like their sulfur-based analogues, selenium- and tellurium-containing compounds can also be readily oxidized by ROS. Wang et al. reported the first degradable selenium-containing polymer based on an ROS-triggered selenoxide elimination reaction [25]. *β*-Selenylated carbonyl moieties were incorporated into a hydrophobic polyurethane and each terminus was functionalized with PEG, resulting amphiphilic triblock copolymers. In the presence of H_2O_2, the polymers underwent controlled degradation through oxidation-induced selenoxide elimination reactions. Furthermore, this approach was also expanded to an analogous tellurium-containing system with enhanced oxidation sensitivity. These ROS-triggered degradable polymer systems

have potential for further exploration in biomedical applications, assuming that the concentrations of selenium and tellurium can be kept sufficiently low to avoid toxicity.

The design of ROS-sensitive polymers has also been adapted for ultrasensitive bioimaging and noninvasive diagnosis. Zhou et al. reported a hydroxyl radical-responsive degradable polymer with fluorophores in the backbone [26]. When formulated into nanoparticles in the presence of a fluorescent quencher (i.e., black hole quencher 2, BHQ2), the fluorescence from the squarylium dye in the polymer backbone was greatly supressed. When activated by $HO^{\bullet}$, these nanoparticles exhibited selective disassembly as a result of complete degradation of the polymer backbone, thus generating free squarylium dye. Notably, the released squarylium dye could bind with cytoplasmic proteins to further enhance its fluorescence intensity, providing a signal-amplifying approach to achieve ultrasensitive detection of $HO^{\bullet}$. Furthermore, these nanoprobes were successfully applied to detect and image endogenously produced $HO^{\bullet}$ in a cardiopathic mouse model.

In other interesting work, Huang et al. developed ROS-activatable polymeric nanoprobes with a superoxide anion-triggered near-infrared (NIR) fluorescence response [27]. The probes also had a renal clearance switch for noninvasive *in vivo* imaging and urinalysis of hepatic ischemia-reperfusion injury (IRI). Hemi-cyanine fluorophore units were covalently connected via self-immolative linkers that were caged with $O_2^{\bullet-}$ cleavable trifluoromethanesulfonate motifs. In addition, 2-hydroxypropyl-β-cyclodextrin moieties to facilitate renal clearance were grafted along the backbone as pendent groups, resulting in an amphiphilic polymer that self-assembled to form 160 nm particles. In the presence of $O_2^{\bullet-}$, a biomarker of oxidative stress during hepatic IRI, cleavage of the self-immolative linker resulted in the release and activation of the fluorophore for NIR imaging, along with disintegration of the particles to release renally clearable fluorophores for urinalysis. Due to their high hepatic accumulation, sensitive response

to $O_2^{\bullet-}$, and efficient release of renally clearable fluorophores, imaging and urinalysis with these materials enabled the diagnosis of hepatic IRI at least 7 h earlier than typical clinical assays in a mouse model.

Enzymes

Enzymes have been one of the most extensively investigated stimuli for the degradation of polymers in biomedical applications as their expression can vary greatly depending on the *in vivo* location and disease state. The first anticancer drug conjugates investigated in clinical trials comprised *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymers with DOX conjugated by cathepsin B (CatB)-cleavable GFLG peptide linkers enabling lysosomal drug release. Since then, the field has expanded to incorporate enzyme-responsive linkers into polymers for a variety of biomedical applications ranging from tissue engineering to imaging and drug delivery [61]. Some commonly investigated enzymes include matrix metalloproteinases (MMPs), hyaluronidases, cathepsins, azoreductases, alkaline phosphatases (ALPs), and esterases. Focusing here on polymers where enzymes have been used to mediate backbone degradation, many of the most interesting recent developments involve systems that incorporate multiple functions or therapeutic mechanisms and which provide versatile platforms that can be tuned for different applications.

