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# Oxidation-Responsive Polymers for Biomedical Applications

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**Abstract**

Reactive oxygen species (ROS) play key roles in many physiological processes such as cell signaling and host innate immunity. However, once they are overproduced, ROS may damage biomolecules *in vivo* and cause diseases such as cardiovascular or neurodegenerative diseases, cancer, and so forth. Oxidative stress is usually implicated in various inflammatory tissues, representing an important target for the development of various therapeutic strategies. Therefore, various probes for *in vitro* detection of ROS or *in vivo* diagnosis of the oxidative stress-relevant diseases have been developed. Oxidation-responsive polymers have also attracted great interest because of their potential applications in biomedical fields. In this feature article, we summarize six types of oxidation-responsive polymers based on different oxidation-responsive motifs. Poly(propylene sulfide)s, selenium-based polymers, aryl oxalate- and phenylboronic ester-containing polymers are discussed in detail, while poly(thioketal)s and proline-containing polymeric scaffolds are briefly introduced.

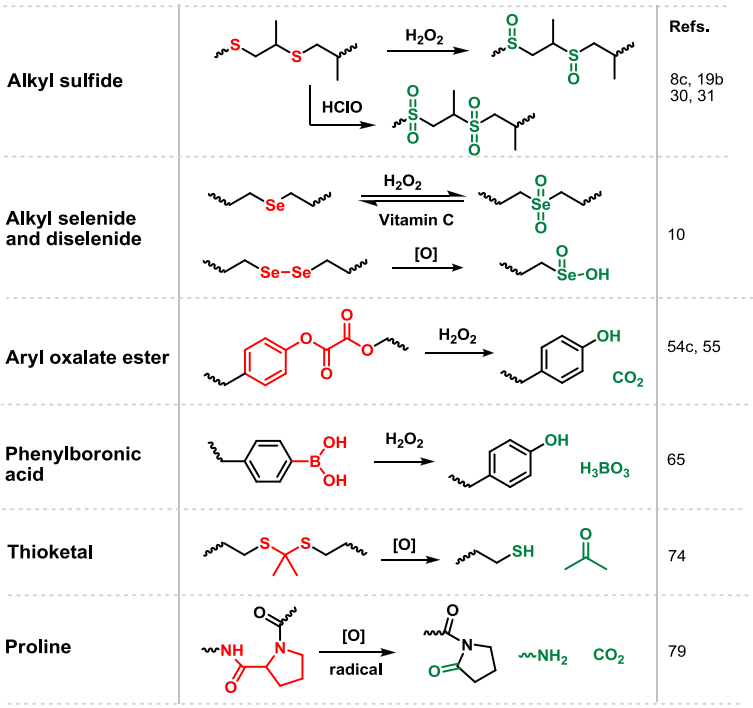
## 1. Introduction

In human body, there are two types of oxidative species: reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS generally include superoxide anion and hydrogen peroxide ($H_2O_2$) which are initially generated by oxygen reduction, as well as their derived reactive species including hydroxyl radical, hypochlorous acid (HOCl), peroxyl radicals, and singlet oxygen. RNS commonly represent nitric oxide and its derivatives such as peroxynitrite ($ONOO^-$) and nitrogen dioxide.[1] ROS or RNS at the appropriate concentrations play important biological functions in a wide range of physiological processes such as cell signaling, apoptosis or proliferation, and in the fight against foreign pathogens. For example, $H_2O_2$ is directly or indirectly involved in many cell signaling pathways mainly *via* redox reactions with thiol-containing proteins. Nitric oxide, known as the endothelium-derived relaxing factor can relax vascular smooth muscle. HOCl, hydroxyl radical and peroxynitrite are the key oxidants for host innate immunity against microbial infection.[2] However, ROS or RNS are a

double-edged sword: if overproduced, these oxidative species may damage biomolecules such as lipids, proteins, and DNAs. Overproduction of ROS may be induced endogenously or by exogenous stimuli such as UV/γ-ray radiation and xenobiotics, resulting in oxidative stress, a biological feature that is closely associated with various pathological disorders including cancers and inflammatory, cardiovascular or neurodegenerative diseases.[3] Oxidative stress plays a pivotal role in initiation, progression, and metastasis of cancer cells; chemoresistance of some cancer cells may also be related to the overproduced ROS. In addition, oxidative stress is usually implicated in inflammatory tissues.[4] These biological features inspired scientists to exploit various probes or sensors for *in vitro* detection of different ROS/RNS or *in vivo* diagnosis of the oxidative stress-relevant diseases.[1a, 5] The abnormal redox states in tumor and inflammatory tissues have also been used as the targets for the development of various therapeutic strategies.[6]

Many anticancer or anti-inflammatory drugs are poorly soluble in water and show undesirable side effects. Therefore, intelligent nanomedicines capable of delivering the drugs/genes specifically to the diseased sites have attracted great interest.[7] In the past decade, various oxidation-responsive polymers have been developed as potential carriers for site-specific drug/gene delivery or bioimaging. In several review papers, Tirelli and coworkers focus on the sulfur-containing aliphatic polymers such as poly(propylene sulfide) (PPS);[8] Sung et al. have summarized the biomedical applications of different types of oxidation-sensitive organic polymers;[9] Xu and Zhang have recently summarized their studies on the selenium-based polymers.[10] In this feature article, we highlight recent developments of oxidation-responsive organic polymers that show potential biomedical applications, in particular as drug vehicles, imaging agents, antioxidants, or coating biomaterials. Four important families of oxidation-responsive polymers, including PPS, selenium-based polymers, aryl oxalate- and phenylboronic ester-containing polymers, are discussed in detail. For each type of polymer, we summarize the synthesis, self-assembly, oxidation property and bio-related

applications. In addition, poly(thioketal)s and proline-containing polymeric scaffolds are also briefly discussed. The six types of oxidation-responsive motifs and their oxidation products are shown in **Scheme 1**. Other types of oxidation- or redox-responsive polymers include organometallic polymers (metallocene-based systems, polymer-metal complexes, etc.) and conjugated polymers (polyaniline, polythiophenes, and so forth). Some of them, for example the ferrocene-containing polymers or mesoporous silica nanoparticle, could be used for chemically triggered drug delivery systems.[11] In most cases, however, the redox properties of these polymers are electrochemically modulated. They may find wide applications in the fields of biosensor, actuator, electrochromic device, artificial muscle, battery, and so forth. These redox-responsive polymers have been summarized in recent review papers and we will not cover them in this article.[12]




