ATRP in the Design of Functional Materials for Biomedical Applications

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Abstract

Atom Transfer Radical Polymerization (ATRP) is an effective technique for the design and preparation of multifunctional, nanostructured materials for a variety of applications in biology and medicine. ATRP enables precise control over macromolecular structure, order, and functionality, which are important considerations for emerging biomedical designs. This article reviews recent advances in the preparation of polymer-based nanomaterials using ATRP, including polymer bioconjugates, block copolymer-based drug delivery systems, cross-linked microgels/nanogels, diagnostic and imaging platforms, tissue engineering hydrogels, and degradable polymers. It is envisioned that precise engineering at the molecular level will translate to tailored macroscopic physical properties, thus enabling control of the key elements for realized biomedical applications.

Keywords: Atom Transfer Radical Polymerization (ATRP), drug delivery, biomedical engineering, biomaterials, imaging, nanoparticles, nanogels, tissue engineering, bioconjugation, polymeric micelles, polymer grafting, functionality, block copolymers, bioactive surfaces

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1. Introduction

Functional polymeric materials are essential components of a variety of biological and biomedical applications including drug delivery, tissue engineering, and medical imaging.[1-4] In nature, proteins exist as an example of perfect polymers. They are composed of precisely placed amino acids with controlled polymer composition, chemical properties, functionality, molecular weight (MW), and monodisperse molecular weight distribution (MWD). A long-standing goal in polymer science is to approach nature's order by aiming to synthesize polymers with as much control as possible[5, 6], where precision engineering at the molecular level can lead to optimal macroscopic physical properties.

Despite the long history of biomedical engineering, polymers used in these applications have historically been polydisperse, with limited control over functionality and architecture.[4, 7] In early stages of development, biomaterial selection focused on inertness and on mimicking the physical properties of the damaged tissue. Later development included design to illicit a specific biological response.[8] Meanwhile, polymer chemistry has experienced increased sophistication in terms of what can be controlled. "Smart" polymers with stimuli-sensitivity, new architectures, and greater control over MW and MWD have driven polymer research over the last 10-15 years.[5, 9, 10] In this context, it is logical that advanced synthetic techniques that can construct precision materials will lead to new applications and uses in biomedical engineering.

Atom Transfer Radical Polymerization (ATRP)[11-15] is one of the most powerful and versatile Controlled Radical Polymerization (CRP) processes. It enables precise control over MW, MWD, and functionality.[16] It can be carried out in a variety of different solvents and conditions, including water at room temperature, and is tolerant of most functional groups. The polymerization conditions and parameters can be tuned, providing control over reaction kinetics. In addition to homogeneous and heterogeneous solution polymerization, polymers can be grown from surfaces, proteins, organic materials, and inorganic materials including nanoparticles (NPs).[17] It is useful in the construction of hydrogels with uniform mesh size, in imaging, diagnostics, and biosensors. In some applications, new ways to enable degradability of ATRP-produced polymers may be required, and multiple strategies have been developed

to render ATRP-produced polymers degradable. Therefore, ATRP is especially well suited to bridge controlled polymer synthesis with biomedical applications. This article reviews recent advances in the preparation of effective multifunctional nanomaterials using ATRP for drug delivery, tissue engineering, and medical imaging applications.

1.1 Method and mechanism of ATRP

ATRP was first reported in seminal 1995 publications.[11, 18] It has strongly influenced the development of many fields of polymer science, invigorating great interest in controlled polymerizations. The interface of ATRP with biology has always been one of the most attractive areas for applications due to ATRP's robust nature and ability to grow polymers from a variety of surfaces. The essential feature of ATRP[11, 12, 18-23] is the equilibrium between a low concentration of active propagating species and a larger number of dormant chains, via an inner sphere electron transfer process promoted by a transition metal complex (**Figure 1a**).[24, 25] As with conventional free radical polymerization, the generated radicals propagate and terminate with rate constants k_p and k_t. In ATRP however, the radicals are generated through a reversible redox process catalyzed by a transition metal complex (M_t^n-Y/Ligand, where Y may be another ligand or the counter ion) which undergoes a one electron oxidation with concomitant abstraction of a (pseudo)halogen atom, X, from a dormant species, R-X. This process occurs with rate constants of activation k_{act}, and deactivation k_{deact}. Upon addition of the intermediate radicals to monomers, polymer chains grow with the rate constant of propagation k_p. Termination reactions (k_t) also occur in ATRP, mainly through radical coupling and disproportionation. However, a very small percentage of polymer chains undergo termination in a well-controlled ATRP. This is due to the low concentration of active propagating radicals and higher concentration of dormant species, which minimizes termination. Although copper is most commonly used metal catalyst in ATRP, iron compounds, which are generally considered to be less toxic, can also be used.[26-29] In addition to normal ATRP, the development of Activator Generated by Electron Transfer (AGET) ATRP,[30] which enables polymerizations to be conducted without freeze-pump-thaw cycles, has poised AGET ATRP to be carried out by biologists and other scientists in jars on the bench top (**Figure 1b-f**).[31] In addition, Activators Regenerated by Electron Transfer (ARGET) ATRP[32, 33] has reduced the amount of required copper catalyst to ppm levels. Application of electrochemistry to ATRP could be another breakthrough that will enable expansion to new applications.[34] Overall, ATRP has witnessed remarkable growth and exploration in the past 15 years, and is poised to continue its usefulness in biomedical applications.

(Insert Figure 1)

Figure 1. (a) The mechanism of transition metal-catalyzed ATRP. (b) Proposed mechanism of ARGET ATRP in the presence of limited amounts of air.[31] Typical setup for grafting polymer chains from silicon wafers using ARGET ATRP with limited air (c) in a large jar and (d) in a sample vial. (e) Illustration of procedures for surface-initiated ARGET ATRP with limited air. (f) Relationship between the grafted poly(butyl acrylate) (PBA) brush thickness measured in air by ellipsometry and M_n of free PBA polymers. In this example, it was demonstrated that polymers could grow with or without stirring. It was also shown that the polymerization could be stopped and re-started with continued growth of PBA chains, or extension of the chains by polystyrene. Adapted from reference[31] with permission of ACS Publications.

