Rational Design of Biomolecules/Polymer Hybrids by Reversible Deactivation Radical Polymerization (RDRP) for Biomedical Applications

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Abstract Hybrids, produced by hybridization of proteins, peptides, DNA, and other new biomolecules with polymers, often have unique functional properties. These properties, such as biocompatibility, stability and specificity, lead to various smart biomaterials. This review mainly introduces biomolecule-polymer hybrid materials by reversible deactivation radical polymerization (RDRP), emphasizing reverse addition-fragmentation chain transfer (RAFT) polymerization, and nitroxide mediated polymerization (NMP). It includes the methods of RDRP to improve the biocompatibility of biomedical materials and organisms by surface modification. The key to the current synthesis of biomolecule-polymer hybrids is to control polymerization. Besides, this review describes several different kinds of biomolecule-polymer hybrid materials and their applications in the biomedical field. These progresses provide ideas for the investigation of biodegradable and highly bioactive biomedical soft tissue materials. The research hotspots of nanotechnology in biomedical fields are controlled drug release materials and gene therapy carrier materials. Research showed that RDRP method could improve the therapeutic effect and reduce the dosage and side effects of the drug. Specifically, by means of RDRP, the original materials can be modified to develop intelligent polymer materials as membrane materials with selective permeability and surface modification.

Keywords Biomolecule-polymer hybrids; RDRP; Biomedical applications; Drug release; Nanotechnology

INTRODUCTION

In recent years, the functional hybridization of biomaterials has attracted complete attention because of its great benefits for disease treatment.[1,2] Polymer science has a significant impact on many scientific research fields. [3] With the increase in knowledge, the design of macromolecules with complex programmable polymer science behaviors becomes essential and attracts scientists' interest. [4–6] Biomacromolecule polymer hybrid is a special polymer designed by using the unique structure reaction of biomacromolecule and synthetic polymer, [7–10] which has the inherent advantages of both biomacromolecule and synthetic polymer. [11–13] The study of living polymerization was started very early. Before 1966, people thought that anionic polymerization was the only means of living polymerization. [14] Until 1974, when Matyjaszewski found two new active species of trifluoromethane sulfonate anion ring-opening polymerization, people gradually combined free radical polymerization with living polymerization and introduced the concept of RDRP. In 1995, Wang and Matyjaszewski et al. realized the “living/controllable radical polymerization” of styrene monomer and named this kind of polymerization atom transfer radical polymerization (ATRP). [15–17] In 1998, the team of Australian scholar reported reverse addition-fragmentation chain transfer (RAFT) polymerization for the first time. [18] In 2011, Matyjaszewski’s team explored the electric mediated atom transfer radical polymerization and then extended the electric mediated reverse addition-fragmentation chain transfer (eRAFT) polymerization [19] and electric mediated nitroxide mediated polymerization (eNMP). [20] In 2013, Hawker et al. studied photo-mediated ATRP, etc. [21] In a word, the research on RDRP methods has been endless in recent years, representing the possibility of more polymers prepared by RDRP. For example, Tao et al. made use of the inherent reactivity of the terminal group of thiocarbonate to carry out RAFT polymerization and then carried out chain transfer reaction with protein azo initi-
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with PISA and designed a new type of water-soluble PEGylated ruthenium alkene catalyst for polymerization.

At present, biomacromolecule polymer hybrids’ research products mainly include nucleotide polymer hybrid,[35] polysaccharide polymer hybrid,[56–59] protein-polymer hybrid,[60,61] etc. Due to the different three-dimensional structures of biomolecules, the properties of the products obtained by conjugation modification of polymers are also significantly different.[3] For example, polysaccharides can resist cancer,[62,63] proteins can recognize,[64] and nucleic acids can encode. All these biomolecules’ properties can be stable or even better developed after hybridization with polymers. Thus, the biomedical applications of biomolecular polymer hybrids in biosensors, drug delivery, and tissue engineering are also introduced in this review. In drug delivery systems, biomolecular polymer hybrids are mainly used as drug carriers, which can be made into drug-loaded nanoparticles or drug-loaded nanotubes.[65,66] In the aspect of the biosensor, biomolecular polymer hybrids can be made into fluorescent nanoprobes for targeted disease therapy.[67,68] In tissue engineering, biomolecular polymer hybrids can be used as scaffolds to promote biomaterialization.[69]

It is gratifying that biomolecular polymer hybrids break through the limitations of pure polymer materials in some aspects. They achieved breakthroughs in the limits of biomolecules themselves. Biomolecular polymer hybrids can control and change the stability of biomolecules, improve the biological activity and reduce the immunogenicity of polymers, making them widely used in biomedical field and driving the development of other sciences as supramolecular science, precision polymer self-assembly, etc.[3] However, there are few intrinsic relations of biomolecular polymer hybrids that have been studied, so it is difficult to explore new conjugates by artificial control.

In this review, the research contents of RDRP applied to biomolecular-polymer hybrids are discussed (Scheme 1). A systematic classification and explanation of biomolecular polymer hybrids are provided. The applications of biomolecular-polymer hybrid in biomedical field was elucidated in detail.

**STRATEGIES FOR BIOMOLECULE/POLYMER SYNTHESIS BASED ON RDRP**

Despite their excellent performances in some aspects, polymer materials have some disadvantages, such as poor biocompatibility and low degradability. Therefore, researchers put forward the idea of hybridizing biomolecules and polymers.[28] At present, there are many methods for preparing biomolecules/polymer hybrids, but only RDRP is introduced in this...
review. RDRP can be commonly divided into RAFT, ATRP and NMP. These three polymerization methods have their advantages, which are suitable for different systems and can be coupled with various biomolecules.

**Reversible Addition-fragmentation Chain Transfer Polymerization**

A significant problem facing the world today is the shortage of resources caused by the rapid consumption of energy resources, which makes the exploration of renewable and degradable resources become the research focus. Lignin has become one of the raw materials to unlock green and sustainable development because of its advantages of simple preparation, low economic cost and wide application. To modify the function of lignin, Bao et al.\[70\] used jute fiber with rich lignin content as raw material and explored a new method combining enzyme-initiated RAFT polymerization and free-radical coupling. In this method, they successfully prepared lignin/polymer copolymer by coupling the regular polymer synthesized by the RAFT method with lignin on the surface of jute fiber in the HRP/ACAC/H₂O₂ system. Although the jute/polymer copolymer synthesized has not solved polymer grafting density out of control, the research is also a bold exploration.

The disadvantages of traditional drug delivery are short drug intervals, long medication cycles, and toxicity caused by drug penetration. Therefore, polymer nanocapsule (NCs) as a drug delivery system has become one of the research hot-spots in the biomedical field in recent years. Ramirez et al.\[71\] reported multi-reactive polysaccharide-based transurf for RAFT polymerization of butyl acrylate and methyl methacrylate. The experiments were mainly divided into the synthesis of DexN3-τ derivatives, the synthesis of DexN3-τ CTA γ transurfs and the RAFT polymerization of MMA in the microemulsion. It is worth mentioning that the oily-core NCs were prepared for the first time in this study. By controlling the hydrophobic and CTA groups numbers, the dextran coverage/PMMA shell/oily core NCs were successfully prepared by R-group mediated RAFT polymerization at the reaction site of transurf.

**Nitroxide Mediated Radical Polymerization**

In the aspect of modified polysaccharides, RDRP has many advantages, such as controlling molecular weight and its distribution, controlling the overall morphology and functionality of conjugates. Some polysaccharides, such as chitosan and dextran, have been modified by NMP. Starch is also one of the polysaccharides that are often changed. But there is little research on the modification of starch by NMP. Starch nanoparticle is a kind of amorphous nanomorphology obtained by starch gelatinization. It may be used in paper coating, adhesive, and as additive of some composite materials in the future. In the research field of NMP modified starch nanoparticles (SNPs), Cazotti et al.\[72\] have broken through the conservative synthesis route of polysaccharides and polymers.
and synthesized polymer-g-SNP for the first time by combining NMP with "grafting to". Specifically, polymer-g-SNP were prepared by the three-step method, including active vinyl modification of SNP, preparation of synthetic polymers by NMP and grafting of synthetic polymers to SNPs. The results show that the reduction of monomer ratio to SNP is beneficial to the surface initiation of NMP and the acquisition of higher conversion. This method proved the possibility of SNP graft modification by NMP for the first time and explored a new way to study polysaccharide modification.