**Scheme 1**. Oxidation-responsive motifs and their oxidation products.

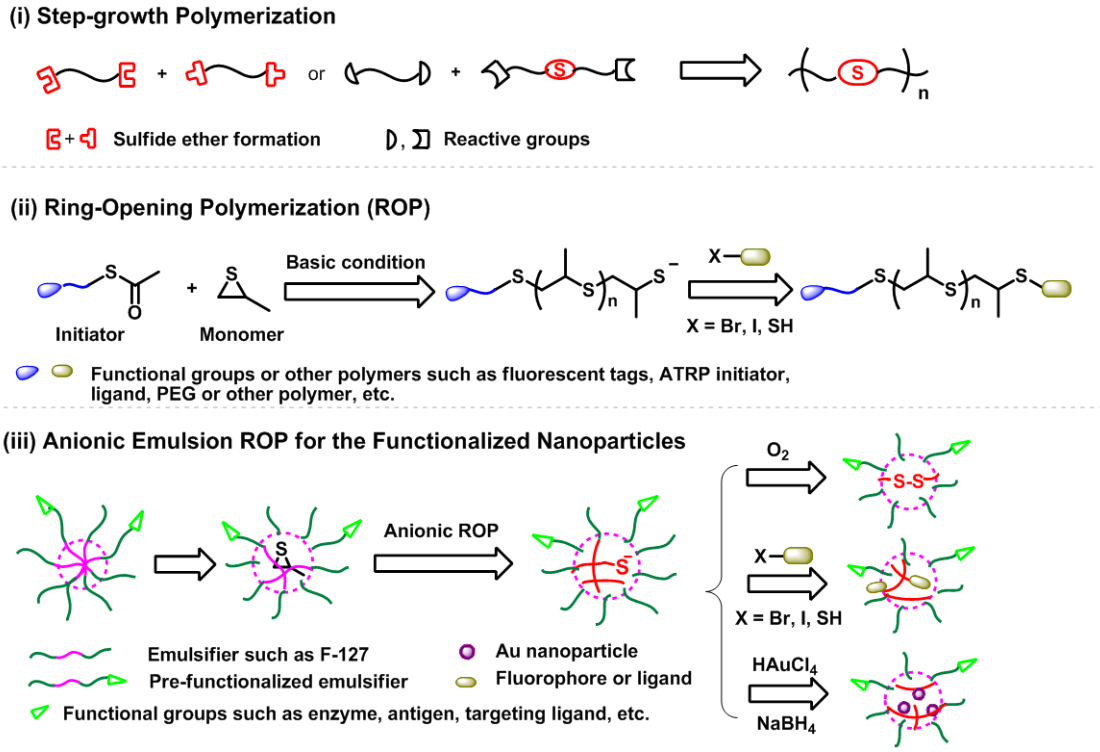
## 2. Poly(propylene sulfide)s

The sulfur(II)-containing polymers including poly(alkylene sulfide)s and poly(arylene sulfide)s have a long history; some of them have been applied as sealants

and high-performance plastic.[8a] However, there was no report on the oxidation sensitivity of poly(alkylene sulfide)s as nanoparticulate drug carriers until 2004 when Tirelli, Hubbell and coworkers found that the polymersomes formed by triblock copolymer PEG-PPS-PEG were readily disrupted in the presence of 10% $H_2O_2$.[13] Inspired by this initial success, the same authors have systematically studied the PPS-based polymers and the relevant nanoparticles (NPs) including their synthesis, self-assembly, oxidation-responsive properties, and the bio-related performances as potential drug carriers for particulate vaccination.

### 2.1. Polymer synthesis and nanoparticle formulation

Poly(alkylene sulfide)s and the relevant NPs can be prepared via three strategies as shown in **Scheme 2**: step-growth polymerization, anionic ring-opening polymerization (ROP), and emulsion anionic ROP combined with the subsequent cross-linking or functionalization. [8a, 8c]




**Scheme 2**. Preparation of the sulfide-based polymers or nanoparticles.

The step-growth polymerization can be used to synthesize both poly(alkylene

sulfide)s and poly(arylene sulfide)s via nucleophilic substitution and nucleophilic or radical addition reactions. However, it is difficult to control the molecular weight and PDI of the polymers.[14]

In the second ROP approach, five-membered or larger cyclic alkylene sulfides undergo neither cationic nor anionic ROP to get poly(alkylene sulfide)s with high molecular weights. Although the four- and three-membered rings (thietane and episulfide) can undergo cationic ROP, this method usually generates cyclic oligomers or polymers with branched structures. The anionic ROP of thietane requires strict conditions, which limits its practical application.[8a] Fortunately, poly(1,2-alkylene sulfide)s can be synthesized in a controlled manner via the anionic ROP of episulfides using the mild thiolates as propagating species.[15] This feature makes it practical to prepare poly(alkylene sulfide)s with complex architectures and diverse functionalities; among them, PPS derivatives are the mostly studied.[16] Using the protected thiols such as thioacetate to *in situ* generate the initiating species can ensure reproducibility of the initiator concentration, which is helpful to better control the polymer molecular weight and structures.[17] A recent work indicates that 2-bromoisobutyryl end-modified PPS can be used as a macroinitiator to perform atom transfer radical polymerization under mild conditions, without significant copper sequestration by the PPS chains.[18] By combination of reversible addition-fragmentation chain transfer and thioacyl group transfer (TAGT) polymerizations, the PPS-containing block copolymers have also been synthesized.[19] These results indicate that living ROP of episulfides combined with other living polymerizations or the end-modification pathways may offer poly(1,2-alkylene sulfide)-containing polymers with different topology and versatile functionalities.

In the third strategy, the oxidation-responsive NPs consisting of PPS core covered by a poly(ethylene glycol) (PEG) corona have been prepared by the emulsion anionic ROP of propylene sulfide using Pluronic F-127 as an emulsifier, 1,3-propanedithiol as a bifunctional initiator, and 1,8-diazabicyclo[5.4.0]undec-7-ene as a basic catalyst. The success of this facile one-pot approach is guaranteed by the hydrophobic character of

the monomer (propylene sulfide) and PPS, and the tolerance of the propagating species (thiolates) to water at the mildly basic pH (<11).[20] In order to improve the long-term stability of the PPS NPs, a tetra-armed hydrophobic initiator was used to provide the star-shaped macromolecules with reactive end-thiols. Upon adding a bifunctional end cap such as tetra(ethylene glycol) diacrylate or simple exposure to air, crosslinked PPS NPs were thus obtained via the Michael-type addition to the acrylate or oxidation coupling of the thiols. The size of the NPs can be easily tuned in the range of 25-250 nm by changing the monomer/emulsifier ratio. In addition, the NPs can be selectively labeled or functionalized in bulk, on surface, or both.[21] When the Pluronic F-127 pre-modified with peptide ligand, model antigen protein, or enzymes was used as a co-emulsifier, versatile surface-functionalized PPS NPs can be achieved.[22] Further covalently incorporation of fluorophores, gold NPs, or antigens into the PPS NPs (in bulk or on the surface) is also facile based on the versatile reactivity of the terminal sulfur anion.[16c, 17a, 23] Besides the backbone-type PPS, polymers with pendent sulfide ether were synthesized by post-modification method or by the ROP of sulfide ether-containing monomers.[24]

### 2.2. Self-assembly of the PPS-containing block copolymers

PPS is much more hydrophobic than its oxygen analogue poly(propylene oxide) due to the low dipole moment. This feature endows the PPS-containing block copolymers with self-assembly property in water. For example, triblock copolymers $PEG_{16}$-*b*-$PPS_{25}$-*b*-$PEG_8$ and $PEG_{16}$-*b*-$PPS_{50}$-*b*-$PEG_{16}$ could self-assemble into hydrogels in concentrated aqueous solution, upon diluting, polymersomes were evolved.[25] These polymersomes were stable over long incubation time (up to months) at ambient temperature but underwent a morphology transition from vesicle to micelle, and finally to water soluble substances in the presence of $H_2O_2$.[13] Further detailed studies reveal that the aggregate morphologies of the triblock copolymer $PEG_{44}$-*b*-$PPS_{76}$-*b*-$PEG_{44}$ are greatly dependent on the protocol of preparation. Only spherical micelles were formed when the samples were fabricated by diluting a polymer-tetrahydrofuran (THF) solution

with buffered saline. By contrast, the direct film hydration produced aggregates of various morphologies ranging from spherical micelles to wormlike micelles, Y-junctions, blackberry micelles, and vesicles. After being aged, these kinetically formed, metastable aggregates gradually changed to the thermodynamically stable spherical micelles or short wormlike micelles because of the low glass transition temperature ($T_g$, ~ -60 $^oC$) of the PPS block.[26] Recent fluorescence resonance energy transfer experiments demonstrated a good kinetic stability of the PPS-based micelles, no significant copolymer exchange could be detected within 24 h even for the micelles formed by the rather hydrophilic block copolymer $PPS_{10}$-*b*-$PEG_{44}$. The hydrophobic payload exchange could be avoided for days at a low storage temperature of ~4 $^oC$.[27] The aggregation profiles of the PPS/PEG-based diblock, triblock and multi-armed block copolymers have been investigated systematically. In general, stability of the aggregates depends mainly on the chain length of the PPS block, while the morphology is controlled by the ratio of the PEG block to the PPS block.[17b, 28]