2. Polymer bioconjugates

Advances in biotechnology have led to a growing number of peptide-, protein-, and antibody-based drugs. The main issues with this set of drugs are a short plasma half-life, poor stability, and immunogenicity. Polymers can enable delivery of these drugs. Moreover, ATRP has the potential to be a major part of the new wave of polymer conjugates are being created that can be collectively called polymer therapeutics.[2] This term is used to describe polymeric drugs,[35] polymer-drug conjugates,[36] polymer-protein conjugates,[37, 38] polymeric micelles to which the drug is bound,[39] and multi-component polyplexes developed as non-viral vectors.[40] Polymer therapeutics can be closely compared to macromolecular drugs (proteins, antibodies, oligonucleotides) and macromolecular prodrugs including immunoconjugates.[2] ATRP and other CRP methods have been explored as a tool to prepare well-controlled polymer-peptide/protein bioconjugates.[41-43]

The process of grafting polymer chains from, to, or onto surfaces can impart new properties to materials in carefully controlled ways. It is an essential technique for the delivery of many drugs[44] and biomolecules.[41, 42] Because ATRP can provide site-specific grafting to a variety of surfaces (essentially any surface containing an ATRP initiator), it is a great method for preparing polymer-grafted materials. Compared to other radical grafting methods, ATRP also minimizes radical-radical coupling at the surface due to site-specific initiation and the ATRP equilibrium, which reduces the radical concentration and thereby reduces termination. The low concentration of persistent radical (deactivator) on the surface, which can lead to rapid initiation and propagation of the growing tethered chain, can be overcome by addition of a sacrificial initiator or external addition of a persistent radical/deactivator. ATRP offers opportunities to improve bioconjugation due to the wide range of polymerizable monomers that can impart new physical properties to the bioconjugate, facile incorporation of functional groups, and the variety of methods for precise conjugation

2.1 PEGylation and bioconjugation

The first example of “PEGylation” was reported in 1977,[45] where methoxy-terminated polyethylene glycols were covalently attached to bovine liver catalase. This resulted in enhanced circulating times in the blood without evidence of an immune response, and stimulated great interest in polymer conjugation in drug and biomolecule delivery. Historically, most polymer grafting was performed using the “grafting to” method. Alternatively, “grafting from” ATRP can provide much greater grafting density, and precise control over grafting location. It is therefore poised to significantly impact a number of areas, including polymer bioconjugation.

Although PEGylation has led to a number of polymer-protein conjugates on the market and in development,[2] advanced polymerization techniques offer opportunities for improvement. The traditional route of bioconjugation involves synthesizing an end-functional polymer and coupling it to a protein. This suffers a major drawback, where two large molecules must react via two small reaction centers immobilized on long chains, often leading to incomplete functionalization. In contrast, ATRP enables conjugation via “grafting from”, where the polymer can be grown from the protein or drug with high site specifically and degree of functionalization.

In addition to the methods of conjugation described in this section, ATRP offers a wide range of polymer possibilities. It is tolerant to most functional groups and can polymerize a diverse set of monomers. PEG mimics, such as acrylates and methacylates with PEG side chains,[41, 46-49] are one of the most attractive classes of ATRP-polymerizable monomers.[50, 51] Zwitterionic monomers are another important area of research, with growing interest for various biomedical applications.[52-54] Both monomer classes can reduce non-specific protein absorption and can increase blood circulation times of polymer bioconjugates.

To enable efficient conjugation, improved chemical reactions are often required. For this purpose, the application of click chemistry[55] to polymer science[56-58] has led to improvements in bioconjugation and opportunities for carrying out reactions in challenging conditions, including *in vivo*.[59-61] Because all polymers chains synthesized by ATRP contain a halogen at the end, conversion of the halogen to azide is

simple and efficient. This is one advantage of ATRP over other CRP methods. Many reports have shown that azide groups can be conjugated to a variety of alkyne-functionalized materials via click chemistry.[57, 58]

2.2 "Grafting from" surfaces, peptides, and proteins using ATRP

Because polymers can be grown from nearly any surface or material that has an ATRP initiating group attached to it, ATRP is well suited for the synthesis of polymer bioconjugates. Polymerization from ATRP initiators containing proteins and short peptide sequences offers an attractive route to produce polymer-protein bioconjugates. Peptide sequences,[62-65] biotin,[66, 67] and proteins such as chymotrypsin,[68] streptavidin[69] and bovine serum albumin (BSA)[70] have been successfully modified to become ATRP initiators (**Figure 2)**. By attaching an ATRP initiating group to biotin[67] and streptavidin,[69] polymer bioconjugates were synthesized in one step. Similarly, poly(*N*-isopropylacrylamide) (PNIPAAm) was grown from BSA, as a model protein, using ATRP.[70] This method resulted in a temperature-sensitive bioconjugate that retained bioactivity. Polymer chains functionalized with biotin, either by "grafting from" or by end group displacement, can also be used as injectable hydrogels upon mixing with streptavidin.[71] Fmoc-protected amino acid building blocks with ATRP initiator functionalities have also been reported.[65] This enabled site-specific incorporation of peptides into polymers and the synthesis of glycopolymer-peptide conjugates.

When "grafting from" ATRP is used for the preparation of peptide-functionalized polymers,[49,50] the attached peptide may have utility in cell attachment to polymer surfaces, or for *in vivo* targeting when used for drug delivery. Gly-Arg-Gly-Asp-Ser (GRGDS)-functionalized poly(2-hydroxyethyl methacrylate) (PHEMA) was synthesized by growing HEMA from a resin supported peptide (**Figure 2a**).[62] After cleavage from the resin, the polymer was cast onto a surface and demonstrated improved cellular adhesion compared to unmodified PHEMA. In another example, the peptide was functionalized with an ATRP initiating group and then cleaved from the bead.[63] Solution phase ATRP was then carried out to prepare the peptide-polymer biohybrid. Low polydispersity and complete functionalization were achieved, illustrating two of the major advantages of this method over traditional PEGylation.

The rapid clearance from systemic circulation is a major obstacle for protein drugs. By combining protein and polymer engineering, polymers have been carefully grown from the N-terminus[72] and C-terminus[73] of proteins to prolong circulation times and enhance drug accumulation in tumors (**Figure 2d**). This elegant process provides a more careful construction of PEGylation, achieving 100% of functionalized protein with high bioactivity. To eliminate multiple attachments of polymers to the protein, a single ATRP initiating group was placed at the terminus of the protein. A long bottlebrush composed of poly(oligo(ethylene oxide) monomethyl ether methacrylate) (POEOMA) was polymerized from the protein. This increased the hydrodynamic radius from 3 to 20 nanometers, with a nearly 300-fold increase in hydrodynamic volume, and ultimately translated to increased circulation times and tumor accumulation.