To improve the hydrophobicity of starch nanoparticles, Cazotti et al. conducted a similar experiment, in which a controllable high activity polymer was formed by non-mediated polymerization. Correct characterization of the grafted nanoparticles was realized by "grafting to". In addition, in this experiment, they changed SNPs' properties by controlling and adjusting the type, molecular weight and grafting density of the grafted polymers.

**Atom Transfer Radical Polymerization**

Although RAFT and NMP are very useful, some biomolecular polymer hybrids are more suitable for other RDRP. Many researchers have chosen to add selective polymer brushes to polymer hybrids are more suitable for other RDRP. Many researchers have chosen to add selective polymer brushes to polymer hybrids. One of the common forms of peptide polymer hybrid is to make hybrid nano-objects. According to the results of previous studies, polymerization-induced self-assembly (PISA) is a simple and effective method for the production of amphiphilic block polymer nanoparticles. Simultaneously, self-assembling peptides (SAPs) have great potential in the preperation of ordered nanostructures. Dai et al. firstly synthesized a peptide-polymer hybrid nano-objects by combining these two methods with the strong self-assembling driving force, as shown in Fig. 1. The experimental part was divided into three steps: (i) synthesis of the methacrylamide-functionalized peptide monomer (MAm-GFF); (ii) synthesis of the copolymer (GMA-stat-(MAm-GFF)) macro-CTA by RAFT; and (iii) P(GMA65-stat-(MAm-GFF)) macro-CTA and poly(2-hydroxypropyl methacrylate) (PHPMA) self-assembly bodies of P(GMA65-stat-(MAm-GFF)) and PHPMA28. They found that the temperature affected the copolymer's self-assembly structure size of peptide monomer and glycerol monomethyl acrylate (GMA). The strong effect of peptide self-assembly and GFF interaction will affect the diblock copolymer's self-assembly process prepared by water dispersed PISA in the third step, leading to the change of the morphology of diblock copolymer.

The peptide has a specific regulatory function on human nutrition and immunity and has gradually attracted people's interest in their research. Among this, the classic example is a glucagon-like peptide. Glucagon-like peptide-1 (GLP-1) has a
remarkable effect in controlling insulin secretion, thereby controlling blood sugar and body weight, but it is inevitably hydrolyzed by enzyme, and its impact is significantly reduced. At present, there are two methods for solving this problem. One is to develop analogs of GLP-1, but there is a problem of immune reaction, and the other is to combine GLP-1 with the

| Materials                  | Biomolecules                  | Methods                       | Structures                          | Advantages                                              | Applications                              | Refs. |
|---------------------------|-------------------------------|-------------------------------|-------------------------------------|---------------------------------------------------------|-------------------------------------------|-------|
| Peptide-polymer hybrid nano-objects | Peptide                  | Polymerization-induced self-assembly peptide | Wormlike, fibrous or spherical nanostructures | Peptide interactions                                   | Peptide polymer nano-objects with different morphologies | [88]  |
| Zwitterionic polymer conjugated glucagon-like peptide-1 | GLP-1                   | “Click chemistry” reaction     | Nanoparticle                        | Active sites of pCB and natural GLP-1                   | Prolonged circulating half-life of GLP-1 | [89]  |
| Protein-polymer          | Protein                       | CuAAC                          | Nanoparticle                        | Chain length, density, and conformation of polymers     | Modify proteins                           | [90]  |
| Polymer-protein          | Bovine serum                  | Electrostatic self-assembly    | Nanoparticles                       | Ultrasonic processing                                   | Stable, tunable polymer-protein nanoparticles | [57]  |
| DNA-polymer conjugates   | albumin                       | Photoinduced RAFT polymerization | Supramolecular architectures        | Photo; monomer to DNA-initiator ratio                   | Customization of DNA polymer conjugates   | [92]  |
| Hybrid DNA-covalent Polymer | DNA                         | Hybridization chain reaction   | Gel phase                           | DNA hairpins                                            | Drive DNA side chain growth on demand    | [93]  |
| Polymer hybrid cell surfaces glycans | DNA                     | Azide-alkyne “click” cycloaddition | –                                   | Azides                                                 | Design of cell surfaces                 | [97]  |
| Glycopolymers            | Sugars                        | DMTMM coupling                 | –                                   | Binding of amino-functionalized carbohydrates to lactose | Glycoprotein from pure sugar β          | [99]  |

**Fig. 1** (a) Synthesis of the P(GMA-stat-(MAm-GFF)) macro-CTA using RAFT and of P(GMA-stat-(MAm-GFF))-b-PHPMA block copolymers under PISA conditions. (b) Schematically drawing of PISA process. (c) Representative TEM image of P(GMA65-stat-(MAmGFF7))-b-PHPMA28 block copolymer structures. (Reproduced with permission from Ref. [88]; Copyright (2020) American Chemical Society).

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polymer to protect the part that may be hydrolyzed by the enzyme. Different from the site-specific conjugation of PEG onto GLP-1, Tsao et al. combined poly-carboxy betaine (pCB) and C-terminus of GLP-1 by thiol-maleimide “click chemistry” to protect the activation point of N-terminus of GLP-1. They realized the combination of GLP-1 with pCB and observed the insulin secretion induced by GLP-1. Under the experimental conditions, the hydrodynamic diameter of the conjugate of GLP-1 and pCB increased, which prevented GLP-1 from being filtered by the kidney, and the solubility of the conjugate was also greatly improved. It is worth mentioning that, firstly, conjugation of pCB with GLP-1 will not affect the secondary structure of GLP-1. Secondly, possible experiment results show that pCB binding will not affect GLP-1 receptor activation, which indicates that PCB may be the best peptide-binding polymer at present.

Proteins

The most commonly modified biomaterials are proteins due to their unique ability to act as signaling agents, structural components, and enzymes in vivo. According to the various proteins and polymers used, there are many kinds of protein-polymer conjugates, however, their applications are limited, such as in drug carriers and biosensors. Like peptide polymer conjugates, protein-polymer conjugates extend the half-life of protein drugs in the blood through polymer modification, thus prolonging the treatment time. However, the research in this field is still in the development stage. It is always challenging to select the polymer that can give the conjugates degradability or improve conjugates’ immunogenicity.

Protein is the main undertaker of human life activities and plays an essential role in antibody immunity. However, biomedical materials are foreign for the human body. To ensure the functions of biomaterials, it is necessary to suppress antigen’s immunogenicity and modify the protein. PEG is one of the most widely used polymers to interfere with natural biomaterials’ immunogenicity, such as proteins. In order to explore the ability of other polymers except PEG to modify protein hybridization, Crooke et al. carried out a comparative test on antibody recognition of poly(ethylene glycol methacrylate), poly(methacryloyl glucosamine) and PEG three immunogenic viruslike particles (VLP). Crooke’s team prepared polymer by RAFT polymerization, and realized the combination of polymer and VLP through CuAAC reaction. The results of size exclusion chromatography, dynamic light scattering and gel electrophoresis showed that the size and hydrodynamic radius of the VLP conjugates were larger than those of the unmodified VLP. In addition, PEG was proved to be the most excellent polymer to modify protein.