### 2.3. Oxidation of PPS

Oxidation of organic sulfide ether into sulfoxide can be performed under mild conditions such as using low $H_2O_2$ concentration at low temperature; whereas under a strong oxidative condition, such as in the presence of organic peroxyacids, sulfone is produced.[24a] In the case of the PPS-containing copolymers, although $H_2O_2$ has already been proven to oxidize the sulfide ether bond and destroy the NPs,[8c, 13, 29] the detailed oxidation products were analyzed only recently by Fourier transformed infrared (FTIR) spectroscopy. In the mixture of THF/water, PPS was mainly oxidized by $H_2O_2$ into poly(propylene sulfoxide) without significant production of sulfone groups. When hypochlorite was applied as the oxidant, a large amount of sulfide ethers was oxidized into sulfones which caused a dramatic depolymerization of the oxidized polymer chains.[30] In addition, hypochlorite oxidized PPS much faster than $H_2O_2$ did as proven by the FTIR and $^1H$ NMR results or the transmittance measurements.[8c, 30, 31] The peroxidases such as chloroperoxidase (CPO) or myeloperoxidase (MPO) catalyze the

conversion of $H_2O_2$ and chloride anion to hypochlorite; therefore, in the presence of MPO (5 U/mL) or CPO (20 U/mL) with 200 mM NaCl, PPS NPs responded quickly to 0.5 mM $H_2O_2$, releasing the loaded Nile red.[31] This work implies that the peroxidases may play an important role in the *in vivo* oxidation of PPS NPs, considering that $H_2O_2$ is the dominant oxidant in the inflammatory sites or in cancer cells. According to another recent paper, PPS is also sensitive to peroxynitrite; the lipopolysaccharide (LPS)-activated macrophages can generate sufficient ROS and/or RNS to trigger the release of hydrophobic fluorescent dyes loaded in the PPS-based micelles.[19b]

### 2.4. Biomedical application of the PPS-containing NPs

PPS is a hydrophobic polymer with a low $T_g$. Oxidation of PPS generates polysulfoxide and/or polysulfone along with a significant solubility-switch, providing an attractive platform for drug/gene delivery specifically to the pathological sites with oxidative stress. In the past decade, the PPS-based polymers have been extensively studied regarding their great potential application as carriers for nanomedicines in the forms of micelles, polymersomes, as well as cross-linked NPs.

The size and surface property of the cross-linked PPS NPs prepared by the third method significantly influence the NPs' performance both *in vitro* and *in vivo*. In an early work, Hubbell, Swartz and coworkers found that the PEG-stabilized PPS NPs with a size of 20 nm can be effectively taken up and trapped in the lymph nodes for at least 5 days after interstitial injection. Particularly, up to 40-50% of the lymph node-residing dendritic cells contained the internalized NPs without using any targeting ligand. By contrast, the 100 nm NPs were difficult to transport into lymph nodes.[32] Further results indicate that the surface-polyhydroxylated PPS NPs (OH-NPs) can function as an adjuvant to activate the complement cascade and stimulate dendritic cell maturation. Using ovalbumin (OVA) as a model antigen, the authors have demonstrated that the antigen-conjugated OH-NPs with a diameter of ~25 nm are able to generate humoral and cellular immunity in mice.[22d] Because of the ease of fabrication and multiple functionalization, high stability, and oxidation-sensitivity, these cross-linked PPS NPs

with suitable sizes and surface properties show great potential for nanomedicines targeting to various tissues or organs such as articular cartilage, lung, and other mucosal airways.[22c, 23c, 33]

Besides the aforementioned PPS NPs prepared by the emulsion ROP, polymeric micelles or polymersomes fabricated from the PPS-containing block copolymers have also been studied as potential drug vehicles. For example, cyclosporine A, a hydrophobic immunosuppressive drug, can be facilely encapsulated into the spherical or wormlike micelles formed by $PEG_{44}$-*b*-$PPS_{10-40}$ block copolymers with up to 19% loading capacity. The *in vitro* release sustained 9-12 days at 37 $^{o}$C and was slightly influenced by the PPS block length.[28a] The micelles (~50 nm) formed from block copolymer $PEG_{115}$-*b*-$PPS_{31}$ are able to encapsulate hydrophobic anti-inflammatory drug (mometasone furoate) or immunosuppressive drugs (rapamycin and tacrolimus), and effectively deliver them to the draining lymph nodes, showing proper immune regulation.[34] Recent results demonstrate that the polymersomes of copolymer $PEG_{17}$-*b*-$PPS_{30}$ can encapsulate the Toll-like receptor agonists (gardiquimod or R848) or the model antigen (OVA) by the combination of film hydration and extrusion method. These oxidation-sensitive polymersomes may function as a vaccination platform for inducing cell-mediated immunity against cancer or chronic viral infection. Importantly, the intracellular payload release was studied by confocal microscopy using calcein as a model compound. It is found that significantly intraendosomal release of calcein was detected within 12 h followed by extensive cytosolic delivery after 24 h. The released calcein was also detected in some endosomes that might not possess a low pH lumen and therefore were not stained with LysoTracker. This may be attributed to the oxidative dissociation of the polymersomes by the NOX2-dependent ROS.[35]

It is well known that glucose oxidase (GOx) catalyzes the conversion of β-D-glucose to D-glucono- 1,5-lactone and $H_2O_2$ in the presence of $O_2$. Therefore, when GOx was physically encapsulated into the PPS polymersomes or covalently conjugated onto the PPS NPs, the GOx-loaded particles were stable for at least several days in the

absence of glucose but gradually dissociated in the presence of D-glucose in air.[22a, 29] Although these PPS-based glucose-sensitive vesicles or NPs might be applied in the fields of drug delivery or glucose detection, no further relevant publication is reported.

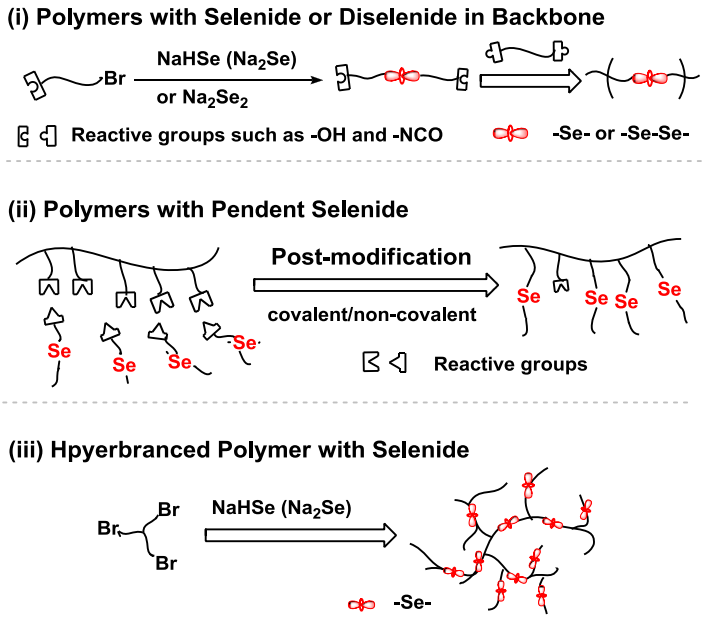
Recently, PPS NPs have found new applications as antioxidant materials to stabilize the encapsulated enzymes such as diisopropylfluorophosphatase.[36] Moreover, by combining superoxide dismutase (SOD) and PPS-*b*-PEG, Hu and Tirelli have developed a micellar system. This system mimics the SOD/catalase combination and is capable of scavenging both superoxide and $H_2O_2$. Since SOD is covalently attached onto the surface of the PPS NPs, it can readily catalyze superoxide anion to form $H_2O_2$, thus formed $H_2O_2$ can be easily cleaned by the proximate PPS NPs. Furthermore, the stability of SOD is improved by the covalent conjugation and PEG-shielding, which is beneficial for their potential *in vivo* use. In principle, this type of hybrid "antioxidant" NPs are able to encapsulate active therapeutics and release the payloads specifically at inflammatory sites or in cancer cells. However, *in vivo* studies are necessary to further confirm both ROS-scavenging activity and stability of this hybrid "enzyme".[22b]