In another example, a genetically encoded initiator was used for site-specific polymer growth from proteins.[74] An unnatural amino acid, 4-(2′-bromoisobutyramido)phenylalanine, was designed as an initiator for ATRP that would provide a stable linkage between the protein and growing polymer (**Figure 2e**). It was incorporated into green fluorescent protein (GFP) and then used as an initiator under standard ATRP conditions to polymerize OEOMA, efficiently producing a polymer−GFP bioconjugate. In another manifestation, this chemistry was used to produce a GFP protein-nanogel hybrid with preservation of the protein structure.[75]

(Insert Figure 2)

Figure 2. Examples of polymer bioconjugates prepared by ATRP using functional initiators. (a) HEMA was polymerized by ATRP from an Initiator-S(tBu)D(tBu)GR(Pbf)G Wang Resin. After cleavage from the resin, GRGDS-functionalized PHEMA promoted cell adhesion.[62] (b) A biotinylated ATRP initiator was used for

the polymerization of PNIPAAm from streptavidin.[69] This approach yielded a temperature-sensitive polymer-protein bioconjugate. In an earlier report, it was used to prepare biotinylated PNIPAAm in one step.[67] (c) Monomethoxy poly(ethylene glycol)-methacrylate was polymerized from 2-bromoisobutyramide derivatives of chymotrypsin as a protein-initiator, resulting in the conjugate containing a single, near-monodisperse polymer chain per protein molecule with polydispersity index 1.05.[68] This site-specific initiation was better than a conventional approach, where multiple chains are randomly grafted to the protein. (d) POEGMA with low polydispersity and high yield, was grown solely from the N-terminus of the protein by in situ ATRP under aqueous conditions from myoglobin, to yield a site-specific (N-terminal) and stoichiometric conjugate (1:1).[72] The myoglobin-POEGMA conjugate showed a 41-fold increase in its blood exposure time compared to the unmodified protein after intravenous administration to mice. (e) A genetically encoded initiator (via the amino acid 4-(2′-bromoisobutyramido)phenylalanine) was used as an ATRP for the site-specific polymer growth of POEOMA from GFP.[74] This figure contains elements from selected references [62, 68, 69, 72, 74], with permission of ACS Publications and the National Academy of Sciences, USA.

2.3 “Grafting to/onto” surfaces and proteins using ATRP

Since ATRP allows for the synthesis of polymers with defined reactive end groups, it is an attractive route for the synthesis of polymer conjugates via “grafting to.” For example, catechol-functionalized ATRP initiators may provide facile attachment to surfaces.[76] Thiol[77] and hydroxyl[71] groups can also be used for bioconjugation. HEMA was functionalized with the elastin-like peptide tropoelastin Val-Pro-Gly-Val-Gly (VPGVG) and homopolymerized by ATRP. It was also polymerized from a α,ω-di-functionalized PEG macroinitiator to form an ABA triblock copolymer.[78] This block copolymer displayed lower critical solution temperature (LCST) exhibited by the peptide sequence due to a transition from random to β-spiral at 40º C.

In addition to applications in drug and protein delivery, site-specific conjugation using well-defined polymers also allows for the modulation of protein binding and recognition properties and is a powerful strategy for mediating the self-assembly of synthetic polymers.[79] In this context, synthetic polymer-protein conjugates show promise for use in bioanalytical applications and bioseparations.

3. Drug delivery systems

The poor water solubility of hydrophobic drugs and systemic toxicity are two of the main limits to therapeutic efficacy of conventional small molecule drug therapeutics. Non-specificity of conventional chemotherapeutics results in side effects and toxicity toward healthy tissues. Targeted drug delivery systems have been extensively explored as effective means to deliver therapeutics to cells. A variety of effective polymer-based drug delivery systems have been proposed. Typical examples include polymer-protein conjugates,[38] polymer-drug conjugates,[44, 80] micelles[81-84] and vesicles[85, 86] based on amphiphilic and doubly-hydrophilic block copolymers, dendrimers,[87] NPs,[88, 89] and cross-linked microgels/ nanogels.[90-92] A variety of polymers for gene delivery synthesized by CRP methods have also been reported and summarized in other reviews.[93-95] This section describes how ATRP has been used to develop well-defined amphiphilic block copolymer-based micelles and nanogels/microgels.

3.1 Amphiphilic block copolymer micelles

Amphiphilic block copolymers consist of both hydrophobic and hydrophilic blocks covalently connected each other. Because of the different solubility of each block in selective solvents, amphiphilic block copolymers self-assemble in water to form micelles. A hydrophobic inner core, capable of carrying a variety of hydrophobic therapeutics, is surrounded with hydrophilic corona, ensuring water solubility and biocompatibility of the micelles. These polymeric micelles offer many advantages as effective drug delivery systems[96, 97] including 1) facile preparation, 2) colloidal stability with low critical micelle concentration

(CMC), 3) tunable sizes with narrow size distribution, 4) the ability to protect drugs from possible deactivation and preserve their activities during circulation, and intracellular trafficking, 5) improved pharmacokinetics, and 6) high physical loading efficiency of drugs without chemical modification.

A variety of well-defined amphiphilic block copolymers with narrow MWDs have been prepared.[98-100] The preparation of amphiphilic block copolymers consisting of naturally occurring polysaccharides has been summarized in other reviews.[101, 102] Hydroxyl groups of polysaccharide chains were modified with 2-bromoisobutyryl bromide to form ATRP macroinitiators. A few examples of polysaccharide-terminated block copolymers have been reported, including oligosaccharide-b-poly(methyl methacrylate)[103] and dextran-b-polystyrene.[104] Aliphatic polyesters based on hydroxyalkanoic acids, such as polylactide (PLA), polycaprolactone (PCL), polyglycolide (PGA), and their copolymers are biodegradable and generally prepared by ring opening polymerization (ROP).[105-110] These copolymers have potential for the use in pharmaceutical and biomedical applications as sutures, implants for bone fixation, drug delivery systems, and tissue engineering scaffolds.[105, 107, 111] ATRP has been utilized to prepare well-defined polyester-based amphiphilic block copolymers with hydrophilic poly(meth)acrylates, including poly(2-methacryloyloxyetheyl phosphorylcholine),[112] poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA),[113-115] and PHEMA.[116]