Similar to peptide polymer hybrid nanoparticles, there are also polymer protein nanoparticles for protein modification. Generally speaking, the bulk mixing method was once a common method for developing nanoparticles. Still, it was gradually abandoned due to its discontinuity and insufficient control of nanoparticles’ size and distribution. Seaberg has studied a millifluidic process as shown in Fig. 2(a) to synthesize polymer-protein nanoparticles to solve the problem of parameter control and scalability of polymer nanoparticle drug delivery system. Specifically, Seaberg used poly(L-lysine) as a cationic polymer and PEG as biocompatibility material. He then grafted them to self-assemble around the protein to realize conjugation of bovine serum protein and poly(L-lysine) grafted PEG (see Fig. 2b). Millifluidic process can realize the control of feed flow rate, tubing material, and ultrasonic power input, and then realize nanoparticles’ control (Figs. 2c, 2d).
It is worth mentioning that the nanoparticles’ activity obtained by this process is higher than that of the nanoparticles and free protein produced by the general process.

**DNA**

It is well known that DNA is programmable and sequence-specific. As a gene carrier, DNA can be hybridized with the polymer to form a DNA polymer hybrid. At present, the hybrid application of DNA and polymer is mainly in cell imaging and cell therapy, which is realized by receptor-mediated gene transfer.[91] DNA polymer hybrid has unique and controllable characteristics of DNA and good biocompatibility, so its application prospect is expected. However, due to the limited solubility of DNA and polymer in organic solvents, the remaining DNA and polymer fragments after reaction are faced with purification problems. Moreover, due to their high requirements for experimental equipment and high preparation cost, DNA polymer hybrids are not suitable for large-scale production.

DNA-polymer conjugated materials combine the characteristics of polymer and DNA, which promote the study of DNA nanostructure and precise structure of the polymer. Using methacrylic acid, acrylate, and acrylamide as raw materials, Lueckerath’s team prepared DNA polymer conjugates via photoinduced RAFT polymerization.[92] The reason why RAFT polymerization was chosen was that Lueckerath believed that RAFT polymerization did not rely on toxic transition metal catalysts, which avoided the problem of the catalysts being difficult to remove. Besides, to eliminate the disadvantage of the steric hindrance effect between the presynthesized polymer and DNA, Lueckerath et al. adopted the method of grafting-from polymerization and obtained more convenient purification and higher yield of DNA-polymer conjugates under the premise of ensuring the DNA chain’s self-assembly characteristics. They used Eosin Y(EY)/ascorbic acid (AscA) as a reducing agent and chose water solvent and blue light-induced experimental conditions by changing the monomer and initiator ratio.

Noteborn et al. successfully prepared DNA graft polymer with another method.[93] Specifically, they used dextran and natural polymer with high biological activity as raw material. They first prepared 5′-sulphhydryl DNA and dextran-VS, and then DNA dextran graft copolymer conjugate by sulphhydryl Michael addition of vinyl sulfone (Fig. 3a). Subsequently, initiator DNA dextran graft copolymer was mixed with two DNA hairpins to carry out gel electrophoresis experiments, fluorescence experiments, etc. (Fig. 3b). Through the analysis of the experimental results, they concluded that the DNA side-chain

![Diagram](https://doi.org/10.1007/s10118-021-2543-x)
extension occurred on the polymer (Figs. 3c and 3d). And the DNA/dextran graft copolymer conjugate was successfully formed. The results showed that DNA graft copolymers could indeed initiate a hybrid chain reaction, which has guiding significance for developing biomedical responsive materials in the future.

Others

In addition to proteins, peptides and DNA, polysaccharides such as chitosan, cellulose and lipids can also be hybridized with polymers. The application direction of conjugates is different according to the characteristics of biomolecules. For example, chitosan has good biodegradability and antifungal properties and can be used as drug carrier particles after hybridization with the polymer. Some polysaccharides have biological recognition, which can be combined with polymers to realize specific accurate recognition of cells. The functional combination of biomolecule and polymer was realized through this method. Besides, the hybrid was non-toxic and performed better biocompatibility than pure polymer. However, it is still a complex problem to select suitable non-toxic polymer and design the polymer’s density.

In recent years, polymer-modified cell surface research is gradually rising, promoting cell surface development in medicine and biological science. Ruben et al. grafted poly(hydroxyethyl acrylamide) onto azide-labelled cell surface glycans by “grafting-to” method (Figs. 4a, 4b and 4c). It controlled the grafting density by adjusting the length and concentration of the polymer chain. The result of flow cytometry and confocal imaging used by Ruben showed that covalently labelling cells' efficiency was more than 95% and showed less heterogeneity (Figs. 4d and 4e). The dissociation of lipid polymer is generally less than 24 h. At the same time, this experiment proves that conjugated polymer can remain in cells for more than 72 h, significantly improving the deficiency of lipid polymer insertion into cells. In conclusion, polymer and cell surface glycan can realize the combination of cell recognition function and polymer characteristics and promote the research on cell surface tracking and treatment.

Figure 4 (a) Synthesis of telechelic poly(N-hydroxyethyl acrylamide) by RAFT polymerization. (b) DBCO-pHEAₙ-FI cell surface conjugation. (c) A549 cells were treated with Ac₄ManNAz and DBCO-pHEAₙ-FI. (d) Flow cytometry analysis. (e) Average fluorescence intensity values. (Reproduced with permission from Ref. [97]; Copyright (2019) American Chemical Society, not subject to U.S. Copyright)
Another polymer-modified biomolecule is a natural carbohydrate polymer. Because of the "cluster glycoside effect", carbohydrate polymers with chain sugar structure, which are distributed along the polymer skeleton, have become a useful tool to detect the glycoprotein interaction in some biological processes. On how to synthesize well-defined glycoproteins, Zhou et al. proposed a strategy based on the conjugation of functionalized sugar derivatives with polymer skeleton.[99] They synthesized poly(acrylic acid) homopolymer by RAFT polymerization. Lactosamine and galactosamine were prepared by amino functionalization of lactose and D-galactose. The glycopolymer was then successfully prepared by graft polymerization of poly(acrylic acid) and two kinds of glycosamines. This experiment is different from the previous preparation of glycopolymer by complex polymer prefunctionalization. From the point of view of sugar modification, it is easier and faster to prepare glycopolymer. Moreover, this method can also control the structure of glycopolymer and the grafting density of sugar. Various combinations of the biomolecules/polymer hybrids were summarized in Table 1.

### BIOMOLECULES/POLYMER HYBRIDS FOR BIOMEDICAL APPLICATION

The development of biomedical materials is in full swing in recent years. The hybrid of polymers and biomolecules undoubtedly solved the problem of the poor biocompatibility of polymers. Therefore, researchers have been studying the application of biomolecular/polymer hybrid materials in many medical fields.[100–102] This review mainly introduces its application of biomolecular/polymer hybrid materials in drug delivery, biosensor, tissue engineering and other medical fields with less research. The biomedical applications of biomolecular-polymer hybrids are summarized in Table 2. The hybrid materials mainly include protein/polymer hybrids, polysaccharide/polymer hybrids, and some lipid/polymer hybrids are also introduced, hoping to provide ideas for the study of other biomedical materials.

### Drug Delivery

Due to the poor permeability, poor stability, low metabolic rate, short half-life and side effects of some drugs, more and more researches on drug carriers have been conducted in recent years. There are a lot of materials used to make drug delivery carriers.[103–106] This review mainly introduces the drug carriers prepared by the hybridization of biomolecules and polymers, including lipid polymer hybrids, chitosan polymer hybrids and protein-polymer hybrids. These natural hybrids are mainly used to treat tumors and other diseases, primarily made into nanoparticles. The drug carriers from biomolecular polymer hybrids have significant advantages in biocompatibility, biodegradability, low toxicity and biological activity. They realized the biological recognition, thus achieving targeted disease treatment. However, polymer-modified biomolecules mechanism and law for synthesizing hybrid compounds are still not clear, and the experience in this field is insufficient, and the research cost is high.