On-demand manipulation of cellular function plays an important role in some rising fields such as personalized therapy, quantitative cell biology, and so forth. By encapsulating the photosensitizer ethyl eosin in the membrane of $PEG_{17}$-*b*-$PPS_{30}$ polymersomes, Hubbell et al. have demonstrated an optical approach to spatially and temporally tuning intracellular delivery of molecules. Upon laser irradiation at 561 nm, PPS was oxidized into polysulfoxide by the *in situ* generated $^1O_2$, inducing polymersome rupture and encapsulated cargo release. This optofluidic technique significantly expands the application fields of this type of oxidation-responsive polymers.[37]

### 3. Selenium-based responsive polymers and supramolecules

Belonging to the family of chalcogens (group 16 of the periodic table), selenium resembles sulfur atom in many aspects including the oxidation-responsive property. However, selenium (II)-containing organic compounds possess a higher sensitivity to

oxidant than the sulfur (II)-based analogues because of the weaker bond energy of C-Se (244 kJ/mol) as compared with that of C-S bond (272 kJ/mol). Furthermore, the smaller bond energy (172 kJ/mol) of the Se-Se bond makes it more labile than the S-S bond (240 kJ/moL) towards reducing reagents; as a result, the diselenide bond can be easily oxidized to selenic acid. These features make C-Se (II) and diselenide bonds very attractive motifs for constructing redox-sensitive organic compounds or polymers.[10] For example, the natural selenoproteins function to reduce cancer risk by preventing ROS-induced cellular damage; they may also negatively affect tumor growth by enhancing immune-cell activity.[38] Various synthetic organoselenium compounds such as Ebselen have been prepared to mimic glutathione peroxidase (GPx).[39] Recently, a family of selenide- or diselenide-containing polymers and supramolecules have been synthesized and investigated on their potential applications as drug carriers or redox enzyme mimics.[10]




**Scheme 3**. Synthesis of the selenide- or diselenide-based polymers.

### 3.1. Polymer synthesis

Early in 1972, the synthetic routes of selenium-containing polymers were ever summarized, with step-growth polymerization being the predominant method.[40] Here, we briefly introduce the syntheses of the selenide- or diselenide-containing polymers

that may find biomedical applications (**Scheme 3**). The main chain selenide- or diselenide polyurethanes (PUSe or PUSeSe) were synthesized via step-growth polymerization of toluene diisocyanate (in slight excess) with selenide- or diselenide-containing diols; the subsequent PEGylation gave the corresponding amphiphilic triblock copolymers, PEG-*b*-PUSe-*b*-PEG and PEG-*b*-PUSeSe-*b*-PEG.[41] Similarly, a positively charged diselenide-containing polyurethane was prepared by using 2,2'-(piperazine-1,4-diyl)diethanol and 1,11'-diselanediylbis(undecan-1-ol) as the comonomers.[42] These PUSe and PUSeSe have relatively high molecular weights as compared to the polymers prepared *via* the reaction of alkylene dihalides with $Na_2Se$ or $Na_2Se_2$.

The second type of polymers with pendent selenide groups can be prepared by post-modification method. For example, esterification of PEG-*b*-poly(acrylic acid) with $PhCH_2Se(CH_2)_{11}OH$ afforded the desired amphiphilic block copolymer PEG-b-PAA-Se.[43] Hyperbranched polymers have also been prepared. For example, Zhang et al. used NaHSe as the AA' monomer and 1,3,5-tris-bromomethyl-2,4,6-trimethylbenzene as the B3 monomer to obtain a hyperbranched polymer with selenides at the branching sites. Yan and coworkers prepared a hyperbranched polyphosphoester with diselenide units from 2-(2-(2-hydroxyethoxy)ethoxy)ethyldiselenide (as A2 monomer) and phosphorus oxychloride (as B3 monomer).[44] Recently, another approach was used to synthesize the selenide-containing hyperbranched polyphosphoesters by self-condensing ring-opening polymerization of the cyclic phosphoesters with pendant hydroxyl groups.[45]

### 3.2. Self-assembly and oxidation of the polymers

All the selenide- or diselenide-containing amphiphilic block or graft copolymers reported by Zhang and Xu et al. can self-assemble into micelle-like NPs with diameters of 60-80 nm. These NPs are stable for at least one month under ambient conditions.[41, 43] Oxidation-sensitive polyelectrolyte NPs can be fabricated via electrostatic interaction between the dually hydrophilic block copolymer PEG-*b*-PAA and a positively charged

selenium-containing surfactant.[46] The redox-responsiveness of these NPs was studied by combination of X-ray photoelectron spectroscopy (XPS), $^{1}H$ and $^{77}Se$ nuclear magnetic resonance, FT-IR, mass spectrometry, transmission electron microscope (TEM), and dynamic light scattering. The results indicated that these selenide-containing NPs were extremely sensitive to $H_2O_2$, dissociating in hours upon exposure to 0.1 wt% $H_2O_2$ in water. The results of drug release profile, XPS and TEM measurements indicated that the selenide-based NPs degraded much faster than their sulfide counterparts. Interestingly, selenide was quickly oxidized into selenone by 0.1 wt% $H_2O_2$ while under the same condition, sulfide was oxidized into sulfoxide first and converted slowly into sulfone.[41a] However, the selenide adjacent to a phenyl group was oxidized to selenoxide but not selenone, which might be due to the effect of the nearby benzene ring.[43, 46]

The diselenide-containing polymers possess a character of dual responsiveness; they are sensitive to both oxidative and reductive agents. A very low concentration (0.01 wt%) of $H_2O_2$ can effectively oxidize the diselenide to selenic acid along with the main chain cleavage, whereas 0.01 mg/mL of glutathione (GSH) are able to disrupt the NPs to release the payloads due to the reductive cleavage of the diselenide bond into selenol.[41b] Another unique feature of the diselenide-based polyurethanes is that they are responsive to low dose of γ-ray radiation (5 Gy) in the presence of oxygen or to red light with the help of porphyrin derivatives as a photosensitizer; both stimuli disrupt the NPs *via* oxidative cleavage of the diselenide bond by the *in situ* generated ROS such as hydroxyl radical, singlet oxygen, etc.[47]

### 3.3. Biomedical applications

Starting from mimicking GPx, the selenium-containing polymers have developed a much broader prospect especially as oxidation-responsive nanocarriers. As aforementioned, oxidative stress may be used as the biomarker of malignant cells distinguished from the normal cells, these selenium-based oxidation-sensitive polymers offer an attractive platform as the delivery vehicles of anticancer drugs. For example, the micelle-like NPs of PEG-*b*-PUSeSe-*b*-PEG are capable of loading doxorubicin

