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Biomedical polymers: synthesis, properties, and applications

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Biomedical polymers have been extensively developed for promising applications in a lot of biomedical fields, such as therapeutic medicine delivery, disease detection and diagnosis, biosensing, regenerative medicine, and disease treatment. In this review, we summarize the most recent advances in the synthesis and application of biomedical polymers, and discuss the comprehensive understanding of their property-function relationship for corresponding biomedical applications. In particular, a few burgeoning bioactive polymers, such as peptide/biomembrane/microorganism/cell-based biomedical polymers, are also introduced and highlighted as the emerging biomaterials for cancer precision therapy. Furthermore, the foreseeable challenges and outlook of the development of more efficient, healthier and safer biomedical polymers are discussed. We wish this systemic and comprehensive review on highlighting frontier progress of biomedical polymers could inspire and promote new breakthrough in fundamental research and clinical translation.

biomedical polymer, nanomedicine, cancer therapy, drug delivery, bioimaging and biosensing, tissue engineering, regenerative medicine, cytotoxicity, biocompatibility

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1 Introduction

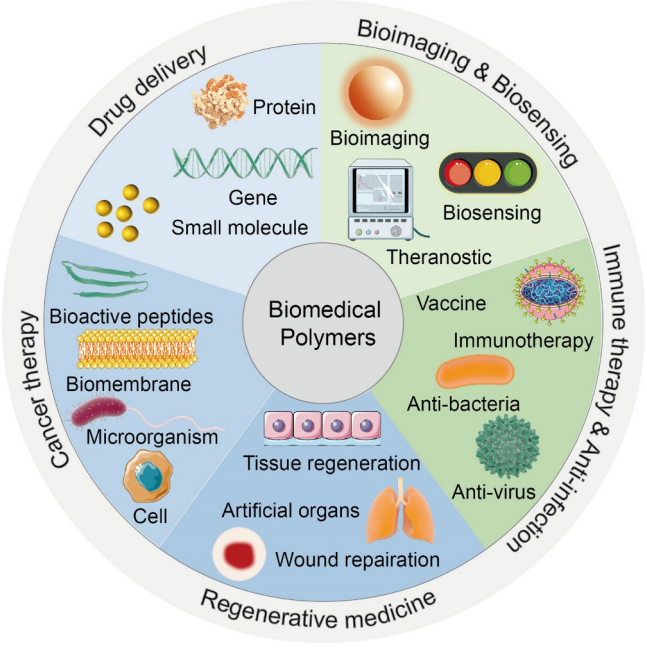
Biomedical polymers are classified into naturally-derived polymers and synthetic polymers according to the sources [1,2]. The main difference between these two kinds of polymers is in structure [3]. Usually, many naturally-derived polymers (*e.g.*, proteins, polysaccharides) spontaneously fold into compact shapes in complex ways depending on their primary structures, which, in turn, determine their biological functions. Instead, most synthetic polymers (*e.g.*, polyesters, poly(ethylene glycol), polycarbonates) have simpler, more random structures. In addition, naturally-derived polymers are generally biodegradable and interact well with biological units (*e.g.*, cells and tissues), yet, they have some disadvantages such as limited mechanical properties, uncontrolled degradation, and possible immunogenicity, which greatly limit their *in vivo* application [4,5]. In contrast, synthetic polymers exhibit good controllability in terms of composition, structure, mechanical properties, and degradation behavior, but they generally lack inherent biological activity [6,7]. Therefore, it is of great significance to give full play to the advantages of natural and synthetic polymers in biomedical fields.

Biomedical polymers have been extensively developed for promising applications in a lot of biomedical fields, such as smart drug delivery, disease detection/diagnosis, biosensing, regenerative medicine, and disease treatment. For example, polymer-based carriers provide major advances in improving the bioavailability and therapeutic outcomes at spatio-temporal drug delivery, greatly benefiting the treatment of diseases, such as cancers, organ grafting, and infections [8–10]. Meanwhile, the rational design of intelligent polymeric carriers can provide the stimuli-responsive ability to respond to the external or intrinsic signals in specific lesions, thereby achieving precise and targeted localization at lesion sites and triggered release of payloads inside diseased cells for enhanced therapeutic efficacy [11,12]. Moreover, biomedical polymers have been extensively applied to carry out the concept of theranostics, either as vehicles for delivering both therapeutic and diagnostic agents or as self-theranostic agents, owing to their biocompatibility, biodegradability, structural diversity, and multifunctionality [13–16]. The flexible design of polymer-based theranostic systems can not only target diseased areas within the body, but also provide information on the extent of the disease, where applicable, to report the disease's response to treatment.

More importantly, some burgeoning bioactive polymers (*e.g.*, biomembrane, cells, microorganisms as well as their natural components) have been highlighted for their intrinsic tumor targeting, immune activation, easy functionalization, and intrinsic therapeutic properties. For example, microbial components containing peptides, proteins, polysaccharides and lipids can be used as natural biomedical polymers to design and prepare effective nanomedicines for cancer-targeted therapy [17]. And functional cells used as direct therapeutic agents (*e.g.*, CAR T cells based immunotherapy) or as drug carriers (*e.g.*, doxorubicin (DOX)-loaded chitosan nanoparticles modified erythrocytes) have been developed

for treating cancers with high specificity and efficiency. Particularly, the integration of synthetic materials (*i.e.*, polymeric materials) with these bioactive polymers can be achieved through various integration methods such as physical assembly, chemical conjugation, and biological ligand recognition, thus greatly enhancing the function and sustainability of bioactive therapeutic platforms [18,19]. As such, the development of biomedical polymers-involved therapeutic strategies may have collective advantages and compensate for the disadvantages of other materials, holding the potential to greatly recommend the clinical translation of biomedical materials.

This review systematically summarizes the latest research advances of preparation and application of biomedical polymers (Scheme 1). The comprehensive understanding of the design principles of biomedical polymers is discussed for the use in various fields, including medicine delivery, bioimaging, biosensing and theranostic, anti-infection, regenerative medicine, and cancer therapy. Moreover, the structure-function relationship of biomedical polymers used as nanomedicines as well as the potential side effects is explicated in detail. In addition, a few emerging strategies are also highlighted such as biomedical polymers for vaccines-based immunotherapy, cytokine therapy, and adoptive T cell therapy. In particular, bioactive polymers, including peptide/biomembrane/microorganism/cell-based biomedical polymers, are highlighted as the smart nanotherapeutics for cancer precision therapy. At the end, some critical challenges and outlook of biomedical polymers-based applications in the future are extensively discussed.



Scheme 1 Schematic illustration of smart polymers for biomedical applications (color online).

2 The synthesis of biodegradable biomedical polymers

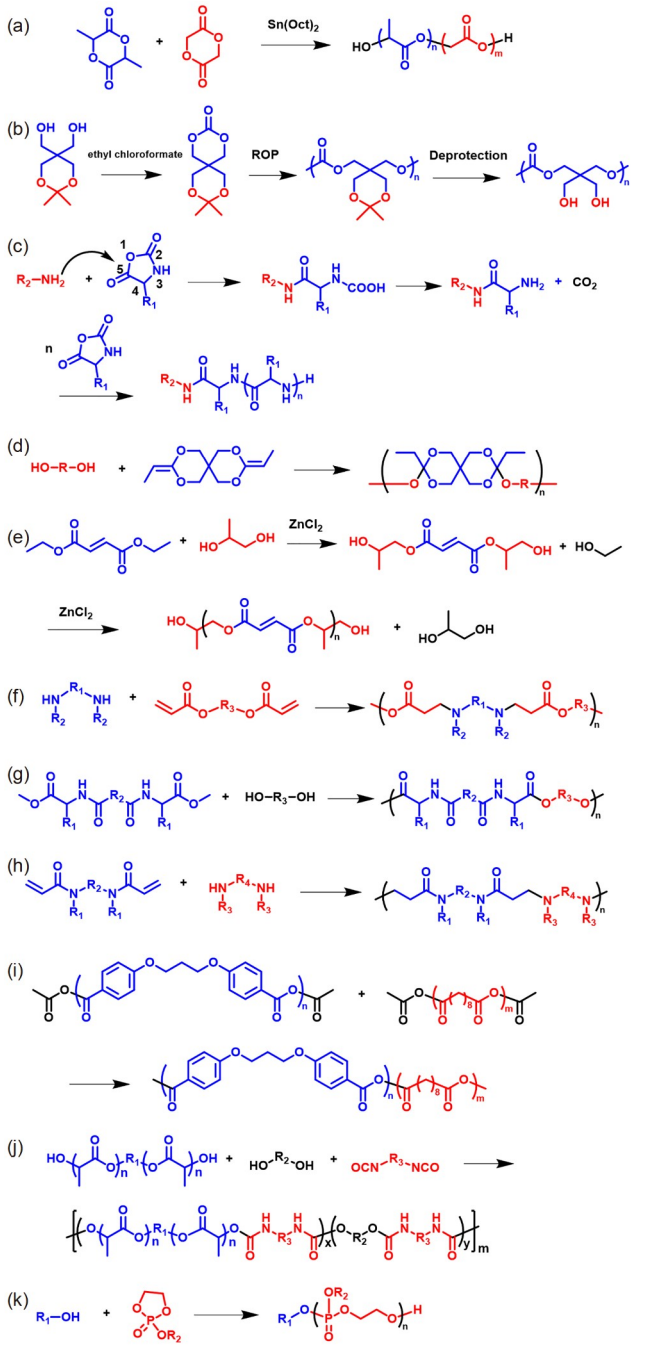
Biomedical polymers have been classified into naturally-derived polymers and synthetic polymers [1,2]. Naturally-derived polymers including proteins and polysaccharides possess biodegradability and interactions with cells and tissues, while they show limited mechanical properties, uncontrollable degradation and possible immunogenicity. In contrast, synthetic polymers display good controllability in compositions, structures, mechanical properties, and degradation behaviours, although they are usually short of innate bioactivities [2]. Additionally, based on the biodegradability *in vivo*, synthetic biomedical polymers can be further categorized into biodegradable synthetic polymers and nonbiodegradable synthetic polymers [20]. A range of nonbiodegradable synthetic polymers have been developed for different biomedical applications, including poly(ethylene glycol) (PEG), ultrahigh molecular weight polyethylene (UHMWPE), polymethacrylate derivatives, poly(tetrafluoroethylene), poly(dimethylsiloxane), poly(urethanes) (PUs)/poly(urethane-urea), polyetheretherketone, polyethyleneimine (PEI), and poly(*N*-isopropylacrylamide). Due to their nonbiodegradability and bioinert nature *in vivo*, many of these polymers are investigated or used as permanent implantable prostheses for partial or complete substitution of the functions of damaged organs. For instance, a synthetic vascular graft based on poly(ether-urethane-urea) has been approved by the US Food and Drug Administration (FDA) for clinical application. In orthopaedic applications, a composite of UHMWPE and a CoCrMo alloy was approved by FDA as an artificial lumbar disk, and a PU-based implant was approved by FDA as a meniscal substitute [21].

In contrast to the permanent implantable prostheses based on the nonbiodegradable polymers, a wide range of biodegradable polymers have also been developed and evaluated in the past decades for different biomedical applications, such as controlled delivery systems, temporary scaffolds for cell culture and tissue regeneration, absorbable devices for wound closure [22]. These polymers may be degraded, metabolized and/or excreted from the body after completing their specific functions *in vivo*, without obvious toxic side-effects, long-term burden to the body and the generation of toxic degradation byproducts. This section will focus on the synthesis of some representative biodegradable polymers that are designed for biomedical applications, including aliphatic polyesters, aliphatic polycarbonates, poly(amino acid)s, poly(ortho esters), poly(propylene fumarate) (PPF), poly(β-amino esters), poly(ester amide)s, poly(amidoamine)s, polyanhydrides, poly(ester urethanes), poly(organo)phosphazenes, and polyphosphoesters. Additionally, the biodegradation behaviours and (potential) biomedical applications of these polymers are briefly introduced.

2.1 Aliphatic polyesters

Synthetic aliphatic polyesters, typically poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic acid-*co*-glycolic acid) (PLGA), and poly(ε-caprolactone) (PCL), are one type of the most studied biodegradable polymers for biomedical applications [23,24]. Based on the residue chirality, there are four types of PLA including poly(*L*-lactic acid) (PLLA), poly(*D*-lactic acid) (PDLA), poly(rac-*D*,*L*-lactic acid), and poly(meso-lactide). PLA, PGA, and PLGA have been approved by FDA for various clinical uses, such as absorbable sutures (DEXON® (PGA-based), Vicryl Rapide® (PLGA(10:90)-based)), bone fixation devices (Biofix® (PGA- or PLLA-based), Fixsorb® (PLLA-based)), facial fillers (Sculptra® (PLLA-based)), and drug delivery systems (Eligard® (Leuprolide acetate/PLGA)) [23–25]. Compared with the aforementioned polyesters, PCL shows obvious longer hydrolytic degradation time for over 2 years. A commercially available monofilament suture is based on the copolymer of ε-caprolactone (ε-CL) and GA [23]. The above aliphatic polyesters are typically synthesized *via* the ring-opening polymerization (ROP) of various cyclic lactones including lactide (LA), GA, ε-CL and their mixed monomers, by using tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) as a catalyst (Scheme 2a).

Additionally, polyhydroxyalkanoates (PHAs), a class of aliphatic polyesters commonly produced by various bacteria, have also received considerable attention for biomedical applications [26]. Poly(3-hydroxybutyrate) (P3HB) is the most widely studied PHA, and has been produced as biodegradable plastics at a commercial scale. Due to its high crystallinity and hydrophobicity, P3HB shows a lower degradation rate compared with the polyesters based on LA and/or GA, with the generation of nontoxic 3-hydroxybutyric acid. The crystallinity and degradation rate can be tuned by the incorporation of other hydroxyalkanoate units. In addition to the microbial source, a chemical route for the synthesis of P3HB through the ROP of β-butyrolactone monomer has also been reported [22]. The investigation on the biomedical applications of PHAs is encouraged by the FDA approval of an absorbable suture based on poly(4-hydroxybutyrate) (P4HB) for clinical applications [26]. It is noteworthy that the content of endotoxin in bacteria-derived PHAs needs to be strictly controlled for clinical uses.



Scheme 2 Synthesis routes for representative aliphatic polyesters (a), aliphatic polycarbonates (b), poly(α-amino acid)s/polypeptides (c), poly(ortho esters) (d), poly(propylene fumarate) (e), poly(β-amino esters) (f), poly(ester amide)s (g), linear poly(amidoamine)s (h), polyanhydrides (i), poly(ester urethanes) (j), and polyphosphoesters (k) (color online).

2.2 Aliphatic polycarbonates

Polycarbonates (PCs) contain a carbonyl bond connecting two ether bonds. The synthesis of PCs is usually through the ROP of cyclic carbonates (Scheme 2b) [27]. Compared with the aliphatic polyesters, aliphatic PCs show the fascinating advantages in the incorporation of functional moieties, due to the facile procedures to obtain functionalized cyclic carbonates through the reactions between diol-containing compounds and triphosgene or ethyl chloroformate. Aliphatic PCs are relatively hydrolytically stable but their degradation can be accelerated in the presence of enzymes. Poly(trimethylene carbonate) (PTMC) is a representative aliphatic PC that has been investigated for soft tissue regeneration and drug delivery systems, attributed to its excellent flexibility

and non-acidic microenvironment caused by degradation byproducts.

2.3 Polypeptides

Synthetic polypeptides, also called poly(α-amino acid)s, are composed of amino acid residues linked by peptide bonds. Polypeptides can be chemically synthesized by ROP of α-amino acid *N*-carboxyanhydrides (NCAs) using amine-containing initiators, or by solid phase peptide synthesis [28–31]. Based on the ROP of α-amino acid NCAs, polypeptides with relatively high molecular weights can be facilely obtained. It is noteworthy that the ROP of α-amino acid NCAs in the presence of an amino-based initiator commonly follows two types of mechanisms, including amine mechanism and activated monomer mechanism. In the presence of primary amines or highly nucleophilic secondary amines, the ROP of NCAs is usually initiated through amine mechanism by the nucleophilic attack of primary amines to CO-5 of NCAs (Scheme 2c) [28]. The primary amine-initiated ROP can result in polypeptides and their copolymers with controlled molecular weights and structures. In contrast, when tertiary amines or some secondary amines containing bulky substation groups are used as initiators, a small fraction of NCAs are first deprotonated at NH-3 by the initiators, and the ROP of remained NCAs is subsequently initiated by the activated NCA monomers. This approach allows the preparation of polypeptides with high molecular weights.

Attributed to their good biocompatibility, enzymatic degradability and unique secondary structures analogous to natural peptides, polypeptides have been extensively investigated for biomedical applications [28–31]. In the presence of proteinases, polypeptides degrade into α-amino acids that are nontoxic, nonimmunogenic and metabolizable. Several ROP-derived polypeptides have been evaluated in phase I, II & III clinical trials [32]. For instance, a polymeric prodrug based on poly(*L*-glutamic acid) (PLG) conjugated with paclitaxel (PTX) through an ester bond (CT-2103) has entered phase III clinical trial in USA for the treatment of advanced non-small cell lung cancer in combination with carboplatin [33]. Additionally, a poly(ethylene glycol)-*block*-poly(*L*-glutamic acid) micelle loaded with cisplatin (NC-6004) has entered phase I/II clinical trials in USA and Europe, for treatment of various types of cancers in combination with an antibody and/or a chemotherapeutics.

2.4 Poly(ortho esters)

Poly(ortho esters) (POE) contain three geminal ether bonds in the backbones that are hydrolysable and sensitive to acid [34]. There are four families of POE that have been investigated. For instance, POE II is synthesized through the reaction between a diol and a diketene acetal by using a trace of an acidic catalyst (Scheme 2d). The molecular weight of the polymerization products can be well controlled by this reaction. To adjust the degradation rate at neutral environment, oligo(lactide)s or oligo(glycolide)s are usually incorporated into the polymer backbone during a preparation process similar to that of POE II. This leads to the formation of POE IV, which obtain more attention for potential biomedical applications compared with other types of POE in the past decades, and has entered Phase I clinical trial. The hydrolytic degradation periods of POE IV range from several days to several months depending on the composition, with the generation of biocompatible pentaerythritol, diol, propanoic acid, and lactic acid (or glycolic acid).

2.5 Poly(propylene fumarate)

PPF is a linear polyester containing an unsaturated bond in the fumarate repeating units [35]. The degradation of PPF arises from the hydrolysis of the ester bonds, which leads to biocompatible degradation byproducts, fumatic acid and 1,2-propane glycol. The unsaturated bonds in the PPF backbone allow the further covalent crosslinking in the presence of a photoinitiator and ultraviolet irradiation, leading to the formation of biomaterials with obviously enhanced mechanical properties. The synthesis of PPF commonly involves a two-step reaction including the formation of a bis(hydroxypropyl) fumarate diester intermediate from diethyl fumarate and propylene glycol, followed by the transesterification of the above intermediate under reduced pressure (< 1 mm Hg) (Scheme 2e) [35].

2.6 Poly(β-amino esters)

Poly(β-amino esters) (PBAEs) are a type of biodegradable polymers containing ester bonds and tertiary amino groups in the backbones [36]. The synthesis of linear PBAEs is typically based on the Michael additions between primary monoamine or secondary diamines and diacrylate-conjugated monomers (Scheme 2f). The incorporation of a multifunctional monomer can result in the formation of a hyperbranch or cross-linked product. Due to the electrostatic interactions with various negatively-charged genes/therapeutic agents and the responsiveness to physiologically relevant pH change of the tertiary amino groups, PBAEs have been investigated as carriers for controlled delivery of genes or other therapeutic agents in the past two decades. This type of polymers usually shows rapid hydrolytic degradation within 3 days with the generation of noncytotoxic diols and bis(β-amino acids) [36].

2.7 Poly(ester amide)s

Poly(ester amide)s (PEAs) are a class of polymers containing

both ester and amide bonds in the backbones [37,38]. This type of polymers has also attracted considerable interest for biomedical applications due to the combination of the thermomechanical properties of polyamides with the biodegradability of polyesters [39]. Based on the different choices of monomers, PEAs can be synthesized through ROP of morpholino-2,5-dione derivative intermediates, polycondensation reactions based on monomers containing diamide (or bis(amino acids)) and diester moieties (Scheme 2g) [39,40], as well as passerini reactions [41].

2.8 Poly(amidoamine)s

Poly(amidoamine)s are synthetic polymers containing both tertiary amino groups and amide bonds in the backbones [42,43]. Poly(amidoamine)s have been investigated for various biomedical applications, due to their biocompatibility, biodegradability and electrostatic interactions with genes and other biomacromolecules. Similar to PBAEs, linear poly(amidoamine)s are typically synthesized by stepwise Michael addition reactions between primary or secondary amines and bisacrylamides. The replacement of diacrylate-containing monomers with bisacrylamides results in an increased hydrolytic stability of poly(amidoamine)s compared with PBAEs. Based on the stoichiometric ratios of the di- or tri-functional amines and bisacrylamides, the linear or hyperbranched polymers can be obtained. As an example, linear poly(amidoamine)s are synthesized by the reaction between primary mono-amine or secondary diamine monomer with bisacrylamide monomer (Scheme 2h) [42].

It is worth mentioning that poly(amidoamine) dendrimers have also attracted considerable interest as carriers for drug and gene delivery due to their advantages including precise controls of size and structure, as well as abundant functional groups [44]. Typical strategies for the synthesis of poly(amidoamine) dendrimers include divergent and convergent approaches [45]. For instance, poly(amidoamine) dendrimers can be prepared through a divergent synthesis strategy by an iterative two-step sequence, including exhaustive Michael addition of the amino groups of primary diamines with methyl acrylate, and subsequent amidation of the surface esters with the primary diamines.

2.9 Polyanhydrides

Polyanhydrides are a class of biodegradable polymers that are composed of anhydride linkages in the backbones [46]. Compared with polyesters and PCs, polyanhydrides show faster hydrolytic degradation, due to the water-sensitivity of anhydride linkages. Other than the precise synthesis processes of the polymers through ROP, the synthesis of polyanhydrides are commonly based on condensation polymerization, which may cause relatively broad polydispersity indexes. For instance, a representative biomedical polyanhydride, poly[bis(*p*-carboxylphenoxy)propane sebacic acid anhydride] (PCPP-SA), is obtained by the melt-condensation of the mixed anhydride prepolymers of 1,3-bis(*p*-carboxyphenoxy)propane and sebacic acid (Scheme 2i) [47]. An absorbable implant based on PCPP-SA for controlled release of carmustine (Gliadel®) has been approved by FDA and commercialized for the treatment of brain tumor [46].

2.10 Poly(ester urethanes)

Polyurethanes (PUs) that contain microphase-separated soft and hard segments have been widely studied as long-term implants attributed to their excellent biocompatibility, hydrolytic stability and good mechanical properties [48]. PUs are commonly synthesized by the polycondensation of diisocyanate-containing monomers with diols or polyols. To adjust the biodegradability of PUs, poly(ester urethanes) have been developed by the incorporation of biodegradable polyester diols or triols as the soft segments in the PU backbones (Scheme 2j) [49]. The degradation rate can be tuned by changing the composition of the polyester segments.

2.11 Poly(organo)phosphazenes

Poly(organo)phosphazenes are a type of inorganic-organic hybrid polymers containing an alternating phosphorus-nitrogen backbone and two organic pendant groups linked to the phosphorus atom [50]. The synthesis of the polymer precursor, poly(dichlorophosphazene), is usually based on the ROP of hexachlorocyclotriphosphazene or living cationic polymerization of a phosphoranimine using phosphorus pentachloride as a catalyst. Biodegradable poly(organo)phosphazenes are then obtained through the substitution reactions between poly(dichlorophosphazene) and monofunctional, sometimes protected nucleophiles, such as amino acid ester derivatives, sodium salts of glycolate or lactate ester, and sodium salts of protected *D*-glucose [51].

Although the phosphorus-nitrogen bonds are hydrolytically stable, the hydrolysis of poly(organo)phosphazenes is imparted by the incorporation of proper organic side groups [52]. Additionally, the hydrolytic degradation rate and physicochemical properties of poly(organo)phosphazenes are also highly dependent on the organic side groups. Due to these advantages, these biodegradable polymers have been investigated for potential biomedical applications. An FDA-approved product based on poly[bis(trifluoroethoxy)phosphazene] (Polyzene-F®) has been tested as stent coatings and embolizing microspheres [53].

2.12 Polyphosphoesters

Polyphosphoesters (PPEs) are composed of repeating phosphoester bonds and two variable groups, one in the backbone and the other in the pendant group. The phosphoester bonds are both hydrolytically and enzymatically degradable. The variable moieties in both the backbone and side group render these polymers highly tunable physiochemical properties and biodegradation behaviours, which have been investigated for various biomedical applications [54]. Different approaches have been developed for the synthesis of PPEs, including ROP, polycondensation, and polyaddition [53]. As an example, PPE can be synthesized by the ROP of cyclic phosphoester monomers in the presence of a hydroxyl-containing molecule and $Sn(Oct)_2$ as the initiator and catalyst, respectively (Scheme 2k) [54].

3 Biomedical polymers for medicine delivery

3.1 Biomedical polymers used for small molecule drug delivery

Hydrogels, micelles, vesicles, and other polymer-based carriers provide major advances in an improving therapeutic index and bioavailability at spatiotemporal drug delivery, greatly benefiting the treatment of diseases, such as cancers, infections, and cardiovascular disease [55–62]. In this field, tremendous progress has been made in the last decades. Among those, the development of anticancer drug delivery systems is a typical representative, and the progress in this area will be mainly focused on in this section.

3.1.1 The correlation between the physio-chemical properties and in vivo fate of nanomedicines

Current nanomedicines for chemotherapeutics can relieve adverse effects but often fail to enhance therapeutic efficacy. For improving the therapeutic outcomes and guiding the design of nano-delivery systems, researchers established the correlations between the physio-chemical properties and *in vivo* fate of nanoparticles. The drug-delivery process of an intravenously administered nanomedicine involves circulation, accumulation, penetration, internalization and release. The nanoproperties, such as size [63–65], shape [66,67], and surface properties [68–70], are crucial to the *in vivo* fate of nanomedicines. Basically, nanoparticles with a size of 100–150 nm have an optimal circulation and tumor accumulation [63,64,71], while nanoparticles smaller than 30 nm are more conducive to tumor penetration [63,71]. Surely, PEGylation is a famed discovery in the development of functionalized nanoparticles, which facilitates the successful clinical application of nanoparticles by prolonging the blood circulation and enhancing the tumor accumulation [72,73]. For example, Wang *et al*. [70,74] established a reliable relationship between surface PEG density or length and nanoparticle's *in vivo* behaviours by using polymeric nanoparticles with controllable PEG density or length but similar other nano-properties *via* incorporating of hydrophobic homopolymer and regulating the PEG block molecular weight. They found that the blood circulation time of nanoparticle is positively dependent on the surface PEG density, which first increases and then decreases along with the increase of surface PEG length. However, a high density of PEGylation prevents the nanomedicines from interaction with tumor cells, showing low drug internalization. In addition, surface charge is another significant influence on nanoparticle behaviours. It confers nanoparticles with the contradictions of short blood circulation, low tumor accumulation, enhanced tumor penetration, and high cellular internalization [69,75–77].

3.1.2 Stimuli-responsive nanomedicines

From the abundant basic studies, it is noted that these needed properties of nanomedicines are often opposing in different steps, most of which can be summarized as the PEG [78], charge [79], size dilemmas [80]. In the past decades, the development of stimuli-responsive nanomedicines enables us to manipulate the properties of nanomedicines to improve drug delivery efficacy. These nanomedicines can be self-adaptive to the requirements during the delivery process and overcome the dilemmas.

Smart nanomedicines have been designed to respond to endogenous stimuli, such as pH [81–83], redox gradients [84,85], enzymes [86,87], and external stimuli including temperature [88], light [89], gamma/X-ray irradiation [90], and ultrasound [91]. Such design significantly reduces the toxicity of drugs to normal tissues and improves the therapeutic efficacy when the kinetics of drug activation is well-controlled.

Nanomedicines can also achieve a stealthy-to-sticky transition from being neutral/PEGylated/shielding functional groups in the normal tissues to being cationic/dePEGylated/exposing functional groups in the lesion sites [82,92,93]. Such design enables the nanomedicines with long blood-circulation half-lives, effective drug accumulation and internalization, and thus promotes therapeutic efficacies. Wang *et al*. [82] developed a powerful tool, tumor-acidity-cleavable maleic acid amide (TACMAA), for designing smart nanomedicines to overcome the dilemmas (Figure 1). Such tool enables nanomedicines achieving tumor specific activation by tumor acidity with negative-to-positive charge transition [87,94], dePEGylated transition [95,96], and shielding/exposing transition of functional groups [97,98]. Shen *et al*. [87] reported that a γ-glutamyl transpeptidase (GGT)-responsive zwitterionic camptothecin-polymer conjugate could actively infiltrate throughout the tumor tissue *via* transcytosis (Figure 2). Under the function of GGT, the

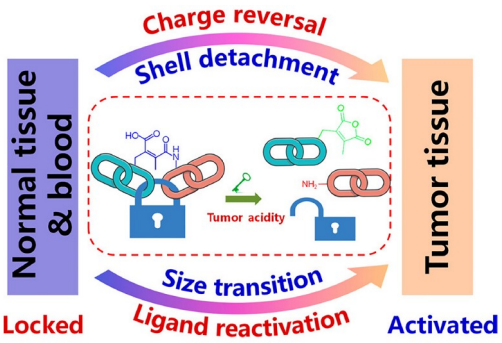


Figure 1 TACMAA is produced by the facile reaction of an amino group with 2,3-dimethylmaleic anhydride (DMMA) and its derivatives and can be cleaved under tumor acidity. By virtue of such characteristics, NPs containing TACMAA enable size or surface charge switching at tumor sites so that they can overcome those delivery barriers for improved drug delivery and cancer therapy [82] (color online).