Recently, Huang et al. developed enzyme-responsive nanoparticle-based sensors for non-invasive NIR imaging *in vivo* and urinalysis to achieve early detection of cancer and liver allograft rejection [17]. The nanosensor design was similar to the superoxide anion-responsive system by the same group described above [27], having caged fluorophores in the polymer backbone and pendent *β*-cyclodextrin moieties for renal clearance. However, in this case the backbone self-immolative moieties were protected with CatB or granzyme B (GzmB) cleavable

peptides. The selective cleavage of the CatB-responsive peptide (Ac-FK) in the presence of elevated levels of enzymes in mice bearing subcutaneous CT26 tumors led to breakdown of the polymer backbone and the release of fluorophores for non-invasive NIR imaging and urinalysis, enabling early-stage cancer detection. Cleavage of the of the GzmB-sensitive peptide (Ac-IEFD) induced by elevated GzmB expression in the presence of activated T lymphocytes enabled the non-invasive detection of acute liver allograft rejection. These nanosensors have strong potential as a versatile platform that can enable early diagnosis of health conditions through a creative combination of NIR imaging and urinalysis, both of which are enabled by the stimuli-responsive breakdown of the polymers.

Wang et al. developed a CatB-responsive polyprodrug nanoplatform for the targeted delivery and release of cisplatin and the photosensitizer indocyanine green (ICG) [28]. A linear polymer composed of alternating cisplatin prodrug units and CatB-degradable GFLG peptides linked by hydrophobic amide spacers was synthesized and terminated with hydrophilic PEG blocks on each end. The resulting amphiphilic copolymers self-assembled into ~200 nm particles that encapsulated 16% (w/w) ICG. Upon cellular uptake and trafficking to lysosomes, CatB-mediated polymer degradation led to the release of cisplatin prodrugs. Concomitantly, irradiation of the ICG photosensitizer with 808 nm light resulted the generation of both ROS and heat, damaging the lysosome and delivering the cisplatin prodrug into the cytosol, where it was reduced by GSH to active cisplatin. Furthermore, the system enabled *in vivo* fluorescence and photoacoustic imaging. *In vitro* and *in vivo* studies demonstrated that the particles could inhibit cisplatin-resistant cancers with minimal side effects *in vivo*, showing the promise of these multi-functional particles.

In another approach to tackle multidrug resistance in chemotherapy, Yao et al. developed micelles that were degraded by ALP, an enzyme overexpressed in certain tumors [29]. They

synthesized hyperbranched polyphosphoesters (hPPE) with hydrophobic segments to form the core of the micelles and hydrophilic moieties to stabilize their peripheries. DOX and IR-780, a photothermal agent, were incorporated into the cores of the micelles, resulting in ~150 nm-diameter particles that selectively accumulated in tumors. Degradation of the hPPE by ALP resulted in accelerated release of DOX and this release could be further increased thermally by NIR irradiation of IR-780. The combination of triggered chemotherapy and hyperthermia resulted in synergistic cytotoxicity *in vitro* and effective ablation of DOX-resistant tumors *in vivo*.

NHD(P)H:quinone oxidoreductase-1 (NQO1) is another enzyme that is highly overexpressed in certain cancer cells [62]. Its role includes maintaining redox homeostasis and inhibiting oxidative stress. Building on prior work showing that NQO1 reduced trimethyl-locked quinone propionic acid (QPA), resulting in lactone formation through intramolecular cyclization, Park et al. developed NQO1-responsive micelles for anticancer drug delivery [30]. They synthesized amphiphilic PEG-PCL block copolymers, where the PCL block had pendent methylamino groups protected with QPA groups. Self-assembly provided 27 nm particles that encapsulated DOX. In the presence of NQO1, cleavage of the QPA moieties revealed the free amines, which could then cyclize to 6-membered lactams, cleaving the polymer backbone and disrupting the micelles, resulting in the release of DOX. The particles exhibited increased accumulation in tumors and enhanced therapeutic effects compared to controls.

Zhang et al. exploited the overexpression of azoreductase in the environment of hypoxic tumors and photodynamic therapy-induced hypoxic environments to design azoreductase-responsive nanocarriers [31]. They prepared a conjugated polymer chain from 4,4'-azodianiline and terephthalaldehyde and then prepared ~100 nm particles encapsulating camptothecin and the photosensitizer Ce6 by a nanoprecipitation process in the presence of polyvinylpyrrolidone.