Consecutive ATRP has been explored for the preparation of poly(meth)acrylate-based amphiphilic block copolymers.[117] In the approach, terminal bromine-bearing poly(meth)acrylates are prepared by ATRP, which can be purified and used as macroinitiators for consecutive ATRP, yielding amphiphilic block copolymers. Block copolymers of styrene (Sty) and a protected tetra-*O*-acetyl-β-$_D$-glucose monomer have been prepared by ATRP.[118] After polymerization, the hydroxyl groups on the resulting polymer were deprotected by hydrolysis. ATRP of unprotected glycomonomers has also been reported.[119-121] The ring structure of $_D$-gluconolactone was opened with 2-aminoethyl methacrylate to give the monofunctional 2-glucanoamidoethyl methacrylate (GAMA). Block copolymers were subsequently made by using a halogen ester functionalized PEO as macroinitiator. To obtain a glycopolymer where the ring structure of the saccharide was preserved, 2-aminoethyl methacrylate was reacted with lactobionolactone to give 2-lactobionamidoethyl methacrylate (LAMA). Homopolymers were prepared via an aldehyde-terminated initiator. Functionalized poly(propylene oxide) (PPO) macroinitiators were used to prepare P(PPO-b-LAMA) copolymers, and by the sequential polymerization of a LAMA block followed by growth of a 2-(diethylamino)ethyl methacrylate (DEAMA) to obtain a P(LAMA-b-DEAMA) copolymer. The P(LAMA-b-DEAMA) copolymers were able to undergo reversible micelle formation with changes in pH. At pH < 6, the polymer chains were completely dissolved, as the amine groups on the PDEAMA block were protonated, whereas by deprotonating the PDEAMA blocks by increase in pH, micelles were formed with the more hydrophobic PDEAMA block in the core and the hydrophilic PLAMA block in the shell. Synthetic glycopolymers exhibiting these types of dynamic response are of potential significance as feedback-controlled drug release materials.[122] One of the best advantages of the ATRP method is that functionality in the initiator group is retained at the chain end. This benefit of ATRP was used to prepare a maltoheptose-terminated polymer.[103] The potential recognition properties of glycopolymers prepared by ATRP were probed by investigating the binding to lectins immobilized on HPLC stationary phases. Galactose containing copolymers with PEG-methacrylates and benzyl methacrylate were found to bind strongly to immobilized RCA-1 lectin, whereas the corresponding protected galactose copolymer and a glucose containing copolymer displayed no affinity for the stationary phase.[123]

Stimuli-responsiveness has been introduced for the design and development of block copolymer micelles via several approaches.[124-126] One approach involves the design of double-hydrophilic block copolymers having a stimuli-responsive block.[86] These block copolymers can form micelles in response to external stimuli, such as pH and temperature.[127] An example is the pH-responsive block copolymer of poly(glycidol-b-poly(4-vinylpyridine)). The polyglycidol block is water-soluble, while poly(4-vinylpyridine) is soluble in acidic pH, but aggregates in basic pH. Hence, the block copolymer forms micelles of poly(4-vinylpyridine) core surrounded with polyglycidol corona in basic water.[128] Another approach involves the design of amphiphilic block copolymers with a hydrophobic pendent cleavable block. Examples of pendent cleavable groups include cyclic orthoester groups (in response to acidic pH)[129] and light-responsive groups such as pyrenylmethyl,[130] o-nitrobenzyl,[131] coumarin,[132] and spiropyran[133] groups (responsive to UV illumination). These block copolymers form micelles with cleavable blocks as a core in

water, but the formed micelles can be disrupted in response to external stimuli (acidic pH and light) upon cleavage of hydrophobic pendent groups of the block copolymers. Such degradation upon external stimuli ensures controllable release of drugs. **Figure 3** illustrates an example of changing hydrophilic-hydrophobic balance of a light-sensitive block copolymer.[134, 135] Coumarin-containing block copolymer micelles are further cross-linked through photodimerizaion of coumarin rings when a visible light is illuminated, yielding core cross-linked micelles. This photodimerization is reversible, such that the cyclobutane dimer can be cleaved upon illumination of UV light.[136, 137] Another approach for stimuli-responsiveness involves the design of stimuli-responsive degradable amphiphilic block copolymers with cleavable linkages within the polymer backbone using ATRP. For example, degradable polyester-based copolymers with multiple disulfide groups positioned between the hydrophobic polymer segments were synthesized by a combination of polycondensation and ATRP.[138] These copolymers formed stable micelles above a CMC of 8-12 μg/mL. Cleavage of the disulfide groups in a reducing environment caused colloidal instability, leading to release of encapsulated model drugs. Core cross-linked multi-star assemblies bridged with disulfide linkages were synthesized by ATRP in the presence of disulfide-labeled PMMA telechelic macroinitiators.[139] Finally, the synthesis and assembly/disassembly of thiol-responsive micelles of symmetric triblock amphiphilic block copolymers has been reported,[140] where micelle disruption was visualized by AFM.

(Insert Figure 3)

Figure 3. Schematic illustration for changing hydrophilic-hydrophobic balance of light-sensitive block copolymers by illumination. Adapted from reference [134] with permission of RSC Publishing.

3.2 Cross-linked microgels/nanogels

Micro-/nanogels are cross-linked hydrogel particles that are confined to micro- or nanoscopic dimensions.[141-143] For drug delivery applications, key features including high water content/swellability, biocompatibility, and adjustable chemical/mechanical properties are particularly attractive. The large surface area provides space for functionalization and bioconjugation. The size of the nanogels[144, 145] can be tuned to an optimal diameter for increased blood circulation time *in vivo* after IV administration. Smaller diameter (<200 nm) enables better cellular uptake and reduced NP uptake by mononuclear phagocyte system (MPS).[146, 147] Finally, the interior network allows for encapsulation of therapeutics. Physical entrapment of bioactive molecules (including drugs, proteins, carbohydrates, and nucleic acids in the polymeric network) and their *in vitro* release kinetics have been extensively investigated. In addition, the incorporation of inorganic materials has been reported. Examples include quantum dots[148, 149] and magnetic NPs[150, 151] for optical and magnetic imaging, and gold nanorods for photodynamic therapy.[152]

CRP techniques have been utilized for the synthesis of gels[153-163] and cross-linked NPs of well-controlled polymers in the presence of cross-linkers.[48, 71, 91, 164-168] Hydrogel NPs of PNIPAAm were prepared by precipitation polymerization via ATRP in water.[169] OEOMA, an analog of PEG has been polymerized by AGET ATRP in homogenous aqueous solution[170] and in heterogeneous conditions.[48] In this context, biodegradable cross-linked nanogels of well-controlled hydrophilic polymers were synthesized using ATRP in inverse miniemulsion in the presence of a disulfide-functionalized dimethacrylate (DMA) cross-linker.[48] The nanogels preserved a high degree of halide end-functionality that enabled further functionalization, including chain extension to form functional block copolymers. The nanogels were nontoxic to cells and degraded in a reducing environment to individual polymeric chains with a relatively narrow MWD ($M_w/M_n < 1.5$), indicating the formation of a uniformly cross-linked network within the NPs. This uniform structure is expected to improve controlled release of encapsulated species. The measured swelling ratio, degradation behavior, and colloidal stability of nanogels prepared by ATRP were superior to those prepared by conventional free radical inverse miniemulsion polymerization. In

another report, these nanogels were loaded with doxorubicin (Dox), an anticancer drug.[164] The nanogels released Dox *in vitro* upon exposure to glutathione, which degraded the nanogels. Glutathione has been reported to exist in cells at mM concentrations,[171-174] which could serve as the releasing agent *in vitro* and *in vivo*. Rhodamine isothiocyanate-labeled dextran (RITC-Dx) was also encapsulated as a model water-soluble biomacromolecular carbohydrate drug.[165] Specific binding of released RITC-Dx from nanogels upon degradation was demonstrated by interaction with lectins such as Concavalin A (ConA) in water.