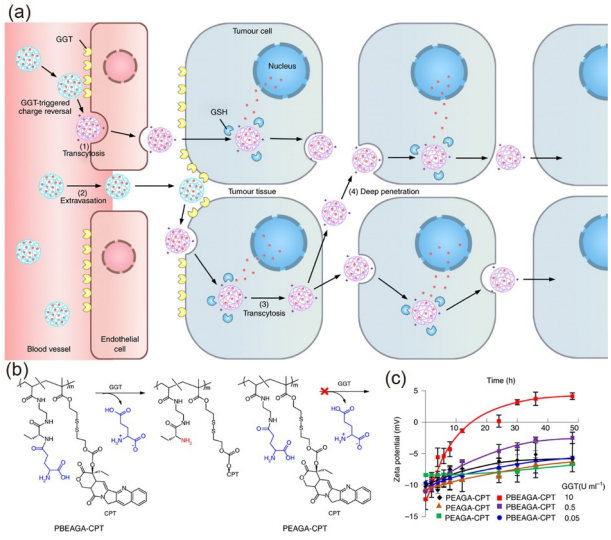


Figure 2 (a) Adsorption-mediated transcytosis (AMT) resulted in active tumor penetration for the trans-endothelial and transcellular transport of the nanomedicine, including enzyme-mediated transformation of the neutral nanomedicine to a cationic one, extravasating into the tumor interstitium, active penetrating *via* the cancer-cell transcytosis and rapidly internalized by cancer cells *via* the AMT. (b) The structures of the GGT-responsive cationizing drug-conjugate PBEAGA-CPT and the non-GGT-responsive conjugate PEAGA-CPT, and their GGT-catalysed γ-glutamylamide hydrolysis to the primary amine. (c) The zeta potentials as a function of incubation time of PEAGACPT and PBEAGA-CPT in the presence of GGT [87] (color online).

zwitterionic prodrug transformed to cationic polymer, which underwent caveolae-mediated endocytosis and transcytosis, enabling tumor penetration and achieving a significantly enhanced therapeutic efficacy. They also reported a polyzwitterion, poly(2-(*N*-oxide-*N*,*N*-diethylamino)ethyl methacrylate) (OPDEA), which exhibited a stealthy-to-sticky transition (Figure 3) [99]. Zwitterionic OPDEA was not sticky towards proteins and bound reversibly to cell membranes through weak interaction with phospholipids. These properties rendered the polymer with long blood-circulation

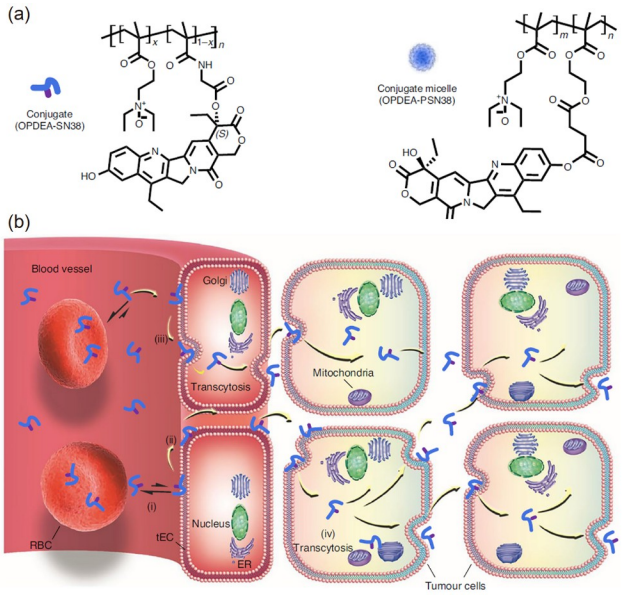


Figure 3 OPDEA-based conjugate or block copolymer with the anticancer drug SN38 and the drug delivery process. (a) Molecular structures of the OPDEA conjugate and conjugate block copolymer. (b) After intravenous injection, the OPDEA conjugate or micelles circulate in the plasma or reversibly attach to RBCs, and may also adsorb on the tECs (i); adsorption on the tECs facilitates the extravasation of the conjugate or micelles *via* the EPR effect (ii), and may also trigger AMT through the tECs into the interstitium (iii). In the tumor interstitium, adsorption on the cancer cell initiates rapid internalization of the nanomedicine, some of which are exocytosed and internalized by the surrounding cells and passed on to cells in deeper layers, leading to infiltration into the avascular regions of the tumor (iv) [99]. ER, endoplasmic reticulum (color online).

half-lives and triggered fast cellular uptake, transcytosis-based active tumor penetration, and the ability to eradicate large tumors and patient-derived tumor xenografts in mice.

Transformable nanoparticles with size or sharp transition also show promise for enhanced therapeutic efficacy. Liang *et al.* [100] developed a proton-driven nanotransformer, which induced a strong immune response without substantial systemic toxicity (Figure 4). The nanotransformer mechanically disrupted the endosomal membrane and directly delivered the antigenic peptide into the cytoplasm after its transition from nanospheres (about 100 nm in diameter) to nanosheets (several micrometres in length or width). Wang *et al.* [101] reported a smart polymeric clustered nanoparticle (iCluster) to systematically overcome the size dilemmas (Figure 5). iCluster had an initiate size of ~100 nm, which was favorable for long blood circulation and tumor accumulation, and released platinum prodrug-conjugated poly (amidoamine) dendrimers (diameter ~5 nm) at tumor extracellular acidity, which greatly facilitated tumor penetration, cell internalization and therapeutic efficacy of the drug.

3.1.3 *Active targeting drug delivery strategies*

Active targeting strategy is another important direction for site-specific drug delivery. Targeting ligands including pro-

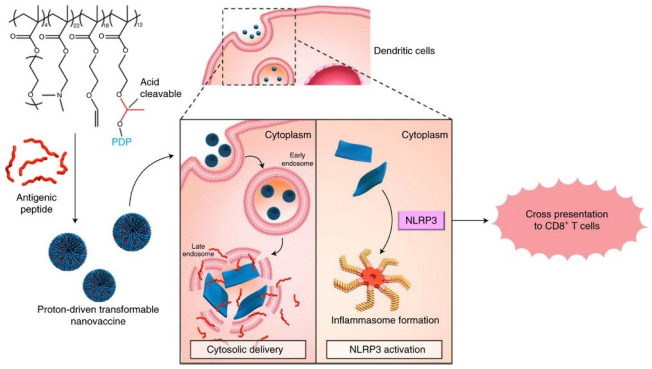


Figure 4 Schematic illustration of a proton-driven NTV for cancer immunotherapy. The nanoparticles transit from nanospheres (about 100 nm in diameter) to nanosheets (several micrometres in length or width) in the acidic lysosome, mechanically disrupt the endosomal membrane and directly deliver the antigenic peptide into the cytoplasm [100] (color online).

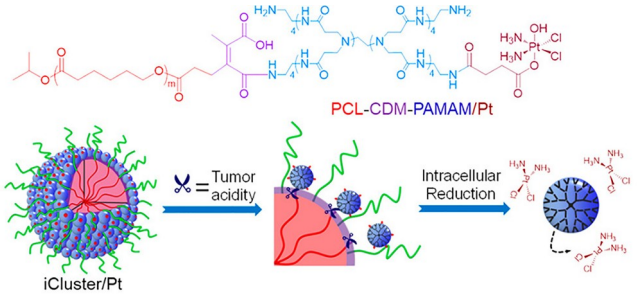


Figure 5 Structure of platinum prodrug-conjugated poly(amidoamine)-graft-poly(ε-caprolactone) (PCL-CDM-PAMAM/Pt); its self-assembly into iCluster/Pt, and iCluster/Pt's response to tumor acidity and the intracellular reductive environment [101] (color online).

teins (such as transferrin [102] and antibodies [103]), peptides [104], aptamers [105], and small molecular ligands (such as folate [106] and monosaccharides [107]) have been reported with encouraging results both *in vitro* and in animal studies. Multiple targeting strategies have been promoted to preclinical and clinical setting [108,109].

Besides molecular targeting ligands, circulating cell-targeting strategies offer the possibility of active accumulation in the target tissues due to the intrinsic stealth properties, natural homing capability, and the intrinsic ability to cross biological barriers of the cells [110–112]. For example, erythrocyte/immune cell-hitchhiked nanoparticles can effectively accumulate in the lesion sites [113–117]. Shuai *et al.* [117] reported another example of using anti-PD-1 antibody conjugated nanocarrier, which could bind to circulating PD-1$^+$ T cells and then follow their infiltration into the tumor, markedly improving antitumor therapeutic effect.

Another interesting strategy is to amplify targeting signal. As an example, Tang and Chen *et al.* [118] reported a self-amplifying tumor-homing nanotherapeutic system, which contained a coagulation targeting peptide-decorated poly(*L*-glutamic acid)-graft-maleimide poly(ethylene glycol)/combretastatin A4 conjugate (A15-PLG-CA4) (Figure 6). In the tumor, A15-PLG-CA4 subsequently released CA4, a vascular disrupting agent that can disrupt the established tumor blood vessels and induce hemorrhage within tumors. Afterwards, the hemorrhage activated the blood coagulation factor XIII (FXIII) to FXIIIa, which further facilitated A15-PLG-CA4 homing to tumors and released more CA4 in the tumors, and then started again to initiate a next cycle (Figure 6). In this way, A15-PLG-CA4 initiated a manner of chain reaction to deliver more drugs to tumor and showed a significantly high antitumor effect against large C26 tumors (≈500 mm^3). Gu *et al.* [119] reported a relay drug delivery strategy through amplifying the targeting signal and enhancing antitumor therapy. A signal transmission nanocarrier that encapsulated tumor necrosis factor α (TNF-α) could trigger tumor vascular damage by initiating the inflammation cascade signal, and then platelet membrane-coated execution biomimetic nanocarrier received the amplified inflammation signal and accumulated at the tumor site (Figure 7).

Overall, important advances have been made in the basic understanding and designing of delivery systems over the years. The field is thriving with rapidly growing number of publications and patents. However, functional nanomedicines with the capability of overcoming the biological barriers are often too complicated to be translational. We should pay much attention to developing nanomedicinal drug products that can eventually deliver on their promise of increased patient benefit.

3.2 Biomedical polymers used for gene delivery

Gene therapy that can rectify pathological abnormality at the

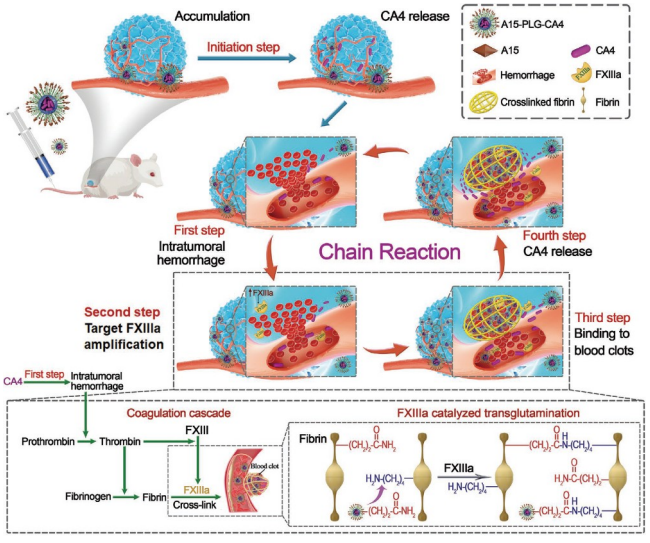


Figure 6 Schematic illustration of the self-amplifying tumor-homing nanotherapeutic platform, A15-PLG-CA4, characterized by chain reactions [118] (color online).

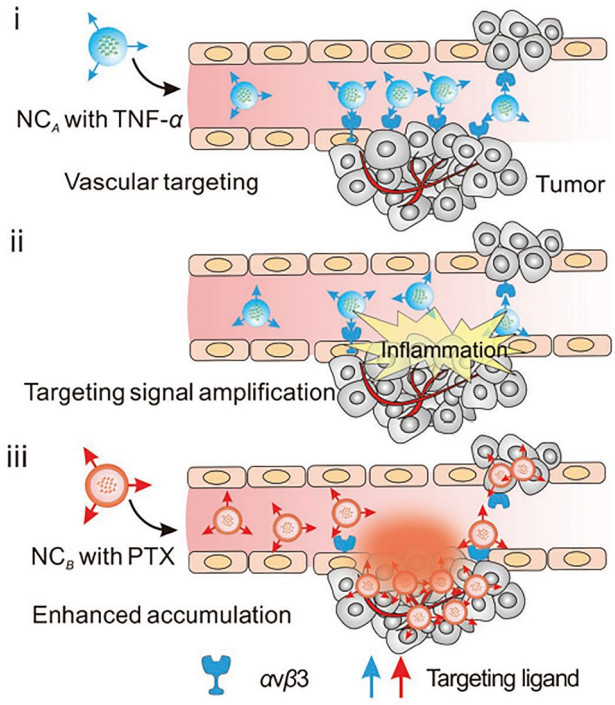


Figure 7 The signalling transmission NC$_A$ is composed of a RGD decorated nanocarrier, which could (i) target the tumor blood vessels, (ii) release encapsulated TNF-α and induce the vasculature inflammation. The execution biomimetic NC$_B$ is made of a platelet membrane-coated dextran nanocarrier with incorporation of an acidity-degradable modality. (iii) NC$_B$ could respond to the amplified targeting signal induced by NC$_A$, accumulate at the tumor site, and subsequently release an encapsulated anticancer drug [119] (color online).

genetic level holds great potentials for disease treatment. Among all therapeutic nucleic acids, plasmid DNA (pDNA) and messenger RNA (mRNA) up-regulate specific genes or proteins; small interfering RNA (siRNA), short hairpin RNA (shRNA), and micro RNA (miRNA) mimics down-regulate gene expression at the mRNA level *via* RNA interference (RNAi); synthetic miRNA inhibitors specifically inhibit miRNA functions. More than 2,000 gene therapy clinical trials are ongoing or completed worldwide, and gene therapies have been approved by FDA for the treatment of acute lymphoblastic leukemia, large B-cell lymphoma, and RPE65 mutation-associated retinal dystrophy. Because nucleic acids are hydrophilic biomacromolecules that are impermeable to cell membranes and vulnerable to hydrolytic degradation, the key to the success of gene therapy is efficient cytosolic delivery into target cells *in vivo*. Polymers represent an important category of nucleic acid delivery materials, mainly due to their desired biocompatibility, low immunogenicity, and structural diversity.

3.2.1 Polymer-based nucleic acid delivery systems

Because nucleic acids are negatively charged, cationic polymers (also terms as polycations) are widely utilized to condense nucleic acids into cell-ingestible, nano-sized complexes (polyplexes) *via* electrostatic interaction. Commonly used polycations include chitosan derivatives, PEI, poly(*L*-lysine) (PLL), polyamidoamine, poly(β-amino esters) (PBAEs) [120], poly(*L*-histine) (PHis), poly(2-dimethylaminoethyl methacrylate) (PDMAEMA), poly[(2-acryloyl)ethyl(*p*-boronic acid benzyl)diethylammonium bromide] (B-PDEAEA) [121], and cholesterol-terminated ethanolamine-aminated poly(glycidyl methacrylate) (CHO-PGEA) [122]. The incorporation of functional moieties into polycations can enhance the binding affinities with nucleic acids. For instance, Chen, Tian and co-workers [123] modified PLL with *p*-toluylsulfonyl arginine to greatly enhance the DNA binding efficiency *via* multiple interactions such as electrostatic interaction, salt bridging, hydrogen bonding, and hydrophobic interaction. A major shortcoming of the polyplexes is their instability in salt, because the ionic screening effect diminishes the electrostatic interaction. The polyplex micelles assembled from copolymers with a hydrophobic block and a positively charged hydrophilic block could greatly enhance salt stability [124]. Polymersomes, also assembled from amphiphilic block copolymers, possess a hydrophilic shell, a robust membrane, and an aqueous cavity that can encapsulate hydrophilic nucleic acids [125]. Such a structure endows them with desired salt stability, and a short, positively charged block could be incorporated into the polymersomal structure, which is preferentially positioned toward the inner aqueous cavity to strengthen the gene encapsulation force. Besides these systems, templated nanoparticles comprised of an inner template (such as inorganic or PLGA nanoparticles) and surface-positioned polymer, are also widely utilized for gene delivery (Figure 8), because of the controllable size/morphology/aspect ratio and the inherited properties from the template, such as photo/thermal/magnetic properties [126].

3.2.2 Polymer designs for overcoming physiological barriers against nucleic acid delivery

To achieve efficient gene transfection, polymeric vehicles need to overcome the multiple intracellular barriers. Cell membrane represents the first intracellular barrier that impedes the cytosolic delivery of nanovehicles. Nanovehicles are often internalized *via* endocytosis, and positively charged nanovehicles are preferentially taken up by cells due to their electrostatic affinity with cell membranes. To reinforce the transmembrane efficiency, cationic polymers can be tailored with higher molecular weight, higher charge density, and multivalent structure. Also, modulating the hydrophobicity/aromaticity of cationic polymers or introducing targeting ligands can greatly enhance the membrane affinity [124,127]. Upon endocytosis, nanovehicles tend to be trapped by endo/lysosomes, and an efficient endo/lysosomal escape mechanism is highly demanded to allow liberation of

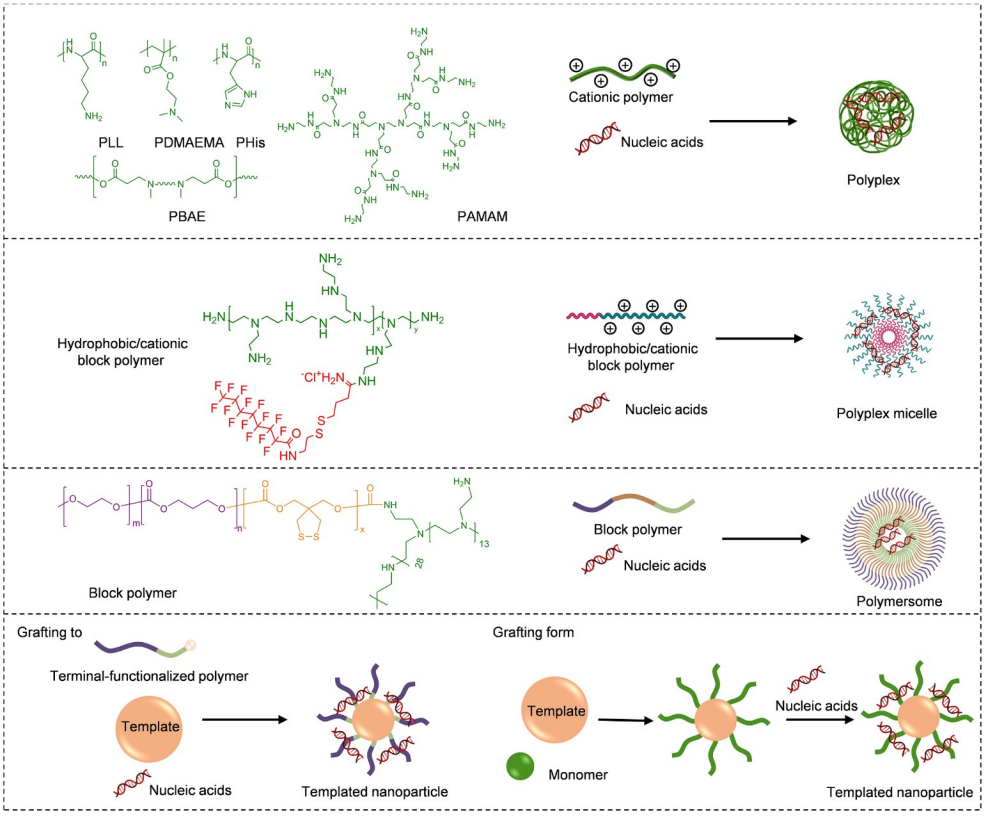


Figure 8 Major categories of nanovehicles based on biomedical polymers for nucleic acid delivery (color online).

the nanovehicles into the cytosol. Polymers carrying buffering domains such as protonatable amines with different pK_a can induce osmotically driven endosome burst, the so-called "proton sponge effect". Alternatively, polymers conjugated with lipids or cell penetrating peptides (CPPs) can mediate endo/lysosomal escape *via* membrane fusion or membrane disruption. Photosensitizer-embedded nanovehicles can also generate reactive oxygen species (ROS) upon light irradiation, destabilizing endo/lysosomal membranes *via* the photo-chemical internalization (PCI) mechanism (Figure 9). Nanovehicles with smaller sizes and higher positive charge densities can more easily escape from endo/lysosomes. Because endocytosis may not be an efficient intracellular gene delivery mechanism, polymeric nanovehicles capable of non-endocytic internalization are more desired. To this end, synthetic cationic polypeptides with guanidine side groups and stable α-helical structure are developed to mimic natural CPPs and provoke direct translocation of gene cargoes into cells [128].

Another critical challenge against intracellular gene delivery is the efficient cytosolic release of gene cargoes. While tight encapsulation of nucleic acids benefits systemic circulation/distribution and cytosolic delivery, the excessive binding affinities between the delivery vectors and the gene cargoes will retard cytosolic gene liberation. To address this dilemma, degradable or transformable polymeric nanovehicles are widely developed. Polymers with built-in trigger-responsive domains are developed to enable degradation into low-MW segments, charge reversal from positive to negative, or dissociation of the nanovehicles upon internal (such as acidic pH in the endo/lysosomes, reductive glutathione in the cytosol, H_2O_2 overproduced in cancer cells) or external (such as light and heat) stimuli, thereby diminishing the binding affinity with nucleic acids and promoting cytosolic release [121,125,126] (Figure 10). For DNA delivery, DNA has to be transported into the nuclei to initiate transcription, and positively charged, hydrophobically modified polyplexes smaller than 50 nm are favorable for nuclei entry. Intranuclear transport of large nanoparticles could be achieved by using nuclear localization signal peptides, which bind importin α and β to target nuclear pore complex.

In the *in vivo* setting, the nanovehicles also need to overcome various extracellular barriers before they can reach the target cells. For systemic injection, the nanovehicles need to resist serum and circulate in the blood for a long time. Because gene delivery often involves the utilization of polycations, surface decoration that can shield the positive charges is often demanded to repel the adsorption of negatively charged serum proteins. Surface PEGylation and polyanion coating are common approaches to improve serum stability and prolong blood circulation [129]. However, the immunogenicity of PEG will cause the accelerated blood

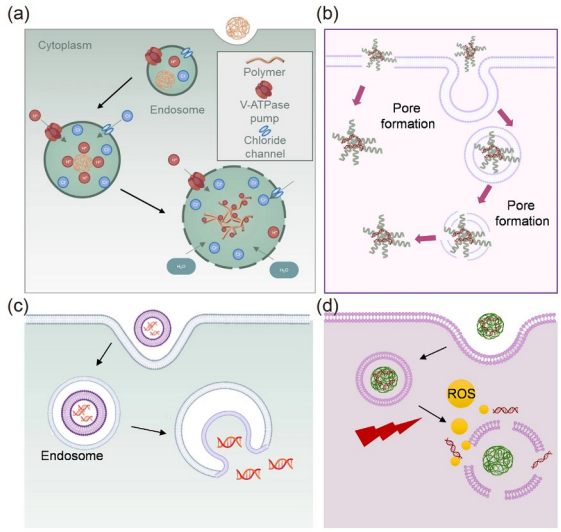


Figure 9 Schematic illustration of different endo/lysosomal escape mechanism. (a) Proton sponge effect; (b) pore formation mechanism; (c) lipid fusion mechanism; (d) photo-chemical internalization (PCI) effect (color online).

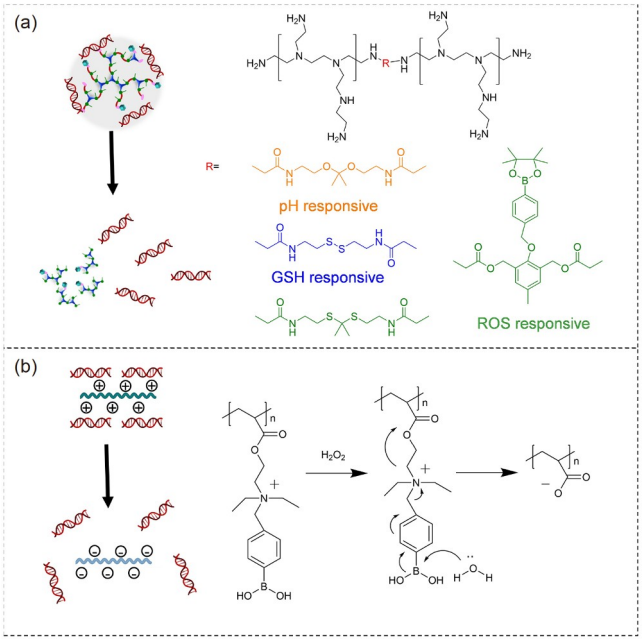


Figure 10 Trigger-responsive intracellular nucleic acid release *via* (a) degradation and (b) charge reversal of cationic polymers (color online).

clearance of PEGylated nanovehicles after repeated injections, and such an issue could be well resolved by the utilization of zwitterionic polymers such as polysulfobetaine (PSB) and polycarboxybetaine (PCB), which adopt an overall neutral charge and have high hydration capability to repel serum proteins. Another issue related to PEGylation or polyanion coating is the compromise of the interaction with target cells. Thus, cleavable PEG or charge reversible polyanions (from negative to positive) are developed, which can shed off in the extracellular environment to expose the positively charged inner core in response to triggers such as the acidic pH or overexpressed matrix metalloproteinases in tumor tissues [130]. Fluorocarbon modification of polycations such as dendrimers and PEI represents another important strategy to resist serum yet enhance membrane activities because of the hydrophobic yet lipophobic nature and low surface energy of fluorocarbons [131]. Besides systemic injection, mucosal delivery is another important administration route with high patient compliance. The mucus layer lining the epithelia is rich of negatively charged mucin glycoproteins, and thus traps positively charged nanovehicles. Again, fluorocarbon modification of cationic polypeptides greatly enhances the dual-penetration across mucus and macrophage membrane, thereby leading to high TNF-α silencing in alveolar macrophages against acute lung injury after intratracheal administration of polypeptide/TNF-α siRNA polyplexes [132]. Alternatively, cationic polypeptide/TNF-α siRNA polyplexes surface-decorated with an acid-responsive, charge reversal polyanion feature potent mucus penetration after intratracheal administration, while in the inflamed alveolar spaces, the polyanion transforms to positively charged and sheds off, exposing the inner polyplexes to enable efficient transfection of alveolar macrophages [133].

3.2.3 *Functional polymers for gene therapy*

pDNA is widely utilized to supplement the deficiency of target genes, which is transcribed into mRNA and translates into protein. pDNA is large, and usually has stronger molecular entanglement with polymers. Thus, efficient cytosolic release mechanism is highly necessitated. Also, the delivery vehicle should be able to deliver DNA into the nuclei where it initiates transcription. You *et al.* [124] reported bioreducible cationic nanomicelles wherein disulfide bonds connected the cationic shell and the fluorocarbon core. Fluorocarbon-assisted assembly allowed the nanomicelles to efficiently condense DNA even at an N/P ratio of 1, and they can release DNA in response to intracellular glutathione (GSH). Shen *et al.* [134] optimized the hydrophobicity of polycations to greatly enhance the stability of polyplexes at low concentrations, and they entered cells *via* macropinocytosis to bypass endo/lysosomes. Whereas, the unmodified polyplexes were dissociated or trapped in the lysosomes at low doses, thereby weakening the transfection efficiency. Wang *et al.* [120] reported highly branched poly (β-amino esters) (HPAEs) with multivalency-reinforced DNA delivery capability. They screened a library of HPAEs containing backbone-embedded disulfides and terminally positioned guanidines, and the optimized HPAEs provoked the transfection efficiencies of 77% and 52% for minicircle DNA in multipotent adipose derived stem cells and astrocytes, respectively. Cheng *et al.* [128] reported cationic polypeptides with rigid, rod-like α-helix, which can puncture

pores on cell membranes to allow non-endocytic internalization of pDNA. The best-performing PVBLG-8 showed 12-fold higher transfection efficiency than commercial reagent PEI and outperformed its random coiled analog by 2 orders of magnitude. Chen *et al*. [123] also reported the helix-assisted DNA delivery by introducing a "molecular string" onto PLL backbone, which not only transformed PLL from random coil to α-helix, but also introduced multiple interactions between polymer and DNA or cell membrane to potentiate the transfection efficiency. The best-performing PLL derivative mediated effective delivery of pDNA-encoding shVEGF *in vivo* to inhibit tumor growth. Furthermore, they developed mPEG-*b*-PLG/PEI-RT3/DNA (PPD) to mediate pDNA-encoding shPD-L1 delivery also by introducing multiple interactions and polyproline II (PPII)-helix conformation [129]. PPD reversed T-cell exhaustion, and combined with zebularine, a DNA methyltransferase inhibitor to increase the levels of tumor antigens and antigens presentation, to greatly inhibit tumor growth and prevent tumor relapse and metastasis.

mRNA is widely adopted for vaccines and protein-replacement therapy. Compared with pDNA, mRNA can be directly loaded into the ribosome to translate into target protein without the need for nuclei transport and transcription. Therefore, mRNA delivery often features higher efficiency and lower risk of insertional mutagenesis than pDNA, while its instability toward enzymatic hydrolysis needs to be carefully tackled with. Kataoka *et al*. [135] reported Gaussia luciferase (GLuc) mRNA polyplexes based on N-substituted polyaspartamides with varied numbers of side-chain aminoethylene repeats, and unraveled that polyplexes with odd number of aminoethylene repeats (PA-Os) but not with even number of repeats (PA-Es) provoked sustained Gluc expression. While PA-Es could mediate efficient cytosolic delivery, the polyplexes suffered from poor stability that led to quick degradation of mRNA. Comparatively, PA-Os with high stability could protect mRNA in the cytoplasm to induce sustainable mRNA translation, even though it had relatively weak endosomal escape capability. Stephan *et al*. [136] reported an mRNA delivery nanocarrier to reprogram tumor-associated macrophages (TAMs) toward cancer treatment. Two mRNAs that encoded interferon regulatory factor 5 and its activating kinase IKKβ were complexed with cationic PBAE, followed by mixing with di-mannose-functionalized PLG to shield the positive charges and allow macrophage targeting. Systemically injected nanosystems led to efficient mRNA transfection in TAMs (M2 phenotype), reprogramming them to the M1 phenotype to induce antitumor immunity. mRNA vaccines that can induce intracellular synthesis of protein/peptide antigens in antigen-presenting cells (APCs) hold great advantages over whole-protein vaccination, because mRNA produces proteins catalytically, and a relatively small dose of mRNA is required to produce many copies of proteins. Sun *et al*. [137] reported an intranasal vaccine system based on mRNA encoding HIV gp120 delivered by using cyclodextrin-modified PEI 2k. Intranasal administration resulted in effective mRNA transfection of APCs, thereby provoking effective local and systemic immune responses. Levy *et al*. [138] developed charge-altering releasable transporters for anti-cancer mRNA vaccines. Oligo(α-amino ester) cations formed polyplexes with mRNA to enable effective delivery into APCs, while they lost the cationic charges *via* charge-neutralizing intramolecular rearrangement to release mRNA. As such, the CART vaccines could activate an antigen-specific immune response against mRNA-encoded viral epitopes *in vitro* and *in vivo*, outperforming conventional synthetic viral peptide mixtures. Even so, polymer-based mRNA vaccines are often less than the reported lipid-based mRNA vaccines, maybe due to the difficulty in polymer synthesis and quality control. Further development and optimization of polymer-based mRNA vaccines will provide more opportunities for the clinical application of mRNA vaccines.

The over-expression of disease-related genes can be down-regulated *via* the RNAi mechanism, mostly realized *via* the degradation of mRNA using synthesized siRNA or miRNA mimics. siRNA or miRNA mimics are small and linear, and they are highly vulnerable to enzymatic degradation. Thus, nanovehicles that can tightly encapsulate the siRNA/miRNA mimics are demanded. They function in the cytosol by recognizing target mRNA, and thus do not require to transport into the nuclei. Ding *et al*. [127] reported a DNA origami-based nanodevice to co-deliver siRNA (targeting Blc2 and P-glycoprotein) and DOX, which was co-assembled from functional moieties including trans-activator of transcription (TAT) and disulfide-containing DNA locks. TAT improved cellular uptake and tumor retention, and DNA locks sealed the nanodevice during circulation but opened the nanodevice in response to cytosolic GSH to liberate siRNA. Xu *et al*. [139] reported a theranostics system composed of gadolinium-chelated tannic acid (TA) for magnetic resonance imaging (MRI), cationic polymer PGEA for the condensation of miRNA-145 (miR-145), and peptide ColIV for targeting thoracic aortic dissection (TAD). miR-145 could stabilize the vascular structure to prevent the progression of TAD, and TA allowed early detection of TAD by MRI. Zhong *et al*. [125] reported virus-mimicking vehicles based on cNGQGEQc peptide-functionalized, reversibly cross-linked chimaeric polymersomes (cNGQ/RCCPs) to deliver Polo-like kinase 1 specific siRNA (siPLK1) for treating orthotopic human lung cancer. cNGQ/RCCPs could encapsulate siPLK1 at an N/P ratio of 0.45 and be efficiently taken up by α3β1-overexpressed A549 cells, thereby inducing potent gene silencing *in vitro* and *in vivo*. Shuai *et al*. [126] reported a pH-sensitive and vitamin A-conjugated copolymer (T-PBP) that was assembled with super-

paramagnetic iron oxide (SPIO) to form cationic micelles for miRNA-29b and miRNA-122 co-delivery. The T-PBP micelles efficiently transported miRNA to hepatic stellate cells in an MRI-visible manner, significantly inhibiting expression of fibrosis-related genes. Zhang *et al*. [140] utilized functional siRNA as the cross-linker to assemble with DNA-grafted poly(ε-caprolactone) (DNA-*g*-PCL) brushes, constructing spherical nanogels *via* nucleic acid hybridization. The nanogels with tunable size showed desired thermostability and enzymatic stability, and they provoked efficient gene silencing and tumor inhibition by delivering siPLK1 *in vivo*. In order to improve the siRNA delivery efficiency in serum, Liang *et al*. [141] prepared a library of fluorinated oligoethylenimines (fxOEIs) with potent endosomal disruption capability, and the optimized f0.7OEI achieved dramatically higher luciferase silencing efficiency (88.4%) than Lipo 2000 (48.8%) in serum-containing medium.