In recent years, controllability and targeting are two essential factors for biomedical intelligent carrier materials. Considering the internal environment of tumor cells, Li et al. studied the dual redox/pH-responsive hybrid polymer-lipid composites as anticancer drug carriers.[107] By controlling PEGylated lipid and disulfide content, three kinds of nanoparticles were prepared, namely DOX-DNPs, DOX-HPLNPs and DOX-HDPLNPs. They prepared the copolymer PAE(-ss-mPEG)-g-Chol and its analogue, and set up DOX-DNPs, DOX-HPLNPs and DOX-HDPLNPs-loaded hybrid polymer lipid nanoparticles as well as free drugs to study the properties of the dual redox/pH-responsive hybrid polymer-lipid composites. They found that the serum stability of drug carrier nanoparticles...
was an essential factor for the carrier. And PEG esterification preparation was conducive to improving the stability of serum. They also conducted the experiment by changing the dosage of PEG-DSPE and obtained the corresponding experimental conclusion under the experimental conditions.

In addition to lipid polymer composite drug-loaded nanoparticles, polysaccharide and polymer hybrid drug-loaded particles are also drug carriers that researchers often study. For example, in the treatment of neovascular age-related macular degeneration, particle injection exposes some problems, such as limited loading capacity and unstable release. Jiang et al. [108] studied a method to solve these problems by preparing chitosan core-polymer-based shell particles with uniform size, high physical integrity, and biodegradability (Fig. 5a). The electrostatic interactions between chitosan core, bevacizumab, and the protective hydrophobic polycaprolactone shell exist. They changed the size and shape of particles and finally achieved the effect of optimizing the uniformity and drug loading of hybrid particles (Figs. 5b and 5c). In this study, bevacizumab was used as the loaded drug, which provided ideas for transmitting other drugs in the human body.

**Tissue Engineering Materials**

Tissue engineering materials generally refer to materials that can be used to reconstruct or repair tissues or organs. [108–113] At present, the hybrid products of biomolecular polymers used in tissue engineering mainly include the hybrid products of gelatin and polymer. The hybrids of natural polysaccharides such as chitosan and sodium alginate with polymers. Biomolecular polymer hybrids are primarily used as biomimetic scaffolds for bone tissue replacement and minimally invasive treatment. The biomimetic scaffolds generally have high porosity, which endows the platforms with good osteogenic and angiogenic properties. Besides, biomolecules provide good biocompatibility and biodegradability, which is conducive to the minimally invasive treatment of tissue engineering and patients’ later recovery. While at the same time, the control of the biodegradation rate is still a big problem. For example, if the degradation rate is too fast, the scaffold’s mechanical integrity will be affected.

The most common form of tissue engineering materials is a biomimetic scaffold. In situ gas foaming method originally refers to generating bubbles in molten metal by thermal decomposition of foaming agent or supersaturation of gas in the melt, cooling molten metal containing bubbles and preventing bubbles from escaping to obtain foamed metal. Mishra used gelatin and poly(vinylpyrrolidone) (PVP) as raw materials. They utilized an in situ gas foaming method for synthesizing biological “foam metal”, a bionic scaffold to replace...
bone tissue. It is of great significance to realize functional graft substitutes for bone reconstruction. Pore is the crucial factor in promoting the migration and proliferation of osteoblasts and supporting vascularization in the scaffold structure applied to bone tissue. The porous sponge structure of bionic scaffold made by Mishra plays a role in controlling the mechanical and physiological characteristics of bone tissue regeneration. Besides, he made an important empirical conclusion that the blending ratio of gelatin to PVP will affect the interconnectivity and shape uniformity of the scaffold pores as well as the overall performance of the bionic scaffold, which has guiding significance for the construction of gelatin-PVP bionic scaffold.

The hole in the biomimetic scaffold is a crucial factor. In addition to the foaming process, the pore structure can also be obtained by the hydrogel's unique design. For instance, Kim et al. reported a bioconjugated hydrogel scaffold, which can promote in situ polymerization biomineralization for bone repair materials. The experimental process can be described as follows: (i) synthesis of PCLA copolymers using ε-caprolactone (CL) and D,L-lactide (LA) as raw materials; (ii) phosphate-modified alginate (Alg-P-PEA) was synthesized by phosphorylation of sodium alginate using ethanolamine phosphate. And then, amine-functionalyzed PCLA copolymers (PCLA-NH$_2$) and Alg-P-PEA were prepared as ALG-PCLA bioconjugates (Fig. 6a). The results of GPC experiments on biological conjugates showed that temperature and concentration affected the sol-gel transition of Alg-PCLA bioconjugated hydrogels, resulting in the application of minimally invasive treatment at specific concentrations and temperatures (Figs. 6b and 6c). The biocompatibility and biodegradability of the synthetic copolymer of natural biopolymer were proved to be useful in human embryonic kidney cells and rats in vivo.

Of course, if the main components of biomimetic scaffolds include the original materials of bone tissue, the scaffolds' performance will become more excellent. At present, studies have shown that hydroxyapatite was an inorganic component of bone. It has certain biocompatibility and can be used as one of the candidate materials for bone tissue engineering. For example, Zou et al. prepared chitosan (CS)/collagen (Col)/polylactic acid (PLA)/NHAP scaffold with nano-hydroxyapatite as raw material. In this experiment, they solved the problem of easy phase separation between the oil phase (PLA) and water phase (CS/Col) by ultrasonic and amidation. XRD results showed that the scaffold had an excellent pore structure and improved the scaffold's mechanical properties. After the osteoblasts were incubated and trypsinized in vitro, the cell viability was measured by MTT assay. The results also showed that the scaffold had good biocompatibility.

**Biosensors**

Enzymes, cells, nucleic acids and other bioactive substances are often sensitive to biological substances and are used as biomimetic components. Using these components to change some important concentrations and then converting the concentration signal into electrical signals by the transducer is called a biosensor. The materials made by the biometric elements and other conversion parts are biosensors, by which people can detect the changes in some substances such as viruses and markers, some enzymes, etc. Biosensors can achieve disease prevention and disease monitoring, and their sensitivities are based on the hybrids of biomolecules. For example, the sensitivity of protein/polymer-based biosensor is...
much higher than that of biosensor based on pure biomolecules. However, the problem of nonspecific binding of impurity molecules remains to be studied.

Protein has its biological recognition function which can be used as a biosensor. However, it has the problem of binding with nonspecific molecules, which affects biosensors’ performance. To solve the problem that the sensitivity of the surface biosensor in the detection solution is reduced due to the nonspecific binding of impurity molecules, Justin studied the factors affecting the protein polymer’s internal diffusion conjugated thin-film biosensor.

Based on the previous studies that the polymer on the surface of biosensor can control the protein diffusion near the biosensor, Justin synthesized poly(N-isopropyl acrylamide) by RAFT, which was conjugated with several purified proteins to set up the experiment as shown in Fig. 7(a). The protein-polymer conjugates prepared in the experiment were used to measure the diffusion coefficients of proteins in protein gel and polymer solution. Compared with the diffusion coefficients obtained by the Stokes-Einstein equation, the diffusion coefficients of most proteins conform to the Stokes-Einstein equation (Figs. 7b and 7c). The diffusion coefficients of a few proteins are influenced by the interaction with poly(N-isopropyl acrylamide), and the interaction with other proteins was controlled by poly(N-isopropyl acrylamide). Using this conclusion, we can make protein-polymer conjugated thin film biosensors with higher sensitivity than biosensors composed of binding proteins in the future.

In the protein-polymer block copolymer films prepared by Justin, proteins capture non-target proteins according to their sizes. In contrast, polymers play a role in limiting the diffusion of the macromolecules, which significantly weakens the background signal problem caused by nonspecific molecules. By comparing the diffusion time of SA and mSA2 on protein-polymer block copolymer thin films, it is concluded that the analyte size affects the absorption rate of the membrane. However, when the exposure time is constant, the larger size of the analyte SA can only bind to the small area of the film. More interestingly, when SA is used as an analyte, it can be observed that the larger the domain spacing, the easier the diffusion of SA into the film and the larger the diffusion thickness, which indicates that the domain spacing of the polymer has excellent control on the distribution of the protein.