(DOX) and Rhodamine B; more than 90% of the loaded Rhodamine B can be quickly released in 4 h upon exposure to 0.01% $H_2O_2$.[41b] Since the PEG-*b*-PUSeSe-*b*-PEG NPs are sensitive to γ-ray radiation, more than 40% of the loaded DOX can be released after 3 h of γ-ray irradiation at a dose of 5 Gy. This irradiation dose is close to the dose received by patients during a single radiotherapy treatment. As expected, further increasing the irradiation dosage can enhance the DOX release.[47a] Recently, a positively charged diselenide-containing polyurethane was used together with a self-assembling peptide amphiphile to provide fibrillar, supramolecular hydrogels. These materials underwent a gel-sol transition when exposed to both γ-ray radiation and UV light, due to diselenide degradation and depolymerization; it is noteworthy that analogous disulfides are not degraded under the same oxidative conditions. [42] Moreover, the negligible toxicity of PEG-b-PUSeSe-b-PEG up to a concentration of 0.1 mg/mL in a human hepatic cell line suggests a general good biocompatibility of these constructs.[47b] These results demonstrate that this type of diselenide-based polyurethanes have great potential as anticancer drug vehicles, in particular for the combination of chemotherapy with radiotherapy or photodynamic therapy.

The selenide-containing copolymer (PEG-*b*-PUSe-*b*-PEG) NPs were also used to encapsulate DOX and release the payload rapidly by 0.1 wt% $H_2O_2$ triggering.[41a] More importantly, this copolymer can complex with platinum cation ($Pt^{2+}$) to form novel coordination-responsive micelles which are capable of loading DOX. Upon exposure to GSH or dithiothreitol (DTT), the micelles are disrupted due to the competitive coordination of $Pt^{2+}$ with GSH or DTT, triggering the encapsulated DOX release. These complex micelles have little cytotoxicity to HUVEC or HepG2 cells. When cisplatin was used instead of $PtCl_2$ to complex with PEG-*b*-PUSe-*b*-PEG, the obtained micelles are able to kill tumor cells. This kind of cisplatin-coordinating micelles are attractive for the combinatorial chemotherapy with dual or multiple drugs.[48]

Small molecular weight selenium-containing compounds play important roles for cancer therapy in the forms of anticancer drug and chemopreventive agent, or as

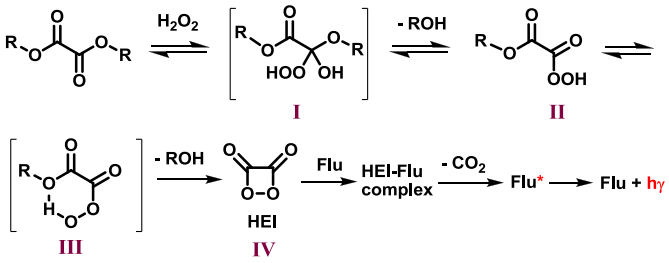
modulator of therapeutic efficacy of other anticancer drugs.[49] However, little work has been dealing with the anticancer activity of selenium-containing polymers. Recently, Yan and Huang et al. found that the hyperbranched polyphosphoesters with alternative hydrophilic phosphate segments and hydrophobic selenide or diselenide units in the polymer framework possess intrinsic anticancer activity by inducing apoptosis of the cancer cells, but exhibiting little toxic effect on normal cells. Furthermore, the amphiphilic hyperbranched polymers can self-assemble into stable NPs with diameters of 50-70 nm and a multi-core/shell structure. The NPs are capable of encapsulating DOX and releasing it under oxidative or reductive stimulus, which has been proven by the intracellular profiles of the DOX-loaded NPs.[44b, 45] These redox-responsive polyphosphoesters may function as both a polymeric therapeutic agent and a drug vehicle for combined chemotherapy of cancer.

The hyperbranched polymers or dendrimers with selenide or diselenide units in the core or at the branching sites have been studied on their activity as GPx mimics.[44a, 50] This topic is not the focus of the present article; readers may find more relevant information in a recent review paper.[51]

## 4. Aryl oxalate-containing polymers

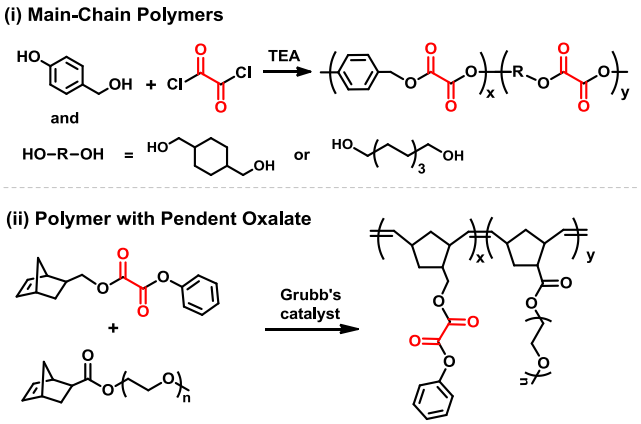
The pioneering work of aliphatic polyoxalates (POXs) was reported early in 1930s. The aliphatic POXs can be prepared by ROP of the six-membered cyclic oxalates of 1,2-glycols or polycondensation between the $\alpha,\omega$-alkylene diols and oxalic diesters or oxalyl chloride with or without catalysts.[52] Although some aliphatic POXs possess mild tissue reaction upon *in vivo* implantation for several days and may find biomedical applications, detailed studies have been performed only recently using various POXs as micro- or nanoparticulate drug carriers.[52d, 53]

Aryl oxalates have been extensively studied since 1960s due to their key function in peroxide-based chemiluminescence systems.[54] The proposed mechanism of the peroxide-based chemiluminescence is shown in **Scheme 4.**[54b, 54c, 55] The oxalates are




Scheme 4. Proposed mechanism of the peroxalate chemiluminescence.

oxidized by $H_2O_2$ to produce 1,2-dioxetanedione or some other kinds of high-energy intermediates (HEI) which interact with an appropriate fluorophore (Flu) to form an activated complex. After decomposition of the complex along with $CO_2$ release, the excited fluorophore (Flu*) decays to the ground state with fluorescence emitting. A unique feature of this system is its high specificity to $H_2O_2$. According to the mechanism shown in **Scheme 4**, a basic environment can promote the oxidation reaction, and thus increasing the subsequent chemiluminescence efficacy. For example, oxidation rate of an aryl oxalate was greatly accelerated in $NaHCO_3$ solution compared to that in pure water, while the reaction proceeded hardly in acidic solution.[56] Besides, the aryl oxalates with electronegative groups at the 2- or 4-position of the aryl ring, not aliphatic oxalates, are preferred to increase the chemiluminescence efficacy.[5f, 54b] The aryl oxalate/$H_2O_2$-based chemiluminescence system is very promising for *in vitro* or *in vivo* $H_2O_2$ detection because of its versatile performance.[5b, 5f, 57] In recent years, a family of main-chain POXs consisting of both aliphatic and aryl segments were prepared by polycondensation of oxalyl chloride with 4-hydroxybenzyl alcohol (HBA) and other aliphatic diols (**Scheme 5**). Varying the structure and ratio of the aliphatic and