The CRISPR/Cas system has emerged as a robust tool for gene editing, and has shown profound potential for treating congenital or acquired diseases. Cas nuclease and single-guide RNA (sgRNA) are two critical components in the CRISPR/Cas system, and Cas and sgRNA expression cassettes can be encoded within one plasmid for delivery. For instance, Xu *et al*. [142] reported a lactose-derived branched cationic biopolymer with plentiful reducible disulfide linkages and hydroxyl groups, which mediated effective delivery of pCas9-survivin for Survivin knockdown for the treatment of orthotopic hepatocellular carcinoma (HCC). The polyplexes could target HCC cells by recognizing overexpressed asialoglycoprotein receptors on cell surfaces, and allow efficient cytosolic payload release *via* GSH-triggered polymer degradation. As such, they achieved the *in vivo* gene editing efficiency of 26.4% in orthotopic HCC tumors. Encoding Cas9 and sgRNA in a single plasmid will make it difficult to screen and optimize different sgRNA sequences to realize multiplex gene editing after vector construction. Thus, co-delivery of Cas9 expression plasmid with sgRNA plasmid, Cas9 expression plasmid with synthesized sgRNA, Cas9 mRNA with synthesized sgRNA, or Cas9 protein with synthesized sgRNA, renders alternative solutions with better maneuverability. For example, Wang *et al*. [143] reported an optimized cationic lipid-assisted nanoparticle (CLAN), constructed from PEG-*b*-PLGA-based nanoparticle assisted by cationic lipid BHEM-Chol, for the delivery of Cas9 mRNA and sgRNA (against NLRP3 inflammasome) into macrophages. By modulating the surface charge and PEG density, they identified the optimal CLAN that provoked efficient disruption of NLRP3 inflammasome, thereby mitigating acute inflammation of lipopolysaccharide (LPS)-induced septic shock, monosodium urate crystal-induced peritonitis, and high-fat-diet-induced type 2 diabetes. Liu, Kang, and Shi *et al*. [144] reported a dual-locking nanoparticle (DLNP) that can release the CRISPR/Cas13a system only at low pH and high H_2O_2. DLNP was prepared from a cationic core assembled from pDNA encoding the CRISPR/Cas13a system and 4-(hydroxymethyl) phenylboronic acid-modified $PEI_{1.8k}$, followed by surface-decoration with *cis*-aconitic anhydride (CA) and sodium glucoheptonate dehydrate (SGD)-modified poly(ethylene glycol)-*b*-poly(*L*-lysine) ($mPEG_{113}$-*b*-PLL_{120}/SGD_5/CA). The outer layer shed off in the acidic and oxidative extracellular environment of tumors, exposing the inner core to enable efficient transfection. In B16F10 tumor models, DLNP delivering Cas13a/PD-L1 significantly reduced exhaustion of T cells to mediate antitumor immunotherapy.

3.3 Biomedical polymers used for protein delivery

Protein is the engine of life and participates in almost all living processes including mitosis, proliferation, apoptosis, metabolism, gene translation and transcription [145]. Many diseases are related to protein dysfunctions, which make restoring protein function the most straightforward therapeutic strategy [146]. Compared with small molecule drugs and gene therapy, protein therapy directly acts on targets and specifically regulates biological processes, thereby can effectively avoid the off-target effect and minimize systemic cytotoxicity [147]. Despite the great potential of therapeutic proteins in diseases treatment, clinical applications of therapeutic proteins remain rare, mainly due to their fragile tertiary structure, short plasma half-life, high immunogenicity, undesired biodistribution, and cell membrane impermeability [148]. For the application of therapeutic proteins, various types of biomedical polymers have been developed to overcome these issues. In this section, the recent advances in the development of biomedical polymers for the extracellular and cytosolic protein delivery are summarized (Table 1).

3.3.1 Biomedical polymers used for extracellular protein delivery

Protein therapy has revolutionized the pharmaceutical industry. According to the reports, seven of the top ten best-selling drugs in 2018 are monoclonal antibodies [169]. However, most exogenous proteins are quickly recognized by the host defense system after intravenous injection, resulting in the clearance and degradation of the protein before exerting their therapeutic effects [152]. Therefore, reducing the immunogenicity, prolonging the plasma half-life and optimizing the biodistribution are essential for the successful application of therapeutic proteins. Recent achievements in this field mainly focus on conjugating hydrophilic polymers onto proteins and encapsulating protein within cross-linked polymer networks, and these polymer-based protein delivery strategies are discussed in this section.

(1) Poly(ethylene glycol)

Table 1 Advanced biomedical polymers for protein delivery

	Polymers	Formulations	Payloads	Applications	Ref.
Extracellular protein delivery	PEG	Polymeric nanogel	Insulin/GOx	Hyperglycemia	[149]
		Multienzyme nanocluster	UOx/CAT	Gout	[150]
		Polymeric nanocapsule	Anti-PD-1	Immunotherapy	[151]
	Zwitterionic polymers	Protein nanocapsule	UO_X	Gout	[152]
		Nanocage	UOx	Gout	[153]
		Nanoparticles	IgG	Immunotherapy	[154]
		Protein nanocapsule	Nimo/Tras	Glioma	[155]
	Polyacrylamide	Protein nanocapsule	AOx/CAT	Alcohol intoxication	[156]
		Protein nanocapsule	AOx/CAT/ALDH	Alcohol intoxication	[157]
Cytosolic protein delivery	Polyethyleneimine	Pyridylthiourea-modified PEI	eGFP/anti-polII/anti-p53	–	[158]
		Guanidyl-modified PEI	BSA/HRP/β-Gal/Ctp/Typ/*etc*.	–	[159]
		Fluoroalkanes-modified PEI	OVA	Immunotherapy	[160]
	Dendrimer	Dipicolylamine/zinc(II)-modified dendrimer	BSA/RNase/GFP/YFP/R-PE/*etc*.	–	[161]
		Phenylboronic acid-modified dendrimer	Cas9	Gene editing	[162]
		Guanidinobenzoic acid-modified dendrimers	BSA/β-Gal	–	[163]
	Other polymers	Poly(*N*-(3-aminopropyl)-methacrylamine)-based nanocapsule	EGFP/CAS	–	[164]
		Man-PEG-*b*-PCL-based mixed-shell polymeric micelles	OVA	Immunotherapy	[165]
		Cell-penetrating poly(disulfide)s	RNase/EGFP	–	[166,167]
		Guanidinium-functionalized poly(oxanorborneneimide)	"E-tags" engineered proteins	–	[168]

PEG is the most widely used polymer for extracellular protein delivery. Currently, direct conjugation of PEG onto protein molecules (PEGylation) is the most widely used strategy for protein delivery. When circulate in the bloodstream, the PEG chains will collapse on the surface of the protein through hydrophobic interaction and bind with water molecules to form a hydration layer around the proteins. Such hydration layer can effectively protect the protein from being recognized and eliminated by the mononuclear phagocyte system (MPS), affording proteins with prolonged circulation time, improved bioavailability and reduced immunogenicity [170]. The shielding effect of PEG is closely related to its molecule weight, chain architecture and density. Generally, higher density, larger molecule weight, and branched architecture offer better shielding effect and longer circulation time. However, a too dense shielding layer may also block the active sites of proteins, resulting in reduced biological activity [171]. Therefore, control of the molecular weight and density of PEG is very important for extracellular protein delivery.

Recently, Shi *et al*. [149] presented a PEG-based polymeric nanogel for the co-delivery of insulin and glucose oxidase (GOx) for smart regulation of hyperglycemia. The coating of PEG layer could effectively hide insulin and GOx from immune clearance during blood circulation, leading to the improved bioavailability and plasma half-life of insulin and GOx. Similarly, Liu *et al*. [150] presented a PEG-based multienzyme nanocluster for the co-delivery of uricase (UOx) and catalase (CAT). The UOx and CAT were confined in nanoscale space, allowing UOx to degrade uric acid without the generation of toxic byproduct H_2O_2. Besides enzymes, PEG-based polymers have also been used for the extracellular delivery of antibodies and cytokines. For example, Shuai *et al*. [151] presented a PEG-based polymeric micelle for the co-delivery of immune checkpoint inhibitor anti-PD-1 and paclitaxel (PTX). In their work, PEG with a molecular weight of 20 kDa was used to provide a shielding effect for anti-PD-1 during blood circulation. As reaching the tumor microenvironment (TME), anti-PD-1 and PTX were released from the micelle, leading to effective immune activation.

Although PEG has achieved great success in enhancing protein stability and improving bioavailability, about 25% of patients will develop anti-PEG antibodies after the first or continuous administration of PEGylated proteins [172]. The as-generated anti-PEG antibodies lead to the activation of opsonization, thereby promoting the rapid clearance of PEG-based protein delivery systems from the blood. Therefore,

the development of novel polymers that can effectively shield proteins in blood circulation while avoiding opsonization is demanded for protein therapy.

(2) Zwitterionic polymers

Zwitterionic polymers refer to polymers that incorporated both negatively charged and positively charged groups into their structure, such as carboxybetaine-, sulfobetaine- and phosphobetaine-based polymers [152]. Different from PEG and other hydrophilic polymers that hydrate through hydrogen bonding, zwitterionic polymers bind surrounding water molecules more strongly through electrostatically induced hydration, leading to the formation of a unique surface that is resistant to protein adsorption. The ability to resist nonspecific protein adsorption and excellent biocompatibility makes zwitterionic polymers as an ideal antifouling coating material for extracellular protein delivery. For example, Lu *et al*. [152] presented a poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC)-based protein nanocapsule and found that this PMPC-based nanocapusule could significantly prolong the circulation time of UOx *in vivo* without causing any immune response. Similarly, Jiang *et al*. [153] presented a poly(carboxybetaine) (PCB)-based nanocage for the systemic delivery of UOx, and no anti-PCB antibodies was detected after four times intravenous injection. Liu *et al*. [154] presented a poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC)-based immunomodulating nanoparticles (IMN) for the tumor-targeted delivery of natural killer cell (NK cell)-activating signals. During blood circulation, PMPC effectively prevented IMN from immune clearance and undesired NK-activation. As reaching TME, PMPC was detached from IMN, resulting in the activation of NK cells for efficient cancer immunotherapy. Besides providing an antifouling surface, Lu *et al*. [155] discovered that MPC could also bind to the nicotinic acetylcholine receptor (nAChRs) and choline transporter (ChT) in endothelial cells. With this discovery, they developed another PMPC-nanocapsule and achieved the efficient delivery of nimotuzumab (Nimo) and trastuzumab (Tras) to central nervous system. These studies demonstrate the great potential of zwitterionic polymers in the development of novel protein therapies.

(3) Other polymers for extracellular protein delivery

Besides PEG and zwitterionic polymers, other hydrophilic polymers have also been investigated for extracellular protein delivery. For example, Shi *et al*. [156] presented a polyacrylamide-based nanocapsule for the co-delivery of multiple enzymes with complementary functions (Figure 11). These complementary enzymes first assembled under template guidance, followed by the *in situ* growth of a thin polyacrylamide layer to provide multienzyme nanocapsule. The polyacrylamide layer can effectively enhance the circulation stability of multienzymes in blood, and the close-proximity architecture of multienzymes ensures that the

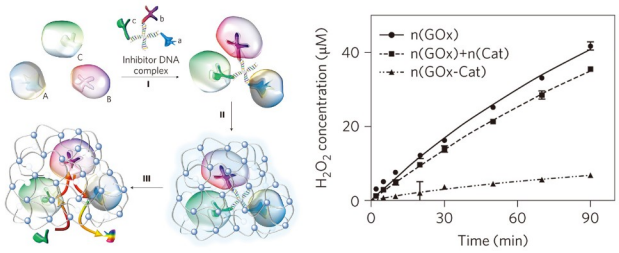


Figure 11 Biomimetic enzyme nanocomplexes as antidotes and preventive measures for alcohol intoxication [156] (color online).

toxic intermediate produced in the enzyme therapy can be effectively eliminated by another enzyme. Continuing this idea, Ji *et al*. [157] presented a polyacrylamide-based hepatocyte-mimicking antidote for the co-delivery of alcohol oxidase (AOx), aldehyde dehydrogenase (ALDH), and CAT. These enzymes work synergistically to catalyze the oxidation of alcohol to acetate without the generation of H_2O_2, thus effectively avoiding acetaldehyde-induced alcoholism and H_2O_2-induced liver damage. In addition, several nature polymers, such as chitosan, dextran, hyaluronic acid, *etc*. can also be used for extracellular protein delivery. For example, Huang *et al*. [173] presented a chitosan-based nanoparticle for the oral delivery of urease. Liu *et al*. [174] presented a dextran-based microsphere for the systemic delivery of vascular endothelial growth factor.

3.3.2 Biomedical polymers used for cytosolic protein delivery

Although protein therapy has achieved great success, it is worth noting that almost all protein drugs approved by FDA were act on extracellular targets such as secretary proteins and membrane proteins. This is mainly caused by the inability of proteins to cross cell membranes due to its inherent hydrophilic and macro-molecular characteristics. However, the numbers of these extracellular proteins only accounts for less than 30% of genome-encoded proteins, and the remaining 70% of intracellular proteins have become unreachable targets for protein therapy [147]. Furthermore, modern biotechnologies related to molecular biology and genome editing pose great demands on the cytosolic delivery of proteins such as cyclization recombinase (CRE) and clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9). To this end, the recent advances in the development of biomedical polymers for cytosolic protein delivery are discussed in this section.

(1) Polyethyleneimine-based polymers

PEI is a kind of synthetic cationic polymer with high charge density and proton buffering capacity, and has been widely used in gene delivery. However, for protein delivery, the delivery efficiency of PEI is greatly compromised due to its low protein loading capacity. Therefore, many PEI derivatives have been developed to improve the protein loading

capacity. For example, Zuber *et al*. [158] reported a pyridylthiourea-modified PEI (πPEI) that has ability to deliver proteins into the cytoplasm. Such modification enhanced multiple interactions between the πPEI and proteins, including hydrogen bonding, hydrophobic and ionic interactions. As a result, πPEI efficiently delivered monoclonal antibodies into cells to regulate biological processes. Guanidyl (GUA) is another commonly used modification group to improve the protein loading capability of polymer by forming hydrogen bonding and salt bridge with protein. For example, Cheng *et al*. [159] presented a series of GUA analogs-modified branched PEI, and found that GUA analogs containing both benzene and guanidyl groups showed the highest protein loading capacity. Furthermore, the same group [175] developed another PEI derivative by introducing fluoroalkanes onto PEI (F-PEI) to achieve efficient cytosolic protein delivery (Figure 12), and discovered that the protein delivery efficiency of F-PEI was highly related to the fluorination degree and fluorous length. By employing ovalbumin (OVA) as model protein, they demonstrated the ability of F-PEI to facilitate the efficient cellular uptake and lysosome escape of OVA, and the potential of F-PEI to promote antigen presentation and immune activation [160].

(2) Dendrimer-based polymers

Similar to PEI, dendrimer is a tree-like polymer with multiple amino groups and great proton buffering capacity. Recently, dendrimer-based polymers have been rapidly developed and shown their potential in cytosolic protein delivery. For example, Cheng *et al*. [161] reported a dipicolylamine/zinc(II) (D-DPA/Zn^{2+})-modified dendrimer. D-DPA/Zn^{2+} was used to bind with glutamic acid through ionic interactions and coordinate with tryptophan, phenylalanine and lysine, thus effectively loading proteins. By optimizing the grafting rate of DPA, they have successfully delivered 30 types of peptides and proteins intracellularly. Similarly, dendrimers modified with phenylboronic acid (PBA), which formed N-B coordination and π-π interactions with lysine and arginine of proteins, were also used to deliver proteins. By employing Cas9 as a model protein, PBA-dendrimer successfully achieved CRISPR/Cas9 gene editing in cells [162]. Recently, guanidinobenzoic acid (GBA) modified dendrimers (DGBA) have been developed for protein delivery [163]. DGBA contained three parts, a dendrimer scaffold, a membrane-disruptive region and a protein binding surface. With the synergy of these three parts, DGBA achieves effective loading and cytosolic protein delivery with several promising features: ① no need to modify proteins; ② high cytosolic delivery efficiency; and ③ general applicability to various proteins.

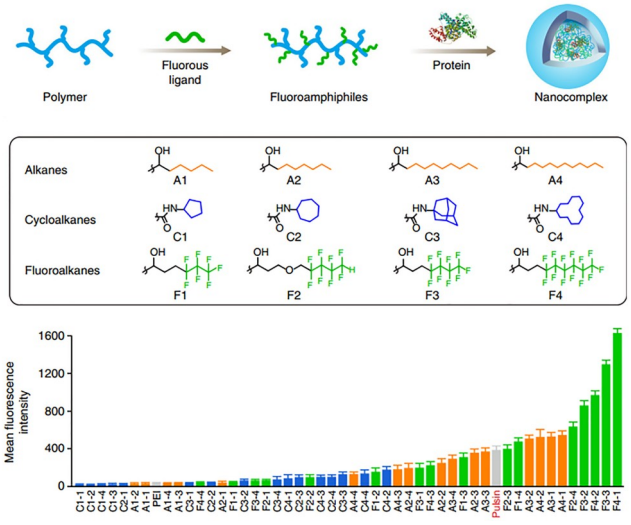


Figure 12 Fluoroamphiphiles for cytosolic protein delivery [175] (color online).

(3) Other polymers for cytosolic protein delivery

Besides PEIs and dendrimers, other cationic polymers have also been investigated for cytosolic protein delivery. For example, Lu *et al*. [164] reported a protein encapsulation method that can form a thin poly(*N*-(3-aminopropyl)-methacrylamine) layer around each protein molecule. Wang *et al*. [176] presented a chitosan-based nanoparticle for protein delivery, and they found that the delivery efficiency predominantly depended on chitosan/TPP mass ratio, molecular weight, concentration and protein feeding ratio. Shi *et al*. [165] presented a mannose-modified poly(ethylene glycol)-*b*-poly(ε-caprolactone) (Man-PEG-*b*-PCL)-based mixed-shell polymeric micelles (MSPMs) for the cytosolic delivery of OVA. The hydrophilic PEG and hydrophobic PAE formed hydrophobic domains on the surface of MSPMs, which were used to load OVA through hydrophobic interaction. After delivering OVA to APCs, MSPMs promoted the uptake of OVA by APCs, and achieved effective lysosome escape after the internalization. The conjugation of cell-penetrating poly(disulfide)s (CPDs) onto proteins can also improve the membrane permeability without compromising protein functions. For example, Yao *et al*. [166] decorated CPDs onto RNase and Lu *et al*. [167] *in situ* modified CPDs around EGFP, demonstrating that cell-penetrating poly(disulfide)s have the capability to facilitate intracellular delivery of native proteins. The resulting CPDs-protein complex could effectively translocate proteins into the cytosol in a thiol-dependent manner. Recently, Rotello *et al*. [168] discovered that guanidinium-functionalized poly(oxanorborneneimide) was able to integrate "E-tags" with engineered proteins and directly inserted into the cell membrane. This approach achieved to translocate protein directly across cell membrane into cytoplasm, thereby avoiding endosome/lysosome degradation and improving the protein delivery efficiency. Since this mechanism generally has much higher requirements for polymers, including a certain degree of molecular rigidity and strong interaction with cell membranes, the development of such vectors is still in its infancy.

4 Biomedical polymers for bioimaging, biosensing, and theranostics

4.1 Biomedical polymers used for bioimaging

Molecular imaging allows real-time and noninvasive visualization of physiological or pathological processes at the cellular or molecular level in living systems, playing a pivotal role in early and accurate disease diagnosis [177]. Probes are essential to correlate signals with molecular status in living subjects [178]. In recent decades, exogenous probes, such as small molecular probes, have been widely developed for bioimaging [179]. However, small molecular probes often suffer poor water solubility, rapid photobleaching, aggregation-induced quenching, and short observation window, which limit their applications *in vivo*. In conjunction with hydrophilic or amphiphilic polymers, polymer probes possess improved water solubility, good photostability, prolonged *in vivo* circulation time, and easy functionalization, which allow probes to accumulate in disease sites for early and accurate diagnosis [180]. Such biomedical polymer-based probes can be obtained through two different routes according to the polymer configuration. Probes are conjugated to hydrophilic polymers *via* a covalent bond to obtain the first type of polymer-based probes. Hydrophilic polymers offer probes that improve solubility in water. The second type is probes encapsulated into amphiphilic polymer micelles *via* physical interactions. In this section, the recent advances in the development of biomedical polymer-based probes equipped with fluorescence, photoacoustic, or other imaging capabilities for *in vivo* bioimaging are summarized.

Real-time fluorescence imaging in living subjects shows the advantages of nonradiative, high sensitivity, and high spatial and temporal resolution, which has gained increasing attention in biomedical research and clinical practice [181]. The fluorescent probe pafolacianine (Cytalux) as an adjunct for intraoperative imaging-guided ovarian cancer surgery has recently been approved by FDA. The development of fluorescence probes is important to impart fluorescence imaging of physiological and pathological processes at the cellular or molecular level in biological tissues [182].

For disease diagnosis, activatable fluorescent probes have been designed according to versatile disease biomarkers (for example, changes in pH, hypoxia, ROS, disease-associated enzymes) induced fluorescence signal changes [183,184]. Gao and co-workers [185] developed an extracellular pH-activatable nanoprobe that consisted of an ultra pH-sensitive copolymer poly(ethylene glycol)-*b*-poly(2-(hexamethyleneimino) ethyl methacrylate) and a near-infrared dye Cy5.5 (Figure 13a). At blood pH (~7.4), the fluorescent signal of Cy5.5 dye was quenched inside the nanoprobe due to homo-fluorescence resonance energy transfer-induced signal quenching. Under acidic pH, the nanoprobe could be dissociated, leading to a marked increase in the fluorescence signals of the Cy5.5 dye. Thus, the nanoprobe showed a sharp pH transition at pH 6.9, with a 102-fold fluorescence enhancement between blood pH (7.4) and the tumor microenvironment pH (6.7) (Figure 13b). Therefore, after conjugation with cRGD, the nanoprobe exhibited an ultra pH response for accurate tumor pH imaging in a broad range of tumor models with diverse cancer phenotypes and is evaluated in clinical tests at present. Hypoxia is also a distinguishing feature of most solid tumors. Jiang and co-workers [186,187] have developed a series of poly(*N*-vinylpyrrolidone) (PVP)-based iridium complex (Ir III) activatable probes for hypoxia imaging. They firstly reported a macromolecular probe (Ir-PVP) by conjugating the biomedical polymer PVP with an Ir complex (Ir-PVP). Ir-PVP was quenched in normal tissues but exhibited strong near-infrared signals under hypoxic conditions, leading to a highly sensitive detection capability for various hypoxic tumor models and even 1,000 cancer cells in the early stage of tumor formation [186]. Furthermore, after coprecipitating Ir-PVP with poly(ε-caprolactone)-*b*-poly(*N*-vinylpyrrolidone) block copolymer (PCL-PVP), the obtained nanoprobe allowed the effective detection of tumor metastasis in the lung or lymph nodes [187]. Moreover, they further modified the iridium complex with PEG through an acidity-sensitive imine bond to show a two-step cascade-amplified response for tumor imaging (Figure 13c) [188]. The redshift of the emission wavelength was first achieved upon response to acidity, and subsequently, the emission intensity was significantly enhanced upon response to hypoxia, achieving highly sensitive detection of small metastatic tumor modules and orthotopic hepatocellular carcinoma. By utilizing polymer PVP's feature, Zhu and co-workers [189] designed a ratiometric probe by conjugating PVP with platinum (II) tetraphenylporphyrin (Pt-TPP) for directly imaging hypoxia *in vivo*. In addition to tumor imaging, biomedical polymer-based fluorescent probes for imaging other disease models have also been reported. Pu and co-workers [190] reported a series of macromolecular renal probes which were composed of (2-hydroxypropyl)-β-cyclodextrin and a hemi-cyanine precursor with different acute kidney injury (AKI) biomarker reactive moieties for the early diagnosis of drug-induced AKI.

Second near-infrared (NIR-II, 1,000–1,800 nm) fluorescence imaging encounters diminished tissue autofluorescence and significantly reduced photo scattering due to the minimal light-tissue interactions, leading to a higher signal-to-background ratio (SBR) relative to NIR-I fluorescence imaging [191]. As most NIR-II organic probes are hydrophobic, hydrophilic or amphiphilic polymers are needed to endow probes with solubility. For instance, Dai and co-workers [192] reported a NIR-II fluorescent nanoprobe for *in vivo* bioimaging. A commercial water-insoluble NIR-II

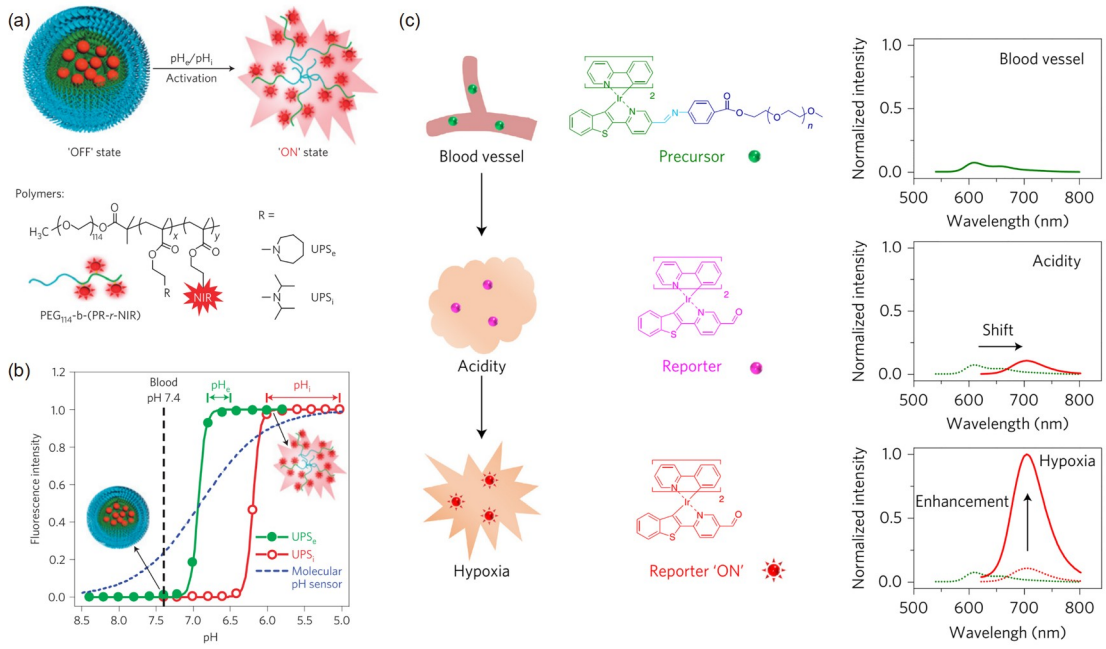


Figure 13 (a) Chemical structure of the pH-activatable nanoprobe [185]; (b) the response of nanoprobe to the change of pH values; (c) schematic illustration of two-step cascade amplification process of the activatable probe to the acidic and hypoxic tumor microenvironment [188] (color online).

dye (IR-1061) was formulated into a water-soluble nanoprobe with the assistance of the amphiphilic polymer 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[methoxy (poly(ethyleneglycol))] (DSPE-mPEG) through nanoprecipitation. The obtained nanoprobe allowed NIR-II fluorescence imaging of lungs, kidneys, and subcutaneous arteries in living mice. To obtain a new NIR-II fluorescent probe, Fan and co-workers [193] selected diketopyrrolopyrrole (DPP) as the donor and electron-withdrawing benzothiadiazole (BT) as the acceptor to narrow the bandgap of the probe (Figure 14a, b). The obtained NIR-II fluorescent probe was subsequently embedded into amphiphilic DSPE-mPEG and lecithin to form water-soluble nanoparticles. The nanoparticles showed a maximum absorption peak at approximately 686 nm and a maximum emission peak at 1,089 nm, allowing for NIR-II fluorescence imaging-guided drug release (Figure 14c). Aggregation-induced emission luminogens (AIEgens) are an emerging material for NIR-II fluorescence imaging due to the large Stokes shift of AIEgens [194]. Tang and co-workers [195] recently designed a series of AIEgens for NIR-IIb (1,500–1,700 nm) imaging through modulation of the effects of twisted intramolecular charge transfer. Benzobisthiadiazole was applied as an electron acceptor, and alkyl thiophene was selected as both the donor and the π-conjugation bridge, and triphenylamine was chosen as both the donor and the molecular rotor to obtain D-A-type NIR-IIb fluorescent AIEgens (Figure 14d). All these AIEgens exhibited maximum emission at approximately 1,030 nm with a tail extended to 1,600 nm, which was suitable for NIR-IIb imaging (Figure 14e). Therefore, with the assistance of DSPE-mPEG, AIEgens were transformed into water-soluble AIE nanoparticles for NIR-IIb fluorescence imaging of the brain vasculature in living mice (Figure 14f). In addition to the classical tetraphenylethylene and TPA structures for constructing AIE molecules, Wu and co-workers [196] developed a new phenothiazine structure with AIE characteristics to fabricate NIR-II fluorescent AIEgens for tumor imaging.