Others

The biomolecular polymer hybrids can also be applied to other aspects. They include biological imaging, nanoreactor and modification of other biomedical materials. There are also improvements in some unique properties, such as antibacterial, immunogenicity, etc. This part mainly introduces peptide polymer conjugates. Other materials, such as protein, DNA and so on, can also produce unexpected effects after hybridizing with polymers, but there are only few studies. Readers interested can refer to other articles.

One of the less popular biological applications of biomolecular-polymer hybrids is natural antibacterial. Qi et al. studied the antibacterial activity of β-peptide polymer-modified biomedical material surface. It was found that the antibacterial property of this method was stable for a long time. Specifically, they first treated the β-peptide polymer-modified thermoplastic polyurethane and unmodified thermoplastic polyurethane with methicillin-resistant Staphylococcus aureus (MRSA) and then implanted the polyurethane sheet subcutaneously into the body. The experimental results showed that the content of MRSA decreased significantly after the modified polyurethane sheet entered the human body, which indicated that the β-peptide polymer had antibacterial property. Besides, the performance of the β-peptide polymer in hemolysis and cytotoxicity also meets the application requirements. The modification method is convenient and straightforward and points out the direction for improving other biomedical materials’ antibacterial properties.
In addition to the study of antimicrobial activity, biomolecular polymer hybrids also have some contributions in biocatalysis. For example, Nishimura et al.\cite{126} reported a peptide polymer vesicle biocatalytic nano-reactor with a negatively charged surface as shown in Fig. 8(a), which partially solved the low permeability of enzyme-substrate in the original vesicle. Specifically, they used oligomeric aspartate and polycyclopropane to synthesize block polymers and then completed self-assembly into vesicles in an aqueous solution. The permeability test for the vesicles showed that the surface charged vesicles significantly improved the permeability to cationic and neutral compounds such as FITCPEG and rhodamine 6G (Figs. 8b and 8c). After hybridizing poly(cyclohexane) and lipid to construct nano-reactor, they further verified the role of the polymer as a molecular channel. The innovation of the method proposed by Nishimura is to introduce charge into the vesicle, which makes the cationic compound and the negative charge produce electrostatic interaction on the surface of the vesicle, facilitating the permeation of the cationic molecules. The biomedical applications of biomolecular-polymer hybrids were summarized in Table 2.

**CONCLUSIONS AND PROSPECT**

In this review, the RDRP methods of biomolecular polymer hybrids are introduced, among which RAFT and NMP methods are presented in detail. The common biomolecular polymer hybrids, such as peptide-polymer, protein-polymer, DNA-polymer and polysaccharide-polymer, are also introduced in detail. Different combinations show different properties by polymer modification due to the various structures and inherent characteristics of the biomolecules used. Polymer modification can control the self-assembly of biomolecules. Under the condition of artificial research, the relationship between macromolecules that have been studied is not clear, and the customization rules of these newly designed hybrids need to be further explored.

Among the methods for the preparation of biomolecular-polymer hybrids, it can be noticed that ATRP polymerization can provide polymerization flexibility. However, the setting of anaerobic conditions remains a problem. RAFT polymerization is easily accessible and widely used, but its reaction kinetics is slow. NMP and RAFT polymerization are popularized RDRP methods. The applications of biomolecular-polymer hybrids in the biomedical fields include biosensors, drug delivery, tissue engineering, and so on. Biomolecular-polymer conjugates have a broad space in the future medical application field, which is of great significance for the personalized development of disease treatment and diagnosis.

**BIOGRAPHIES**

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REFERENCES

1. Wang, C. Y.; Jiao, K.; Yan, J. F.; Wan, M.C.; Wan, Q. Q.; Breschi, L.; Chen, J. H.; Tay, F. R.; Niu, L. N. Biological and synthetic template-directed syntheses of mineralized hybrid and inorganic materials. Prog. Mater. Sci. 2020, 100, 100712.

2. Maghshoudi, S.; Shahrazi, B. T.; Rabiee, N.; Afshari, R.; Fatahi, Y.; Dinavand, R.; Ahmadi, S.; Bagherzadeh, M.; Rabiee, M.; Tayebi, L. Recent advancements in aptamer-bioconjugates: sharpening stones for breast and prostate cancers targeting. J. Drug. Deliv. Sci. Technol. 2019, 53, 101146.

3. Chen, C.; Ng, D. Y. W.; Wei, T. Polymer bioconjugates: modern design concepts toward precision hybrid materials. Prog. Polym. Sci. 2020, 100, 101241.

4. Meng, F.; Hasan, A.; Babadaei, M. M. N.; Kani, P. H.; Talaei, A. J.; Sharifi, M.; Cai, T.; Falahat, M.; Cai, Y. Polymer-based microneedle arrays as potential platforms in development of drugs delivery systems. J. Adv. Res. 2020.

5. Paredes-Ramos, M.; Sabin-López, A.; Peña-García, J.; Pérez-Sánchez, H.; López-Vilariño, J.; de Vicente, M. S. Computational aided acetaminophen-phthalic acid molecularly imprinted polymer design for analytical determination of known and new developed recreational drugs. J. Mol. Graph. Model. 2020, 107627.

6. Kim, Y. M.; Lee, Y. S.; Kim, T.; Yang, K.; Nam, K.; Choe, D.; Roh, Y. H. Cationic cellulose nanocrystals complexed with polymeric siRNA for efficient anticancer drug delivery. Carbohydr. Polym. 2020, 247, 116684.

7. Messina, M. S.; Messina, K. M.; Bhattacharya, A.; Montgomery, H. R.; Maynard, H. D. Preparation of biomolecule-polymer conjugates by grafting-from using ATRP, RAFT, or ROMP. Prog. Polym. Sci. 2020, 100, 101186.

8. Xiong, Q.; Zhang, X.; Wei, W.; Wei, G.; Su, Z. Enzyme-mediated reversible deactivation radical polymerization for functional materials: principles, synthesis, and applications. Polym. Chem. 2020, 11, 1673–1690.

9. Wei, W.; Zhang, X.; Zhang, S.; Wei, G.; Su, Z. Biomedical and bioactive engineered nanomaterials for targeted tumor photothermal therapy: a review. Mater. Sci. Eng. C. 2019, 104, 109891.

10. Gong, C.; Sun, S.; Zhang, Y.; Sun, L.; Su, Z.; Wu, A.; Wei, G. Hierarchical nanomaterials via biomolecular self-assembly and bioinspiration for energy and environmental applications. Nanoscale 2019, 11, 4147–4182.

11. Glasing, J.; Champagne, P.; Cunningham, M. F.raft modification of chitosan, cellulose and alginate using reversible deactivation radical polymerization (RDRP). Curr. Opin. Green Sust. 2016, 2, 15–21.

12. Shipp, D. A. Reversible-deactivation radical polymerizations. Polym. Rev. 2011, 51, 99–103.

13. Ghadban, A.; Albertin, L. Synthesis of glycopolymer architectures by reversible-deactivation radical polymerization. Polymers 2013, 3, 431–526.

14. Webster, O. W. Living polymerization methods. Science 1991, 251, 887–893.

15. Xia, J.; Gaynor, S. G.; Matyjaszewski, K. Controlled/"living" radical polymerization. Atom transfer radical polymerization of acrylates at ambient temperature. Macromolecules 1998, 31, 5958–5959.

16. Xia, J.; Matyjaszewski, K. Controlled/"living" radical polymerization. Atom transfer radical polymerization using multidente amine ligands. Macromolecules 1997, 30, 7697–7700.

17. Matyjaszewski, K.; Gaynor, S.; Greszta, D.; Mardare, D.; Shigemoto, T. ‘Living’ and controlled radical polymerization. J. Org. Chem 1995, 8, 306–315.