Upon laser irradiation, the particles could kill cancer cells through the generation of singlet oxygen from molecular oxygen. In addition, the consequent depletion of oxygen would intensify hypoxia, resulting in enhanced expression of azoreductase, enabling polymer degradation, breakdown of the particles, and the release of camptothecin. *In vitro* and *in vivo* studies suggested a favorable synergistic effect of these multiple mechanisms on cancer cell killing.

MMPs have been a widely investigated stimulus for enzyme-responsive polymeric systems as they play key roles in tissue remodeling and their dysregulation is associated with a wide range of conditions from cancer to cardiovascular and musculoskeletal disease [63]. In one recent example, Aziz and coworkers developed PEG hydrogels with MMP-cleavable peptide crosslinkers as well as the cell adhesive RGD motif [32]. IDG-SW3 cells, which are capable of the production of a mineralized collagen matrix as well as transitioning from osteoblasts into osteocytes were encapsulated in the hydrogels. Their differentiation and cell density were improved in the degradable gels, compared to control, which was attributed to MMP2 and MMP3 production by the cells. Overall, this hydrogel platform is promising for the studying IDG-SW3 cell maturation and their ability to deposit a bone extracellular matrix.

Electromagnetic fields

While the many intriguing systems discussed above aimed to harness endogenous stimuli, much effort has also been placed on approaches that leverage exogenous stimuli such as light (e.g., ultraviolet, visible, or NIR light), ultrasound, X-rays, and γ-rays to stimulate controlled degradation of polymers [64]. In principle, since these stimuli enable spatiotemporal control over the activation of polymers, desired functions (e.g., delivery of diagnostic or therapeutic agents) can be achieved at the target sites, suppressing background interference and minimizing side effects in healthy tissues.

Light-triggerable functionalities, including *ortho*-nitrobenzyl (*o*NB)- and perylene-based moieties, have been extensively incorporated into polymeric backbones and networks [64]. For instance, Raman et al. described the development of a modular and tunable light-triggerable hydrogel system [33]. A PEG-based crosslinker which contained a light-cleavable *o*NB moiety and was capped by acrylate functional groups, and was used to prepare diverse polymeric networks (e.g., single- and double-network hydrogels) that relied on acrylate crosslinking chemistry. They demonstrated the use of these light-degradable hydrogels as dynamic, on-demand triggers for to control the deflation of bariatric balloons as well as collapse and removal of esophageal stents *in vivo*.

In another interesting study, ultrasound was explored as a stimulus to release active drugs from polymeric prodrugs [34]. Specifically, disulfide-centred poly(oligo(ethylene glycol) methyl ether acrylate) (POEGMEA) bearing the anticancer drug camptothecin (CPT) on a carbonate linker in *β*-position of the disulfide moiety was synthesized. Subsequent ultrasound irradiation cleaved the mechanochemically labile disulfide into thiols, allowing an intramolecular cyclization to form a 5-membered cyclic thiocarbonate, releasing free CPT. This design was also expanded to multifunctional theranostic polymers with built-in fluorescence-reported drug release [35].

Distinct from light and ultrasound irradiation, ionizing radiation (i.e., X-ray or *γ*-ray) can trigger a series of water radiolysis reactions in biological milieu, generating highly reactive species such as free electrons and ROS [65]. To take advantage of these highly reactive species, diselenide-based amphiphilic block copolymers functionalized with tumor-targeting RGD peptides were synthesized and then formulated into core-shell nanoparticles encapsulating the anticancer drug doxorubicin (DOX) [36]. *γ*-Ray radiation cleaved and oxidized the diselenides into seleninic acid, which exhibited immunomodulatory activity and a synergistic antitumor

effect by enhancing natural killer (NK) cell function. Moreover, the degradation of polymers facilitated DOX release and enhanced chemotherapy efficiency, showing the potential of this multifunctional system.