Photoacoustic (PA) imaging, which combines optical and ultrasound imaging, detects acoustic wave signals with much less attenuation than photons, and enables increased tissue penetration up to 5 cm [197]. Under pulsed laser irradiation, exogenous or endogenous probes transform absorbed photoenergy into heat, and in turn, the generation of acoustic waves through thermoelastic expansion can be detected by ultrasonic transducers and converted into PA images [198]. Recently, Liu and co-workers [199] reported a pH-responsive PA probe for ratiometric tumor pH imaging (Figure 15a). The PA probe was composed of a benzo[α]phenoxazine (BPOx) dye and an IR825 dye serving as the pH inert matrix and pH indicator, respectively. BPOx and IR825 were then embedded into human serum albumin to generate albumin-dye complexes after chemical cross-linking using glutaraldehyde. The PA signal at 680 nm (assigned to BPOx) increased gradually with decreasing pH, while the PA signal at 825 nm (assigned to IR825) remained nearly unchanged, affording the quantitative analysis of tumor pH using ratiometric PA imaging. In another study, the same group developed a sensitive "turn-on" PA nanoprobe for imaging H_2O_2 that was overexpressed in inflammation and tumor

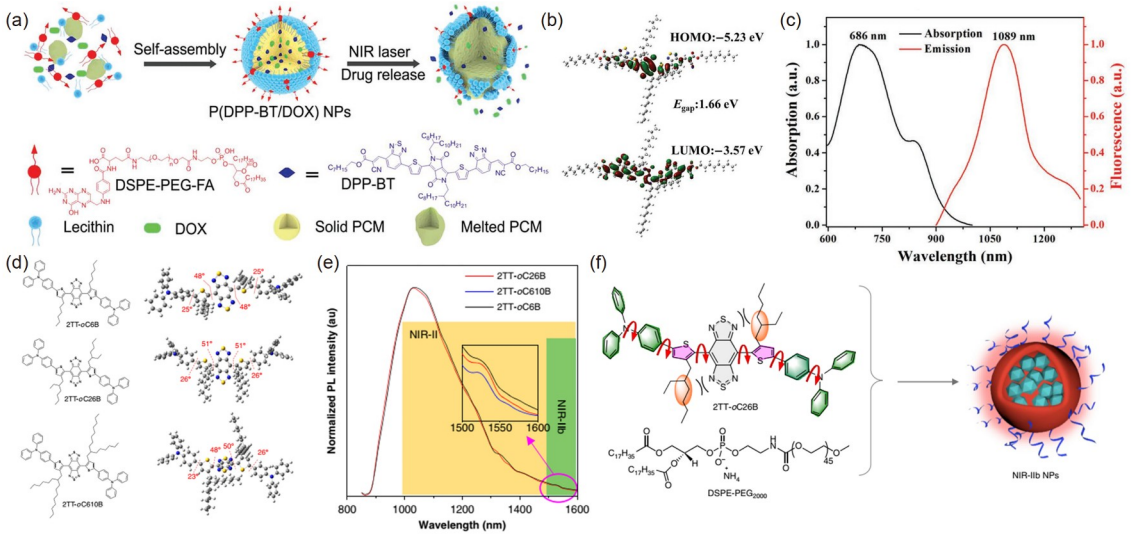


Figure 14 (a) Schematic illustration of the preparation of NIR-II fluorescence probe-based nanoparticles [193]; (b) calculated highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of NIR-II fluorescence probe using DFT B3LYP/6-31G(d) method; (c) absorption and emission spectra of NIR-II fluorescence probe; (d) chemical structures and optimized geometric structures of the AIEgens [195]; (e) fluorescence spectra of the AIEgens; (f) schematic illustration of the preparation of AIEgens nanoparticles (color online).

regions [200]. Horseradish peroxidase, an H_2O_2-activatable probe, and its substrate, 2,20-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), were chosen to dope with liposomes to form a liposomal nanoprobe for PA imaging of LPS-induced inflammation, subcutaneous 4T1 tumors, and orthotopic brain glioma. Wang and co-workers [201] developed an enzyme-responsive PA probe that was composed of an enzyme-responsive peptide (Pro-Leu-Gly-Val-Arg-Gly (PLGVRG)) linked vancomycin (Van) and pyropheophorbide-α (Ppa) as targeting ligand and PA imaging probe, respectively. The peptide could be cleaved in gelatinase overexpressed by gelatinase-positive bacteria to enhance the hydrophobicity of Ppa. Thus, Ppa was self-assembled into twisted fibers, resulting in an enhanced PA signal for bacterial infection detection. Tang and co-workers [202] synthesized an activatable "turn-on" PA nanoprobe for *in vivo* imaging of nitric oxide (NO) in encephalitis. Octyloxysubstituted triphenylamine (OT) was selected as the electron donor, planar thiophene ring was utilized as both the donor and π-conjugation bridge, and diamine-substituted benzothiadiazole (AB) was applied as the reaction-tunable acceptor to afford an activatable PA probe. The *o*-phenylenediamino unit of the probe could react with NO to obtain a triazole product, forming a more electron-deficient 5H-[1,2,3]triazolo[4′,5′:4,5]benzo[1,2-c][1,2,5]thiadiazole (TB) structure that benefits intramolecular motion to facilitate nonradiative relaxation to generate PA signals (Figure 15b). Thus, the activatable PA probe was transformed into water-soluble nanoparticles with the assistance of DSPE-PEG through the nanoprecipitation method (Figure 15c), affording the capability of detecting encephalitis of different severities (Figure 15d). Ding and co-workers [203] reported a new strategy to boost PA signals of probes *via* intramolecular motions to specifically enhance thermal-to-acoustic conversion efficiency for PA imaging-guided cancer surgery. Moreover, semiconducting polymer nanoparticles (SPNs) made from π-conjugated semiconducting polymers through the nanoprecipitation method have been developed as PA imaging probes by several different labs, including Li's group [204], Pu's group [205], Wang's group [206], and Fan's group [207].

The phosphorescence intensity and lifetime of room-temperature phosphorescence (RTP) organic materials can hardly be maintained in the aqueous solution, which hinders *in vivo* imaging applications [208]. A top-down approach to fabricate water-soluble RTP nanoparticles with improved phosphorescence in an aqueous solution with the assistance of the amphiphilic triblock copolymer PEG-poly(propylene glycol)-PEG (PEG-PPG-PEG) was developed by Li and co-workers [209] for *in vivo* bioimaging.

The biomedical polymer could also be used to improve the MRI properties of probes. For instance, Yang and co-workers [210] designed a scaffold protein, named ProCA32 with high Gd^{3+} affinity and metal selectivity as both a T_1- and T_2-weighted probe, allowing early detection of micrometastatic liver tumors. Gao and co-workers [211] utilized albumin to load glycyrrhetinic acid modified Gd-DOTA derivatives, significantly improving relaxivity due to geometric confinement, leading to an 8-fold enhancement of the relaxivities relative to those of Gd-DOTA chelates, achieving the sensitive detection of liver tumors. Shuai and co-workers [212] prepared a novel pH-sensitive nanocarrier based on the diblock copolymer of monomethoxy poly(ethylene glycol) and 2-(diisopropylamino)ethanol grafted poly(*L*-aspartic

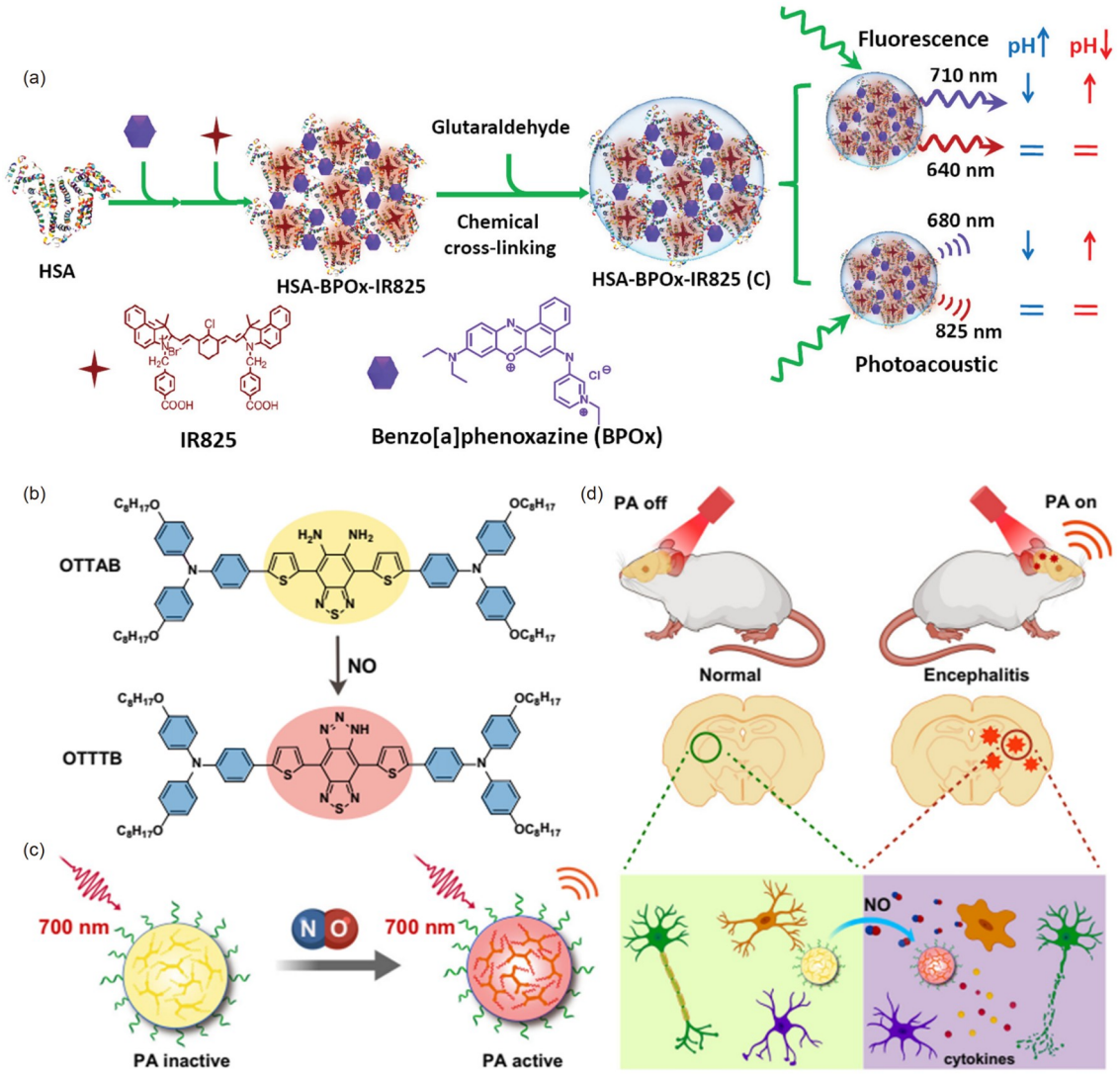


Figure 15 (a) Schematic illustration of the preparation of pH-responsive PA probe and its response mechanism to pH [199]; (b) chemical structures and (c) molecular mechanism of NO-responsive PA nanoprobe [202]; (d) schematic illustration of PA imaging of encephalitis using NO-responsive nanoprobe (color online).

acid) (PEG-PAsp(DIP)) to encapsulate SPIO and anticancer drug DOX, demonstrating its potential for monitoring the intracellular drug release using MRI. Chen and co-workers [213] transformed iron ions into water-soluble nanoparticles with the assistance of PLG-*g*-methoxy poly(ethylene glycol) (PLG-*g*-mPEG) for imaging-guided therapy. Shi and co-workers [214] designed pyridine (Pyr)-functionalized amine-terminated generation 5 (G5) poly(amidoamine) dendrimers to coordinate Cu(II) for MRI-guided cancer therapy. Moreover, the introduction of biomedical polymer could change the signals of MRI probes for stimuli-responsive imaging. The aggregation of iron oxide nanoparticles (IONPs) can change the relaxation of water protons, leading to a drastic γ2 enhancement. Inspired by this phenomenon, Ling and co-workers [215] manipulated the aggregation states of IONPs *via* pH-responsive i-motif DNAs. INOPs with anchor DNAs were first prepared and then were cross-linked by pH-responsive i-motif DNAs to form pH-responsive iron oxide nanocluster assembly (RIA). In the acidic tumor environment, the disassembly of RIA occurred and transformed into well-dispersed INOPs, leading to the initiation of MRI modular switch from T_2 to T_1 enhancement, achieving a significant MRI contrast enhancement between normal liver and HCC.

The biomedical polymer-based probes have good water solubility, long circulation time and high specificity and sensitivity for bioimaging. Due to the facile preparation method, biomedical polymer-based probes could be further functionalized to broaden their bioimaging applications. Although significant advances have been explored, there remains much improvement that needs to be addressed. For instance, biomedical polymer-based probes could be taken up by the mononuclear phagocyte system (MPS), leading to high accumulation in the liver and spleen and slow clearance

from the body due to their large size, inducing potential *in vivo* cytotoxicity effects. The *in vivo* safety issues of biomedical polymer-based probes, including long-term physiological effects, pharmacokinetics, and pharmacology, require further investigation. In general, with these promising achievements, biomedical polymer-based probes show the potential to be translated from bench to bedside.

4.2 Biomedical polymers used for biosensing

Biosensing uses electrical, optical, and other strategies to detect biomarkers *in vitro*, on the body surface and *in vivo*. Among them, implantable biosensors have received increasing interest due to their real-time and accurate detection at the targeted position. Generally, long-term stable monitoring relies on a robust interface between implanted biosensors and surrounding tissues, supposing the biosensor owns high biocompatibility, miniaturized size and mechanical matching with tissues in flexibility. However, traditional biosensors are based on rigid silicon substrates and metal electrodes, and they are liable to induce strong inflammation during *in vivo* chronic monitoring [216]. Therefore, flexible thin-film and fiber biosensors are designed from various polymers with several orders of magnitude lower moduli, making it available for long-term stable monitoring *in vivo* [217,218]. Polymers with different properties have been introduced into biosensors for different functions including substrates, insulation layers, electrodes, active materials, surface modifications, and assisted implantations (Figure 16).

4.2.1 *Polymer-based substrates and insulation layers*

Generally, flexible biosensors need polymer substrates to support electrodes and active materials as well as thin insulation layers to completely insulate non-detection sites. Polyimide (PI), polycarbonate (PC), SU-8, and polydimethylsiloxane (PDMS) have been widely explored for film biosensors due to their combined high biocompatibility, stability and compatibility with fabrication processes of biosensors [219–221]. Nylon fibers have been used as flexible fiber substrates to make organic field effect transistor (OECT) biosensors to monitor dopamine in long term *in vivo*, resulting in negligible inflammation and maintaining the interface stability [222]. Parylene can be vapor-deposited to form thin self-standing films has been widely used as flexible substrates for film biosensors and as insulation layers for both film and fiber biosensors [223].

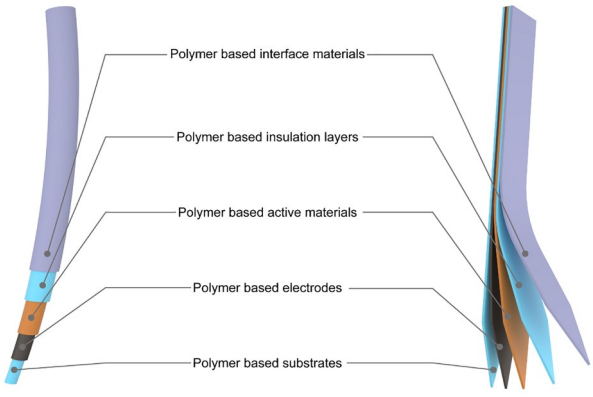


Figure 16 Polymer materials in flexible fiber and film biosensors. Polymer based interface materials indicate surface modification materials for antibiofouling and mechanical matching, or polymers for assisted implantation. Sometimes, substrates and electrode materials are composited as one part (color online).

4.2.2 *Polymer-based electrodes*

The electrodes should be flexible and conductive for the mechanical match with tissues and rapid transport of electron signals. Therefore, conducting polymers such as polypyrrole (PPy) and poly(3,4-ethylenedioxythiophene) (PEDOT) [222] have been studied as electrodes by coating them on polymer substrates. Their conductivity and flexibility usually need to be balanced by adjusting the process methods. Blending flexible non-conductive polymers with conductive nanomaterials, *e.g.*, carbon nanotubes and graphene, is another effective strategy for polymer electrodes, which has more space in selecting materials and designing fabrication processes [224]. In addition, winding aligned carbon nanotube films on polymer fibers or assembling them into macroscopic hierarchical fibers represents a new and effective strategy developed in recent years, which provides high electrical conductivity while ensuring flexibility [225].

4.2.3 *Polymer-based active materials*

Active materials can recognize the target analytes and are core parts of biosensors, which directly determine the performance, *e.g.*, sensitivity, selectivity, limit and range of detection. For the detection of neural signals, the low impedance of electrode/neural interface will lead to a high signal to noise ratio, and PEDOT:poly(styrene sulfonate) (PEDOT:PSS) has been thus widely investigated to reduce the interface impedance due to its high capacitance [226]. For the detection of specific ions, *e.g.*, calcium ions, the potential change of the sensor is attributed to the ion-electron transduction from ion selective membrane. Thus, PEDOT:PSS was also used as the middle ion-electron transduction layer for ion sensors [227]. Moreover, the ion-doping capability along with the simple processability made PEDOT:PSS is perfectly suitable for the channel of OECTs [228–230]. In enzyme-based biosensors such as glucose sensor, glucose is oxidized by O_2 catalyzed by glucose oxidase, and the generated H_2O_2 can then be reacted on platinum nanoparticles and induce current changes. Some polymers such as chitosan were used to immobilize enzyme for stability, and conducting polymers of polyaniline (PANI) with redox properties were usually used as intermediate to improve the

sensitivity and widen the linear range, and they mainly served as three-dimensional conductive scaffolds to immobilize enzyme and platinum nanoparticles [231,232]. Furthermore, enzyme-based biosensors might face stability challenges *in vivo* and some non-enzyme sensors have also been explored to realize specific detections. Specially, molecularly imprinted polymers have been obtained by polymerizing polymer, *e.g.*, PPy, with the analyte and then removing the analyte [233]. Although molecularly imprinted polymers are very promising, their application *in vivo* still needs to be verified clearly. Overall, conducting polymers are used most as active materials of biosensors.

4.2.4 Polymer-based surface modification materials

The surface of the biosensor is often modified with a polymer to improve the anti-interference property [234,235], interface stability, and anti-biofouling. Microporous (0.2 μm) polysulfone membrane and hydrophilic zwitterionic polymer are often studied to resist biofouling including blood cells and proteins *in vivo* [236]. For example, zwitterionic polymers were linked to the surface of biosensors by mussel-inspired polydopamine, resulting in the increasing sensing performance and stability while decreasing inflammatory response [237].

4.2.5 Polymer-assisted implant materials

Flexible ribbon and fiber biosensors face a contradiction, *i.e.*, rigid biosensors can be directly implanted but the mechanics do not match with tissues, while soft ones can be mechanically matched but cannot be directly implanted. The use of some responsive polymers can solve this contradiction, such as the degradable PEG and silk protein [238,239]. These materials coated on flexible biosensors were rigid before implantation and would be dissolved and degraded after implantation. Some temperature-sensitive polymers, which were rigid below body temperature and soft at body temperature, were also used as the assisted layer [240]. Furthermore, a hydrogel of calcium ion cross-linked sodium alginate with good biocompatibility has been reported as the outermost layer of fiber sensors. It was rigid with the modulus of more than 1 GPa *in vitro*, so it could be directly implanted. In the body, after being in contact with body fluid for a certain period, the hydrogel layer became soft with the modulus reduced to kPa level for mechanical matching with the tissues [241]. These responsive polymer layers ensued the effective implantation and stable interfaces between biosensors and tissues.

A lot of implanted biosensors with polymers as different components have been reported to monitor various physical and chemical information *in vivo*, while all-polymer biosensors are rare. In the future, we should design and synthesize biomedical polymers in response to the demand for implantable all-polymer biosensors by considering flexibility, performance and processability, while with high sensitivity and low limit of detection. It will also be possible to take advantage of the easy modification of polymers to achieve multifunctional integrated sensing systems for the simultaneous detection of multiple biomarkers, *e.g.*, ion, neurotransmitter, and blood glucose. High performing semiconductor polymers should be developed and introduced to realize *in-situ* amplification of signals in the body because some biomarkers have ultra-low concentrations with tiny changes. Finally, the combination of implantable biosensors with other imaging methods might reveal more complex physiological mechanisms. For example, some efforts were made to develop fMRI-compatible polymer based biosensors and study the brain in multiple models with complementary temporal and spatial resolutions (Figure 17).

4.3 Biomedical polymers used for theranostics

Theranostics is a combination of the terms “therapeutics” and “diagnostics”. Essentially, it describes a multifunctional system that enables diagnosis, therapy, and simultaneous monitoring of the therapeutic response [242,243]. This approach not only offers the opportunity to distinguish patients or disease types for the selection of therapy, but also potentially allows one to bypass some of the unpleasant adverse effects that may otherwise arise when these strategies are implemented separately.

Due to their biocompatibility, biodegradability, structural diversity, and multifunctionality, biomedical polymers have been extensively used to implement the concept of theranostics, either as vehicles shipping both therapeutic and diagnostic agents or as self-theranostic agents [244]. The polymer-based theranostic systems can target diseased areas within the body, thus avoiding damage to healthy organs or tissues. Once the site of interest has been pinpointed, the theranostic systems may then provide information on the extent of the disease, and report disease response to treatment if applicable. In this section, the applications of bio-

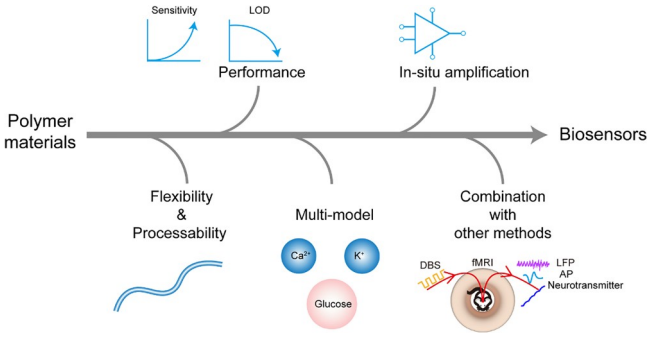


Figure 17 Outlook of polymer materials improving biosensors. LOD: limit of detection. DBS: deep brain stimulation. fMRI: functional magnetic resonance imaging. LFP: local field potential. AP: action potential (color online).

medical polymers in theranostics are briefed in terms of imaging modalities, which include optical, ultrasound, photoacoustic, nuclear, and MRI.

4.3.1 Optical imaging-based theranostics

Optical imaging, particularly fluorescent imaging, is favorite for guiding drug delivery as it can provide the real-time, noninvasive, and nonionizing readout of disease information at the cellular or even molecular level. However, most fluorescent theranostic systems rely on emitted photons as the signal readout and thus inevitably suffer from limited tissue penetration and low SBR arising from light absorbance, scattering, and autofluorescence of the tissues [245]. The use of near-infrared (NIR) fluorophores may effectively overcome these issues for *in vivo* applications [246]. Currently, many polymer-based theranostic systems have been developed with NIR fluorophores for imaging [247–251]. Mechanisms of photon emission including conventional fluorescent dyes or nanocrystals, and aggregation-induced emission (AIE) dyes have been exploited.

Li *et al*. [247] reported a GSH-responsive turn-on theranostic nanoparticle, which consisted of a disulfide bond-linked hydroxyethyl starch paclitaxel conjugate (HES-SS-PTX) and a NIR-I cyanine fluorophore DiR (Figure 18a). As DiR was encapsulated within the hydrophobic core formed by HES-SS-PTX, its fluorescence was quenched by the aggregation-caused quenching effect. However, once the nanoparticles were internalized by tumor cells, the disulfide bond of HES-SS-PTX would be broken by intracellular GSH, leading to the release of the conjugated PTX and encapsulated DiR. The released PTX could elicit its therapeutic efficacy, and DiR could integrate onto endosome/lysosome membranes and regain its fluorescence. Thus, the therapeutic systems could monitor the release and therapeutic effect of PTX through the fluorescence recovery of DiR. In addition to the NIR-I dyes, many NIR-II dyes have also been used in polymeric theranostic systems. For example, Li *et al*. [248] reported a macromolecular theranostic agent, which was prepared by conjugating a NIR-II cyanine dye (Flav7) with an amphiphilic polypeptide. The theranostic agent could form uniform micelles in an aqueous solution, leading to prolonged blood circulation time and enhanced accumulation in tumors. *In vivo* studies demonstrated that this system could achieve a potent photothermal ablation effect on tumors with a low dose of NIR-II dye and light irradiation, and the process could be monitored by NIR fluorescence imaging.

Compared with conventional molecular fluorophores that are typically subjected to fluorescence quenching in the aggregated state, the AIE dyes show many advantages for theranostics [252]. AIE-active semiconducting polymer nanoparticles (SPNs), also known as polymer dots and conjugated polymer nanoparticles, are emerging as a promising

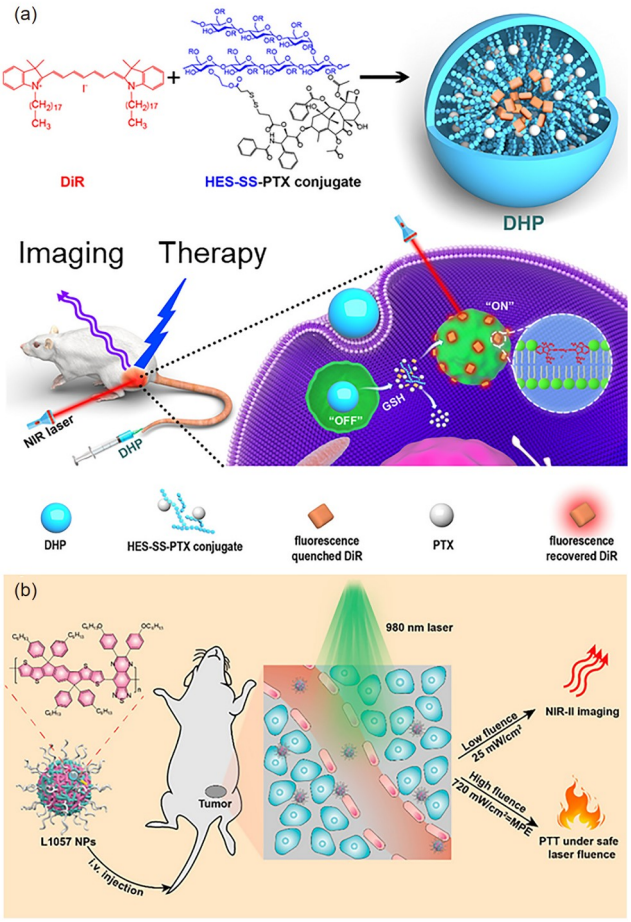


Figure 18 (a) Schematic illustration of the GSH-responsive turn-on theranostic system and the theranostic applications [247]; (b) schematic illustration of the AIE-active SPNs as a theranostic agent [249] (color online).

theranostic platform given their high extinction coefficient, large Stokes shift, efficient photothermal conversion, and excellent photostability [253]. Yang *et al*. [249] presented an SPN-based theranostic system for NIR-II fluorescence imaging and photothermal therapy (PTT) (Figure 18b). Despite the use of a weak electron acceptor, the donor-acceptor polymer still exhibited red-shifted absorbance profiles by increasing the conjugation length of the backbones. Moreover, the SPNs showed much higher effective NIR-II brightness than most reported organic NIR-II fluorophores, allowing for real-time imaging of the whole body and brain vessels and the detection of cerebral ischemic stroke and tumors with high resolution. The excellent photothermal conversion capacity and high maximal permissible exposure limit enable the SPNs for PTT of tumors under safe laser fluence. Besides PTT, SPNs have also been used for guiding other therapies [250,251]. Liu *et al*. [250] developed an SPN-based theranostic system for siRNA delivery *in vivo* and simultaneous real-time tracking of tumor accumulation. The SPNs exhibited long blood circulation and high tumor ac-

cumulation. Systemic siRNA delivery using these SPNs could efficiently silence BRAF expression in tumor tissues and thus significantly inhibit tumor growth and metastasis.

Fluorescence imaging needs real-time light excitation, which also excites tissue autofluorescence and thus compromises imaging sensitivity and specificity in living subjects. Afterglow luminescent probes can trap excitation energy in defects and slowly release photons after cessation of light excitation [254]. As such, afterglow imaging has no autofluorescence interference from biological specimens and greatly improves signal-to-background ratio *in vivo*. Pu *et al*. [255] reported poly(1,4-phenylenevinylene) (PPV)-based SPNs that could emit long-NIR afterglow luminescence with a half-life of ~6 min. The afterglow intensity of SPNs was over 100-fold higher than that of inorganic afterglow agents. High-contrast lymph node and tumor imaging in living mice could be enabled with a SBR up to 127-times higher than that obtained by conventional NIR fluorescence imaging. The afterglow luminescence of these PPV-based SPNs also showed temperature dependency, which was utilized for real-time monitoring of temperature during photothermal therapy.

4.3.2 *MRI-based theranostics*

MRI is another powerful diagnostic tool for its high resolution, non-exposure to radiation, and noninvasive imaging. To increase the sensitivity, MRI often requires contrast agents, which can be classified into positive agent (gadolinium complexes for T_1-weighed imaging) and negative contrast (SPIO particles for T_2-weighed imaging).

Gd(III) chelates are the most common T_1 MRI contrast agents in clinical use, however, most of these chelates including diethylenetriaminepentaacetic acid-Gd (DTPA-Gd, Magnevist) [256] and Gd-diethylenetriaminepentaacetic acid bismethylamide (Gd-DTPA-BMA, OmniScan) [257] are small molecules with typical drawbacks of non-specificity and rapid renal clearance. Macromolecular Gd chelates, particularly polymer-based ones, have been demonstrated higher imaging quality and longer blood circulation times, and are able to preferentially accumulate in diseased sites [258]. Integration of polymer-based MRI with cancer therapies can enable real-time monitoring of treatment response. Cai *et al*. [259] reported an enzyme-responsive polymeric prodrug-based theranostic system with cyanine 5.5 and Gd-chelates as the imaging agents and PTX as the chemotherapeutic drug (Figure 19). The theranostic nanoparticles demonstrated excellent biocompatibility, and high stability under physiological conditions, but released PTX rapidly in the tumor microenvironment. While exhibiting high cytotoxicity to cancer cells similar to free PTX, the nanoparticles greatly improved MRI contrast. The imaging-guided chemotherapy in 4T1 mouse tumor models demonstrated potent anticancer efficacy. Moreover, this system allowed for real-time accurate monitoring of the chemotherapeutic response.

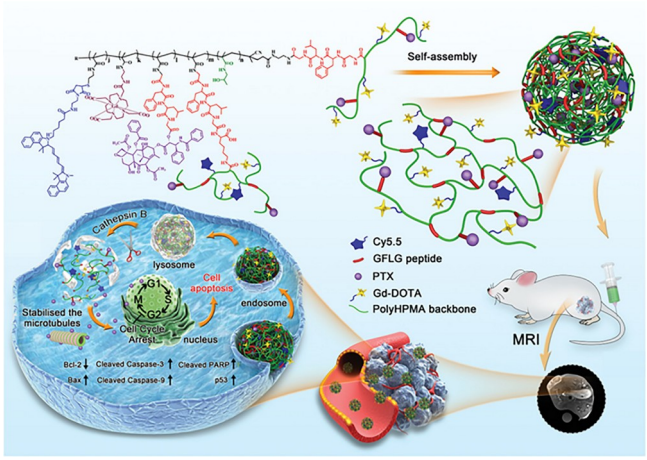


Figure 19 Schematic illustration of the enzyme-responsive biodegradable theranostic nanomedicine and its theranostic applications [259] (color online).

Concerns of nephrotoxicity and long-term brain deposition of Gd-based T_1 contrast agents have prompted the development of T_2-type theranostic agents [260]. Luque-Michel *et al*. [261] developed polymeric nanoparticles loaded with both SPIO nanoparticles (SPIONs) and DOX. SPIONs were used for noninvasive MRI imaging and also tumor targeting with the use of magnets. This theranostic system was expected to map the real-time characteristics of the tumor in each patient and allowed for earlier disease detection, more accurate prognostic information, and an enhanced ability to monitor the efficacy of treatment. Once administered into tumor-bearing mice, a significant accumulation of the nanoparticles was observed within the tumor tissue under static magnetic field as observed by MRI, leading to significantly inhibited tumor growth.

4.3.3 *Ultrasound imaging-based theranostics*

Ultrasound imaging represents another clinically routine technique for disease diagnosis and monitoring. This modality uses the nano- and micro-bubbles as the contrast imaging agents that help distinguish diseased tissues from normal tissues [262]. Bubbles are generally formed from lipids, proteins, and biodegradable polymers. In contrast to lipids and proteins, polymer-based bubbles display an excellent stability during circulation that ensures biosafety [263]. Polymeric backbones also permit drug loading and targeting ligand attachment for their multiple functional groups. Moreover, the explosive effect of the bubbles triggered by ultrasound wave can facilitate drug extravasation and cell internalization by enhancing the permeability of blood vessel and cell membrane [264]. For instance, Fan *et al*. [265] proposed a boron-polymer/microbubble complex (B-MB)-assisted focused ultrasound (FUS) treatment for brain glioma. B-MBs could simultaneously achieve the safe opening of the blood-brain tumor barrier and enhance boron

drug delivery into the tumor tissue using FUS sonication.