18. Moad, G.; Anderson, A. G.; Ercole, F.; Johnson, C. H.; Kristina, J.; Moad, C. L.; Rizzardo, E.; Spurling, T. H.; Thang, S. H. Controlled-growth free-radical polymerization of methacrylate esters: reversible chain transfer versus reversible termination. ACS Symp. 1998, 685, 352–360.

19. Wang, Y.; Fantin, M.; Park, S.; Gottlieb, E.; Fu, L.; Matyjaszewski, K. Electrochemically mediated reversible addition–fragmentation chain-transfer polymerization. Macromolecules 2017, 50, 7872–7879.

20. Magenau, A. J.; Strandwitz, N. C.; Gennaro, A.; Matyjaszewski, K. Electrochemically mediated atom transfer radical polymerization. Science 2011, 332, 81–84.

21. Fors, B. P.; Hawker, C. J. Control of a living radical polymerization of methacrylates by light. Angew. Chem. 2012, 124, 8980–8983.

22. Tao, L.; Kaddis, C. S.; Loo, R. R. O.; Grover, G. N.; Loo, J. A.; Maynard, H. D. Synthetic approach to homodimeric protein-polymer conjugates. Chem. Commun. 2009, 2148–2150.

23. Corrigan, N.; Jung, K.; Moad, G.; Hawker, C. J.; Matyjaszewski, K.; Boyer, C. Reversible-deactivation radical polymerization (controlled/living radical polymerization): from discovery to materials design and applications. Prog. Polym. Sci. 2020, 101311.

24. Yeow, J.; Chapman, R.; Gormley, A. J.; Boyer, C. Up in the air: oxygen tolerance in controlled/living radical polymerization. Chem. Soc. Rev. 2018, 47, 4357–4387.

25. Chenal, M.; Boursier, C.; Guillauneuf, Y.; Taverna, M.; Couvreur, P.; Nicolas, J. First peptide/protein PEGylation with functional polymers designed by nitroxide-mediated polymerization. Polym. Chem. 2011, 2, 1523–1530.

26. He, P.; He, L. Synthesis of surface-anchored DNA-polymer bioconjugates using reversible addition?fragmentation chain transfer polymerization. Biomacromolecules 2009, 10, 1804–1809.

27. Wilks, T. R.; Bath, J.; de Vries, J. W.; Raymond, J. E.; Herrmann, A.; Turberfield, A. J.; O’Reilly, R. K. ‘Giant surfactants’ created by the ‘living’ recombination of biocompatible biopolymers. Chem. Commun. 2016, 52, 9403–9405.

28. Averick, S.; Mehl, R. A.; Das, S. R.; Matyjaszewski, K. Well-defined biohybrids using reversible-deactivation radical polymerization procedures. J. Control. Release 2015, 205, 45–57.

29. Matyjaszewski, K.; Tserkezov, N. V. Macromolecular engineering by atom transfer radical polymerization. J. Am. Chem. Soc. 2014, 136, 6513–6533.

30. Zhang, H.; Deng, J.; Lu, L.; Cai, Y. Ambient-temperature RAFT polymerization of styrene and its functional derivatives under mild long-wave UV-Vis radiation. Macromolecules 2007, 40, 9252–9261.

31. Baner-Kowollik, C.; Perrier, S. The future of reversible addition fragmentation chain transfer polymerization. J. Polym. Sci., Part A-Polym. Chem. 2008, 46, 5715–5723.

32. Smith, A. E.; Xu, X.; McCormick, C. L. Stimuli-responsive amphiphilic (co)polymers via RAFT polymerization. Prog. Polym. Sci.
mediated radical polymerization (NMP) processes: their understanding and optimization. Chem. Rev. 2008, 108, 1104–1126.

50. Liu, D.; He, J.; Zhang, L.; Tan, J. 100th Anniversary of macromolecular science viewpoint: heterogeneous reversibility of radical polymerization at room temperature. Recent advances and future opportunities. ACS Macro Lett. 2019, 8, 1660–1669.

51. Torres-Rocha, O. L.; Wu, X.; Zhu, C.; Crudden, C. M.; Cunningham, M. F. Polymerization-induced self-assembly (PISA) of 1,5-cyclooctadiene using ring opening metathesis polymerization. Macromol. Rapid Commun. 2019, 40, 1800326.

52. Dai, X.; Yu, L.; Zhang, Y.; Zhang, L.; Tan, J. Polymerization-induced self-assembly via RAFT-mediated emulsion polymerization of methacrylic monomers. Macromolecules 2019, 52, 7468–7476.

53. Tan, J.; Xu, Q.; Zhang, Y.; Huang, C.; Li, X.; He, J.; Zhang, L. Room temperature synthesis of self-assembled ab/b and abc/bc blends by photoinitiated polymerization-induced self-assembly (photo-PISA) in water. Macromolecules 2018, 51, 7396–7406.

54. He, J.; Cao, J.; Chen, Y.; Zhang, L.; Tan, J. Thermoresponsive block copolymer vesicles by visible light-initiated seeded polymerization-induced self-assembly for temperature-regulated enzymatic nanoreactors. ACS Macro Lett. 2020, 9, 533–539.

55. Kedracki, D.; Maroni, P.; Schlaad, H.; Vebert-Nardin, C. Polymer-aptamer hybrid emulsion templating yields bioresponsive nanocapsules. Adv. Funct. Mater. 2014, 24, 1133–1139.

56. Adhikary, P.; Tiwari, K.; Singh, R. Synthesis, characterization, and flocculation characteristics of polyacrylamide-grafted glycogen. J. Appl. Polym. Sci. 2007, 103, 773–778.

57. Seaberg, J.; Kaabipour, S.; Hemmati, S.; Ramsey, J. D. A rapid millifluidic synthesis of tunable polymer-protein nanoparticles. Eur. J. Pharm. Biopharm. 2020, 154, 127–135.

58. Baldwin, A. D.; Klick, K. L. Polysaccharide-modified synthetic polymeric biomaterials. Peptide Sci. 2010, 94, 128–140.

59. Fujita, M.; Shoda, S. I.; Kobayashi, S. Xylanase-catalyzed synthesis of a novel polysaccharide having a glucose-xylene repeating unit, a cellulose-xylan hybrid polymer. J. Am. Chem. Soc. 1998, 120, 6411–6412.

60. Vicent, M. J.; Duncan, R. Polymer conjugates: nanosized medicines for treating cancer. Trends Biotechnol. 2006, 24, 39–47.

61. Lutolf, M.; Hubbell, J. Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. Nat. Biotechnol. 2005, 23, 47–55.

62. Lin, J.; Bao, Y. X.; Lam, W.; L. W. W.; Lu, F.; Zhu, X.; Liu, J.; Wang, H. P. Immunoregulatory and anti-tumor effects of polysaccharopeptide and astragalus polysaccharides on tumor-bearing mice. Immunopharmacol. Immunotoxicol. 2008, 30, 771–782.

63. Mladoková, E.; Svitlová, S.; Všišková, V.; Kogan, G.; Rauko, P. The role of microbial polysaccharides in cancer prevention and therapy. J Cancer Integr Med. 2004, 2, 1738.

64. Deeley, R. G.; Westlake, C.; Cole, S. P. Transmembrane transport of endo-and xenobiotics by mammalian ATP-binding cassette multidrug resistance proteins. Physiol. Rev. 2006, 86, 849–899.

65. Xu, X.; Cui, Y.; Bu, H.; Chen, J.; Li, Y.; Tang, G.; Wang, L. Q. A photosensitizer loaded hemoglobin–polymer conjugate as a nanocarrier for enhanced photodynamic therapy. J. Mater. Chem. B 2018, 6, 1825–1833.

66. Mkwana, H.; Mastroatto, F.; Magnusson, J. P.; Sleep, D.; Hay, J.; Nicholls, K. J.; Allen, S.; Alexander, C. Engineered polymer-transferrin conjugates as self-assembling targeted
drug delivery systems. *Biomacromolecules* 2017, 18, 1532–1543.