**Scheme 5.** Syntheses of the $H_2O_2$-responsive polyoxalates with both aliphatic and aryl segments.

aromatic diols can produce POXs with a proper hydrolytic stability but quickly responding to the low concentration of $H_2O_2$. Selected fluorescent dyes can be encapsulated into the polyoxalate NPs (~550 nm) via the oil/water (o/w) emulsion technique. Upon exposure to $H_2O_2$, the POXs degraded along with HEI production and the subsequent dye emitting. The dye-loaded NPs possess a high sensitivity to $H_2O_2$ because of the close proximity of the oxalate groups and the dye molecules in the same NP; they can linearly detect $H_2O_2$ *in vitro* in the range of 0.25-10 μM. The additional attractive properties of the polyoxalate NPs include tunable emissive wavelength (460-630 nm) by encapsulating different dyes, excellent specificity to $H_2O_2$ over other ROS, deep-tissue imaging capability, and continuous detection of the *in situ* produced $H_2O_2$ for a long time. These dye-loaded NPs have the ability to image endogenously generated $H_2O_2$ in the peritoneal cavity or exogenously injected $H_2O_2$ (1 μM) in the leg of mice.[5f] To optimize the system, stable micelle-like polyoxalate NPs with a hydrophilic PEG shell and a diameter of ~150 nm were prepared by using Pluronic F-127 as an emulsifier. The improved micellar NPs can detect $H_2O_2$ as low as 100 nM; and interestingly, they function as antioxidants by scavenging $H_2O_2$ and suppressing the intracellular production of ROS. In other words, this type of micellar NPs may be applied as theranostic nanomedicines for the ROS stress-associated diseases.[58] Alternatively, a polynorborene-type copolymer with pendent phenyl alkyl hybrid oxalate group and oligo(ethylene glycol) chain was synthesized by the ring-opening

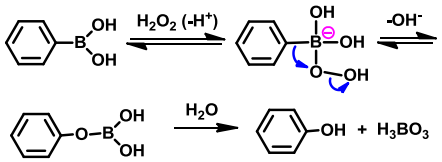
metathesis polymerization (**Scheme 5**). The micelle-like NPs formed by the copolymer was able to detect $H_2O_2$ as low as 50 nM, probably due to the smaller size (33 nm) as compared to that of the main-chain polyoxalate NPs.[59] Although this copolymer was designed to make $H_2O_2$-specific imaging NPs with suitable physicochemical characteristics for intravenous injection, more *in vivo* studies are necessary in the future.

4-Hydroxybenzyl alcohol (HBA) is one of the active components in some herbal agents that have been used to treat oxidative stress-related diseases such as ischemic brain injury and coronary heart disease. It is reported that HBA possesses anti-inflammatory and neuroprotective activity.[60] Besides the applications for *in vivo* $H_2O_2$ detection, recently, it was found that the HBA-derived polyoxalate copolymers (HPOX) show potential as polymeric antioxidants. The HPOX prepared by the polycondensation of oxalyl chloride with HBA and 1,4-cyclohexanedimethanol (1:4 in molar ratio) can be formulated into ~500 nm NPs by the o/w emulsion method; and the formed NPs can be hydrolyzed in a buffer solution (pH 7.4) to release HBA. *In vitro* studies on LPS-activated RAW 264.7 cells demonstrate that the HPOX NPs are able to inhibit the nitric oxide production by suppressing the induced nitric oxide synthases (iNOS) expression, and thus reducing the level of tumor necrosis factor-α (TNF-α) in a dose-dependent way.[61] Furthermore, HPOX NPs exhibit an obvious $H_2O_2$-scavenging capability and are capable of reducing significantly intracellular oxidative stress because the oxidation of aryl oxalates is $H_2O_2$-consuming. *In vivo* test results reveal that the HPOX NPs can greatly reduce pulmonary inflammation upon intranasal delivery. The promising features, including low cytotoxicity, significant antioxidant property, and biodegradability, make HPOX and some other aliphatic/aryl copolyoxalates very potent for the therapy of ROS stress-associated disorders.[53, 62]

## 5. Phenylboronic ester-containing polymers

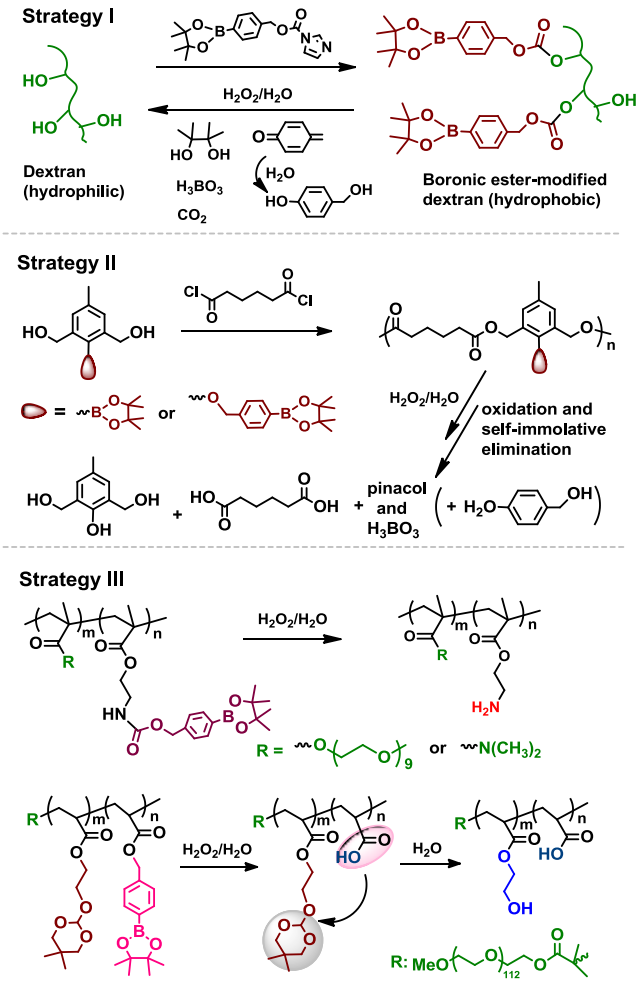
Phenylboronic acid and its derivatives are important building blocks for constructing organic compounds, functional polymers, supramolecules and network that have great potential applications in sensing, separation, catalysis, and drug delivery.[7e, 63]

One of the unique features of phenylboronic acid (ester) is its susceptibility towards $H_2O_2$, generating phenol and boronic acid as the oxidation products.[64] The oxidation mechanism proposed by Kuivila et al. in the 1950s is shown in **Scheme 6**.[65] Since the nucleophilic addition of $H_2O_2$ is a key step of the sequential reactions, phenylboronic acid can be oxidized into phenol only by $H_2O_2$ but not other ROS such as superoxide, hypochlorous acid, hydroxyl radical and so forth. This character makes the phenylboronic esters or arylboronic esters very promising as caging groups for the development of various $H_2O_2$-specific imaging agents [1a, 5a, 66] and $H_2O_2$-sensitive prodrugs.[67] Furthermore, phenylboronic acid or esters can also be applied as the $H_2O_2$-sensitive triggers to construct self-immolative dendritic fluorescent probes by using suitable adaptors. Upon exposure to $H_2O_2$, the probes decompose in a domino manner to release the fluorescent reporters, showing an amplifying effect.[68]




**Scheme 6.** Oxidation of phenylboronic acid by $H_2O_2$.

In principle, all of the polymers containing arylboronic acid or arylboronic ester motifs are oxidation-responsive, at least to $H_2O_2$. Although there are numerous publications reporting the polymers with phenylboronic acid or phenylboronic ester groups, most of them deal with the glucose- and/or pH-sensitivities of these polymers.[69] In recent years, several research groups have reported $H_2O_2$-responsive polymers that possess phenylboronic ester moiety. The polymers can be prepared via three strategies: polymer post-modification method,[70] step-growth polymerization of the phenylboronic ester-based monomers,[71] and free radical polymerization of the phenylboronic ester-containing vinyl monomers.[72] Upon $H_2O_2$-induced oxidation and the subsequent self-immolative elimination, the polymers either degrade totally or their properties change significantly (**Scheme 7**).