Chen *et al*. [266] reported on theranostic polymer microcapsules composed of hydrogen bonded multilayers of tannic acid and poly(*N*-vinylpyrrolidone) for ultrasound imaging and DOX delivery (Figure 20). These capsules exhibited excellent imaging contrast in both brightness and harmonic modes and showed prolonged contrast over six months, unlike commercially available microbubbles. Controlled DOX release could also be achieved by tuning ultrasound irradiation. Moreover, the imaging contrast of the microcapsules could be tailored by changing the number of layers, polymer type (relatively rigid tannic acid versus more flexible poly(methacrylic acid)), and polymer molecular weight.

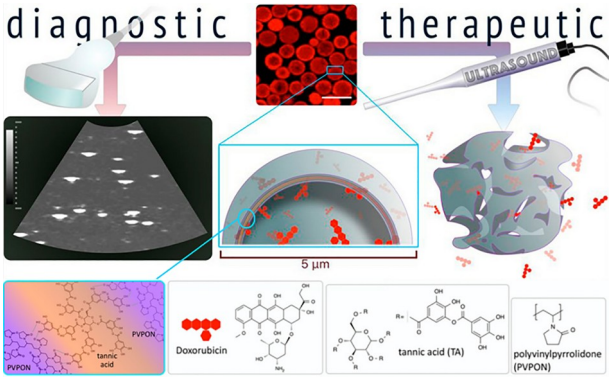


Figure 20 Schematic illustration of hydrogen-bonded tannic acid/poly(*N*-vinylpyrrolidone) multilayer capsules loaded with DOX for theranostic applications [266] (color online).

4.3.4 *Photoacoustic imaging-based theranostics*

While ultrasound can provide real-time tissue imaging, it can only distinguish tissue interfaces *via* differences in the speed of sound. Photoacoustic imaging can extend the contrast of ultrasound from the anatomical to the molecular by augmenting the spatiotemporal resolution of ultrasound with the spectral contrast of optics [267]. This technique relies on the photoacoustic effect—optical energy is absorbed by a material and released as an acoustic vibration [268]. This combination has led to applications in photoacoustic diagnostics, drug delivery, and theranostics [269,270].

Wang *et al*. [271] reported photosensitizer-free polymeric nanocapsules formulated from NIR light-absorbable amphiphilic polymers and a NO-releasing donor, DETA NONOate (Figure 21). Controlled NO release and nanocapsule dissociation were triggered in acidic lysosomes of cancer cells. More importantly, upon pulsed laser irradiation, the photoacoustic cavitation could excite water to generate significant ROS, which further reacted with the *in situ* released NO to produce highly cytotoxic peroxynitrite in cancer cells. The generated peroxynitrite induced significant mitochondrial damage and DNA fragmentation, thus initiating programmed cancer cell death.

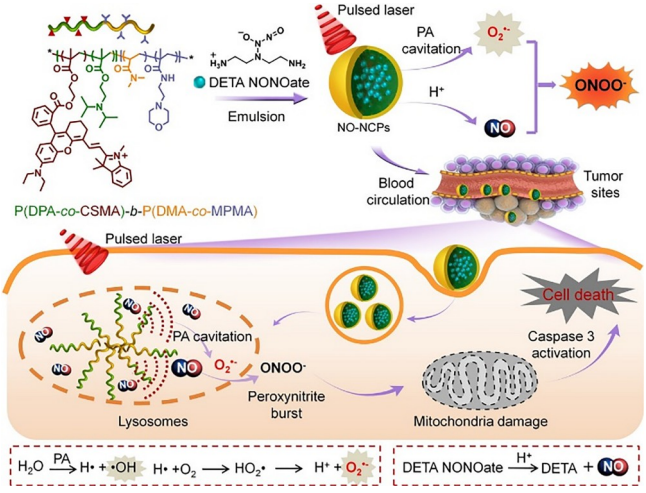


Figure 21 Schematic illustration of NIR light absorbable polymeric nanocapsules for photoacoustic imaging and peroxynitrite burst-induced cancer therapy [271] (color online).

4.3.5 *Nuclear imaging-based theranostics*

Nuclear imaging techniques are powerful tools to quantify the distribution of radiotracers in the whole body with deep tissue penetration. As mostly performed modalities, single-photon emission computed tomography (SPECT) measures gamma rays during radioisotope compound (^{99m}Tc, ^{111}In, ^{123}I, ^{177}Lu, *etc*.) decay process, and positron emission tomography (PET) counts the photons produced by the isotopes (^{11}C, ^{18}F, ^{64}Cu, ^{68}Ga, *etc*.) [272]. However, most of the radiotracers are small molecules, which may be subjected to rapid renal excretion and exhibit no tissue selectivity *in vivo*. To improve the tissue specificity, biomedical polymers have been utilized to deliver radiotracers along with anticancer drugs to form theranostic systems.

Xiao *et al*. [273] developed unimolecular micelles made of hyperbranched amphiphilic block copolymers for cancer-targeted drug delivery and PET imaging (Figure 22a). This block copolymer employed Boltorn® H40 as the core, DOX-conjugated-poly(*L*-glutamate) as the hydrophobic segments, and PEG with targeting ligand cRGD and PET probe ^{64}Cu as the hydrophilic shell. The uniform-sized unimolecular theranostic micelles exhibited pH-sensitive drug release profiles and also high cellular uptake. Moreover, PET scanning enabled facile quantitative measurement of tumor-targeting efficiency and *in vivo* biodistribution. Zhu *et al*. [274] presented ^{131}I-labeled multifunctional dendrimers for targeted SPECT imaging and radiotherapy of tumors (Figure 22b). Amine-terminated poly(amidoamine) dendrimers were introduced with PEG chains, folic acid, and radioactive ^{131}I. The generated dendrimers enabled targeted SPECT imaging and simultaneous radiotherapy *in vivo*.

Collectively, these polymer-based theranostic systems provide high selectivity towards diseased tissues and enable

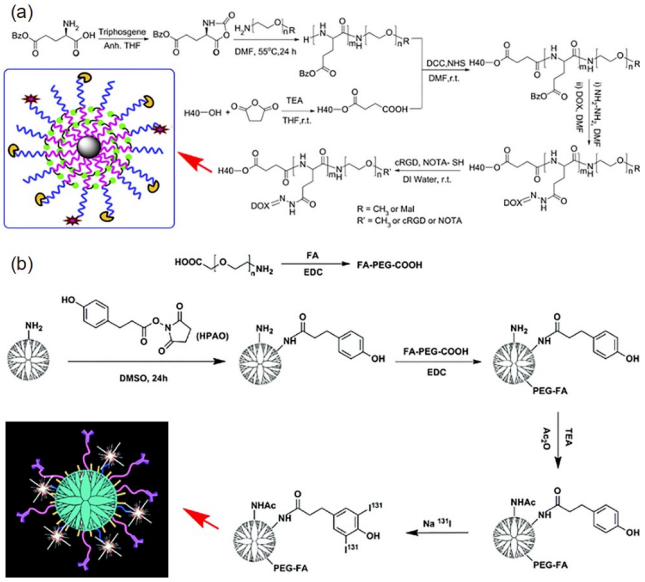


Figure 22 (a) Schematic illustration of the synthesis of the multifunctional H40-DOX-cRGD nanocarriers for tumor-targeted drug delivery and PET imaging [273]; (b) schematic illustration of the synthesis of ^{131}I-labeled multifunctional dendrimers for targeted SPECT imaging and radiotherapy [274] (color online).

imaging-guided disease treatment. However, none of them have been approved for clinical use. One of the major reasons is that these systems do not achieve well balanced and satisfactory therapeutic and diagnostic outcomes, especially for cancer theranostics, given the much increased complication of the combined two modalities. Similar to intravenously (*i.v.*) administered nanomedicines for cancer therapy, the *in vivo* transport process of *i.v.* administered theranostic agents also need to complete the *CAPIR* cascade [92], sequentially comprising circulation in the blood compartments, accumulation in the tumor, deep penetration into avascular tumor tissue to reach tumor cells followed by cellular internalization and intracellular drug release. Although penetrating the tumor and entering cells may not be necessary for the diagnostic modality functioning, the two steps may enhance its tissue concentration and thus the contrast. Thus, the efficient completion of the *CAPIR* cascade, in the context of polymer-based theranostic systems, may not only increase the therapeutic outcomes, but also improve the diagnostic quality.

Two critical steps, namely tumor extravasation and tumor penetration, dictate the efficiency of the *CAPIR* completion. Conventional polymer-based theranostic systems rely on tumor's enhanced permeation and retention (EPR) effect to extravasate through the hyper-permeable tumor vasculature and accumulate into tumor lesion. However, the absence of the EPR effect in human tumors [275,276], and moreover, its heterogeneous and dynamic nature [277] severely limit such passive diffusion-based extravasation [278,279]. Once extravasate into the periphery of tumor vasculature, the dense extracellular matrix (ECM), crowded cellular entities, and high interstitial fluid pressure restrict these macromolecular theranostic agents from infiltrating into the tumor lesion towards avascular regions [280]. So, the two barriers limit the diagnostic and therapeutic efficacies of most theranostic systems.

Recently, Shen *et al.* [87,99,280–282] reported fast transcytosis-inducing polymers as drug delivery carriers, which leverage the intrinsic active transport pathways of endothelial cells and tumor/stromal cells and overcome the difficulties in passive extravasation and penetration of conventional nanomedicines, which greatly enhanced the tumor accumulation and infiltration and therapeutic efficacy (Figure 23). They envision that such polymers-based theranostic systems may promise higher diagnostic and therapeutic effects.

5 Biomedical polymers for immune therapy and anti-infection

5.1 Biomedical polymers used for vaccines and immunotherapy

Immunotherapy has become a powerful strategy to treat and even cure certain types of cancer in the clinic by leveraging the patient's coordinated and adaptive immune system [283,284]. In cancer immunotherapy, therapeutic substances are used to boost the immune system to attack cancer cells through natural mechanisms [285]. Thanks to the unique feature of immunotherapy, it exhibits many advantages encountered by traditional chemotherapy, radiotherapy and others that directly kill cancer cells [286]. Representative cancer immunotherapies include tumor vaccines, immune checkpoint blockade (ICB), cytokine therapy, and engineered T cell therapy [287]. Although it has numerous advantages, immunotherapy may face challenges in both efficacy and safety, thus limiting its clinical application [288]. For example, most patients do not respond to ICB inhibitors *via* various escape mechanisms, resulting in lim-

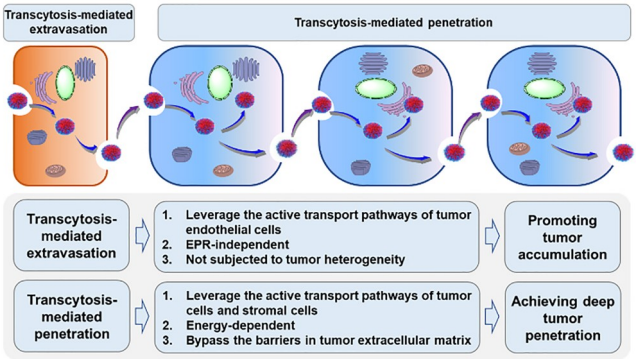


Figure 23 Concept of transcytosis-mediated active tumor extravasation and penetration (color online).

ited therapeutic efficacy [289]. In addition, immune-related adverse events (IRAEs) often occur during immunotherapy, including renal dysfunction, liver dysfunction, colitis, interstitial pneumonia, fever and other potentially lethal adverse effects [290]. Thus, it is still pressing to develop additional strategies to safely and effectively promote immunotherapy to benefit a wider range of patients.

Considering these advantageous characteristics of biomedical polymers for drug delivery to tumors, much effort has been devoted to promoting cancer immunotherapy using biomedical polymers [291,292]. Biomedical polymers have been investigated as efficient delivery systems for vaccines and other immunotherapeutics or immunologic stimulants to activate the immune system [293,294]. As a delivery system, biomedical polymers can passively or actively deliver immune-bioactive agents and protect them from the surrounding environment, increasing their circulation time, reducing systemic side effects and eliciting strong immune responses [294]. For vaccines, a nanosized delivery system based on biomedical polymers is able to mimic pathogens, allowing efficient delivery of antigens to APCs [295]. Moreover, large polymeric carriers exhibit a depot effect, increasing the local concentration of antigens at specific sites through timely release without multiple vaccinations [296]. More interestingly, various polymers with immunostimulating properties have been developed, which can be identified by specific receptors expressed on immune cells to activate specific immune pathways [297]. Immunostimulating polymers with the ability to activate the immune system could also simultaneously serve as efficient delivery systems to induce synergistic immune responses. [298]. In this section, the current advances in biomedical polymers used for vaccines and immunotherapy have been surveyed.

5.1.1 Biomedical polymers used for cancer vaccines

Vaccination is an active immunization strategy to induce specific immune responses against specific pathogens [299]. Cancer vaccines usually consist of appropriate antigens and adjuvants to induce strong immune responses [300]. Cancer vaccines not only treat existing tumors but also prevent the onset of a specific cancer. According to the type of antigen, cancer vaccines are usually classified as whole cancer cell vaccines, subunit vaccines, dendritic cell vaccines and nucleic acid vaccines (such as mRNA) [301]. Effective cancer vaccines require successful delivery of antigens and adjuvants to APCs, which can effectively induce T cells to produce cytotoxic antitumor effects after maturation [302]. Recently, biomedical polymers after specific engineering have been reported to effectively promote cancer vaccines in different ways, including increasing the stability of antigens by preventing their degradation, incorporating multiple adjuvants and antigens to enhance the immunogenicity, enhancing the uptake and cross-presentation of antigen by APCs, and enabling active targeting of APCs *via* specific recognition receptors or activating endosomal Toll-like receptors (TLRs) [303]. Therefore, various biomedical polymers have been investigated for vaccine development.

For cancer vaccines, effective delivery of antigen to APCs is essential for APC activation and antigen presentation [304]. Biomedical polymers have been widely used to effectively deliver antigens to APCs with improved antigen presentation [305]. For example, various antigens, including peptides, proteins, cell lysates or nucleic acids, have been successfully encapsulated in PLGA nanoparticles, realizing prolonged release of antigen to induce more effective immune responses [306,307]. PLGA could also simultaneously encapsulate antigens and adjuvants and co-deliver them into the same APC, which would induce strong T cell responses even at very low dosages. In addition to simply encapsulating antigens and adjuvants, Lynn and co-workers [308] synthesized a library of polymers bearing adjuvants with different densities and demonstrated how polymeric carriers could enhance the efficacy of cancer vaccines (Figure 24a). Moreover, some pH-sensitive polymers have been discovered to enhance antigen presentation *via* endosomal escape and enhance cross-presentation of antigens. Qiu *et al*. [309] developed polyplex nanoparticles by mixing pH-sensitive poly(propylacrylic acid) (pPAA) and antigenic peptides (Figure 24b). It was found that pPAA can change from hydrophilic to hydrophobic in acidic environments to allow endosomal escape, achieving enhanced antigen uptake and presentation by DCs. In addition to a single nanovaccine, different release behaviors of nanovaccines may induce stronger antigen-specific immune responses. Dong *et al*. [310] developed a novel nanovaccine combined with antigens in the inner and outer layers, which could trigger a stronger antigen-specific immune response through the programmed release of antigens. Moreover, Luo *et al*. [311] recently synthesized an immune stimulative PC7A copolymer that could generate a strong cytotoxic T cell response after loading with antigens through efficient cytosolic delivery of antigens and simultaneous activation of type I interferon-stimulated genes.

In addition to the sustained release of antigens, an appropriate administration route is another key factor affecting vaccine efficacy. According to previous studies, intradermal administration of vaccines exhibited stronger immune responses. Recently, Zaric *et al*. [312] developed a microneedle containing antigen loaded with PLGA nanoparticles. Interestingly, after the microneedle was dissolved in the skin, antigen-encapsulated PLGA nanoparticles could be released into the skin layers containing abundant APCs, achieving efficient activation of DCs. Apart from novel administration routes, using cancer cell membranes as novel antigens is another important strategy to induce strong immune responses. Kroll *et al*. [313] utilized cancer cell membranes to

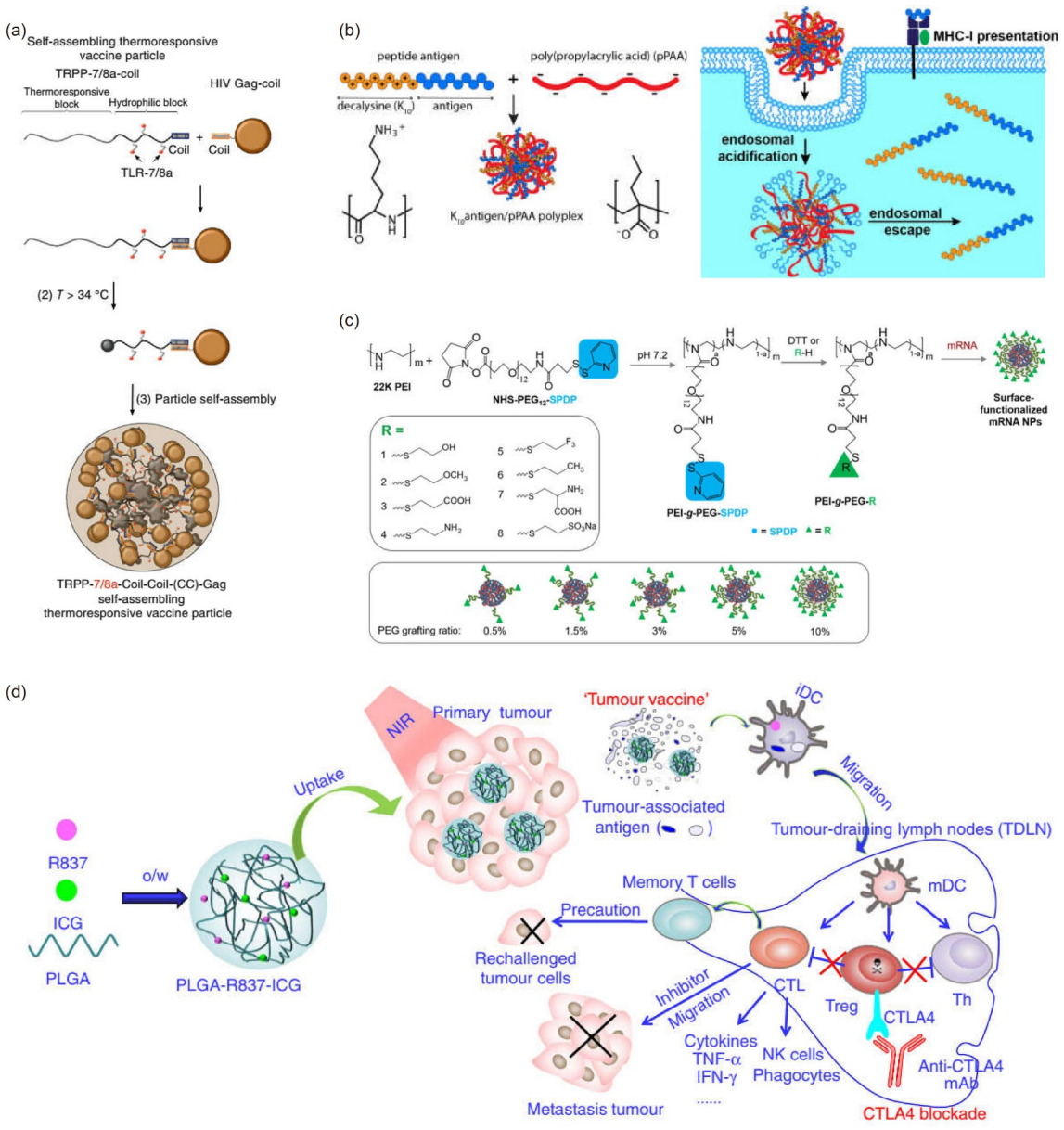


Figure 24 Biomedical polymers used for cancer vaccines. (a) Temperature-responsive Poly-7/8a modified with a coil peptide that forms heterodimers with a recombinant HIV Gag-coil fusion protein to form TRPP-7/8a-(CC)-Gag [308]; (b) assembly of antigen-loaded nanoplexes *via* simple and rapid mixing of decalysine-modified antigenic peptides and pPAA, which generates electrostatically-stabilized nanoparticles as cancer vaccine [309]; (c) preparation of PEI-g-PEG/mRNA NPs with various PEG terminal groups and PEG grafting ratios [316]; (d) anti-tumor immune responses induced by PLGA-ICG-R837-based PTT [318] (color online).

coat adjuvant-containing PLGA nanoparticles, realizing vigorosomal and multiantigenic antitumor immune responses. Moreover, Liu's group [314] also developed a cancer cell membrane-coated cancer vaccine. They found that after further modification with mannose, the nanovaccine could specifically target APCs due to the interaction between mannose and its receptor on APCs, leading to significantly enhanced immune responses.

Recently, mRNA-based nucleic acid vaccines have attracted wide attention due to their unique advantages over conventional vaccines. However, mRNA is a relatively fragile macromolecule, so it is not stable in physiological environments and can not easily pass through physiological barriers to enter target cells. To improve the immunogenicity of mRNA vaccines, many biomedical polymers have been used to deliver mRNA. PEI, one of the most commonly used cationic polymers, has been used for nucleic acid delivery [315]. Considering its toxicity, various modified PEIs have been synthesized for mRNA vaccine delivery. Mao's group [316] synthesized PEI-PEG with different grafting ratios and PEG terminal groups to deliver mRNA (Figure 24c). They demonstrated that PEI-PEG condensed mRNA with amino or

amino acid terminal groups showed the highest transgene expression in the lungs of mice after systemic administration. Additionally, Anderson's group [317] demonstrated that degradable poly(β-amino esters) after conjugation with PEG-lipid could also systemically deliver mRNA to the lungs of mice. Moreover, some pH-responsive polymers have also been synthesized for mRNA delivery. A series of poly-aspartamide derivatives with ionizable aminoethylene side chains were synthesized to deliver mRNA.

In addition to these classic vaccines, *in situ*-generated vaccines based on polymeric nanoparticles have been reported recently. Liu's group [318] developed therapeutic nanoparticles using PLGA, indocyanine green (ICG) and the TLR-7 agonist R837 (Figure 24d). Upon photothermal ablation of the tumor injected with PLGA-ICG-R837, the generated tumor-associated antigens working together with PLGA nanoparticles could act as vaccines to induce strong immunological responses. Min *et al*. [319] also developed antigen-capturing PLGA NPs, which were able to capture the released tumor-associated antigens after radiotherapy and deliver them to nearby APCs, thereby exhibiting vaccine function to activate the immune system. In addition to PLGA nanoparticles, He *et al*. [320] developed nanoscale coordination polymer (NCP) nanoparticles containing chemotherapeutic drugs and photosensitizers. They also found that chemotherapy and photodynamic therapy of the primary tumor injected with NCP nanoparticles could act as vaccines to release tumor-associated antigens and induce antitumor immune responses. Chen's group [298] developed a supramolecularly assembled polymeric nanoparticle based on poly-[(*N*-2-hydroxyethyl)-aspartamide]-Pt(IV)/β-cyclodextrin and CpG/polyamidoamine-thioketal-adamantane. They found that after intravenous injection, polymeric nanoparticles could also induce tumor-associated antigen release and act as a tumor vaccine to activate the immune system.

5.1.2 Biomedical polymers used for ICB

Although employing biomedical polymers to promote cancer immunotherapy has mainly focused on cancer vaccines by efficiently delivering antigens and adjuvants, inefficient immune responses remain due to immune resistance [321]. Immune checkpoint therapy is a common mechanism of immune resistance that plays an important role in protecting normal tissues against immune system attack [322]. ICB therapy has achieved outstanding therapeutic results in treating various types of tumors by blocking regulatory signals expressed on immune cells or tumor cells. There are various ICB inhibitors, such as anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) and anti-programmed cell death protein 1 and its ligand (anti-PD-1/anti-PD-L1) antibodies [323]. Although some of these ICB inhibitors have achieved outstanding therapeutic effects, the current ICB still has a few challenges, such as improving the efficacy and reducing immune-related side effects [324]. Therefore, various strategies based on biomedical polymers have been developed to promote the efficacy of ICB while reducing its side effects.

Li *et al*. [325] synthesized a biocompatible and biodegradable poly(ethylene glycol)-*block*-poly(*D*,*L*-lactide) (PEG-PDLLA) copolymer to encapsulate CTLA-4 siRNA (siCTLA-4) with the help of *N*-bis(2-hydroxyethyl)-*N*-methyl-*N*-(2-cholesteryloxycarbonyl aminoethyl) ammonium bromide (BHEM-Chol) (Figure 25a). They demonstrated that siCTLA-4-loaded polymeric nanoparticles could promote antitumor immune responses by successfully silencing CTLA-4 molecules expressed on activated T cells. In addition to polymeric nanoparticles, some hydrogels based on polymers have also been developed to promote the delivery of ICB inhibitors. Li *et al*. [326] used alginate hydrogels to locally and simultaneously deliver anti-PD-1 and anti-inflammatory drugs. Thanks to the efficient delivery of anti-PD-1 and anti-inflammatory drugs, strong immune responses and antitumor effects were achieved. Yu *et al*. [327] prepared a functionally injectable polypeptide gel based on ROS-responsive triblock copolymer containing PEG, *L*-methionine and dextro-1-methyl tryptophan (D-1MT), an inhibitor of indoleamine-2,3-dioxygenase, which could successfully deliver and achieve sustained release of anti-PD-L1 and D-1MT, leading to enhanced antitumor efficiency (Figure 25b). In addition to polymeric hydrogels, Gu's group [328] developed a biodegradable microneedle patch based on hyaluronic acid (HA) for local and sustained delivery of ICB inhibitors, including anti-PD-1, anti-CTLA-4 or D-1MT, in a melanoma tumor model (Figure 25c). Compared with free ICB inhibitors, this strategy could trigger more effective antitumor immune responses to inhibit the growth of tumors.

5.1.3 Biomedical polymers for cytokine therapy

In contrast to ICB, cytokine therapy is a direct immunotherapeutic strategy to stimulate different immune cells to kill cancer cells. Cytokines, secreted proteins, play an important role in regulating both the innate and adaptive immune systems [329]. To date, three main types of cytokines, interferons (IFNs), interleukins (ILs), and granulocyte-macrophage colony-stimulating factor (GM-CSF), have been pursued cancer immunotherapy [330,331]. Despite the strong antitumor immune responses achieved by cytokine treatments, there are still many side effects, such as acute inflammation and autoimmune diseases. Utilizing biomedical polymers to efficiently deliver cytokines has also attracted wide attention.

IL-2, which is a growth factor for T cell proliferation and activation, has been approved by FDA for the treatment of renal cell carcinoma and melanoma [332]. In past years, IL-2 has been encapsulated into polymeric nanoparticles to promote T cell activation and infiltration. For example, Pork and

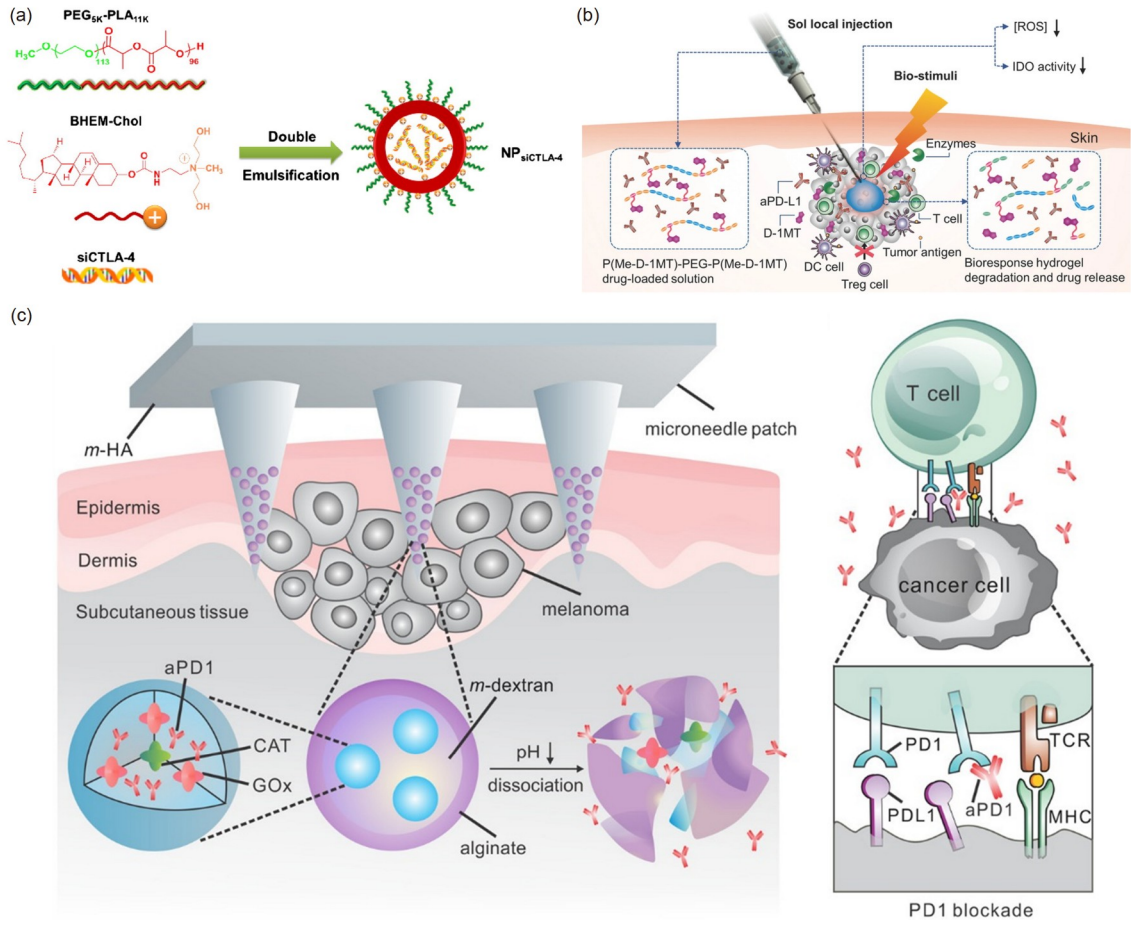


Figure 25 Biomedical polymers used for ICB. (a) Poly(ethylene glycol)-*block*-poly(*D*,*L*-lactide) and BHEM-Chol used for siCTLA-4 delivery to promote antitumor immune responses [325]; (b) the injectable polypeptide gel based on triblock copolymer containing polyethylene glycol (PEG), *L*-methionine (Me) and dextro-1-methyl tryptophan (D-1MT) was used to deliver anti-PD-L1 and D-1MT [327]; (c) microneedle patch for local and sustained delivery of ICB inhibitors, including anti-PD-1, anti-CTLA-4 or D-1MT [328] (color online).

co-workers [333] encapsulated IL-2 and transforming growth factor-β (TGF-β) inhibitors into biodegradable polymers. The sustained release of IL-2 and TGF-β inhibitors obviously increased the infiltration of natural killer cells and $CD8^+$ T cells and significantly delayed the growth of tumors. IL-2 could also be conjugated to the surface of hydroxyethyl starch nanocapsules, realizing efficient targeting of T cells relying on IL-2 receptor-mediated internalization. In addition to IL-2, IL-7 is another important cytokine for T cell proliferation and can also be encapsulated into polymeric nanoparticles together with antigens to induce strong humoral and cellular immune responses to inhibit tumor growth [334]. Moreover, various biodegradable polymer-based nanoparticles, including PLGA, PLA, polysaccharide chitosan, and PBAE, have been used to encapsulate IL-12 to promote the activation of T cells to inhibit the growth and metastasis of tumors [335,336].

5.1.4 Biomedical polymers for adoptive T cell therapy

Adoptive T cell therapy is a kind of passive immunotherapy that transfuses T cells with additional expansion and modification to patients [337]. During this treatment, T cells from patients are collected and activated by cytokines or genetic engineering and then reinfused into patients to kill cancer cells. Currently, adoptive T cell therapies, including tumor-infiltrating lymphocyte (TIL) therapy, cytotoxic T lymphocyte (CTL) therapy and engineered T cell therapy, have been used for cancer therapy [338]. Considering the elaborate procedures and high costs required to generate adoptive T cells, biomedical polymer-based strategies to promote the efficiency of adoptive T cells are now being investigated [339].