67 Duro-Castano, A.; Lim, N. H.; Tranchant, I.; Amoura, M.; Beau, F.; Wieland, H.; Kingler, O.; Herrmann, M.; Nazerê, M.; Plettenburg, O. In vivo imaging of MMP-13 activity using a specific polymer-FRET peptide conjugate detects early osteoarthritis and inhibitor efficacy. *Adv. Funct. Mater.* 2018, 28, 1802738.

68 Gao, D.; Zhang, P.; Liu, Y.; Sheng, Z.; Chen, H.; Yuan, Z. Protein-modified conjugated polymer nanoparticles with strong near-infrared absorption: a novel nanoplatform to design multifunctional nanoprobes for dual-modal photoacoustic and fluorescence imaging. *Nanoscale* 2018, 10, 19742–19748.

69 Faust, H. J.; Sommerfeld, S. D.; Rathod, S.; Rittenbach, A.; Banerjee, S. R.; Tsui, B. M.; Pomper, M.; Amzel, M. L.; Singh, A.; Eliseeff, J. H. A hyaluronic acid binding peptide-polymer system for treating osteoarthritis. *Biomaterials* 2018, 183, 93–101.

70 Bao, X.; Fan, X.; Yu, Y.; Wang, Q.; Wang, P.; Yuan, J.raft modification of lignin-based cellulose via enzyme-initiated reversible addition-fragmentation chain transfer (RAFT) polymerization and free-radical coupling. *Int. J. Biol. Macromol.* 2020, 144, 267–278.

71 Ramirez, L. M. F.; Babin, J.; Boudier, A.; Gaucher, C.; Schmutz, M.; Er-Rafik, M.; Durand, A.; Six, J. L.; Nouvel, C. First multi-reactive polysaccharide-based transurf to produce potentially biocompatible dextran-covered nanocapsules. *Carbohydr. Polym.* 2019, 224, 115153.

72 Cazotti, J. C.; Fritz, A. T.; García-Valdez, O.; Smeets, N. M.; Dubé, M. A.; Cunningham, M. F. Grafting from starch nanoparticles with synthetic polymers via nitroxide-mediated polymerization. *Macromol. Rapid Commun.* 2019, 40, 1800834.

73 Song, W.; Xiao, C.; Cui, L.; Tang, Z.; Zhuang, X.; Chen, X. Facile construction of functional biosurfaces via SI-ATRP and “click glycosylation” *Colloids Surf. B* 2012, 93, 188–194.

74 Rowland, G.; O’Neill, G.; Davies, D. Suppression of tumour growth in mice by a drug-antibody conjugate using a novel approach to linkage. *Nature* 1975, 255, 487–488.

75 Cazotti, J. C.; Fritz, A. T.; Garcia-Valdez, O.; Smeets, N. M.; Dubé, M. A.; Cunningham, M. F. Grafting from starch nanoparticles using nitroxide-mediated polymerization and the grafting from approach. *Carbohydr. Polym.* 2020, 228, 115384.

76 Porter, C. J.; Werber, J. R.; Ritt, C. L.; Guan, Y. F.; Zhong, M.; Eimelech, M. Controlled grafting of polymer brush layers from porous cellullosic membranes. *J. Membr. Sci.* 2020, 596, 117719.

77 Ding, Z.; Fong, R. B.; Long, C. J.; Shayton, P. S.; Hoffman, A. S. Size-dependent control of the binding of biotinylated proteins to streptavidin using a polymer shield. *Nature* 2001, 411, 59–62.

78 Qi, G. B.; Gao, Y. J.; Wang, L.; Wang, H. Self-assembled peptide-based nanomaterials for biomedical imaging and therapy. *Adv. Mater.* 2018, 30, 1703444.

79 Zhang, L.; Beatty, A.; Lu, L.; Abdalrahman, A.; Makris, T.; Wang, G.; Wang, Q. Microfluidic-assisted polymer-protein assembly to fabricate homogeneous functional nanoparticles. *Mater. Sci. Eng. C* 2020, 110768.

80 Kapischon, V.; Whitney, R. A.; Champagne, P.; Cunningham, M. F.; Neufeld, R. J. Polymerization induced self-assembly of alginates based amphiphilic graft copolymers synthesized by single electron transfer living radical polymerization. *Biomacromolecules* 2015, 16, 2040–2048.

81 Johnson, J. A.; Finn, M.; Koberstein, J. T.; Turro, N. J. Construction of linear polymers, dendrimers, networks, and other polymeric architectures by copper-catalyzed azide-alkyne cycloaddition “click” chemistry. *Macromol. Rapid Commun.* 2008, 29, 1052–1072.

82 Meldal, M.; Tornoe, C. W. Cu-catalyzed azide-alkyne cycloaddition. *Chem. Rev.* 2008, 108, 2952–3015.

83 Lutz, J. F.; Zarafshani, Z. Efficient construction of therapeutics, bioconjugates, biomaterials and bioactive surfaces using azide–alkyne “click” chemistry. *Adv. Drug. Deliv. Rev.* 2008, 60, 958–970.

84 Bao, H.; Li, L.; Gan, L. H.; Ping, Y.; Li; J.; Ravi, P. Thermo- and pH-responsive association behavior of dual hydrophilic graft chitosan terpolymer synthesized via ATRP and click chemistry. *Macromolecules* 2010, 43, 5679–5687.

85 Zhang, K.; Zhuang, P.; Wang, Z.; Li, Y.; Jiang, Z.; Hu, Q.; Liu, M.; Zhao, Q. One-pot synthesis of chitosan-g-(PEO-PLLA-PEO) via “click” chemistry and “SET-NRC” reaction. *Carbohydr. Polym.* 2012, 90, 1515–1521.

86 Canning, S. L.; Smith, G. N.; Armes, S. P. A critical appraisal of RAFT-mediated polymerization-induced self-assembly. *Macromolecules* 2016, 49, 1985–2001.

87 Karagot, B.; Esser, L.; Duong, H. T.; Basuki, J. S.; Boyer, C.; Davis, T. P. Polymerization-induced self-assembly (PISA)–control over the morphology of nanoparticles for drug delivery applications. *Polym. Chem.* 2014, 5, 350–355.

88 Dao, T. T.; Vezenkov, L.; Subra, G.; Amblard, M.; Im, M.; Le Meins, J. F. O.; Aubrit, F.; Moradi, M. A.; Ladmiral, V.; Semsarali, M. Self-assembling peptide-polymer nano-objects via polymerization-induced self-assembly. *Macromolecules* 2020, 53, 7034–7043.

89 Tsao, C.; Zhang, P.; Yuan, Z.; Dong, D.; Wu, K.; Niu, L.; McMullen, P.; Luozhong, S.; Hung, H. C.; Cheng, Y. H. Zwitterionic polymer conjugated glucagon-like peptide-1 for prolonged glycemic control. *Bioconjug. Chem.* 2020, 31, 1812–1819.

90 Croke, S. N.; Zheng, J.; Ganevater, M. S.; Guldberg, S. M.; Reinke, T. M.; Finn, M. Immunological properties of protein–polymer nanoparticles. *ACS Appl. Biomater.* 2018, 2, 93–103.

91 Nandi, S.; Kundu, A.; Das, P.; Nandi, A. K. Facile synthesis of water soluble, fluorescent DNA-polymer conjugate via enzymatic polymerization for cell imaging. *J. Nanosci. Nanotechnol.* 2017, 17, 5168–5174.

92 Lueckerath, T.; Strauch, T.; Koyenk, K.; Barner-Kowollik, C.; Ng, D. Y.; Weil, T. DNA–polymer conjugates by photoinduced RAFT polymerization. *Macromolecules* 2018, 20, 212–221.

93 Noteborn, W. E.; Wondergem, J. A.; Iurchenko, A.; Chariey-Prinz, F.; Donato, D.; Voets, I. K.; Heinrich, D.; Kielytk, R. E. Grafting from a hybrid DNA–covalent polymer by the hybridization chain reaction. *Macromolecules* 2018, 51, 5157–5164.