**Scheme 7.** Different oxidation-responsive polymers containing phenylboronic esters.

By modifying the hydroxyl groups of dextran with the imidazoyl carbamate-activated phenylboronic ester, Fréchet and coworkers prepared oxidation-responsive dextran derivatives that are biocompatible and can be formulated into spherical NPs (100-200 nm) via the o/w or w/o/w emulsion procedure (**Strategy I**). These NPs were stable in water in the absence of $H_2O_2$ with a half-life of more than one week; upon exposure to 1 mM $H_2O_2$, the NPs dissociated quickly in 2 h due to the solubility-switch caused by the oxidation reaction. Interestingly, the OVA encapsulated NPs demonstrated a much higher MHC I presentation as compared to the oxidation insensitive PLGA (poly(lactic-co-glycolic acid) NPs loaded with OVA. The facile protocol of fabrication and biocompatibility enable these NPs to be promising vehicles for nanoparticulate vaccine or anticancer drug delivery.[70]

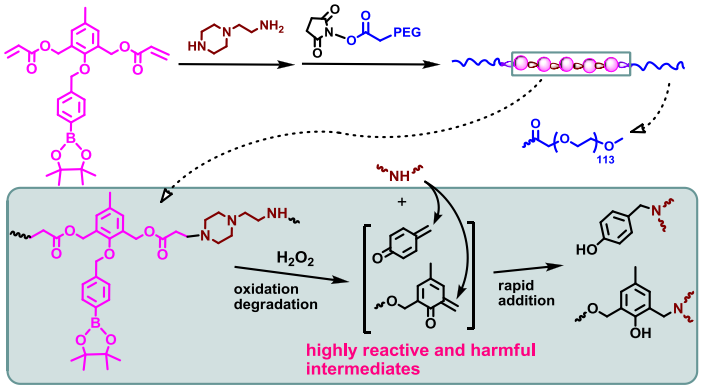
Two main chain-degradable, $H_2O_2$-responsive polymers were prepared by polycondensation of adipoyl chloride with two different oxidation-sensitive diols (**Strategy II**). Both polymers can be formulated into NPs through o/w emulsion technique and the NPs can be cleaved by $H_2O_2$ at the physiologically relevant concentrations. However, the polymer with a benzyloxy adaptor between the backbone and the boronic ester group degraded much faster than the other one. More importantly, the polymer NPs showed considerable degradation in the activated neutrophils with a 2-fold enhancement of the cargo release compared to the non-responsive PLGA NPs.[71a] The oxidation-responsive polymer NPs can encapsulate gadolinium (Gd) oxide NPs which show a low relaxation rate in the hydrophobic polymer matrix. These Gd-loaded NPs are stable over 5 days at physiological pH in the absence of $H_2O_2$. Upon oxidative degradation of the polymer NPs by $H_2O_2$, the Gd NPs were gradually released, generating a corresponding increase in $T_1$ relaxation rates within 10 min. Although these activatable imaging agents enable a relatively rapid $H_2O_2$ sensing, the lowest detection limit (6 mM) is not satisfactory, probably due to the slow degradation of polymer at a low $H_2O_2$ concentration.[71b] This synthetic route can also be used to prepare oxidation-triggerable polymeric prodrug. In a recent paper, 10-hydroxycamptothecin was used as a model diol-containing drug and incorporated into the polymer backbone to develop a class of chain-shattering polymeric therapeutics that have pendant o-nitrobenzyloxyl-1-carbonyl or phenylboronic pinacol ester protecting group. The drug release can be initiated by UV irradiation or $H_2O_2$ exposure. The results of *in vitro* cytotoxicity and *in vivo* tumor cell apoptosis measurements confirmed the key function of the stimuli.[71c]

Switchable protection of some functional groups such as hydroxyl, amino, or carboxyl groups is a versatile approach for the construction of various stimuli-responsive polymers or relevant materials. Liu et al. reported a hybrid colorimetric system for the detection of $H_2O_2$ and glucose by combining the negatively charged gold NPs and a water-soluble oxidation-responsive charge-generation polymer

(CGP). Upon oxidation by $H_2O_2$ and the followed self-immolative elimination, the amino groups were uncaged and protonated in the buffer of pH 7.4 to form a positively charged polymer. The charged polymer can induce aggregation of the gold NPs, and therefore changes in UV-vis spectrum was observed in a $H_2O_2$ concentration-dependent manner (**Scheme 7, Strategy III**). This system can detect $H_2O_2$ as low as ~30 μM, and with the help of GOx, ~70 μM glucose can be sensed.[72a] The CGPs were also used to construct fluorogenic sensors for $H_2O_2$ by combining with negatively charged fluorescent dyes which possess aggregation-enhanced emission property.[72b] However, this detection system may not be ideal for *in vivo* use due to the presence of complicated (poly)electrolytes in human body. We have developed a family of pH/oxidation dual-responsive micelles that were formed by the amphiphilic block copolymers containing pendent ortho ester and phenylboronic ester groups. In the presence of $H_2O_2$, the phenylboronic ester was rapidly oxidized to release the catalytic carboxylic acid groups which can significantly increase the polarity of the micellar core, facilitate water uptake, and promote hydrolysis of the ortho ester groups. Degradation of the micellar NPs can be finely tuned by changing the copolymer composition, $H_2O_2$ concentration, and pH of the media. Importantly, some of the micellar NPs are extremely sensitive to $H_2O_2$ and able to release the payloads under trigger of a bio-relevant concentration (50 μM) of $H_2O_2$ at pH 7.4. This type of dual-responsive NPs possess great promise for anticancer therapeutics and inflammation specific drug delivery.[72c]

An appropriate biocompatibility is a key factor for biomaterials regarding their *in vivo* applications. The $H_2O_2$-induced degradation of these arylboronic ester-containing polymers generates highly active quinone methide intermediates that can react efficiently with biomolecules in principle and may cause undesired side effects *in vivo*. Recently, we reported a new type of amphiphilic poly(amino ester)s containing phenylboronic ester motifs (**Scheme 8**). These oxidation-responsive polymers are sensitive to stimulation of as low as 0.2 mM of $H_2O_2$. More importantly, the *in situ* generated quinone methides can be captured by the build-in amino groups.[73] This wok

provides a possible strategy to improve biocompatibility of the arylboronic ester-based oxidation-responsive biomaterials.




**Scheme 8.** Oxidation-responsive poly(amino ester)s containing phenylboronic ester.

## 6. Others

Thioketals can be oxidized into ketone and organic thiols (or disulfide) by superoxide or some other oxidants.[74] Recently, two thioketal-based oxidation-degradable polymers synthesized by step-growth polymerization were applied for oral delivery of siRNA to intestines and for DNA delivery to the prostate cancer cells, respectively.[75] In the former case, poly(1,4-phenyleneacetone dimethylene thioketal) was prepared by polycondensation of 1,4-benzenedimethanethiol and 2,2-dimethoxypropane, and formulated into siRNA-loaded microparticles with a diameter of ~600 nm. These NPs bind easily to the inflamed colonic mucosa and can be efficiently internalized by phagocytes.[76] Since the particles are tolerant to acid, base and proteases, they can protect the complexed siRNAs against the harsh condition of the gastrointestinal tract and deliver them to the intestinal inflammation sites. Using a murine model with ulcerative colitis, it was demonstrated that the orally delivered particles loaded with siRNA targeting tumor necrosis factor-α (TNF- α) gene can efficiently reduce the TNF-α mRNA level in the inflamed colon and exert protective effect against ulcerative colitis.[75a] In another case, thioketal units were incorporated into the backbone of a poly(amino thioketal) (PATK) which is degradable by ROS such as hydroxyl radical or superoxide. The cationic feature makes PATK capable of condensing