One of the promising strategies is attaching drug-loaded particles to the membrane of T cells. For example, Irvine's group [340] loaded cytokines into nanoparticles and conjugated them to T cells, resulting in efficient expansion of T cells in the tumor. Such an approach could also be utilized to deliver other molecules to promote T cell activation. In a subsequent work, they also conjugated NSC-87877-loaded nanoparticles to tumor-specific T cells, achieving sig-

nificantly enhanced T cell expansion in the tumor [341]. Recently, Tang *et al*. [342] conjugated a 'backpack' containing disulfide-crosslinked cytokine nanogels (NGs) and PEG-*b*-PLL onto T cells (Figure 26a). They found that activated T cells exhibited increased free thiols on their surface, which could trigger antigens to release cytokines within the tumor, realizing selective expansion of T cells in the tumor with low off-target toxicity.

In addition to attaching drug-loaded particles to the membrane of T cells, polymeric platforms are now being developed to target and engineer T cells *in situ*. Smith *et al*. [343] modified biodegradable PBAE with peptides containing nuclear localization signals and microtubule-associated sequences to form lymphocyte-targeting nanoparticles (Figure 26b). After systemic administration, the nanoparticles selectively targeted circulating T cells and effectively delivered leukemia-specific chimeric antigen receptor (CAR) genes *in situ* to achieve sufficient CAR expression.

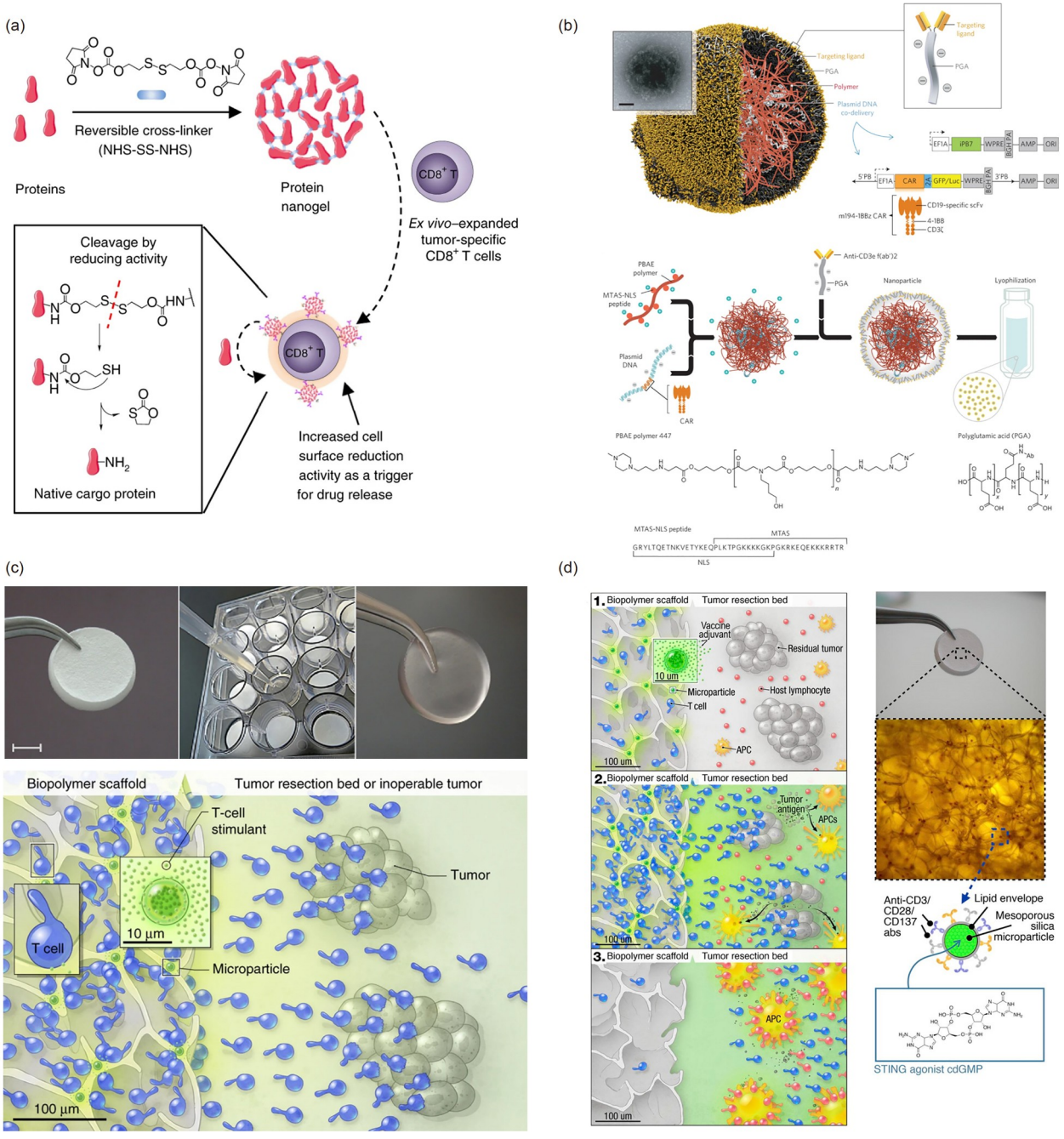


Figure 26 Biomedical polymers for adoptive T cell therapy. (a) Cytokines loaded 'backpack' conjugated on T cells for selective expansion of T cells in the tumor [342]; (b) peptides modified biodegradable poly(β-amino esters) to selectively target circulating T cells and effectively delivered leukemia-specific chimeric antigen receptor (CAR) genes *in situ* to achieve sufficient CAR expression [343]; (c) collagen-mimetic peptide-modified polymerized alginate scaffolds to deliver T cells [345]; (d) implantable biopolymer devices used to deliver CAR T cells [346] (color online).

Importantly, this strategy achieved comparable therapeutic efficiency to traditional CAR T cell therapy.

Although adoptive T cell therapy has shown promising therapeutic results for hematologic malignancies in the clinic, its efficacy against solid tumors remains modest due to the complex tumor microenvironment [344]. Recently, various polymeric hydrogels have been explored to deliver T cells into solid tumors. Stephan and co-workers [345] developed collagen-mimetic peptide-modified polymerized alginate scaffolds to deliver T cells and IL-15-encapsulated silica microparticles, which could stimulate and promote the proliferation of T cells (Figure 26c). In the mouse breast cancer resection model, local delivery of scaffolds containing T cells successfully prevented tumor relapse and prolonged the survival of mice. In a subsequent work, they used implantable biopolymer devices to deliver CAR T cells (Figure 26d) [346]. They found that CAR T cells could be released from the scaffolds and accumulated in solid tumors at high concentrations for a substantial time period, thus successfully eradicating the tumor. They also found that co-delivery of stimulator of interferon genes (STING) agonists could further activate the immune system to eliminate remaining cancer cells. In a recent work, Gu's group [347] developed a polymeric porous MN patch based on biocompatible PLGA to accommodate CAR T cells and allow sustained release of T cells into solid tumors.

5.2 Biomedical polymers used for anti-bacteria

Bacterial infections are threatening the health and life safety of human. According to the statistical data of the World Health Organization, the number of infected diseases is about 80 billion person-time, leading to 10 million deaths. With the abuse of antibiotics, drug resistance is becoming a serious problem that reduces the efficacy of antibacterial drugs. Therefore, various types of antibacterial materials are being intensively studied worldwide to fight against bacterial infections [348,349]. Due to the high flexibility and diversity, polymers have attracted increasing attention. It is noteworthy that, among more than 20,000 articles about antibacterial polymers based on the up-to-date database of Web of Science, the Chinese scientists contributed more than 8,000 articles, which reflects their active and important role in this field.

Many types of novel antibacterial polymers have been developed by Chinese researchers in polymer science and engineering to achieve excellent performances. To fight with drug-resistant bacteria, a series of β-peptide polymers were designed and constructed. The amine group variation, including primary, secondary and tertiary amines, exhibited significant impact on the antibacterial performances of β-peptide polymers against methicillin-resistant *Staphylococcus aureus* (Figure 27a) [350]. The β-peptide polymers with different C-terminal functional groups were synthesized by a ROP reaction of *N*-substituted *N*-carboxyanhydrides, which provided various efficient antibacterial polymers against biofilm formed by drug-resistant bacteria [351]. In order to promote the antibacterial efficiency, multimodal antibacterial polymers, such as quaternary ammonium/photodynamic combination, were developed to treat severe infections (Figure 27b) [352]. Because of the varieties of sources and functions, natural polymers and their derivatives, such as dopamine-modified hyaluronic acid, were also widely used for constructing antibacterial materials [353]. Poly(ionic liquid) and their copolymers are another category of novel antibacterial polymers, which have high antibacterial efficiency, and are used for a wide range of applications (Figure 27c) [354–356]. In addition, the chirality of polymers is an important factor of antibacterial activity, which has been studied to fabricate antiadhesive and bactericidal polymers [357]. The above antibacterial polymers improve the bactericidal efficiency, and provide effective candidates for infection prevention and treatment.

The acting mechanisms and structure-property relationships are essential for the design and regulation of molecular structures of antibacterial polymers. To study the bactericidal mechanisms of antimicrobial peptides, aggregation-induced emission probes were conjugated to visualize the accumulation on the bacterial membrane and disruption of the membrane structure by light-up fluorescence [358]. The interactions between cationic bactericidal agents with different molecular structures and bacteria were well investigated, and the acting mechanisms of cell membrane disruption were demonstrated by ultra-high resolution laser confocal microscopic images and molecular dynamics simulations (Figure 27d) [359]. The antibacterial mechanisms of photodynamic polymers were also studied to detect the attacking sites of ROS [360]. These research works provided theoretical guidance for the development of novel antibacterial polymers.

Biofilm is a primary cause of medical device-induced infections, which could not be eradicated by ordinary antibiotic treatment. Therefore, varieties of high-performance polymeric nanosystems were developed to deal with biofilm. By a pH-responsive PBAE-based copolymer, bactericide-loaded micelles were constructed with enhanced biofilm penetration and acid-triggered charge conversion properties, which could accumulate in biofilm and release antibacterial content induced by bacterial enzymes [361]. Similarly, based on the charge conversion of poly(quaternary-amino-ester) with pH values, a pH-responsive PCL-*b*-poly(quaternary-amino-ester) was assembled with PEG-*b*-PCL to prepare zwitterionic polymeric micelles with self-targeting, penetrating and accumulating properties, and the *in vivo* anti-biofilm properties were directly visualized in a living mouse [362]. Azithromycin-conjugated clustered polymeric nanoparticles with charge- and size-adaptive properties were constructed

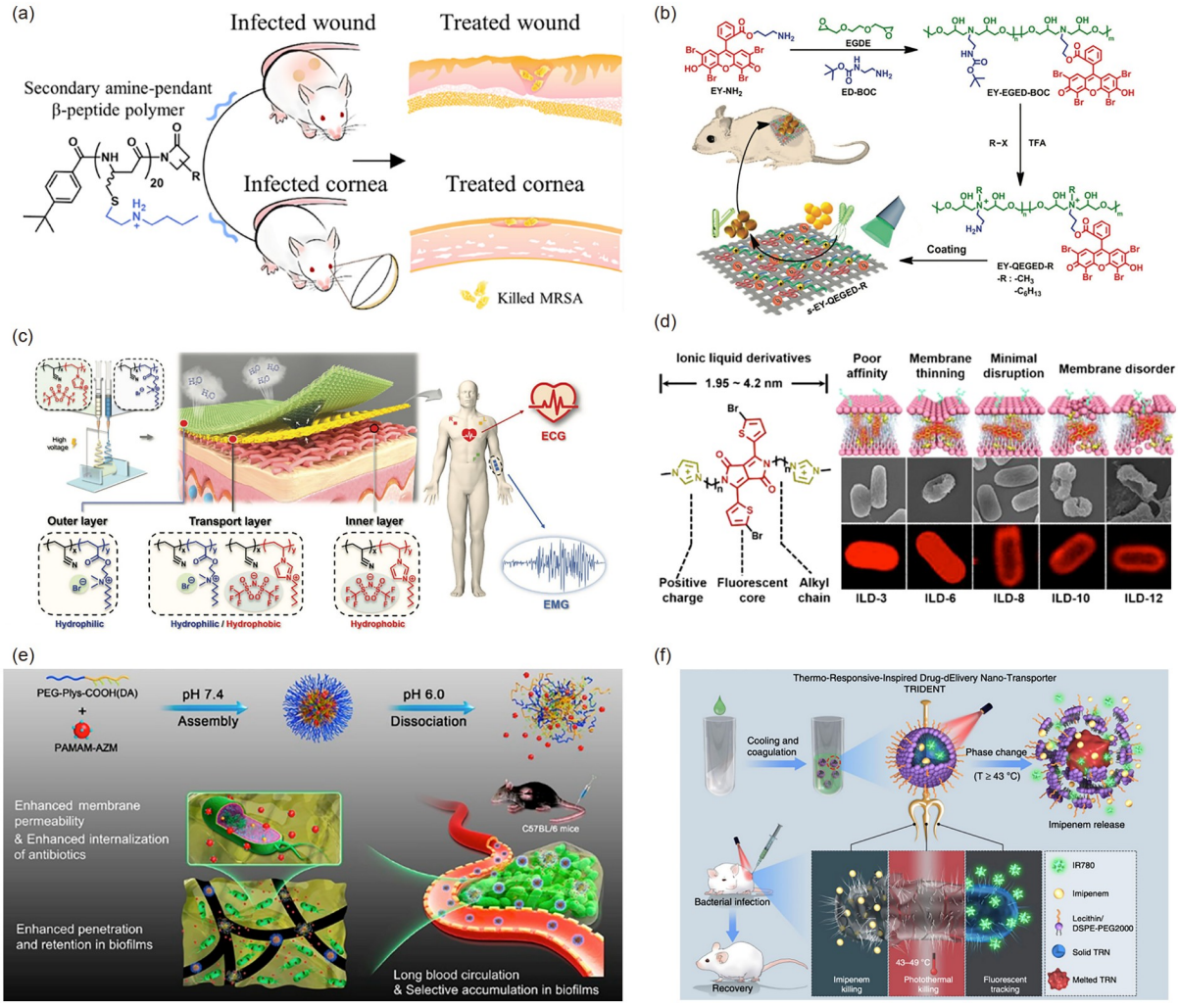


Figure 27 (a) β-Peptide antibacterial polymers [350]; (b) multimodal (quaternary ammonium/photodynamic) antibacterial polymers [352]; (c) poly(ionic liquid) antibacterial polymers [354]; (d) antibacterial mechanism study on cationic materials [359]; (e) size and charge adaptive clustered polymeric antibacterial nanoparticles [363]; (f) thermo-responsive triple-function nanotransporters for antibacterial drug delivery [365] (color online).

based on amino-ended poly(amidoamine) dendrimers, and the nanoparticles could disassemble in the acidic biofilm microenvironment to realize enhanced antibiofilm performances in both *in vitro* and *in vivo* (Figure 27e) [363]. Polymyxin B-functionalized Rose Bengal polydopamine nanoparticles could penetrate biofilm at low pH values, and bind to bacteria to exhibit bactericidal property by the combined activity of antibiotic and reactive oxygen species [364]. Thermo-responsive-inspired drug-delivery nanotransporters could realize integrated fluorescence monitoring and synergistic chemo-photothermal antibacterial properties, which enhanced antibiotic permeation to kill drug-resistant bacteria (Figure 27f) [365]. Such polymeric nanomaterials promoted the delivery efficiency of antibiotics inside biofilms. Some nanosized antibacterial polymers could also possess outstanding performances. For example, imidazolium-based block copolypeptides were synthesized *via* facile ring-opening polymerization and click chemistry methods, and such polymers could self-assemble into nanoparticles with high antibacterial activity and low hemolysis [366]. Moreover, with the introduction of inorganic components, the antibacterial performances of polymeric nanomaterials could be further improved. Antibiotic-loaded polymeric vesicles associated with ceria could inhibit bacterial infection and eliminate superoxide free radicals simultaneously, which was promising for the treatment of infected chronic wounds [367]. The polymeric nanomaterials have become powerful tools to treat stubborn infections induced by biofilms.

Interventional or implanting medical devices are applied in many clinical departments, such as orthopedics, dentistry and plastic surgery. However, the high morbidity of medical device-induced infections leads to failure of treatment and great pain for patients. Because the perquisite of such infections is the attachment and growth of bacterial on the surfaces of medical devices, various types of polymer coatings are fabricated to prevent or treat medical device-related

infections. Catechol-based strategy is efficient for antibacterial coating on various types of medical devices, such as titanium implants (Figure 28a) [368]. Because the medical devices are directly contact with human body, their biocompatibility is important. The hemocompatibility of quaternary ammonium coating could be improved by adjusting the ratio of positively and negatively charged groups in copolymers [369]. A fluorinated copolymer-based water dispersible nanoparticles containing hexamethylene biguanide component could be applied as a transparent coating on medical catheters, which showed excellent antibacterial activity and biocompatibility [370]. Another strategy to improve biocompatibility is constructing polymer coatings that are responsive to internal or external stimuli. Many external stimuli, such as irradiation, could trigger the transformation of molecular configuration, which enabled surfaces with bactericidal-release switching property [371]. By the rational combination of polymers and inorganic components, such as super hydrophilic polymer and gold nanorods, the surface coating could possess balanced bactericidal and antifouling properties to meet the requirement of specific medical devices (Figure 28b) [372]. Owning to the difference of microenvironments between normal and infected tissues, such as pH values and enzymes, infection-responsive antibacterial polymeric coatings could be developed. The responsive antibacterial coating could be fabricated by hierarchical structures with a bactericidal bottom layer and a multi-carboxyl polymeric top layer, because the top layer could collapse under the low pH environment to expose the bactericidal components [373]. By surface-initiated living polymerization and Schiff base reaction, aminoglycoside antibiotics could be decorated onto the surface of medical implants with high amount, and the loaded antibiotics could be released by the triggering of weak acidic environment of infection, showing a self-adaptive antibacterial profile [374]. Bioswitchable antibacterial coatings were prepared by a triblock copolymer that contained a polyester block and two quaternary ammonium blocks, in which the polyester block could be degraded by bacterial lipase to expose the quaternary ammonium groups for infection-responsive antibacterial applications (Figure 28c) [375]. Under the catalysis of horseradish peroxidase, aminoglycosides and protocatechualdehyde could form a stable "smart" coating with high drug loading amount, pH-responsiveness, and on-demand drug release behaviors, showing high antibacterial efficiency both *in vitro* and *in vivo* (Figure 28d) [376]. These infection-responsive polymeric coatings not only possess good biocompatibility, but also have stable and long-term antibacterial activity.

Besides antibacterial activity, the bioactivity is also important for implanting medical devices, especially for tissue restoration materials. To improve the bioactivity of surface antibacterial coating, a fusion peptide engineered "statically-versatile" surface was developed by combing antibacterial and angiogenic sequences into one peptide, which could efficiently eliminate bacterial infection and promote vascularization and osseointegration [377]. The osseointegration bioactivity of antibacterial coating could also be enhanced by regulation of surface chemical characteristics, such as surface charge and bioactive functional groups [378]. Through

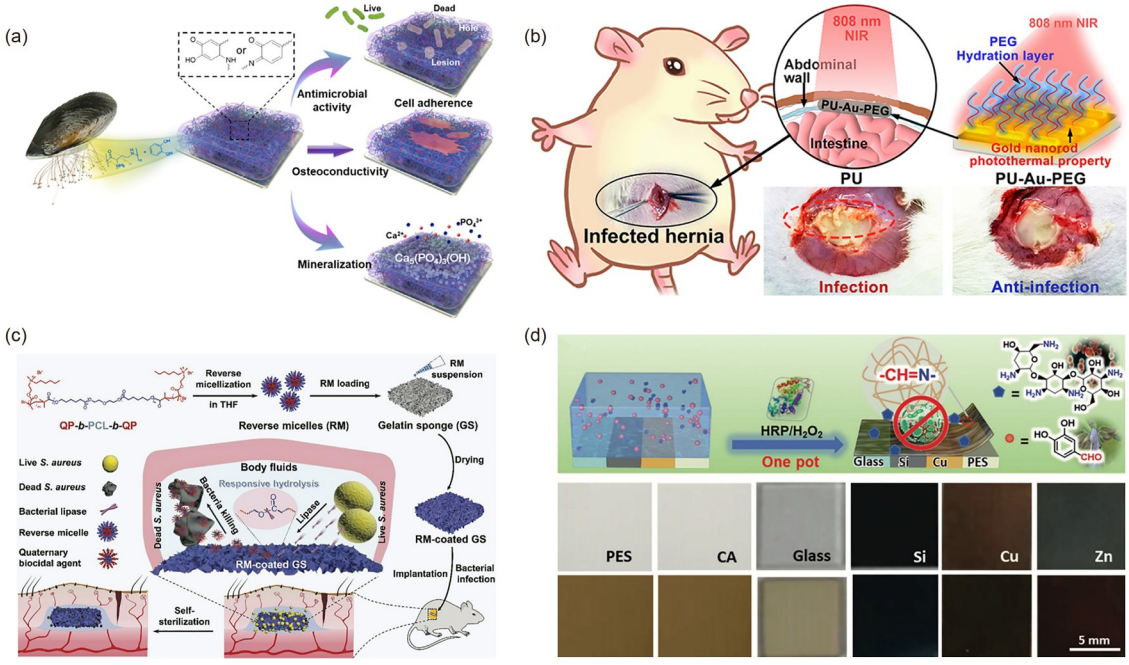


Figure 28 (a) Catechol-based antibacterial coating [368]; (b) near infrared light-triggered antibacterial coating [372]; (c) lipase-responsive antibacterial coating [375]; (d) acid-responsive antibacterial coating [376] (color online).

these strategies, the anti-infection and tissue-integrating properties are improved simultaneously.

At present, the antibacterial efficiencies of antibacterial polymers have been greatly improved. In future, the development trends of antibacterial polymers includes broad-spectrum application, functionalization, theoreticalization, and industrialization, which might promote the upgrading of novel high-performance antibacterial medical devices to protect human health.

5.3 Biomedical polymers used for anti-virus

The novel coronavirus pneumonia epidemic by the SARS-CoV-2 has spread almost all over the world, resulting in great loss to human society. As generally defined, virus is a kind of non-cellular and individually small organism with simple structure that contains only one type of nucleic acid (DNA or RNA), which proliferates through replication and parasitizes in living cells to survive. Infectious diseases are responsible for about 20% of the annual global deaths, and nearly one third of them are caused by virus infections [379]. In order to control the spread of virus, accurate and rapid detection, efficient disinfection, effective personal or collective protective equipment, and timely and effective therapies are extremely required, which ultimately calls for multi-disciplinary solutions [380]. Chemistry, material science and related technology have developed rapidly in recent years and achieved remarkable development. Numerous new chemical reactions, substances, and materials with unique properties have been developed and applied in people's daily life. Especially, these chemical substances and materials can be used to tackle biosafety problems such as pathogen detection and disintegration, *etc*., which have been recently defined as biosafety chemistry and biosafety materials [381–383]. Polymers are characterized by the ease of synthesis, adjustable compositions, tunable structures and morphologies, multifunctionality, *etc*. They can be widely used in biomedical and biosafety fields. Here in this part, we only focus on the use of polymer materials for anti-virus applications, such as virus detection and diagnosis, disinfection, prevention and treatment.

5.3.1 *Biomedical polymers for detection and diagnosis of virus*

Facing the disaster of human society induced by infectious diseases, the first challenge is to detect an unknown pathogen, which has the characteristics of epidemics and may emerge in various ways [384]. Conventional immunoassays such as ELISA and paper-based LFAs have limited sensitivity to virus and may produce false-positive results, which are difficult to distinguish from real-positive samples. Accordingly, optical immunosensors including colorimetry, fluorescence and surface plasmon resonance, have been developed to overcome such limitations (Figure 29) [385]. For instance, the conjugated polymer polydiacetylene (PDA) has unique chromatic characteristics. Once the specific antigen-antibody interaction leads to the conformational change of PDA and shortens the π-π conjugated bonds on the molecular skeleton, its color will instantly shift from blue to red [386]. This excellent behavior can be applied to design PDA as optical immunosensors used for efficient virus detection as the color change can be evidently perceived by the naked eyes.

5.3.2 *Biomedical polymers for disinfection*

Disinfection of the virus in the environment to prevent it from infecting the human beings is the main means to suppress the spread of the virus. Biomedical polymers used for virus disinfection can be mainly synthetic polymers with antiviral properties *via* incorporating antiviral components (such as metal ions), functional organic chains and charged groups such as quaternary ammonium polymers as well as natural polymers and their derivatives.

Natural polymers and their derivatives *via* chemical

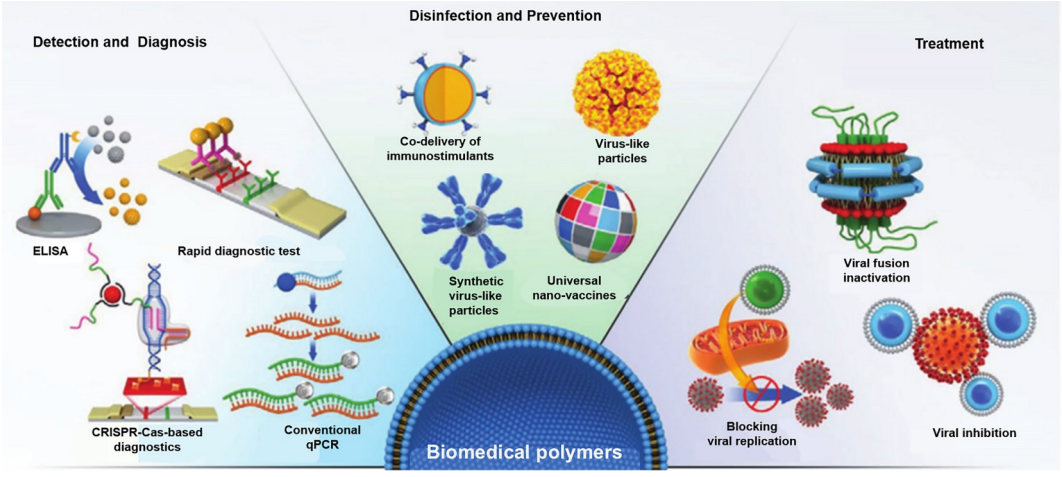


Figure 29 Biomedical polymers for virus detection, diagnosis, disinfection, and prevention and treatment drugs [385] (color online).

modification are possible to be used as anti-virus materials. The modification approaches include grafting with functional groups, ligands and chains [387]. Chitosan is an organic polysaccharide abundant in natural resources, which can be obtained chemically by modifying chitin, another polysaccharide derived from animals or fungi, through removing part of its acetyl groups [388]. Chitosan and its derivatives have already been proved to have direct antiviral activity due to the electrostatic interaction between this positively charged polycation and the negatively charged surface of the virus which can inhibit the infection of virus or directly kill the virus by destroying its protective membrane [389,390]. Moreover, for synthetic polymers, the anti-virus mechanism of PEI is similar to chitosan, as its positive charge can attract the inherently negatively charged virus, intervening its genomic content or structural units, eventually leading to the complete disintegration of the virus [391].

In order to prevent the spread and transmission of viruses through ambient liquid, a sustainable and biodegradable antiviral filter membrane has been developed [392], which is composed of amyloid nanofibers made from food-grade milk proteins and iron oxide nanoparticles. The filter membrane has demonstrated excellent disinfection outcomes towards enveloped, non-enveloped, air- and water-borne viruses, such as SARS-CoV-2, influenza A (H1N1), and enterovirus 71 (EV71), which provides a very promising way of virus-polluted water treatment.

5.3.3 *Biomedical polymers for virus prevention*

Masks, gloves, protective suits and other protective equipments are physical barriers that prevent human beings from infection. People can reduce the adhesion and viability of virus through material surface modification, endowing materials with superior antiviral capacities [393]. Representative antiviral coatings and surfaces are shown in Figure 30a, including surfaces coatings with metal and inorganic nanomaterials, polymeric and organic materials. Moreover, some inorganic substances such as copper, silver, gold, zinc and TiO_2 nanoparticles have broad-spectrum antiviral effects. Researchers can embed these nanoparticles into textiles and films to prepare organic composites with anti-virus effect by surface modifications [394]. Zhou *et al.* [395] developed a new plastic film using AgNPs and CuNPs, the surface of which was covered with a large number of nanopillars (Figure 30b). Such three-dimensional nanopatterns increase the contact area between AgNPs, CuNPs and viruses with improved antiviral performance. Specifically, it was found that the film could inactivate SARS-CoV-2 by two orders of magnitude within the first hour, thus greatly reducing the possibility of virus transmission. Therefore, the above-mentioned materials could be applied in packaging, protective shields, handles, elevator covers *etc.* with excellent antiviral performance.

Chitosan, which can kill viruses, can also be used as virus-prevention materials. Chitosan hydrogels were prepared and used for antiviral spray and antiviral liquid gloves [396]. Another antiviral material that can kill surface viruses is the materials with photodynamic effect. Stable and reusable vitamin K-containing nanofiber membranes (VNFMs) were prepared, which could produce ROS under both ultraviolet (UV) and sunlight with high antiviral effect (>99.9%) upon a

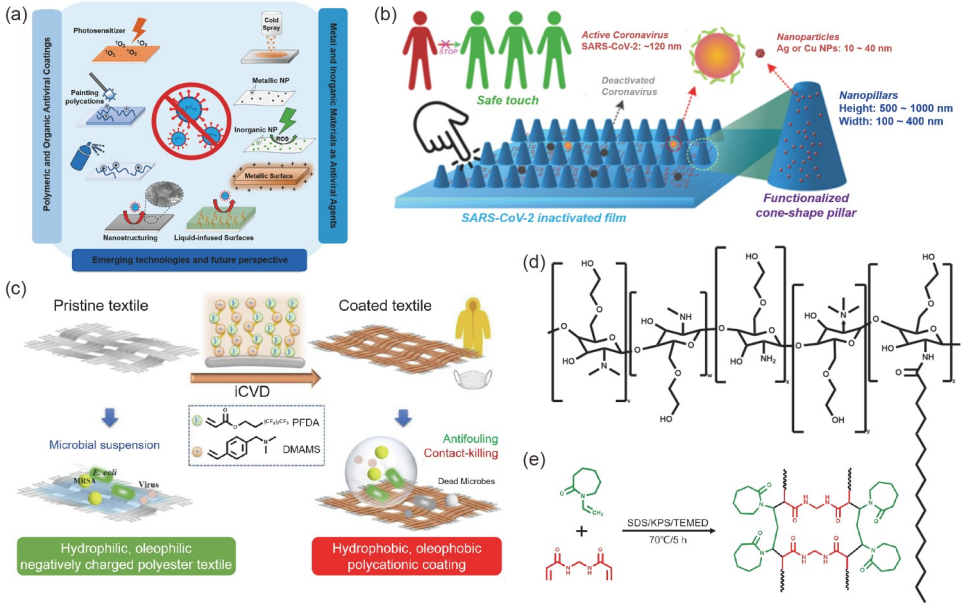


Figure 30 (a) Antiviral coatings and surfaces, including surfaces covered with metal and inorganic nanomaterials, polymeric and organic materials [394]; (b) anti-SARS-CoV-2 film materials embedded with nanopatterns [395]; (c) synthesis of fluorinated polycationic coating and its germicidal effects [398]; (d) the structure formula of GCPQ [399]; (e) synthesis of poly(*N*-vinyl caprolactam) [400] (color online).

relatively short irradiation exposure time (<90 min) [397]. In addition to killing the viruses attached to the surface of the materials, antiviral adhesion is also a strategy for materials design. Moreover, it is reported that a hydrophobic and oleophobic fluorinated polycationic coating on hydrophilic negatively charged polyester fabric was prepared by exploiting a one-step vapor deposition (Figure 30c) [398]. Results showed that this coating could be ideal as antiviral material which can effectively inactivate negatively charged viruses but has good biocompatibility with NIH 3T3 fibroblasts.