94 Hadinoto, K.; Sundaresan, A.; Cheow, W. S. Lipid–polymer hybrid nanoparticles as a new generation therapeutic delivery platform: a review. *Eur. J. Pharm. Biopharm.* 2013, 85, 427–443.

95 Wong, H. L.; Bendayan, R.; Rauth, A. M.; Xue, H. Y.; Babakhanian, K.; Wu, X. Y. A mechanistic study of enhanced doxorubicin uptake and retention in multidrug resistant breast cancer cells using a polymer-lipid hybrid nanoparticle system. *J. Pharmacol. Exp. Ther.* 2006, 317, 1372–1381.

96 Woodside, M. C.; Newman, M. S.; Cohen, J. A. Sterically stabilized liposomes: physical and biological properties. *J. Drug. Target.* 1994, 2, 397–403.

97 Tomaas, R. M.; Gibson, M. I. Optimization and stability of cell–polymer hybrids obtained by “clicking” synthetic polymers to metabolically labeled cell surface glycans. *Biomacromolecules* 2019, 20, 2726–2736.

98 Mammen, M.; Choi, S. K.; Whitesides, G. M. Polyvalent
interactions in biological systems: implications for design and use of multivalent ligands and inhibitors. Angew. Chem. Int. Ed. 1998, 37, 2754–2794.

99 Zhou, C.; Reesink, H. L.; Putnam, D. A. Selective and tunable galectin binding of glycopolymers synthesized by a generalizable conjugation method. Biomacromolecules 2019, 20, 3704–3712.

100 Yang, L.; Sun, H.; Liu, Y.; Hou, W.; Yang, Y.; Cai, R.; Cui, C.; Zhang, P.; Pan, X.; Li, X. Self-assembled aptamer-grafted hyperbranched polymer nanocarrier for targeted and photoresponsive drug delivery. Angew. Chem. 2018, 130, 17294–17298.

101 Mansur, A.; Mansur, H.; González, J. Enzyme-polymer conjugated to quantum-dots for sensing applications. Sensors 2017, 17, 9951–9972.

102 Liu, Y.; Nevanen, T. K.; Paananen, A.; Kempe, K.; Wilson, P.; Johansson, L. S.; Joensuu, J. J.; Linder, M. B.; Haddleton, D. M.; Milani, R. Self-assembling protein–polymer conjugates for surfaces with antifouling features and low nonspecific binding. ACS Appl. Mater. Interfaces 2018, 11, 3599–3608.

103 Ha, D.; Yang, N.; Nadithe, V. Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: current perspectives and future challenges. Acta. Pharm. Sin. B 2016, 6, 287–296.

104 Mathiowitz, E.; Saltzman, W.; Domb, A.; Dor, P.; Langer, R. Polyanhydride microspheres as drug carriers. Il. Microencapsulation by solvent removal. J. Appl. Polym. Sci. 1988, 35, 755–774.

105 Hawkins, M. J.; Soon-Shiong, P.; Desai, N. Protein nanoparticles as drug carriers in clinical medicine. Adv. Drug. Deliv. Rev. 2008, 60, 876–885.

106 Wahajuddin, S. A. Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers. Int. J. Nanomedicine 2012, 7, 3445.

107 Li, J.; Ma, Y. J.; Wang, Y.; Chen, B. Z.; Guo, X. D.; Zhang, C. Y. Dual redox/pH-responsive hybrid polymer-lipid composites: synthesis, preparation, characterization and application in drug delivery with enhanced therapeutic efficacy. Chem. Eng. J. 2018, 347, 450–461.

108 Jiang, P.; Jacobs, K. M.; Ohr, M. P.; Swindle-Reilly, K. E. Chitosan–polycaprolactone core–shell microparticles for sustained delivery of bevacizumab. Mol. Pharm. 2020, 17, 2570–2584.

109 Suh, J. K. F.; Matthew, H. W. Application of chitosan-based polysaccharide biomaterials in cartilage tissue engineering: a review. Biomaterials 2000, 21, 2589–2598.

110 Ma, P. X. Biomimetic materials for tissue engineering. Adv. Drug. Deliv. Rev. 2008, 60, 184–198.

111 Soltchaga, L. A.; Dennis, J. E.; Goldberg, V. M.; Caplan, A. I. Hyaluronic acid-based polymers as cell carriers for tissue-engineered repair of bone and cartilage. J. Orthop. Res. 1999, 17, 205–213.

112 Huttmacher, D. W. Scaffolds in tissue engineering bone and cartilage. Biomaterials 2000, 21, 2529–2543.

113 Ohgushi, H. Tissue engineering using bioceramics. In Bioceramics and their Clinical Applications, Woodhead Publishing 2008, 718–736.

114 Mishra, R.; Varshney, R.; Das, N.; Sircar, D.; Roy, P. Synthesis and characterization of gelatin-PVP polymer composite scaffold for potential application in bone tissue engineering. Eur. Polym. J. 2019, 119, 155–168.

115 Kim, S. H.; Thambi, T.; Phan, V. G.; Lee, D. S. Modularly engineered alginate bioconjugate hydrogel as biocompatible injectable scaffold for in situ biomineralization. Carbohydr. Polym. 2020, 233, 115832.

116 Zhou, L.; Zhang, Y.; Liu, X.; Chen, J.; Zhang, Q. Biomimetic mineralization on natural and synthetic polymers to prepare hybrid scaffolds for bone tissue engineering. Colloids Surf. B 2019, 178, 222–229.

117 Nelson, R. W.; Nedelkov, D.; Tubbs, K. A. Biosensor chip mass spectrometry: a chip-based proteomics approach. Electrophoresis 2000, 21, 1155–1163.

118 Cornell, B. A.; Braach-Maksyvits, V.; King, L.; Osman, P.; Raguse, B.; Wieczorek, L.; Pace, R. A biosensor that uses ion-channel switches. Nature 1997, 387, 580–583.

119 Pandey, C. M.; Malhotra, B. D. Biosensors: fundamentals and applications. Walter de Gruyter GmbH & Co KG. 2019.

120 Gu, T.; Zhang, Y.; Deng, F.; Zhang, J.; Hasebe, Y. Direct electrochemistry of glucose oxidase and biosensing for glucose based on DNA/chitosan film. J. Environ. Sci. 2011, 23, 566–569.

121 Yoo, E. H.; Lee, S. Y. Glucose biosensors: an overview of use in clinical practice. Sensors 2010, 10, 4558–4576.

122 Yang, Y.; Nam, S.; Lee, W. Y. Tris(2,2′-bipyridyl) ruthenium(II) electrogenerated chemiluminescence ethanol biosensor based on ionic liquid doped titania-Nafion composite film. Microchem. J. 2018, 142, 62–69.

123 Paloni, J. M.; Olsen, B. D. Polymer domains control diffusion in protein-polymer conjugate biosensors. ACS Appl. Polym. Mater. 2020, 14, 4481–4492.

124 Paloni, J. M.; Dong, X. H.; Olsen, B. D. Protein–polymer block copolymer thin films for highly sensitive detection of small proteins in biological fluids. ACS Sensors 2019, 4, 2869–2878.

125 Qi, F.; Qian, Y.; Shao, N.; Zhou, R.; Zhang, S.; Lu, Z.; Zhou, M.; Xie, J.; Wei, T.; Yu, Q. Practical preparation of infection-resistant biomedical surfaces from antimicrobial β-peptide polymers. ACS Appl. Mater. Interface 2019, 11, 18907–18913.

126 Nishimura, T.; Shishi, S.; Sasaki, Y.; Akiyoshi, K. Substrate-sorting nanoreactors based on permeable peptide polymer vesicles and hybrid liposomes with synthetic macromolecular channels. J. Am. Chem. Soc. 2019, 142, 154–161.

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