Multiple stimuli

Because of the small differences in physiological conditions between normal tissues and diseased sites as well as the significant heterogeneity and dynamics of the microenvironment within diseased sites, intelligent polymer systems with single responsiveness may not achieve the desired goals. Instead, polymers responsive to multiple endogenous and/or exogenous stimuli are highly promising for advanced biomedical applications, including selective drug delivery and diagnostics, spatiotemporal control of drug activation, and combination therapy [66]. As discussed above, endogenous stimuli such as changes in pH, oxidative stress, reductive milieu, and overexpressed enzymes as well as exogenous electromagnetic fields have been extensively employed to design degradable polymers. Here, some exciting developments in multi-stimuli-triggered polymer degradation are briefly summarized. While some of the polymeric systems discussed above involved multiple stimuli in their mechanisms of action (e.g., enzyme and light-responsive photosensitizer), we will focus in this section on examples where the polymer backbones themselves are cleavable by multiple stimuli.

To overcome the spatiotemporal barriers to endogenous glutathione-responsive polymers, Weng et al. developed a photo-responsive self-reducible polymer system [37]. The dually responsive polyurethane was prepared from the copolymerization of *o*NB-caged dithiothreitol (DTT) and *L*-cystine dimethyl ester diisocyanate, followed by termination with PEG. The resulting amphiphilic block copolymers self-assembled into polymersomes. In addition to the possibility for direct cleavage of the *L*-cystine disulfides by reducing agents, uncaging of the

DTT thiol moieties by UV light led to self-cleavage of the backbone *L*-cystines. The photo-triggered *in situ* generation of multiple reducing moieties in the particle core could potentially alleviate the steric hindrance and temporal limitations, resulting in a site-specific and ultrasensitive delivery of theranostic agents.

Zeng et al. introduced a dually responsive Pt(IV)/Ru(II) bimetallic polymer to treat cisplatin-resistant tumors [38]. Through amino-yne "click" polymerization, amphiphilic bimetallic polymers were prepared from a primary amine-bearing Pt(IV) monomer and a propiolate-containing Ru(II) monomer, followed by functionalization with amine-terminated PEG. These triblock copolymers self-assembled into nanoparticles that were efficiently taken up by cisplatin-resistant cancer cells. Upon irradiation with red light, the nanoparticles generated singlet oxygen, thereby inducing complete polymer degradation, and triggering the release of the Ru(II) anticancer agent. Concurrently, active cisplatin was generated and released via intracellular reduction of the Pt(IV) motifs. The released Ru(II) and cisplatin, as well as the generated $^1O_2$ exhibited synergistic effects to inhibit the proliferation of drug-resistant cancer cells.

Imparting degradable polymers with precise degradative responsiveness by leveraging multiple environmental cues to trigger Boolean logic gate-programmed reactions would enable unprecedented selectivity over controlled therapeutic release and/or activation. To demonstrate this approach, Badeau et al. reported modular multi-stimuli-responsive hydrogel platforms that could perform tailored and user-specified biocomputation for programmable degradation [18]. Seventeen discrete, monodisperse, stimuli-responsive crosslinkers that could collectively yield all possible YES/OR/AND logic outputs from multiple orthogonal inputs involving enzyme, reducing agent, and light were synthesized. By incorporating these orthogonal stimuli-labile crosslinkers into cytocompatible hydrogels, selective hydrogel dissolution and the consequent

release of drug- and cell-based therapeutics were accomplished. Using these creative hydrogel platforms, the first sequential and environmentally-triggered release of multiple cell lines in well-defined combinations was demonstrated. In other interesting work, Zhang et al. established a programmable polymer library that enabled the construction of multi-stimuli-responsive nanocarriers containing logic gates for combinatorial tumor therapy [39]. A series of monomeric building blocks responsive to UV/visible light, ROS, GSH, acidic pH, esterase and phosphatase with similar chemical structures and reactivities by self-immolative linkages were constructed. Then, a library of degradable polymers consisting of a pH-detachable PEG segment, a responsive hydrophobic block, and a positively charged polyethylenimine block were synthesized. These polymers were co-assembled with small interfering RNA (siRNA) into smart nanocarriers with logic gates and hierarchical structures. Moreover, small-molecule (pro)drugs and inhibitors could also be encapsulated into such logic nanodevices, allowing for efficient combinatorial anti-tumor therapies. Taken together, logic gate-based smart platforms hold great potential in diverse fields including precision drug delivery, diagnostics, and regenerative medicine.