Since ATRP results in polymers with a high degree of halide end-functionality, facile functionalization with various molecules is possible. When preparing functional nanogels using ATRP in inverse miniemulsion, functional ATRP initiators such as 2-hydroxyethyl 2-bromoisobutyrate (HOEtBriB)[71] and copolymerization with functional monomers offer two approaches towards bioconjugation. Hydroxyl-functionalized nanogels have been prepared using HOEtBriB and by copolymerizing with 2-hydroxyethyl acrylate (HEA). The nanogels were then conjugated with biotin, and further bioconjugated with fluorescein isothiocyanate (FITC)-labeled avidin. The number of biotin molecules in each nanogel was determined to be 142,000 and the formation of bioconjugates of nanogels with avidin was confirmed using optical fluorescence microscopy.[164] The uniform network of POEOMA nanogels prepared by ATRP in inverse miniemulsion enables encapsulation of a range of molecules, including gold NPs, BSA, RITC-Dx, and fluorescein isothiocyanate-dextran (FITC-Dx).[166] The control over functionality that ATRP provides was utilized to functionalize the nanogels with peptides (**Figure 4a**). Flow cytometry experiments showed that peptide functionalization increased cellular uptake *in vitro*.[166, 175] FITC-Dx-loaded nanogels were also able to effectively internalize into a spheroidal co-culture of human umbilical vascular endothelial cells (HUVECs) and human mesenchymal stem cells (hMSCs), which validated cellular endocytosis into a more complex system (**Figure 4b**). One future goal of nanogel research should be the improved design of micro-/nanogels with specific targeting residues to enable highly selective uptake into specific cells, particularly cancer cells. Polymer chemists and biologists can learn from each other to elucidate the specific interactions between biomolecules and cellular integrin receptors, which in turn can be carefully attached to advanced delivery systems. Through collaboration, advanced nanogels with careful control over stability, size, biodegradability, and functionality for bioconjugation can be realized.

(Insert Figure 4)

Figure 4. Preparation of stable nanogels of well-controlled POEOMA with low polydispersity. (a) The inclusion of RITC-Dx molecules inside of the uniform POEOMA network (gray bars) functionalized with GRGDS peptides is schematically illustrated. (b) Merged fluorescent confocal images of co-culture cell spheroids cultured in the presence of FITC-Dx-loaded nanogels with GRGDS after 2 hours of incubation. The cell nuclei have been stained blue, and the nanogels are green. (c) The optical section shown was taken at 28 μm cell depth into the co-culture spheroid. Adapted from reference[166] with permission of ACS Publications.

4. Diagnostic and imaging platforms

Colloidal inorganic NPs (or nanocrystals) have attracted interest as building blocks for the development of advanced nanomaterials in nanoscience, nanotechnology, and biotechnology. This is because inorganic nanocrystals have unique electronic and optical properties. Thus, they have been explored as diagnostic and imaging platforms for biological and biomedical applications. Typical examples include superparamagnetic iron oxide nanoparticles (SNPs) for magnetic resonance imaging (MRI);[176-181] quantum dots (QDs) for fluorescent imaging of living cells;[182-185] and gold nanorods for photodynamic therapy.[152] Towards these biomedical applications, one of the requirements for these nanocrystals is water solubility or water dispersibility. The general way to achieve this is the modification of nanocrystalline surfaces with water-dispersible ligands.[186] The ligands that have been widely explored are small organic molecules and biomolecules having one or two anchoring sites (called monodentate or

bidentate). For example, well-defined CdSe QDs were synthesized by a thermal decomposition of organometallic precursors in hot organic coordinating solvents, typically trioctyl phosphine oxide (TOPO), at high temperature.[187, 188] As a consequence, native QDs stabilized with organic TOPO layers are not soluble in water or protic solvents. In order to render TOPO-capped QDs to be water-soluble, one approach is the ligand exchange of TOPO stabilizing ligands with various water-soluble thiols including mercaptoacetic acid,[189] cysteine,[190] and dihydrolipoic acid (DHLA).[191, 192] In general, the anchoring groups include sulphur (S), nitrogen (N), oxygen (O), and phosphorous (P).

Polymers, compared with mono- and bidentate ligands, can act as multidentate ligands with more than one group capable of binding to the surface of metal NPs, thus enhancing the properties of inorganic nanocrystals. Most polymers are transparent in the visible range of electromagnetic spectrum, and therefore do not interfering with biological processes and imaging modes. In addition, polymers provide mechanical and chemical stability to the nanomaterials. Furthermore, polymeric particles and micro-/nanogels enable the encapsulation of therapeutics and imaging agents such as nanocrystals for drug delivery system to specific cells.[92, 193] Several approaches to prepare polymeric inorganic nanomaterials using ATRP have been reported.

One approach involves the direct adsorption of block copolymers onto nanocrystals during and after the synthesis of nanocrystals. This approach requires the synthesis of well-controlled multifunctional block copolymers consisting of a block with pendent anchoring groups that enable binding to nanocrystals surfaces. CdSe/ZnS core/shell QDs were passivated with well defined P(EG-b-DMAEMA) via ligand exchange, yielding water-soluble CdSe/ZnS QDs. ^{31}P-NMR spectroscopy was used to characterize the ligand exchange. No P signal was observed for purified TOPO-capped QDs. When P(EG-b-DMAEMA) block copolymer was added, sharp P signals appeared at 30-50 ppm, corresponding to free TOPO released from the QD surfaces.[194-196] In addition, pyrene-end-functionalized PDMAEMA was used to quantify the ligand exchange using gel permeation chromatography (GPC).[197] SNPs were synthesized by co-precipitation of Fe(II) and Fe(III) ions in the presence of poly(OEOMA-b-(methacrylic acid)) (P(OEOMA-b-MAA)), which was yielded by hydrolysis of P(OEOMA-b-(t-butyl acrylate)). The PMAA block was anchored to the SNP surface and the POEOMA block rendered the assembly water-dispersible and biocompatible. These SNPs stabilized with P(OEOMA-b-MAA) could be useful as MRI contrast agents.[198] Surface-initiated ATRP yields a brush-like morphology. This approach requires the immobilization of ATRP initiating groups on nanocrystal surfaces. Two routes for immobilization of halide-initiating species have been reported. One route involves the physical absorption of acid-functionalized halides on SNPs. They include 2-chloropropionic acid,[199, 200] 2-bromoisobutyric acid,[201, 202] and 10-carboxydecanyl-2-bromo-2-methyl-thiopropanoate,[203] to yield single SNPs coated with hydrophobic polystyrene or water-soluble POEOMA. The other route involves the covalent attachment via silanization.[204-206] Examples of this route include the immobilization of 2-(4-chlorosulfonylphenyl)ethyltrichlorosilane for PMMA,[207] [11-(2-bromoisobutyryloxy]undecyltrichlorosilane for PSt,[208] and [4-(chloromethyl)phenyl]trichlorosilane for POEOMA.[209] Another approach involves silanization that requires the preparation of copolymers bearing trimethoxysilyl groups capable of cross-linking reactions on SNPs. One example includes copolymers consisting of poly((3-trimethoxysilyl)propyl methacrylate) and poly(*N*-acryloxysuccinimide) (PNAS).[210] Since CRP methods enable dyes to be easily incorporated,[211] the PNAS block was further functionalized with Cy5.5 fluorescent dye for *in vivo* tumor detection by dual magnetic resonance and fluorescence imaging.[212]