In addition to the above materials that can form physical barriers, some polymers are directly used in the human body to prevent human from viruses. For aerosol-borne viruses, one best approach to reduce the transmission could be preventing them from entering mammalian nasal to contact epithelial cells. To address this, a positively charged polymer chitosan with long lipid side chains and ammonium groups was prepared (GCPQ, Figure 30d) and showed the ability to prohibit the binding of COVID-19 to host cells, resulting in blocking virus invasion into the body [399].

For HIV and other sexually transmittable viruses, vaginal administration can prevent the virus from invading the human body [400]. For example, a poly(*N*-vinyl caprolactam)-responsive nanoscale gel was prepared (Figure 30e), which demonstrated nearly no cytotoxic effect on cervix vaginal epithelial cells but the gel can inhibit the replication of intracellular HIV-1 and plays a significantly protective role in preventing HIV infection.

5.3.4 *Biomedical polymers for the treatment of virus infection*

The last step for virus prevention and control is the development of treatment drugs and vaccines. Antiviral drugs include small molecule-based drugs and polymeric drugs. Recently, polymers have attracted much attention because of exclusive properties compared with small molecule drugs. This is because the tunability of chemical composition and topology structure of polymer is diverse. Moreover, polymers are characterized by "multivalence", which might adopt their multiple pendent groups or polymer main chains even the self-assembled nanostructures to simultaneously bind to multiple complementary receptors on biological targets, significantly enhancing the antiviral ability of the drugs [401]. Therefore, it is highly prospective to develop polymeric materials for anti-virus infection.

Marine-derived sulfated polysaccharides, such as carrageenan, agar, fucoidan and alginate, possess broad-spectrum antiviral activity against a wide range of enveloped and non-enveloped viruses, which are becoming one of the potential sources for the development of novel antiviral drugs (Figure 31a). The mechanism of these sulfated polysaccharides inhibiting different stages of virus infection in host cells has also been studied [402], including blocking the initial virus entry, suppressing the transcription and translation by regulating the immune response of host cells [403]. Moreover, the potential of highly sulfated synthetic glycomimetic as inhibitors of virus binding/infection was studied (Figure 31b) [404]. Results demonstrated that both long-chain glycopolymers and short-chain ones could inhibit the infection of herpes simplex virus (HSV), influenza A virus (IAV) and Merkel cell polyomavirus (MCPyV).

Multivalent binding inhibitors are another promising class of antiviral drugs, which inhibit the binding of viruses with host cell membranes by simulating mucin for anti-viral in-

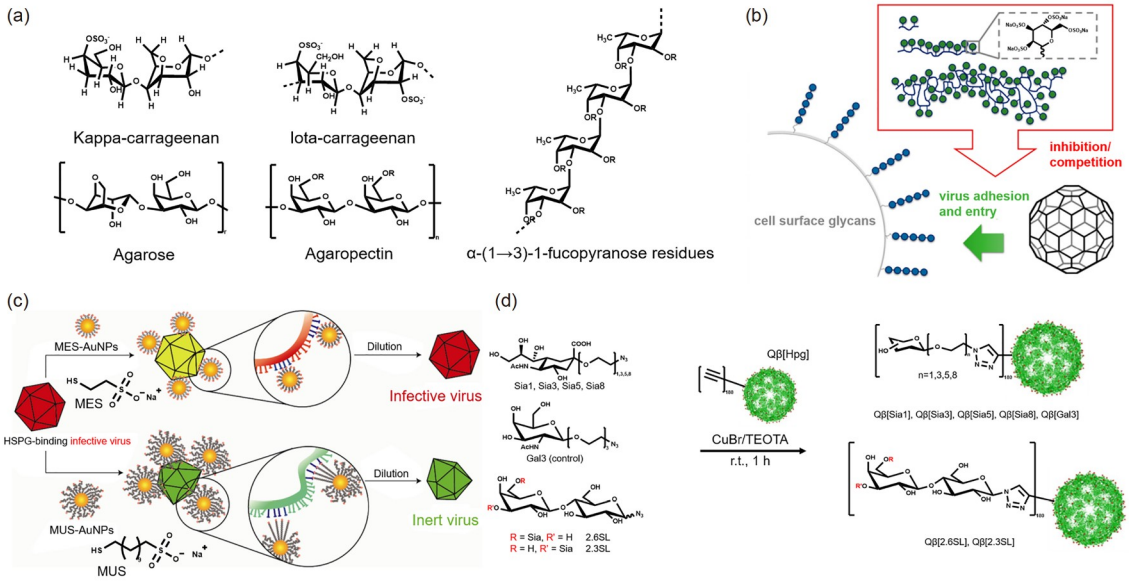


Figure 31 (a) Chemical structures of some marine-derived sulfated polysaccharides [402]; (b) the inhibition of viruses entering host cells *via* competitive binding of highly sulfated synthetic glycomimetic [404]; (c) the reversible and irreversible inhibition of short-chain, long-chain sulfates-covered gold nanoparticles towards VALs [406]; (d) structure and synthesis of functionalized bacteriophage capsid [407] (color online).

fection [405]. For example, heparan sulfated proteoglycan (HSPG) is a highly conserved target of virus attachment ligands (VALs). Some polymers can block the interaction and cross-talk between viruses and cells by simulating the proteoglycan [406]. For example, gold nanoparticles with polymeric sulfonates were prepared to simulate HSPG, in which the long-chain sulfonates in gold nanoparticles with polymeric sulfonates could help to produce strong multivalent binding to VALs and deform the viruses, finally resulting the irreversible loss of viral infectivity (Figure 31c). Moreover, the nanoparticles barely have cytotoxicity and can be applied in treating HSV, human papillomavirus (HPV), respiratory syncytial virus (RSV), and dengue virus infection.

Hemagglutinin, a kind of mucin, plays an essential role in the process of virus invasion in the host cells. To this end, a multivalent polymer-functioned bacteriophage capsid with hemagglutinin ligand was prepared (Figure 31d), which could simulate a ligand arrangement of hemagglutinin on the surface of influenza A virus in order to match the geometry of hemagglutinin binding site. In this way, it helps to bind to the virus in a predetermined multivalent mode. In a word, the capsids can cover the whole virus envelope, preventing the binding of virus with host cells to inhibit virus infection [407]. In a word, polymer is very promising as a drug for the treatment of viral infection.

6 Biomedical polymers for regenerative medicine

6.1 Biomedical polymers used for tissue repair and regeneration

Biomedical polymers for tissue repair and regeneration are defined as biomedical polymer materials, combined with cells and biological factors, alone or together, that can treat disease and injury by regeneration or repair of functional tissues. There are several fundamental considerations in the design of biomedical polymers for tissue repair and regeneration [408]. They should: (1) induce few foreign-body reactions; (2) interact with the microenvironment through biophysical or biochemical approaches to activate beneficial utilities; (3) control or regulate specific cell behaviors.

The biomedical polymers used for tissue repair and regeneration can be divided into two classifications: *ex vivo* and *in situ*. The *in situ* approach, also defined as endogenous regeneration, requires biochemical or biophysical factors in combination with self-adaptive and bioresponsive materials [408], which can modulate or respond to multiple cell behaviors such as directional cell migration [409,410], selective cell adhesion [411], extracellular signal pathways [412], and intracellular gene programming [413].

Biomedical polymers of various formulations including scaffolds, sponges, micro- and nano-particles, fibers, films and hydrogels *etc*. have been developed for different applications. Each physical architecture or chemical component varies in stiffness, topology, porosity, and degradation, which in turn influences the interactions between cells/tissue and biomaterials [408].

The micro- and nano-particles (MNPs) are capable of: (1) promoting cell-mediated transportation and interaction with individual cells; (2) targeting or permeating into tissues or cells [414]. The MNPs-based strategies show potential in biomedical applications, especially in immunomodulation and tissue regeneration [415].

The hydrogel is a soft material with excellent biocompatibility, biodegradability, and adjustable mechanical properties [416]. Synthetic polypeptides are a newly devised kind of hydrogel polymers, which possess a great biomimetic secondary structure compared with natural proteins [417].

Polyurethane (PU) possessing excellent elasticity, biocompatibility, biodegradability and modifiable chemical structure is widely used in biomedical field [418]. A novel unsaturated PU, also known as PPFU, is synthesized from PPF diol and diisocyanate. By subsequent modification *via* the high reactive unsaturated double bonds, the PPFU can be grafted with molecules such as peptides, leading to selective cell adhesion and migration [419].

6.1.1 Surface and interfacial properties of biomedical polymer materials

Protein adhesion, cell behavior, and tissue response are distinctly modulated by biomaterials, particularly surface and interfacial properties. The modification of surface and interfacial properties of biomaterials, such as chemical or physical structures, hydrophobic and hydrophilic performance, cell affinity, and selectivity, may remarkably influence their interactions with biological systems. A surface facilitating cell-selective adhesion and directional migration is of great significance in tissue repair and regeneration, in particular for the repair and regeneration of blood vessels, nerves, dermis, cartilage, bone, and so on.

The cell-selective biomaterials can be designed from the perspective of physical cues (stiffness, charges, topology, and hydrophilicity), biochemical cues (peptides and antibodies), and physiological cues (chemokines and cytokines) [420]. The cell-selective surfaces can promote desired cell proliferation, differentiation, adhesion, and migration, benefiting the process of tissue repair and regeneration [420].

Gradient surfaces, which can mediate cell adhesion and migration, are of vital importance in tissue repair and regeneration. Li *et al*. [421] designed a thickness gradient material of temperature-responsive poly(*N*-isopropylacrylamide) (PNIPAAm) covalently fixed on a silicon substrate *via* surface-initiated atom transfer radical polymerization (SI-ATRP). The thickness of the polymer brushes can be chan-

ged linearly along with position, and can thus regulate cell adhesion and detachment. The nerve regeneration process is determined by the upregulated migration of Schwann cells and downregulated migration of fibroblasts. Therefore, the surface selectively mediating cell migration is a novel target in nerve regeneration. Zhang *et al*. [422] designed a poly(*D*, *L*-lactide-*co*-caprolactone) (PLCL) substrate with peptide gradients and microgrooves. The *in vivo* experimental results demonstrated its significant advantages in peripheral nerve regeneration (Figure 32).

6.1.2 *Biomedical polymer biomaterials/cell and tissue interactions in the framework of immunomodulation*

Numerous forms of biomaterials are implanted for tissue repair and regeneration, either alone or in combination with other bioactive components that will interact with the immune system, including various immune cells, cytokines, and chemokines. Polymeric biomaterials, whether naturally sourced or synthetically prepared, can modulate the immune cell activity because of their molecular scale contact with cells and their interpretation at the bulk scale [423]. During the acute inflammation phase, innate immune cells arrive sequentially to the implanted biomaterials. The most essential players are neutrophils and monocytes originating from blood, as well as monocyte-derived and tissue-resident macrophages [424]. The surface characteristic of biomaterials can influence neutrophil activation. For example, neutrophils react differently to titanium implants when their surface roughness or wettability (hydrophilicity) alters [425]. The rough or smooth hydrophobic surfaces increase the level of pro-inflammatory cytokines and enzymes secreted by neutrophils compared with those rough hydrophilic surfaces. The roughness also affects how neutrophils respond to polymers. The rough regions of polytetrafluoroethylene and Dacron on polymeric cardiovascular implants can elicit

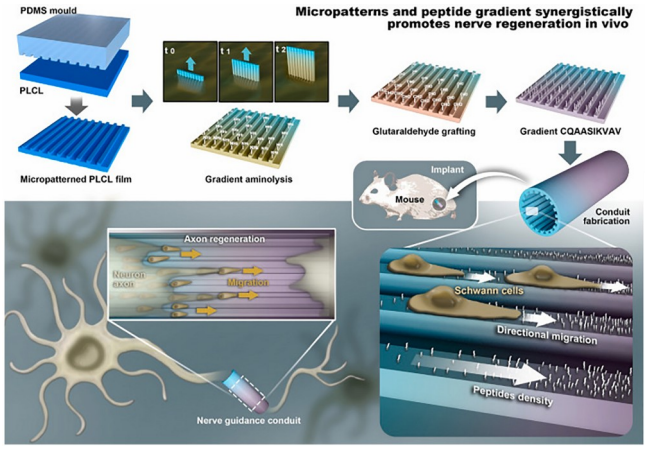


Figure 32 Schematic drawing to delineate the preparation of micropatterned PLCL film incorporated with a CQAASIKVAV peptide density gradient, which is manufactured into a conduit for peripheral nerve regeneration [422] (color online).

significantly more neutrophil death and ROS generation than smooth regions [426]. A similar effect has been observed on electrospun scaffolds with a small fiber diameter, which produces a higher traps formation response of neutrophils than those with a large fiber diameter [427]. Therefore, the biomedical polymers have unique immunomodulatory effects, leading to tissue repair and regeneration by modifying their mechanical, chemical, and morphological properties.

6.1.3 *Applications of biomedical polymers in tissue repair and regeneration*

The polymeric materials have been used in diagnoses and treatments of various diseases, especially by modulating the microenvironment to stimulate the inherent capability of tissues with respect to repair and regeneration (Figure 33).

(1) Skin repair and regeneration. Neutrophils and monocytes/M1-like macrophages are the predominant cell types in the cutaneous wound microenvironment during the early acute inflammatory phase of wound healing. Biodegradable polyurethane antimicrobial hydrogel and cryogel show an immunomodulation effect by improving the M2-macrophage population ratio in diabetic skin wounds [428]. Moreover, some amphiphilic NPs are also used to polarize macrophages from M1 to M2 confirmed by the lower expression of CD80 (M1 marker) [429].

(2) Myocardial repair. As a result of ischemia and hypoxia, cardiomyocyte damage and necrosis occur during the onset of myocardial infarction (MI), leading to an increase in ROS. ROS-responsive biomaterials are regarded as a promising candidate for MI therapy because their fast ROS-scavenging capability can reduce tissue damage by removing excess ROS from inflammatory sites. For example, polyurethane (PFTU) synthesized from poly(thioketal) (PTK), PPF, and 1,6-hexamethylene diisocyanate (HDI) was electrospun with gelatin to prepare fibrous patches [430]. The material successfully scavenges excessive ROS, decreases cell apoptosis, and alleviates inflammation, leading to a better restoration of myocardial functions with the least infarction area.

(3) Bone defects. The dual function of antibacterial and osteointegration is in high demand in orthopedics, particularly for individuals who have diabetes and osteoporosis at the same time. Although single-purpose coatings have been widely developed, there is a lack of a simple and reliable approach for producing therapeutically useful implants with this dual function. Yang *et al*. [431] grafted hyperbranched poly(*L*-lysine) (HBPL) covalently onto titanium substrate, resulting in antibacterial activity against various pathogens and promotion of adhesion, spreading, proliferation, and osteogenic differentiation of MC3T3-E1 cells *in vitro*. The *in vivo* results confirm the good antimicrobial and anti-inflammatory response in a rat model, thereby resulting in better osteointegration than control group.

(4) Treatment of osteoarthritis (OA). The high concentra-

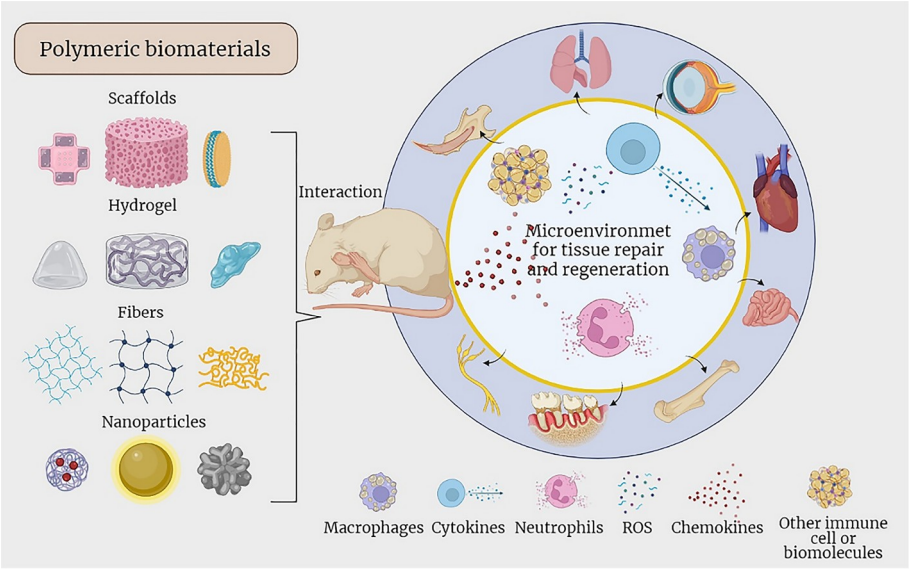


Figure 33 Implantation of polymer biomaterials with an ability to modulate the immune microenvironment (immune cells or biomolecules including macrophages, neutrophils, cytokines, chemokines and ROS) for repair and regeneration of different types of tissues or disease therapy (color online).

tion of ROS in the osteoarthritis microenvironment represents a novel and potential trigger for responsive drug release. Zhang and co-wokers [432] synthesized a new polyurethane featuring ROS-responsive thioketal groups, which was further formulated into NPs loaded with dexamethasone. This nanoplatform effectively suppresses the ROS level and increases the phenotype of M2 macrophages in the monosodium iodoacetate-induced OA model.

(5) Biomaterials in bowel diseases. Comparatively, gastroenterology attains minimal attention in the context of biomaterials. Targeted protein delivery to the colon is beneficial in the treatment of inflammatory diseases such as irritable bowel diseases. The IL-1 cytokine expression is very high in the inflamed colonic mucosa, which can be neutralized by the alginate/chitosan microcapsule loading IL-1 receptor antagonist [433]. The expression of TNF-α, IL-1, and myeloperoxidase (MPO) is reduced in the colitis mice model after oral delivery of alginate/chitosan microcapsules.

(6) Attenuation of pneumonia. NPs carrying proteins, peptides, and anti-inflammatory drugs have become a viable strategy to target macrophages, dendritic cells, and B-cells in pneumonia to alleviate inflammation and other complications. The biodegradable polymers and lipid-based nanomicelles have extraordinary abilities including being easily converted to aerosol, biocompatibility, targeting specific areas in the lung cell population, stability, and release of encapsulated drugs in a specific manner [434]. Hesperidin/chitosan NPs were administrated *via* nasal to acute lung injury (ALI) mice to reduce the level of cytokine storm syndrome [435]. The NPs dramatically reduce lung damage and cytokine levels as well as suppress vascular permeability compared with free hesperidin.

(7) Periodontal tissue regeneration. Cytokines and other biomaterials are combined with collagen to establish a unique property for an immune response to enhance the bioactivity of periodontal regenerations. Chitosan can also be used as an alternative to encapsulate drugs or growth factors to boost the immune system for periodontal regeneration [436].

(8) Corneal repair and regeneration. Current corneal wound healing research has concentrated on corneal characteristics such as immune response, avoiding angiogenesis, and modulating cell signaling. Immunocompatibility of different compositions of elastomeric biodegradable poly(glycerol sebacate) (PGS)-PCL nanofibrous scaffolds was investigated [437]. These scaffolds have well-defined mechanical properties and an immediate effect on the viability of human corneal endothelial cells and human conjunctival epithelial cells. None of the PGS/PCL mixtures induce effects on granulocytes, such as naïve and activated peripheral blood mononuclear cells (PBMCs), while the scaffolds with a higher PGS/PCL ratio show the best cell organization, and cyto- and immuno-compatibility.

(9) Neuroregeneration. When a hydrogel containing repeating units of the tetrapeptide, Arg-Ala-Asp-Ala, poly (RADA) with a C-terminal IKVAV sequence have been utilized to transport neural stem/progenitor cells (NSPC), and it stimulates better tissue healing in the rat brain following a resection-type injury compared with saline alone [438]. In comparison to poly(RADA) alone, the combination of IKVAV peptide with poly(RADA) dramatically improves the differentiation of transplanted NSPC into neurons. Furthermore, NSPC transplantation into the rat *in vivo* in fibrous PCL scaffolds immobilized with glial cell line-derived neurotrophic factor improves the NSPC survival, proliferation, and differentiation into neurons and oligodendrocytes com-

pared with NSPC transplantation in the absence of PCL [439].

In summary, the polymeric biomaterials including scaffolds, hydrogels, fibers, and NPs have the potential to modulate various immune cells and/or biomolecules, resulting in better tissue repair and regeneration. Physical or chemical modifications to these biomaterials may further speed up the healing properties of various tissues.

6.2 Biomedical polymers used for cardiovascular regeneration

For the last two decades, cardiovascular stents have been frequently performed to treat cardiovascular diseases (CVDs), and have been proven to be the golden standard around the world [440]. Although the drug-eluting stent with releasing of antiproliferative drugs has been shown to be effective in preventing the restenosis, the incomplete endothelium regeneration raises a huge risk for late stent thrombosis (ST) which is extremely dangerous for patients [441,442]. In this context, the next generation of coating requires better endothelium regeneration while maintaining the inhibition of restenosis. Biomedical polymers, such as polyelectrolyte and amphiphilic block copolymer, represent promising candidate to realize medical coating to modulate cell responses including adhesion, migration, proliferation, and promote tissue regeneration [443–445].

6.2.1 Polyelectrolyte coating with bioactive agents

Polyelectrolyte coating contained with bioactive species has attracted considerable research interests in cardiovascular disease therapeutics. Combined with medical devices, bioactive agents (*e.g.*, drugs, DNAs/RNAs, antibodies, peptides, growth factors, and enzymes) can be delivered into the desired site to control essential cellular behaviors and regulate the occlusion site [446]. Over the years, various strategies aim to construct functional polyelectrolyte coating with bioactive species over stent surfaces, which can be classified into chemical modification and physical absorption.

Owing to the multi-electrostatic interaction, polyelectrolyte coating shows considerable stability to mimic the ECM both *in vitro* and *in vivo*. Therefore, a large variety of charged biomacromolecules such as protein, DNAs, RNAs, and heparin, could be directly adopted as one of the components to construct coating and influence cell behaviors [446]. Ji *et al*. [447] have prepared protamine sulfate/plasmid DNA encoding hepatocyte growth factor (PrS/HGF-pDNA) coating through layer-by-layer (LbL) assembly technology, which selectively promoted the proliferation of human umbilical vein endothelial cells (ECs), and achieved to enhance ECs competitiveness over smooth muscle cells (SMCs). Furthermore, the coating exhibited favorable protection of functional genes, anticoagulation, and antibacterial properties *in vitro*, and reduced the in-stent restenosis *in vivo* (Figure 34) [448]. Lynn *et al*. [449] reported a localized delivery of plasmid DNA (pDNA) to vascular tissue *via* the LbL coating on catheter balloons, suggesting a promising approach to preventing restenosis after the intervention. The pDNA as the available delivery of genetic information can be easily encoded with different information to perform specified functions. Based on the study of PrS/HGF-pDNA multilayers, Ji *et al*. [450] have used functional pDNA encoding short hairpin RNA as the substitution of HGF-pDNA to present a new functional polyelectrolyte coating, which reduced the secretion of fibronectin and collagen, inhibited cell proliferation *in vitro*, and downregulated the expression of transforming growth factor-β1 and effectively inhibited neointimal hyperplasia *in vivo*. Another typical biomacromolecule system is heparin/collagen coating, which was used to specifically promote attachment and growth of vascular ECs [451]. Notably, bioactive agents are inclined to influence cells by surface contact rather than released in solution, which realize a surface-mediated delivery of functional agents and effectively reduce excessive ECM production [451].

Chemical grafting is frequently performed to stabilize the small bioactive agents (including drugs, antibodies, and peptides, *etc*.) over polymer coating to functionalize the medical devices [452–454]. Polyelectrolytes contain abundant functional groups, possessing intrinsic functionalization potential [455]. Bioactive agents have also been successfully modified into polyelectrolyte coating to treat cardiovascular disease [456]. Ji *et al*. [451] have succeeded in immobilizing

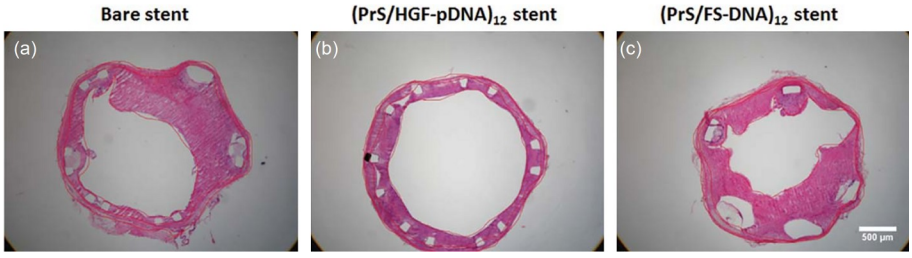


Figure 34 Typical optical micrograph of the cross section slices of the rabbit femoral arteries with bare metal stent (a), (PrS/HGF-pDNA)12 stent (b), and (PrS/FS-DNA)12 stent (c) after implantation for 28 days [448]. The scale bar is 500 μm (color online).

anti-CD34 antibody onto heparin/collagen coating through glutaraldehyde crosslinking. The introduction of anti-CD34 significantly inhibited neointimal hyperplasia as compared with the bare metal stents and the heparin/collagen-modified stents. Mela *et al*. [457] adopted LbL approach with click chemistry to introduce elastin-like recombinamers onto stents and suggested the potential to realize the exclusion of the atherosclerotic plaque while providing a non-thrombogenic luminal surface and promoting endothelialization.

Directly incorporating bioactive agents into polyelectrolyte coating through a "matrix-bound" strategy is also an effective way to construct functional coatings for disease treatment [458]. Ji *et al*. [459] have realized the matrix-bound of vascular endothelium growth factor (VEGF) within the PLL/HA multilayer and demonstrated the ability to enhance the competitive growth of ECs. More recently, Ji and co-workers [460] focused on the preparation of functional polyelectrolyte coatings for drug delivery applications. Based on the spray and relaxation of polyelectrolyte complex (PEC) nanoparticles, they have reported a robust approach to fabricating polyelectrolyte coatings with high efficiency and flexible functionalization (Figure 35). The controllable incorporation of VEGF promoted adhesion and proliferation of ECs on the stents, which suggested a huge potential for industry applications. Utilizing acid treatment and freeze-drying, the same group have generated amounts of micropores in polyethylenimine/poly(acrylic acid) (PEI/PAA) coating. Functional species (dyes and triclosan) solutions were absorbed into the film *via* wicking action, after solvent evaporation, the agents were stored in PEI/PAA coating. After diminishing the micropores under a saturated humidity environment, functional species were encapsulated and achieved sustained release [461,462]. It is a reliable and effective strategy for loading and long-term releasing bioactive agents over stents. After loading VEGF, ECs adhered much better than the VEGF-free coating *in vitro* [463].

6.2.2 Polyelectrolyte coating with specific mechanical properties

ECM plays an important role in regulating the development, function, and homeostasis of all eukaryotic cells. Many studies have suggested that biophysical cues (*e.g*., topographical features, stiffness) in the extracellular microenvironment are vital in regulating cell proliferation, differentiation, migration, and so on [464].

Stiffness, as an important mechanical factor of the ECM, is known to remarkably impact cellular behaviors. In recent decades, diversified ways have been developed to achieve biomimetic stiffness and modulate cell behaviors. Ji *et al*. have realized the modulation of substrate stiffness of PrS/DNA polyelectrolyte coating. The study indicated that, through decreasing stiffness, the coating suppressed cell adhesion of both SMCs and ECs. Interestingly, SMCs were more sensitive than ECs to the stiffness decreasing [465]. Adding covalent bonds into polyelectrolyte coating is another robust and simple method to manipulate coating stiffness for cell regulation. For the coating containing amino and carboxyl groups, it can be effectively cross-linked by amidation, and the coating stiffness can be controlled through the concentration of catalysts. Ji *et al*. [466] have found that ECs showed a better adhesion on the stiffer surface while showing impairment of endothelial function, indicating soft coating was beneficial for keeping the original phenotype of ECs (Figure 36). Based on these findings, the same group developed a growth factor loaded polyelectrolyte coating with different stiffness for combining the biochemical and biophysical ques, and suggested that polyelectrolyte coating with the lower stiffness and matrix-bound growth factors

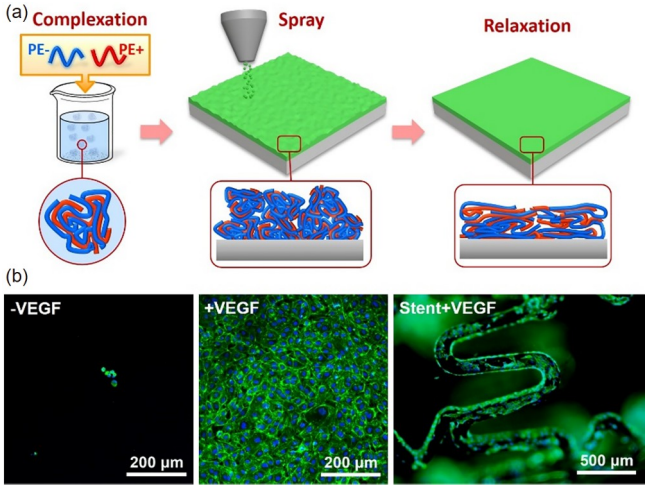


Figure 35 Prepration of PEC functional coating based on spray and relaxation of PEC nanoparticles. (a) Illustration of preparation of PEC films; (b) fluorescence micrographs of EC proliferation on PEC coatings before and after incorporation of VEGF, respectively [460] (color online).

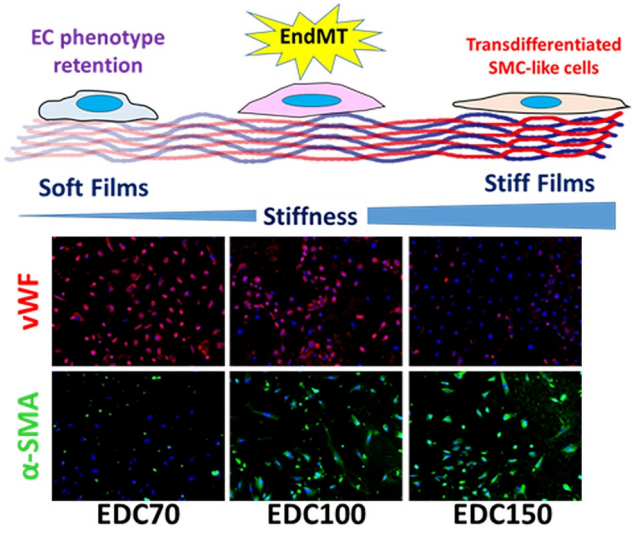


Figure 36 Schematic representation of the effect of substrate stiffness on EndMT by using the PLL/HA polyelectrolyte multilayer films with controlled stiffness [466] (color online).

realized a better regeneration of ECs [460,467].

Considering that ECs show a better adhesion on stiffer substrates but remain their healthy phenotype on softer substrates, the dynamic modulation of substrate stiffness is reasonable to combine the benefits for better ECs growth. Ji *et al*. [468] have introduced matrix metalloproteinase (MMPs) sensitive peptides as dynamic covalent bonds into polyelectrolyte coating and developed a stiffness-adaptive system to study EC behavior. After cross-linked by the MMPs sensitive peptides, the stiffness of the PLL and methacrylated hyaluronic acid (HA-MA) coating was responsive for MMP. Their results demonstrated that the initial stiffer substrates enhanced the adhesion of ECs, and the subsequent MMP-sensitive degradation induced softness of substrate that improved the endothelial morphology and function of ECs. Based on this adaptive platform, autophagy of ECs and SMCs on the coating with different stiffness was further studied, suggesting that the softer substrates promoted ECs autophagy [469]. Besides, bringing different stimuli-responsive cross-linked bonds in polyelectrolyte coating can make film stiffness responsible for different external stimuli. After grafting thiol moieties into hyaluronan (HA-SH), the PLL/HA-SH coating can be cross-linked in chloramine T solution and de-cross-linked in GSH solution [470]. The addition of azobenzene moieties would endow the reversible cross-linking property into polyelectrolyte coating [471]. These strategies broaden the window of stiffness controllability in cardiovascular disease therapeutics.