Lai et al. developed a programmable hydrogel with a double-locked domain (DLD) [40]. The domain could undergo rapid degradation if and only if two stimuli were introduced in a defined sequence. Reversing the order or presenting only one stimulus did not result in comparable degradation. The DLD consisted of an *o*-nitrophenyl ethanol with an acetal in the para position to the nitro group. The electron-withdrawing effect of the nitro group made the acetal stable at low pH. However, exposure of the nitro group to light led to intramolecular photocyclization and reduction to form an electron-rich oxindole. This electron-donating group made the acetal much more susceptible to cleavage at mildly acidic pH (i.e., pH 5). The DLD was incorporated into hydrogels, resulting in hydrogels that were rapidly degraded by the

sequential exposure to light and then acid. These materials have potential to provide a high level of spatiotemporal control in biomedical applications.

Amplifying degradation in response to stimuli

The stimuli-responsive degradation of polymers provides an additional level of selectivity for biomedical applications beyond that afforded by conventional biodegradable polymers. Nevertheless, the range of accessible physiological conditions such as pH, redox potential, and enzyme concentrations is small relative to that accessible in a laboratory, limiting in practice the design and application of such systems. Furthermore, the penetration of light through tissues is limited [64]. Therefore, the possibility of amplifying an event such as a single bond scission mediated by an endogenous or exogenous stimulus is very attractive. Over the past several years, new approaches to exploit single stimulus-mediated bond cleavage events have been introduced and are beginning to be explored for biomedical applications.

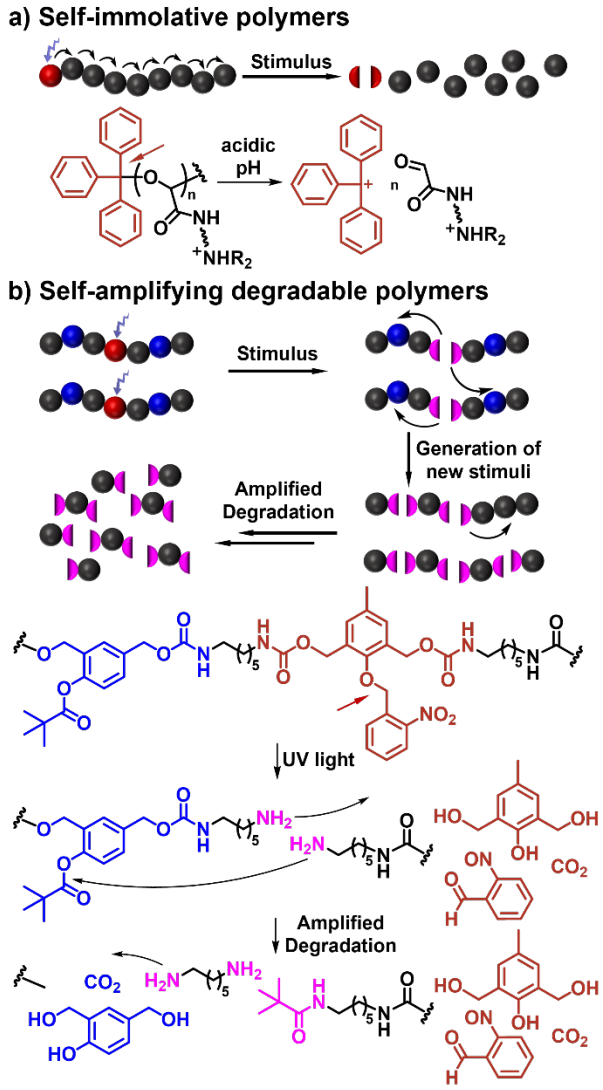

Figure 3. Schematic illustration of degradable polymers exhibiting amplified degradation in response to stimuli: a) Self-immolative polymers with amplified head-to-tail chain depolymerization after cleavage of responsive end-caps [45]. b) Self-amplifying degradable polymers with stimuli-triggered generation of new reactive stimuli or catalytic species [51].