In contrast to the three approaches above that lead to hybrid nanomaterials consisting of a single metal core surrounded with a shell layer, the next two approaches allow for the preparation of another type of hybrid nanomaterial, in which nanocrystals are embedded inside. The first approach involves the self-assembly of amphiphilic block copolymers in the presence of hydrophobic nanocrystals. This approach enables the preparation of core-shell nanoparticles consisting of hydrophobic inner core embedded with nanocrystals, surrounded with hydrophilic corona. One example is the synthesis of well-controlled poly(lactide-b-OEOMA) (P(LA-b-OEOMA)) amphiphilic block copolymer by a combination of ROP and ATRP from 2-hydroxyethyl-2'-bromoisobutyrate, a difunctional initiator. The copolymer self-assembled in the presence of Fe_3O_4 NPs, and was further functionalized with folate for cell targeting.[213] The other approach is the incorporation of nanocrystals into cross-linked microgels, nanogels, or hydrogels. It has been reported that the gel network prepared by ATRP is uniform, exhibiting higher swelling behavior in

solvents including water, compared to counterparts of free-radical polymerization.[48] Such high swelling leads to increased pore sizes in gels, facilitating loading and release of NPs (<50 nm). Gold NP (AuNP)-loaded nanogels were prepared by mixing AuNPs dispersed in water with hydrophilic POEOMA-based nanogels prepared by ATRP of OEOMA in inverse miniemulsion. The AuNP-loaded nanogels were then cultured with MC3T3 cells and TEM was used to image the ultra-section of cells with internalized AuNP-nanogels.[166] In another example, thermo-responsive magnetic degradable microgels were prepared by stirring oleic acid-stabilized Fe_3O_4 NPs with disulfide-functionalized microgels of poly(di(ethylene glycol) methyl ether methacrylate) ($PM(EO)_2MA$) prepared by ATRP in miniemulsion. These disulfide-functionalized microgels are designed to be degradable in the presence of reducing agents such as glutathione. $P(M(EO)_2MA)$-based microgels are designed to respond to temperature, exhibiting volume change at LCST. **Figure 5** illustrates the scheme for the preparation of these thermo-responsive magnetic degradable microgels. Thermogravimetric analysis was used to determine the MNP content in the microgels to be 12%. Rhodamine B as a model for hydrophilic drugs was loaded to study the release kinetics in response to temperature and thiols.[214] Thermo-responsiveness has also been explored for PNIPAAm grafted nano- and microparticles.[215]

(Insert Figure 5)

Figure 5. (a) Schematic illustration for the preparation of $PM(EO)_2MA$-based magnetic degradable microgels and images of their aqueous solutions at 40 °C (b), in ice bath without (c) and with an applied magnetic field (d).[214] Reproduced from reference [214] with permission of ACS Publications.

5. Tissue engineering hydrogels and bioactive surfaces

Polymeric scaffolds play an important role in tissue engineering. They can mimic the roles of extracellular matrixes found in tissues, regulating the function of cells, and allowing the diffusion of nutrients, metabolites, and growth factors. To function properly in the body and promote new tissue formation, polymers for tissue engineering must be biocompatible and degradable, while still maintaining certain physical properties helpful to cell growth. By molecular modification, polymer systems equipped with signals such as growth factors can generate specific interactions with cellular components and thereby direct cell proliferation, differentiation, and extracellular matrix production and organization.[7]

One challenge is to create biodegradable polymeric materials with appropriate mechanical properties that can be modified to incorporate biological activity, such as growth factors and structural adhesive proteins.[216, 217] These polymers can be natural materials such as collagen gels, intestinal submucosa, and carbohydrate-based hydrogels. Alternatively, polymer scaffolds can be made from synthetic materials, and combinations of natural and synthetic materials. Synthetic materials offer the greatest range of physical properties and functionalities. Additionally, the mechanical characterization of materials for tissue engineering must be understood to tailor physical properties with the needs of the application. Finally, new ways to process materials into three-dimensional structures, and how to populate these structures with surface-bound biological signaling is also needed to construct advanced biomaterials.

5.1 Bioactive surfaces

The interaction of cells to material surface properties is an important issue for cell adhesion, growth, signaling, and differentiation. Material surface chemistry and physical properties have a defining

impact and present opportunities for various applications. ATRP has been used in a number of ways to prepare bioactive surfaces.[218, 219] For example, surface-initiated ATRP was used to graft POEOMA from magnetic NPs.[209] The uptake of NPs by macrophage cells *in vitro* was greatly reduced from 158 pg/cell to <2 pg/cell after grafting with POEOMA. Grafting of polymer chains to a variety of NPs can greatly affect their interaction with cells.

In an example of using ATRP for smart cell culturing surfaces, thermo-responsive and biocompatible oligo(ethylene glycol)-based copolymers were grafted onto planer gold substrates, which enabled control of cell adhesion.[220] At physiological temperature, the polymer brushes are collapsed and enable fibroblast adhesion and cultivation. While at room temperature, the hydrated oligo(ethylene glycol) segments become cell-repellent, thus allowing cell harvesting under mild conditions (**Figure 6**).

(Insert Figure 6)

Figure 6. DIC microscopy images of L929 mouse fibroblasts on poly(OEGMA-co-MEO2MA)-modified gold substrates after 44 h of incubation at 37° C (a) and 30 min after cooling the sample to 25° C (b). The surface presented was prepared using the macroinitiator "grafting-from" ATRP approach.[220] The scale bars correspond to 100 μm. Adapted from reference [220] with permission of Wiley.

Surfaces can be coated with a variety of materials, including glycopolymers[221] and zwitterionic polymers.[222] Zwitterionc polymers are particularly attractive because they have shown impressive non-fouling properties. Using a catechol end group for surface anchoring, poly(sulfobetaine methacrylate) (pSBMA) was synthesized by ATRP. This polymer was able to attach to various surfaces, including amino-, hydroxyl-, and methyl-terminated self-assembled monolayers (SAMs) along with bare gold. Under optimized conditions, the coated surfaces were resistant to non-specific protein adsorption, including fibrinogen, lysozyme, and complex media of 10-100% blood plasma and serum. These materials may also have application for reducing bacterial adhesion and biofilm formation.