DNA to form polyplex NPs which can be destroyed by ROS to efficiently liberate DNA. In human prostate cancer (PC3) cells that generate high levels of ROS, DNA/PATK polyplexes dissociated effectively and liberated DNA intracellularly, showing significantly higher transfection efficiency than the non-oxidation-responsive counterpart polyplexes. Interestingly, PATK showed higher transfection efficiency in PC3 cells than in the non-cancerous Chinese hamster ovary cells that produce much lower levels of ROS; however, the oxidation-insensitive counterpart cationic polymers displayed similar efficiencies for both the cell lines. The transfection efficiency of PATK was further improved by conjugation with a peptide ligand that can be recognized specifically by tumor cells. These preliminary results demonstrate that the oxidation-responsive polymers may find potential applications for gene delivery targeted to malignant cells possessing oxidative stress.[75b] The oxidation-degradable scaffolds of poly(thioketal)-derived polyurethanes were also prepared and studied on their mechanical property, *in vitro* and *in vivo* degradation profiles, and the capability of supporting cellular infiltration and tissue formation in subcutaneous rat wounds. As compared to non-responsive poly(ester urethane) analogues, the ROS-responsive scaffolds showed a superior biological performance, which is probably due to the cell-mediated scaffold degradation that may well-match rates of tissue ingrowth.[77] Some amino acid residues of proteins undergo metal-catalyzed oxidation.[78] Particularly, proline residue is susceptible to free radical oxidation and can be oxidized by hydroxyl radicals as shown in **Scheme 1**.[79] In a recent work, oxidation-responsive, biodegradable porous scaffolds composed of PEG-*b*-polycaprolactone copolymers crosslinked by proline-containing linker were prepared using NaCl crystal as the pore-forming agent. The scaffolds are readily degradable under ROS produced *in situ* by the embedded 3-morpholinosydnonimine or activated macrophages, which was proved by scanning electron microscopy and X-ray microtomography imaging. The scaffolds can persist for weeks-to-months depending on local ROS concentration. Slow degradation of the scaffolds makes them suitable as coating materials for tissue engineering and sustained

release of inflammatory modulators at implantation site.[80]

## 7. Summary and perspective

Oxidation-responsive polymers and their relevant materials showing great potential in the biomedical field have advanced significantly in the past decade. PPS and the corresponding NPs have been extensively investigated on their synthetic strategy, self-assembly in water, oxidation-responsive property and the application as delivery vehicles of drug, antigen, and gene in the forms of micelle, polymersome and cross-linked nanoparticle. The PPS-based block copolymers or NPs demonstrate great potential for nanoparticle-facilitated vaccination and immune regulation, or as hybrid antioxidants. The selenide- or diselenide-containing polymers with different topologies have been developed and studied on their potential use as redox-responsive drug vehicles or antioxidants. The selenium-based polymers are much more sensitive to $H_2O_2$ than their sulfide-containing counterparts. Moreover, the diselenide-containing polymers may be applied as drug carriers for combination of chemotherapy with radiotherapy or photodynamic therapy. The intrinsic and selective anticancer activity makes the selenium-based polymers promising candidates, as both a polymeric drug and a delivery vehicle of anticancer drug, for combined chemotherapy.

The oxalate-based polymers consisting of both aliphatic and aryl motifs represent another important type of oxidation-responsive polymers. The HBA-derived polyoxalate micro- or nanoparticles loaded with fluorescent dyes can detect *in vitro* or image *in vivo* $H_2O_2$ in a highly sensitive and specific manner. Considering the additional ROS-scavenging and drug-loading capability, the HBA-based POXs are attractive biomaterials that can be used for theranostic nanomedicines. The exploitation of arylboronic ester-based oxidation-responsive polymers is still in their infancy. The effects of chemical structure and topology of the polymers on their oxidative degradation behaviors have not been studied systematically. However, the preliminary data demonstrate that these polymers may find applications in the fields of nanoparticulate vaccine, $H_2O_2$ detection, and selective cancer therapy.

The oxidation-responsive polymers as promising biomaterials are still far away from real applications despite of the aforementioned advances. More detailed studies are necessary regarding some basic issues such as biocompatibility, analysis of intracellular oxidation products, *in vivo* performance, and so forth. To date, most of the oxidation-responsive polymers and NPs have been evaluated only on their cytotoxicity. It is needed to evaluate the *in vivo* biocompatibility of these polymeric materials in future. Moreover, as a challenging task, the clarification of intracellular fate of these polymers in normal and malignant cells will be helpful for designing new redox-responsive nanomedicines.

Selective killing of cancer cells rather than normal cells by using proper caging groups that can be specifically activated at the diseased sites represents an attractive strategy for the development of new anticancer drugs. Although several $H_2O_2$-activated prodrugs that show potential to selectively kill cancer cells have been developed,[67c, 81] there is no report regarding polymeric prodrug that can be triggered by ROS stress. DNA interstrand crosslink (ICL)–inducing agents which can react with DNA and block its transcription and replication have been used in cancer therapy.[67a] If the ICL precursor motifs are incorporated into a polymer that can release the active ICL-inducing agents upon exposure to $H_2O_2$, one may develop a new type of polymeric anticancer prodrugs. Some small molecules, such as piperlongumine, can selectively kill malignant cells by increasing the intracellular concentration of $H_2O_2$ and nitric oxide.[6b] By combination of piperlongumine and oxidation-responsive polymeric drug vehicles, nanomedicines that target to cancer cells may be developed.

On the whole, oxidation-responsive polymers have intrinsic advantages to treat or diagnose oxidative stress-related diseases. They may also be applied as nanoparticulate imaging agents to study intracellular or in vivo redox homeostasis. Future researches of oxidation-responsive polymers are suggested to focus on elucidation of detailed degradation mechanism of the polymers and the fate of their degradation products within cells or *in vivo*, evaluation of *in vivo* biocompatibility (short term and long term),

development of different nanopaticulate formulations for various specific uses, and design of more sensitive polymer structures that well respond to low concentrations of the biologically relevant ROS.

**Abbreviations**

| | |
|---|---|
| CGP | charge-generation polymer |
| CPO | chloroperoxidase |
| DOX | doxorubicin |
| DTT | dithiothreitol |
| Flu | fluorophore |
| FTIR | Fourier Transformed Infrared |
| Gd | gadolinium |
| GOx | glucose oxidase |
| GPx | glutathione peroxidase |
| GSH | glutathione |
| HBA | 4-hydroxybenzyl alcohol |
| HEI | high-energy intermediate |
| HPOX | HBA-derived copolyoxalate |
| ICL | interstrand crosslink |
| LPS | lipopolysaccharide |
| MPO | myeloperoxidase |
| iNOS | nitric oxide synthase |
| NPs | nanoparticles |
| OH-NPs | surface-polyhydroxylated PPS NPs |
| OVA | ovalbumin |
| $ONOO^-$ | peroxynitrite |
| PATK | poly(amino thioketal) |
| PC3 | prostate cancer |
| PEG | poly(ethylene glycol) |
| PLGA | poly(lactic-co-glycolic acid) |
| POXs | polyoxalates |
| PPS | poly(propylene sulfide) |
| PUSe | selenide polyurethane |
| PUSeSe | diselenide polyurethane |
| RNS | reactive nitrogen species |
| ROP | ring-opening polymerization |
| ROS | reactive oxygen species |
| SOD | superoxide dismutase |
| TAGT | thioacyl group transfer |
| TEM | transmission electron microscope |
| THF | tetrahydrofuran |

| | |
|---|---|
| TNF-α | tumor necrosis factor-α |
| $T_g$ | glass transition temperature |
| XPS | X-ray photoelectron spectroscopy |

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