Self-immolative polymers

Self-immolative polymers (SIPs) are a class of degradable polymers with the capability to transduce a single bond scission event at the polymer terminus or within the backbone into a domino-like fragmentation that leads to complete depolymerization, resulting in an amplification of the triggering event (Figure 3a) [67]. Here, we will present some recent SIPs designs for biomedical applications.

Building on research establishing that cationic polymers can exhibit antibacterial properties [68], Ergene and Palermo prepared self-immolative cationic poly(benzyl ether)s [41]. In addition to cationic ammonium groups, OEG side chains were introduced to lower the toxicity to mammalian cells. By tuning the OEG graft density and chain length, polymers with enhanced bacterial selectivity were obtained. Additionally, these antibacterial polymers underwent sensitive and specific triggered depolymerization into small molecules when exposed to fluoride ions. While only a model stimulus, the depolymerization has the potential to enhance clearance of the polymers *in vivo* and further lower their toxicity.

Ding et al. reported amphiphilic block copolymers containing side chain-functionalized depolymerizable poly(benzyl carbamate)s and PEG, which could self-assemble into micellar nanoparticles [42]. Upon triggering with ROS or acidic pH, depolymerization induced transformation of the nanoparticles into highly reactive electron-deficient azaquinone methide derivatives, which could react with biologically relevant nucleophiles, such as GSH and proteins, providing a novel *in situ* covalent trapping strategy. Using nanoparticles composed of copolymers functionalized with both a ^{19}F-containing moiety and DOTA-*Gd*, stimuli-activatable ^{19}F magnetic resonance imaging (MRI) and ^{19}F/^{1}H dual-modality MRI were achieved. With the DOTA-*Gd*-functionalized nanoparticle system, long-term *in vivo* ^{1}H MRI of tumor-bearing mice was demonstrated. The long-term retention in tissues was attributed to trapping of azaquinone

methides by protein thiols, although the eventual elimination of the lanthanide agent from the body will need to be investigated.

Many SIP backbones have questionable toxicity for *in vivo* applications due to the generation of reactive species such as quinone methides. On the other hand, polyglyoxylates [69] and related polyglyoxylamides [70] can be degraded to glyoxylic acid hydrate, a metabolic byproduct that can be processed in the liver and should exhibit low toxicity [71]. These SIPs have been incorporated as stimuli-responsive components in delivery systems using different designs. For example, poly(ethyl glyoxylate) (PEtG)-PEG block copolymers were prepared containing end-cap-linkers between the blocks, that were responsive to stimuli including GSH, ROS, and UV light. The copolymer self-assembled into nanoparticles [43] that released hydrophobic cargo from their cores on demand. Hybrid nanoparticles were also prepared from PEtG/PLA blends [44]. Depending on the end-cap, degradation of the PEtG could be selectively triggered by UV light or DTT, leading to the release of loaded celecoxib from these domains, while leaving drug in the PLA domains for slow drug release. The percentage of triggered release could be controlled by tuning the PEtG/PLA ratio. Most recently, polyglyoxylamide (PGAm) SIPs were developed by Sirianni et al. as a platform for nucleic acid delivery [45]. The cationic PGAms complexed nucleic acids through multivalent charge interactions in their polymeric form, resulting polyplex nanoparticles, but released it upon depolymerization under the acidic conditions encountered in the endosomes and lysosomes of cells to facilitate delivery. PGAms with different pH-sensitive triphenylmethyl and control end-caps as well as variable cationic pendent groups were explored to tune nucleic acid binding and rate of depolymerization [72]. *In vitro* studies demonstrated promising transfection capabilities and low cytotoxicity for selected PGAms, when compared to a commercial non-degradable linear polyethyleneimine (jetPEI) transfection agent. Further scope still exists to tune the structures of these polymers. In

addition to signal amplification, this work on PEtGs and PGAms demonstrated a key advantage of SIPs over other stimuli-responsive degradable polymers, which is that the stimulus to which the polymer responds can be easily changed just by changing the end-cap, while keeping the polymer backbone and pendent groups unchanged.