Materials surfaces grafted with polymers containing quaternary ammonium (QA) groups possess great antibacterial activity.[223] Well defined PDMAEMA was grown from the surface of polypropylene (PP) via surface-initiated ATRP using a benzophenonyl-functionalized ATRP initiator.[224] Similar polymers were grown from inorganic supports.[225-228] PDMAEMA was converted poly(quaternary ammonium) (PQA) in the presence of ethyl bromide. Antibacterial activity tests against Escherichia coli (E. coli) demonstrated that the biocidal activity of the resultant surfaces depends on the amount of the grafted polymers (the number of available quaternary ammonium units). With the same grafting density, the surface grafted with relatively high MW polymers (M_n > 10,000) showed ~100% killing efficiency, whereas a lower biocidal activity (85%) was observed for the surface grafted with shorter PQA chains (M_n = 1,500).

5.2 Composite tissue engineering scaffolds

The discovery of CRP methods enables creation of well-defined polymers with incorporated reactive groups and complex architectures. An important discovery in the area of scaffold adhesion was that of adhesion domains in fibronectin and other extracellular glycoproteins, which contain the amino acid sequence Arg-Gly-Asp (RGD). This has allowed the design of synthetic materials that can modulate cell adhesion.[229, 230] The physical properties of the material, as well as placement, density, and clustering of the peptide regulate cell adhesion, motility, and ingrowth.[231-236] As a way to control the placement of peptides within a scaffold, and to enable multiple modes for controlled release, nanostructured hybrid hydrogels were developed by incorporating well-defined POEOMA nanogels of sizes 110-120 nm prepared by ATRP into a larger three-dimensional (3D) matrix. RITC-Dx- or FITC-Dx-loaded nanogels with pendant hydroxyl groups were prepared by AGET ATRP in cyclohexane inverse miniemulsion. The hydroxyl groups were then functionalized with methacrylate groups to generate photo-reactive nanogels

that could be incorporated into 3D hyaluronic acid-glycidyl methacrylate (HAGM) hydrogels after free radical photopolymerization (**Figure 7a-b**). Disulfide bonds permitted controlled release of nanogels from cross-linked HAGM hydrogels under reducing conditions. GRGDS contained in the nanogel structure promoted cell-substrate interactions. These nanostructured hydrogels have potential as an artificial ECM impermeable to certain biomolecules and with controlled pharmaceutical release capability. In addition, the nanogels can control drug or biomolecule delivery, while hyaluronic acid based-hydrogels can act as a macroscopic scaffold for tissue regeneration and regulator for nanogel release. Similar RITC-Dx-loaded nanogels could be embedded into a polyurethane network (**Figure 7c**), demonstrating that the hydrogel matrix can be tuned to match the physical properties of the tissue engineering application (unpublished results).

(Insert Figure 7)

Figure 7. (a) Fluorescent dye-loaded GRGDS-POEOMA nanogels were synthesized using AGET ATRP in inverse miniemulsion of water/cyclohexane at ambient temperature. The nanogels were subsequently modified to enable incorporation into macroscopic HAGM or poly(ethylene oxide) dimethacrylate (PEODM) hydrogels via FRP under UV irradiation, forming nanostructured hybrid hydrogels. (b) Confocal microscopy was used to image the nanostructured hybrid hydrogel. RITC-Dx-labeled nanogels (1% wt/v, red spots) are covalently bound and dispersed in the scaffold stained with FITC (10% wt/v, green clusters). (c) A hybrid hydrogel of RITC-Dx-labeled nanogels (red) inside of a polyurethane matrix was synthesized. Differential interference contrast (DIC) and florescence images were merged to show the polyurethane foam network (grey, 300-400 μm pore diameter) and nanogels (red, 150 nm diameter). (a) and (b) are reproduced from reference [237] with permission of Elsevier.

Some polymers are known to drastically change in water solubility at a certain temperature. Such polymers are useful due to their LCST behavior in aqueous solutions (liquid at room temperature, gel at body temperature). The thermo-sensitivity of PNIPAAm, which has an LCST at 32°C has been extensively studied.[238, 239] The LCST can be predictably tuned by forming copolymers and thus used for different applications.[240] The thermo-sensitivity of the polymers can be controlled by the relative hydrophobicity of the copolymers. Poly(*N*-isopropylacrylamide-co-5,6-benzo-2-methylene-1,3-dioxepane) (P(NIPAAm-co-BMDO) was synthesized by ATRP for use an injectable material for bone fracture repair.[241] Cross-linked scaffolds with degradable units within the polymer backbone and at the cross-linking sites were prepared using an ester-containing diacrylate cross-linker. Furthermore, incorporation of a GRGDS peptide sequence improved cell attachment to the gels.

6. Degradable polymers

Although ATRP has led to a number of biomedically relevant bioconjugates, drug delivery systems, diagnostic and imaging systems, tissue engineering hydrogels, and bioactive surfaces, ATRP is generally a technique for the polymerization of vinyl monomers. In some cases, non-degradable polymers are desired (e.g. cell encapsulation, permanent biomedical implants and coatings, etc.). However, in most biomedical situations, degradable polymers are required. Efforts towards rendering ATRP vinyl polymers degradable via combination with radical ring-opening polymerization (RROP), degradable cross-linkers, initiators,[242] and other methods are important for the practical use of ATRP in biomedical applications.

The discovery of new monomers that can be polymerized directly by ATRP and yield degradable polymers would constitute a major advance in the field.

6.1 ATRP and radical ring-opening polymerization

Since ATRP proceeds via a radical chain growth mechanism, it can therefore be combined with RROP[243-245] to introduce degradability into ATRP-produced polymers. In this way, hydrolytically or photodegradable R-ketoester units can be introduced in the polymer backbone by ROP of cyclic esters or anhydride monomers with an exocyclic double bond. One such example that has been combined with ATRP is 5-methylene-2-phenyl-1,3-dioxolan-4-one (MPDO).[246] Another example of a radically polymerizable cyclic monomer is 5,6-benzo-2-methylene-1,3-dioxepane (BMDO).[247] This monomer can be polymerized by ATRP and yields a linear polyester.[248] It can also be combined with other monomers, rendering the copolymer biodegradable by introduction of ester linkages through RROP. Copolymerization of BA[249], MMA[246, 250], Sty[251], POEOMA[49], NIPAAm[241, 252] with BMDO has been reported. Star polymers have also been synthesized by combining living anionic polymerization and ATRP.[253] Furthermore, ATRP enables significant structural and degradation fragment size control. Low cytotoxicity of the material and degradation products, along with incorporation of peptide sequences and polymerization into a cross-linked hydrogel has been reported.[241]