Self-amplifying degradable polymers

Upon exposure to specific stimuli, the aforementioned polymer degradation mechanisms proceeded through either a one-to-one or cascade self-immolative degradation. To achieve efficient degradation, the one-to-one degradation model required a high concentration of specific stimuli, whereas the cascade degradation rendered it possible to amplify external stimuli. Notwithstanding such enhanced sensitivity, cascade degradation only proceeded within the activated molecules. Since the degraded fragments cannot trigger the residual chains, complete degradation of SIPs can only be accomplished in the presence of a stoichiometric amount of stimulus relative to the end-cap. To further increase response sensitivity, amplified cascade degradation has been proposed, in which the degraded products of a trace number of activated chains could further drive the degradation of the residual polymers, enabling exponential amplification of the specific stimulus to actuate self-amplifying degradation (Figure 3b).

To chemically amplify the degradation of polymers, Lee et al. designed a ROS-triggerable polymer containing ketal moieties along the backbone, which could be cleaved by acid-catalysis [46]. Upon triggering with H_2O_2, the polymer exhibited a hydrophobic-to-hydrophilic transition, revealing a carboxylic acid that catalyzed ketal hydrolysis. Notably, the chemical amplification approach accelerated the polymer degradation up to 17-fold when compared to a ROS-responsive polymer without the amplification design. Moreover, ROS-dependent payload release from the nanoparticles formulated from these polymers was demonstrated using a NIR fluorophore, IR-780. However, no further biomedical applications were explored.

Cao et al. developed a polymeric ROS-triggerable nanocarrier with encapsulated chlorin e6 (Ce6) and DOX, which was self-assembled from a ROS-sensitive poly(thioketal phosphorodiamidate) with the help of an amphiphilic PEG-poly(*ε*-caprolactone) block copolymer (PEG-*b*-PCL) [47]. Upon irradiation with 660 nm red light, the photosensitizer Ce6 generated ROS and the ROS rapidly degraded the poly(thioketal phosphorodiamidate) backbone at the thioketal sites, leading to a size shrinkage for the nanocarrier and concomitant release of DOX. This photo-initiated amplified degradation of ROS-triggerable polymers provided a general approach to design self-amplifying degradable polymer systems.

In another interesting contribution, Powell et al. described H_2S-responsive self-immolative poly(benzyl thiocarbamate)s with aryl azides as end-caps for potential H_2S delivery [48]. In the presence of trace H_2S, the polymers depolymerized and generated carbonyl sulfide (COS), which was transformed into H_2S by carbonic anhydrase (CA). Thus, newly formed H_2S further participated in the depolymerization of other polymers, amplifying endogenous H_2S production.

Miller et al. reported acid-responsive degradable macromolecules with a self-amplified degradation mechanism [49]. In their design, a 3-iodopropyl acetal moiety underwent acid-catalyzed acetal hydrolysis with stoichiometric formation of hydroiodic acid, a very strong acid that could catalyze ensuing degradation. When these 3-iodopropyl acetal moieties were incorporated into linear polymers or hydrogels, autocatalytic, acid-amplifying degradation was successfully verified. Subsequently, the same group expanded this approach to design self-amplifying degradable polyurethanes via light or base-triggered and base-mediated degradation [50]. It should be noted that the degradation of these self-amplifying degradable polymers involved relatively harsh activation conditions (organic solvents, high temperature, strong acids/bases, etc.), and this aspect would need to be addressed before they could be used for potential biomedical applications.

Very recently, Tan et al. reported the preparation of amphiphilic polyurethane nanoparticles containing both external and built-in triggers, exhibiting stimuli-triggered self-amplifying degradation [51]. The activation of external triggers by stimuli (i.e., reductive milieu, light, esterase) led to the generation of highly reactive primary amines, which subsequently activated the built-in triggers (i.e., esters) with the liberation of more primary amines in a positive feedback loop, thereby triggering the degradation of micellar nanoparticles in a self-propagating manner. More importantly, it was confirmed that the esterase-responsive nanoparticles could discriminate cancer cells from normal ones by amplifying the esterase stimulus that is overexpressed in cancer cells, thereby enabling the selective release of encapsulated therapeutic agents and inhibiting proliferation of cancer cells.