6.2 Polymers with incorporated disulfide bonds by ATRP

In addition to incorporation of ester groups, disulfide bonds are another attractive option for degradation that can be incorporated into ATRP-produced polymers in a variety of ways. Functional telechelic initiators can be used to grow polymers in two directions, resulting the existence of certain functionality in the middle of each polymer chain.[16] In this way, polymers with a disulfide group within the chains have been prepared by ATRP, resulting in polymers that can be cleaved into two thiol-terminated chains upon exposure to a variety of reducing agents. Examples include the polymerization of linear PSty,[254] polymethacrylates[154, 255, 256], hydrogels,[154] branched polymers,[257] and miktoarm star polymers.[258] Reduction and oxidation of these polymers has been demonstrated. In addition, the living nature of the bromine-terminated chains ends can reinitiate polymerization. In this way, chain extension could be performed within degradable gels.[154] These dangling chain ends can also be used for bioconjugation. This is especially attractive in the case of nanogels prepared in inverse miniemulsion ATRP, as previously described. Since ATRP also enables control over architecture, block copolymers based on temperature-sensitive polymers combined with disulfide functionality[174, 259] offer additional ways to enable “smart” responsiveness and degradation for biomedical applications.

6.3 Combination of degradable polymers and ATRP-produced polymers

The coupling of polymer chains is another way to introduce degradable bonds into polymers prepared by ATRP. These methods include Atom Transfer Radical Coupling (ATRC)[260-262] and click coupling.[263] As mentioned above, “grafting from” ATRP is a powerful approach for the formation of structured copolymers, including brush shaped macromolecules. In this way, polymers can be grown using ATRP from degradable polymer backbones. For example, 2-methacryloyloxyethyl phosphorylcholine (MPC) was polymerized from a linear polyphosphate ester backbone.[264] The grafting density could be tuned by adjusting the monomer feed in forming the backbone. Polycondensation of 1,4-butanediol and 2-bromoadipic or 2-bromosuccinic acid catalyzed by $Sc^{III}(OTf)_3$ yielded bromine-containing polyesters that were used as multifunctional initiators in the ATRP of MMA to prepare polymer brushes.[265] Hyperbranched polymers with degradable ester linages were prepared as well.[266] Polysaccharides can also be used as degradable backbones for ATRP. Examples of polysaccharides modified with synthetic polymer side chains include cellulose[267-269] or ethylcellulose,[270] chitosan,[271-274] pullulan,[275] and dextran.[275]

7. Future perspectives

Advanced polymer chemistry and materials science, combined with knowledge of biology, will realize the full potential of polymer therapeutics in the post-genomic era. In this way, controlled synthetic chemistry will allow careful tailoring of molecular weight, polydispersity, and the addition of biomimetic and bioresponsive elements. The interface of chemistry and biology is pivotal for the development of this field. The development of new monomers that can be polymerized by ATRP and yield fully degradable polymers would constitute a major advance in the field. Advances in polymer chemistry have led to the formation of carefully constructed and complex architectures of defined molecular weight and polydispersity. It is now feasible to construct, on the molecular level, multivalent polymers,[276] branched polymers,[277] graft polymers,[278] dendrimers,[87, 279-281] dendronized polymers,[281] block copolymers,[282] stars,[283] and hybrid glyco- and peptide derivatives.[284] These types of complex polymers and polymer systems are organized on the nanoscale level, and also dictate macroscale organization. New strategies to obtain sequence control within the polymer are an exciting attempt to approach nature's order[6, 285, 286]. We believe that sophisticated polymers with precise nano- and macroscopic morphologies and "smart" responsiveness to stimuli *in vivo* will lead to the development of the polymer therapeutics of the future.

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Abbreviations. Activator Generated by Electron Transfer (AGET) ATRP, arginine - glycine - aspartic acid (Arg-Gly-Asp) (RGD), Activators Regenerated by Electron Transfer (ARGET) ATRP, Atom Transfer Radical Coupling (ATRC), Atom Transfer Radical Polymerization (ATRP), 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), bovine serum albumin (BSA), Concavalin A (ConA), Controlled/living Radical Polymerization (CRP), critical micelle concentration (CMC), 2-(diethylamino)ethyl methacrylate (DEAMA), differential interference contrast (DIC), dihydrolipoic acid (DHLA), doxorubicin (Dox), fluorescein isothiocyanate (FITC), fluorescein isothiocyanate-dextran (FITC-Dx), 2-glucanoamidoethyl methacrylate (GAMA), glycine - arginine - glycine - aspartic acid - serine (Gly-Arg-Gly-Asp-Ser) (GRGDS), green fluorescent protein (GFP), human mesenchymal stem cells (hMSCs), human umbilical vascular endothelial cells (HUVECs), hyaluronic acid-glycidyl methacrylate (HAGM), 2-hydroxyethyl acrylate (HEA), 2-hydroxyethyl 2-bromoisobutyrate (HOEtBriB), 2-lactobionamidoethyl methacrylate (LAMA), lower critical solution temperature (LCST), magnetic resonance imaging (MRI), methacrylic acid (MAA), 2-methacryloyloxyethyl phosphorylcholine (MPC), 5-methylene-2-phenyl-1,3-dioxolan-4-one (MPDO), molecular weight (MW), molecular weight distribution (MWD), mononuclear phagocyte system (MPS), nanoparticles (NPs), poly(butyl acrylate) (PBA), polycaprolactone (PCL), poly(di(ethylene glycol) methyl ether methacrylate) ($PM(EO)_2MA$), poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA), poly(ethylene oxide) (PEO), poly(ethylene oxide) dimethacrylate (PEODM), polyglycolide (PGA), poly(2-hydroxyethyl methacrylate) (PHEMA), polylactide (PLA), poly(*N*-isopropylacrylamide) (PNIPAAm), poly(oligo(ethylene oxide) monomethyl ether methacrylate) (POEOMA), polypropylene (PP), poly(propylene oxide) (PPO), poly(quaternary ammonium) (PQA), poly(sulfobetaine methacrylate)

(pSBMA), poly((3-trimethoxysilyl)propyl methacrylate) and poly(*N*-acryloxysuccinimide) (PNAS), quantum dots (QDs), quaternary ammonium (QA), rhodamine isothiocyanate-labeled dextran (RITC-Dx), radical ring-opening polymerization (RROP), ring opening polymerization (ROP), self-assembled monolayers (SAMs), styrene (Sty), superparamagnetic iron oxide nanoparticles (SNPs), trioctyl phosphine oxide (TOPO), valine - proline - glycine - valine - glycine (Val-Pro-Gly-Val-Gly) (VPGVG)

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