Current Status, Challenges and Opportunities

As highlighted by the examples described in this article, tremendous progress has been made in the development of stimuli-responsive degradable polymers. In the area of pH-degradable polymers, the chemistry and pH-dependence of different chemical linkages have been well established for a number of years now, due to the extensive use of these groups in organic chemistry and their early applications in drug delivery. However, creative uses of these linkers in new polymer backbones and multifunctional gated systems are still emerging. Reduction-responsive polymers have also been extensively investigated to date, but a new emerging trend in the last several years has been their combination with multiple drugs to address the remaining challenge of drug resistance in cancer therapy. Polymers that are responsive to ROS are of particular interest, in terms of new chemistries and functions still being developed. Not only have new ROS-responsive linkages been incorporated into polymers, but the resulting polymers can perform multiple functions, including triggered breakdown to release drugs concomitant with the

scavenging of harmful ROS. Such systems have excellent potential for imaging, as well as the treatment of inflammatory conditions, wounds, and cancer. Furthermore, enzymatically-triggered polymer degradation is also highly attractive due to the chemical specificity of enzymes and the multitude of different enzymes that are involved in the progression of various diseases. Many opportunities in this area for imaging, drug delivery, and tissue regeneration applications remain unexploited and we will certainly see new developments in the coming years. However, a key challenge is the higher chemical complexity of peptide-based linkages compared to simpler linkages such as acetals, disulfides, and thioketals. The introduction of peptides generally requires the use of multiple protection and deprotection steps that bring cost in terms of time and finances. Furthermore, as highlighted by Alor and Amir, the accessibility of the enzyme to the cleavage site is an important consideration [73].

The initiation of polymer degradation with exogenous stimuli is of growing interest as this approach would allow drugs to be released on demand by patients or physicians. So far, UV light has been most widely explored as a trigger. It is an excellent model system for proof-of-concept studies, as the time, intensity, and location of irradiation can be easily controlled in the lab, and light-responsive moieties such as *o*NB are easily incorporated into polymers. However, its application to real *in vivo* conditions is limited due to very poor tissue penetration. This limitation can be overcome to some extent by the use of NIR chromophores and two-photon processes. However, even NIR light can only penetrate several mm into tissues [74]. Ionizing radiation can fully penetrate tissues, but suffers from poor chemical specificity and may induce other undesirable effects. In this regard, ultrasound-responsive systems may be promising, assuming a good balance between responsiveness and side effects can be achieved.

Many of the creative developments over the past few years were in the area of multi-responsive polymer systems. Such systems can potentially account for the limitations of mono-

responsive polymers in terms of heterogeneity in the biological environment *in vivo* and patient-to-patient variability. They can also provide enhanced control over degradation through logic-gated approaches. Nevertheless, a couple of aspects warrant further attention. First, these systems will be broken down into multiple different products. For translation to the clinic, it will be important to understand and fate and biological activity of these different degradation products. In addition, as polymeric systems become increasingly complex, so does their manufacturing. When one considers simple drug-loaded homopolymer particles, there is already dispersity in terms of the size and drug loading of different particles. Each additional parameter that is added (e.g., additional drugs, stimuli-responsive units in the polymer) will also bring dispersity, such that in the final system it is possible that most bioactivity arises from a small fraction of the sample that has ideal composition and properties. Batch-to-batch reproducibility will become increasing challenging but also even more important as the complexity of the polymeric system increases, which may pose challenges for clinical translation.

As highlighted in this article, much of the past research on stimuli-responsive degradable polymers has been directed towards the delivery of cytotoxic small molecule anti-cancer drugs. Polymers offer many opportunities to enhance the efficacy and reduce the side effects of these treatments. However, the growing trend towards immunotherapy - harnessing the body's immune system to fight the disease - should be recognized [75]. It will be important to design and optimize polymer systems that can effectively deliver cells, antibodies, and other biotherapeutics. Furthermore, as the biology behind other conditions, such as autoimmune and musculoskeletal disease, becomes increasingly well understood, researchers can exploit established polymer chemistries and develop new ones to address therapeutic challenges in these areas. Polymer and biomaterials scientists have developed an impressive array of chemical tools

over the past couple of decades and it will be exciting to see this expanded and applied in the coming years!

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