Topographical features of polyelectrolyte coating are another important biophysical cue for regulating cells' behaviors [472,473]. Alternately depositing on a patterned substrate to obtain a patterned polyelectrolyte LbL coating is a versatile way, which has been used to study cell adhesion, differentiation, and spread behaviors [474,475]. The roughness of polyelectrolyte coating can be manipulated through pH, ionic strength, molecular weight, and so on. Based on this, the coating is a good model of stochastic topographic cues for exploring cell behaviors. Möhwald *et al*. [476] controlled the salt concentration during LbL assembly to affect the rigidity and roughness of reducible hyperbranched poly(amidoamine)/DNA coating. Eventually, a crucial adjustment of viability, cell adhesion, transfection activity, and also stress-fiber orientation was gained. Also, Murphy *et al*. [477] used the PAA/poly(allylamine hydrochloride) (PAA/PAH) coating as the model of soft lithography, and surprisingly found a decrease in expression of several cardiovascular disease-related genes of the ECs that cultured on the rough surface.

6.2.3 Synthetic polymer coating with porous structure

The last two decades have witnessed the fast development of interface science that promotes the remarkable improvement of cardiovascular stents for less hyperplasia and better regeneration of endothelium [478]. The basic strategies of these researches generally require the combination of the stents with biofunctional species including peptides, proteins, DNAs/RNAs, *etc*. [479,480]. However, current coating materials for cardiovascular stents in industry are limited to a few kinds of synthetic polymers, which are typically dissolved in organic solvents during manufacture. Therefore, despite the huge success in concept fields, the combination of biofunctional species with the coating materials in practical applications remains challenging.

More recently, porous materials with interconnected pore structures provide an alternative for bioactive agents delivery [481]. The highlighted feature of this capillarity-based wicking process is simple, gentle, and generally independent of the solute in the adsorbed solution [482–484]. Inspired by these spongy materials, Ji *et al*. [485,486] have proposed a hierarchical stent coating architecture composed of a drug coating base layer and a porous cap layer for improving the in-stent regeneration of endothelium. The spongy cap-layer achieved controllable loading of biofunctional agents with satisfied bioactivity. It was demonstrated that the sustained release of rapamycin from the base layer inhibited the restenosis process after stent implantation, while the spongy cap-layer realized a real-time loading of VEGF that promoted the endothelium regeneration. In order to modulate the release profile of encapsulated agents, the same group has reported a self-healable spongy coating platform based on the cross-linked poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL, PCEC) triblock amphiphilic copolymer [487]. The PEG chain endowed the coating material swelling capacity in water, which formed porous structures by the freeze-drying process. By adjusting the ratio of PEG and PCL segments in the networks, the PCEC networks performed an ultrafast activation of polymer chain mobility, thus realizing the self-healing behavior of the porous structure. Based on this self-healable property, Ji *et al*. [488] have presented a miR-22 encapsulated stent coating for suppression of neointimal hyperplasia without interfering the endothelium regeneration (Figure 37). The self-healing of porous structure dramatically prolonged the release profile of miRNAs, therefore realizing a remarkable inhibition of phenotype switching of smooth muscle cells after artery injury. These spongy coating platforms offer a promising opportunity for combining biofunctional species with medical devices and improving the therapeutic effects in real-life applications.

6.3 Biomedical polymers used for wound sealing and hemostasis

Sutures have always been considered as the first choice for hemostasis and wound closure during surgery; however, they cause secondary tissue damage and increase patient trauma.

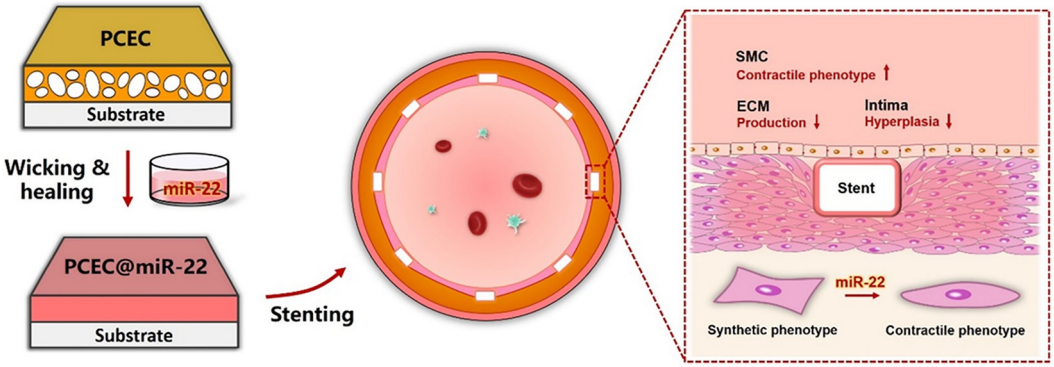


Figure 37 Schematic illustration of the preparation of the PCEC@miR-22 coated stent. The miR-22 was loaded into PCEC spongy coating based on a wicking action and subsequent self-healing encapsulation [488] (color online).

Fast-acting and strong bio-adhesives are expected to be potential alternatives to sutures for tissue sealing and hemostasis owing to their considerable biocompatibility, biodegradability, and ease of use [489]. In recent years, the importance of bio-adhesives in the field of biomedicine has been realized, inspiring worldwide researchers to improve their structure and performance and apply them to many fields such as stomach/intestinal tissue repair, hemostasis, and treatment of myocardial infarction [490,491]. Given the emerging importance of bio-adhesives, a comprehensive review of important findings to date is relevant at this point to facilitate easy access to the available information for researchers and clinicians. Therefore, the current state of research on bio-adhesives for tissue-sealing and hemostasis is reviewed, and the advances in the development of glue- and tape-type bio-adhesives and limitations in their clinical translation are discussed.

Bio-adhesives are primarily divided into two types: glue (Figure 38) [492–495] and tape (Figure 39) [496]. *In situ* curing of glue-type adhesives is conducive to removing moisture from the tissue surface and achieving close adhesion. Therefore, they are often used for adhesive filling of tissue defects and rapid hemostasis [493,494]. In addition, the injectability of glue-type adhesives enables their fair use in minimally invasive surgery [495]. Injectable glue-type bio-adhesives are commonly obtained by combining curing methods such as light, temperature and self-assembly with adhesive groups such as aldehydes, isocyanates, *N*-hydroxy succinimide (NHS)-activated esters, and catechols [492]. For example, Zhu, Zhang, Ouyang, and co-workers [497] designed a photo-reactive injectable adhesive hydrogel by combining methacrylylated gelatin, *o*-nitrobenzyl modified hyaluronic acid, and a photoinitiator. The hydrogel precursor underwent rapid crosslinking to form a gel that could adhere to and seal bleeding arteries and hearts under ultraviolet irradiation to achieve hemostasis. Emergency sealing of bleeding sites is essential for patients with uncontrolled bleeding or blood clotting disorders. However, body fluid or blood on the surface of the tissue prevents the adhesives from contacting the tissue surface, causing them to lose their adhesion. That is, when blood covers the tissue, the ineffective connection between the adhesive and the surface of the tissue significantly reduces the adhesion efficiency. Therefore, removing the blood cover is the first and most important step to achieving ideal adhesion. Since the water content in blood is greater than 90%, combining an adhesive with a hydrophobic structure is the most direct way to remove blood from the surface of the tissue. Inspired by the adhesion mechanism of barnacles, Zhao *et al*. [498] designed an injectable paste by combining a hydrophobic oil matrix with bio-adhesive nanoparticles. Under slight pressure, the hydrophobic oil matrix drained the blood, allowing the bio-adhesive nanoparticles to achieve close adhesion with the tissues. In another development, Liu *et al*. [499] mimicked the adhesion mechanism of mussels and combined catechol groups with a hydrophobic hyperbranched structure to obtain a water-triggered adhesive. The hydrophobic skeleton shrank in contact with water to remove blood on the surface of the tissue and achieve rapid hemostasis on non-compressible and deeply irregular wounds. An injectable and spreadable adhesive that is both hydrophobic and oleophobic has also been prepared by the same group of scientists by using anionic polymers to accelerate spontaneous polymerization of 4-aminostyrene initiated by zwitterions. This adhesive showed proper adhesion to bone tissue and is expected to be used for treatment of fractured bones [500]. Several other injectable glue-type adhesives have been reported to be coated with stem cells, cell growth factors, or nano-hydroxyapatite/bioactive glass and used for peri-implantitis treatment, abdominal wall defect repair, and bone defect repair [501–503]. However, for glue-type adhesives, there are still many drawbacks that need to be overcome in the following research, including the curing time which can take minutes/hours/days, relatively poor adhesive properties, and non-reversibility.

Tape adhesives are often used as tissue repair patches,

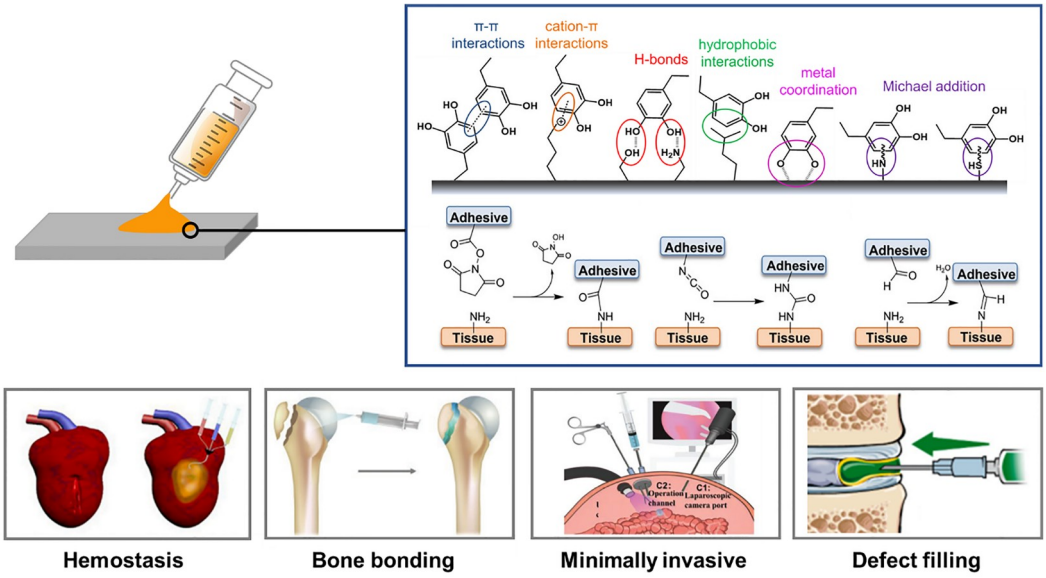


Figure 38 The main adhesion modes and applications of glue-tape adhesives [492–495] (color online).

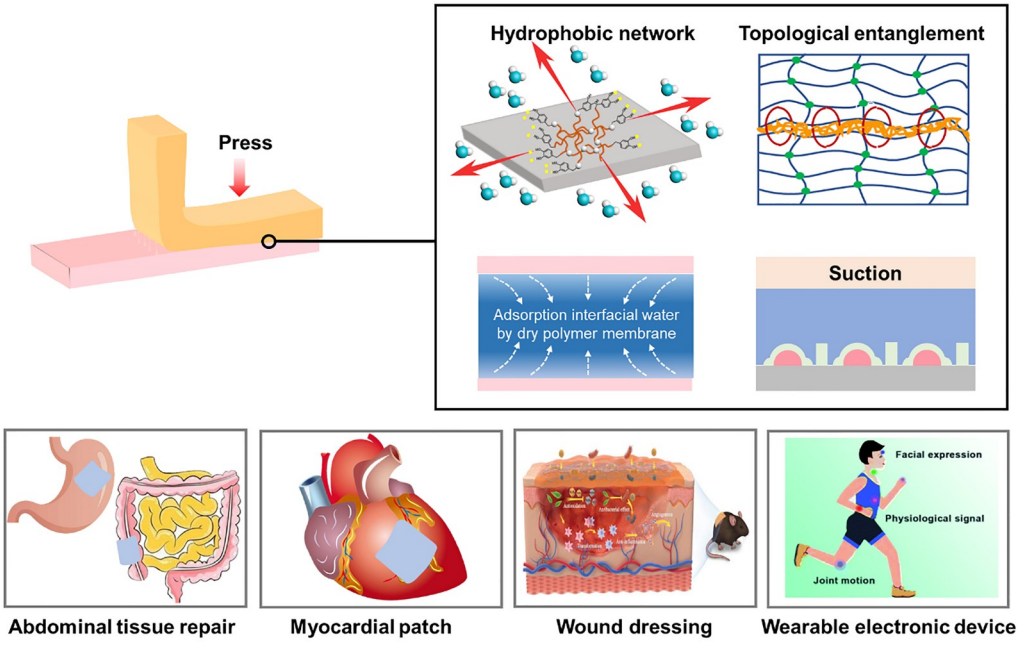


Figure 39 The applications of tape-type adhesives [504] and the main drainage modes [511] (color online).

myocardial patches, wound dressings, antifouling coatings, and wearable electronic devices [504,505]. Since the tape-type bio-adhesives do not require additional stimulation and long-term curing as compared with the glue-type adhesive, they exhibit a faster bonding speed. However, because they cannot be cured *in situ* to remove moisture on the tissue surface, effective drainage of liquid is the key for these products to achieve proper adhesion onto the surface of tissues covered with blood, body fluids, or sweat. To improve the wet tissue adhesion of tape-based bio-adhesives, researchers have made great efforts and put forward many new concepts. For example, Suo's group [506,507] proposed topological adhesion by combining the adhesive surface and the dissipative matrix, which thus forms a topologically entangled network with the dissipative matrix and the wet tissue *via* electrostatic interactions, covalent bonds, and physical interpenetration, stitching them together like a suture at the molecular scale. This provides new ideas for the

development of myocardial patches and tissue repair patches; nevertheless, instantaneous adhesion may not be achieved because the diffusion and entanglement of polymer chains require time. Zhao's group [508] designed a dry double-sided tape (DST) by combining a biopolymer with NHS-modified poly(acrylic acid). It showed instant and excellent adhesion to various wet tissues owing to the rapid absorption of the interface moisture, resulting in fast and temporary physical crosslinking with the surface of the adhered tissue *via* forming hydrogen bonds and electrostatic interactions. Subsequent covalent crosslinking of NHS with amine groups on the tissue further improved the adhesion stability. The DST could instantly seal broken intestines, stomach tissues, and the lung lobes or trachea, and it could also be used as a strain sensor carrier to detect the motion law of dynamic and deformable tissues.

Bio-adhesives inspired by nature are also constantly being developed. In addition to catechol-based adhesives inspired by mussels/sandcastle worms, oyster adhesive cement also prompted the design of novel bio-adhesives. Inspired by the acidic adhesion protein secreted by oysters, Liu *et al*. [509] designed a series of adhesives with carboxyl groups as adhesion groups. They developed the Janus adhesive hydrogel using one-sided dipping and gradient electrostatic complex method. The two faces of the Janus adhesive hydrogel demonstrated strikingly distinct adhesive and non-adhesive properties, and the phase separation caused by electrostatic interaction increased the hydrophobicity and drainage capacity of the adhered side. This Janus hydrogel was used to treat gastric perforations as a substitute for surgical sutures. The adhesive side of the adhesive hydrogel firmly adhered to the gastric tissue to seal the perforation site and promote wound healing, while the other side played a role in preventing postoperative adhesions [510]. In addition, integrating the hydrophobic hyperbranched structure into the carboxyl adhesive not only rendered excellent drainage characteristics, but also significantly increased the carboxyl content on the surface of the adhesive, which significantly improved its wet tissue adhesion strength [499,511]. In addition to oysters, bio-adhesives derived from nature-inspired topological microstructures have also been widely reported, such as hexagonal papillae, suction patches, and spider silk fibers. These adhesives have been used in myocardial patches and wearable electronic devices and have facilitated significant progress in the relevant fields [512].

Although the importance and potential of bio-adhesives have been continuously explored, the ultimate goal is to achieve their clinical translation. Therefore, in addition to focusing on the adhesive performance of bio-adhesives, researchers also need to pay attention to their curing conditions, degradation cycle, and impact of their degradation products on the human body. Research still has a long way to go to realize clinical applications of bio-adhesives.

7 Bioactive biomedical polymers for cancer precision therapy

7.1 Bioactive peptides for cancer therapy

Peptides are covalently linked structures of less than 50 amino acids, which process multiple biological functions in human body. The application of peptides for cancer therapy has been under extensive investigation due to their good biocompatibility and biosafety as well as excellent biological functions, such as targeting ability, stimuli-responsiveness, and therapeutic capability [513]. The peptides could achieve their anti-cancer effects either as monomer or assembling state.

7.1.1 Peptide monomer for cancer therapy

Many peptide-based drugs for cancer therapy were approved by FDA or European Medicines Agency (EMA), which were listed in Table 2. In addition, 1167 studies of peptide-based drugs for cancer therapy are still under pre-clinical and clinical studies [514]. Peptide-based drugs for cancer therapy could be obtained from different resources. Natural hormone or analogues, for instance, gonadotropin-releasing hormone (GnRH) analogues have been directly utilized for the therapy of prostate, breast cancer and so on [515]. Peptide-based drugs could also be screened from natural environment, such as terrestrial and marine environments [516]. The development of high throughput screening method, *i.e*., phage display and one-bead-one-compound, contributed to the screening of peptide-based drugs for cancer therapy [517]. Peptide would activate or antagonize the protein and related signaling pathways, such as inhibiting the secret of testosterone, achieving the anti-cancer effects.

Besides direct therapy, peptides could also act as carriers

Table 2 Peptide-based drugs for cancer therapy

Name	Application	Company
Leuprolide	Prostate, breast cancer	Takea/Abbive
Buserelin	Prostate	Sanofi
Goserelin	Prostate, breast cancer	Astrzeneca
Gonadorelin	Prostate, breast cancer	West-Ward
Nafarelin	Leiomyoma	GD Serie
Triptorelin	Prostate	Allergan
Histrelin	Prostate	Endo
Cetrorelix	Prostate, Uterine leiomyoma	Emd Serono
Degarelix	Prostate	Ferring
Abarelix	Prostate	Emd Serono
Lanreotide	Neuroendocrine tumor	Epsen
Octreotide	Vasoactive intestinal peptide tumor	Novartis
Lutathera	Neuroendocrine tumor	AAA USA
Romidepsin	Cutaneous T-cell lymphoma	Celgene
Mifamurtide	Osteosarcoma	Takeda

for precise drug delivery through targeting tumor site. It is well known that tumor microenvironment is different from normal physiological microenvironment. Multiple components are overexpressed and even specifically expressed in newly formed blood vessel of tumor, ECM, membrane of stromal and cancer cells, providing targets for binding of peptides. For example, new blood vessels of tumor have overexpressed proteins, such as CD13 (aminopeptidase N) and CD105 (endoglin) as targets [518]. Besides, fibronectin, and hyaluronic acid, *etc*. in ECM in tumor could act as targets for peptide binding [519,520]. The membrane protein on stromal cells, such as bombesin receptors [521], as well as on membrane protein of tumor cells, such as epidermal growth factor receptor family, and integrin *etc*. [522], are overexpressed and function as targets for peptide-based drug delivery and cancer therapy.

The select of targets relies on the characteristics of microenvironment in different type of tumor. For instance, the target in new blood vessel of tumor is generally chosen for highly vascularized tumor, such as hepatocellular carcinoma and renal cell carcinoma. Subsequently, the targeting peptide increases the accumulation and retention of the anti-cancer agents in tumor site. The efficacy of cancer therapy would be enhanced regardless of photothermal, photodynamic as well as chemotherapy.

The controlled drug release for cancer chemotherapy is highly needed post-targeting. It is found that there are some overexpressed enzymes including matrix metalloproteases, protein phosphatase, and lactate dehydrogenase, in tumor site, which could enzymolyze specific peptide sequences. Therefore, targeting sequence, enzyme cleavable sequence and drug conjugate, a kind of typical peptide drug conjugate, *i.e*. PDC, is finally designed for precise drug delivery [523]. Compared with antibody-drug conjugate, the PDC with small molecular weight has higher penetrating ability, showing great advantages for drug delivery of solid tumor.

7.1.2 Self-assembled peptide for cancer therapy

There are still some limitations for peptide-based drug or delivery system for cancer therapy due to the poor circulation time and low enzyme degradation resistance. Therefore, self-assembled peptides are intensively developed for further applications.

Driving forces for self-assembled peptides are intermolecular interactions, such as hydrophobic interactions, electrostatic interactions, π-π stackings, and hydrogen bonds, leading to the formation of ordered structures (Figure 40), such as hydrogel, nanoparticles, nanofibers, and nanomicelles [524]. The anti-cancer agents can be loaded into the nanostructures for targeting and sustained drug release [525].

The self-assembled peptide-based hydrogel has been widely used in interstitial chemotherapy of cancer accompanied with a surgery. The drug could be released with the degradation of hydrogel for long-term chemotherapy. The nanostructure carriers could be administrated *via i.v*. injection. The drug-loaded nanostructures passively and actively accumulated in tumor site with sustained drug release. Higher ordered nanostructure, such as higher quantity of β-sheet structure, had lower release rate of drug [526].

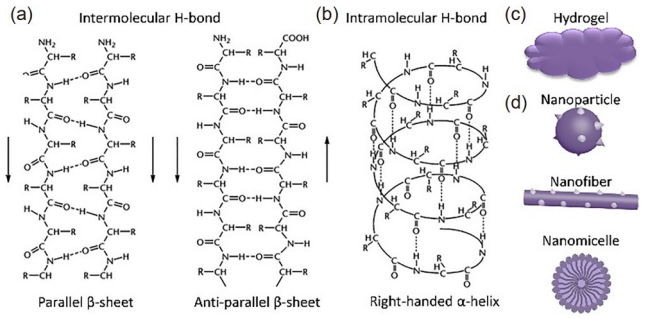


Figure 40 Structure of pre-formed self-assembled peptide. Schematic illustration of (a) β-sheet and (b) α-helix structure of peptide [524]; (c) peptide hydrogel for interstitial chemotherapy; (d) peptide nanostructures administration *via* systemic drug delivery (color online).

The performance of pre-formed self-assembly of peptides may be declined due to the undesired disassembly, or further aggregation. In addition, it is well known that nanostructures with large size exhibit long-term retention, while nanostructures with small size would penetrate in tumor tissues deeply. The programmable self-assembly is desirable for the high performance of drug delivery. Therefore, the concept of "*in vivo* self-assembly" is proposed, which is aiming to precisely modulate peptide self-assembly *in situ in vivo*.

Based on the specific tumor microenvironment, peptide can be modulated by *in vivo* self-assembly strategy for cancer therapy (Table 3). For instance, a peptide consisting of PA agent purpurin18 (P18), enzyme cleavable sequence PLGVRG and targeting sequence RGD was prepared for PA imaging and cancer therapy [527]. The peptide was injected into tumor-bearing mice through *i.v*. injection, followed by targeting tumor site through RGD sequence. The PLGVRG sequence was cleaved by the over-expressed gelatinase in ECM, leading to *in vivo* self-assembly of the hydrophobic residue. The resultant self-assembled nanofibers showed long-term retention and enhanced performance of PA imaging and photothermal therapy (Figure 41).

Some amino acids, such as histidine, arginine, and lysine, could be protonated at low pH value, which disrupt the hydrophilic-hydrophobic balance of self-assembling peptides and induce *in situ* self-assembly in tumor. *In situ* formed assemblies of peptide under acidity of tumor could act as drug depot for loading and releasing drugs [528]. The *in situ* self-assembly process and resulting assembly structures, for example, in lysosome acidity, was able to disturb lysosome and kill cancer cell directly [529]. The peptide was self-assembled into fibers on cell membrane through β-sheet

Table 3 *In vivo* self-assembled peptide for cancer therapy

Stimulator	Assemble location	Application	Ref.
pH	ECM	Chemotherapy	[528]
	Lysosome	Chemotherapy	[529]
Membrane receptor	Tumor cells	Apoptosis of cancer cells	[530]
Enzyme	ECM	Chemotherapy	[531]
	Lysosome	Migration inhibition and anti-angiogenesis	[532]

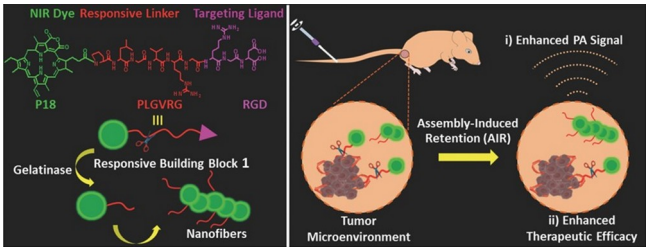


Figure 41 The molecular structure of peptide and *in vivo* self-assembly behavior of peptide to nanofibers for PA imaging through enzyme cleavage [527] (color online).

sequence, which was triggered by binding to some specific receptors on cancer cells. The peptide fibers blocked the receptor related pathway and inhibited the growth of tumor [530]. Enzyme over-expressed in ECM as well as in cancer cells could lead to *in situ* self-assembly of peptide through enzyme cleavage, *i.e.*, enzyme induced self-assembly (EISA) [531–536]. The peptide residue conjugated with drug self-assembled into hydrogel and performed sustained drug release. The peptide solution could be intratumorally injected rather than implanted by surgery to *in situ* form peptide hydrogel, which was a minimally invasive way [537].

The construction of self-assembled peptide *in vivo* remains a huge challenge due to complicated microenvironment *in vivo*. Therefore, the mechanism of self-assembly should be paid much more attention. The self-assembly behavior under different stimuli should be carefully studied and summarized systematically *in vitro* as the basis for the self-assembly *in vivo*.

The degradation of the self-assembling peptides should be evaluated, which are closely related with their side effects, such as immunogenicity and cytotoxicity. The side effect could be firstly inhibited when *in vivo* self-assembly peptides are applied. The proper "side effects" are finally expected to be utilized for cancer therapy.

We believe the peptides would further benefit the therapy of cancer in the future with precise modulation of structure and function.

7.2 Biomembrane-based biomedical polymers

Tremendous efforts have been made to bestow polymeric materials, particularly polymeric nanomaterials (PNs) with more and better functions to meet various requirements for *in vivo* biomedical applications. Unfortunately, increasing complexity in functionalization manipulation appears to make these PNs far away from clinical translation due to the great difficulty in large-scale production. Moreover, these artificially designed functions are still far from satisfactory when facing severe *in vivo* conditions. Researchers start to seek help from nature because the naturally occurring biofunctions have experienced a long evolution. Inspired by the fact that the membrane-membrane interactions between cells play significantly important roles in many cellular biological processes, the cell membrane coating strategy has recently emerged as a cutting-edge nanotechnology, permitting PNs to share the entire biointerfacing functionalities with source cells. Another rationale underlying this strategy is to address the issues of cell-based therapeutics, including the difficult manufacture and storage, and the safety concern, such as the carcinogenicity of cancer cells and the pro-metastatic risk of stem cells in tumors. The cell membrane coating onto PNs is mostly accomplished *via* physical extrusion method [538]. The regulation over membrane-PN adhesion have also been attempted, such as the enhanced affinity through the interaction between the ligand grafted on PNs and the transmembrane receptor expressed on cell membranes [539]. Taking advantage of the proton sponge effect commonly used for the endosomal escape of PNs, dynamically variable affinity between cell membranes and PNs core was achieved, by which PNs core shed the outer membranes for the promoted uptake by tumor cells resulting from the protonation of amine-rich PNs in acid tumor microenvironment [540].

As the provider of coating membranes, the exploited cell types cover red blood cells (RBCs), B cells, cancer cells, immune cells, leukocytes, stem cells, platelets, and even bacterium. In general, the biofunctions conferred by cell membranes are closely related to the innate roles of source cells in host body. The diversity of cell bank allows for the establishment of a toolbox of biofunctions belonging to various cell membranes, offering a powerful arsenal for arming PNs with the naturally derived biofunctions on demand. Till now, the documented biofunctions originating from cell membranes are focused on several aspects including prolonged circulation duration, targeting cells/tissues and immune activation.

7.2.1 Biomembrane-based biomedical polymers used for prolonged circulating duration

The prolonged circulation duration of foreign PNs determines the promotion of not only the *in vivo* efficacy of carried cargoes (*e.g.*, therapeutics, imaging agents) but also the chance to reach targeted sites. This aim can be accessible by coating RBC membrane onto PNs for the biomimetic camouflage to escape the surveillance of complement system, reticuloendothelial system and immunological system due to the presence of "do not eat me" signals, such as CD47, on RBC membranes [541]. This stealthy strategy is apparently superior over the well-known PEGylation in view of the immunogenicity of PEG segments and the tedious PEGylation process. Notably, the membranes of almost all the cell lines have been documented to contribute more or less to the long-term circulating of the coated PNs. The results seem reasonable based on the consideration that these cells could survive and proliferate in host body. Actually, even cancer cells express a high density of "do not eat me" signals to prevent themselves from immune clearance.

7.2.2 Biomembrane-based biomedical polymers used for targeting biotaxis

Cell membranes are featured with dynamic lateral fluidity, allowing multivalent interactions of one or more ligand-receptor pairs between membranes for the strengthened recognition of the membrane-coated PNs by the targeted cells. With this in mind, the cell membrane driving biotargeting may be a preferred option for the site-specific transport compared with the conventional targeting strategy. For instance, like the parent cells, the platelet membrane coated PNs showed strong tendency to accumulate in the injured blood vessels, therefore being potential for the targeted therapy toward thrombotic diseases such as ischemic stroke and myocardial ischaemia-reperfusion injury [542]. Blood vessel in tumors was intentionally destructed to create a new target for the tumor-tropic attract of the platelet membrane coated nanomaterials [543]. Besides, circulating tumor cells (CTCs) would attract platelets to surround them *via* specific biomolecular binding such as P-Selectin and CD44 receptors, enabling them survive and spread to new metastatic niches. Depending on this characteristic, the platelet membrane coated PNs were directed at the CTC capture for cancer diagnosis and tumor metastasis inhibition [544]. Likewise, platelet membranes also exhibited the capability of targeting cancer cells in tumors [545].

Benefiting from the roles of immune cells that routinely patrol the body to capture infected or tumor cells, the coating with the membranes originating from the immune-associated cells (macrophages, neutrophils, natural killer (NK) cells, T cells, dendritic cells (DCs), leukocytes) are being intensively studied for the hitchhiking biotaxis of the therapeutic-carried PNs particularly toward tumors. In addition, the cell membranes from leukocytes, neutrophils and NK cells have been proved to be able to target CTCs [546,547]. Therefore, neutrophils membranes supported the dual targeting of PN-based drug delivery toward both CTCs and metastatic niche to deplete CTCs and inhibit metastasis development [548]. Due to the presence of self-adhesion proteins on cell membranes, the cancer cell membrane coated nanomaterials showed an interesting capability of targeting the homotypic cancer cells [549]. This self-recognition has proven highly specific in targeting homologous tumors *in vivo* even in the coexistence of heterologous tumors [550]. The cancer cell membrane coating strategy has thus been widely applied to enable PNs to target the tumors developed from the same source of cancer cells [551]. Stem cells are highly migratory and attracted by inflamed areas, therefore, the coating with human umbilical cord-derived mesenchymal stem cells contributed to the tropism of the coated PNs toward tumors [552].

7.2.3 Biomembrane-based biomedical polymers used for cancer immunotherapy

Immune systems suffer from various immunosuppression mechanisms generated along with tumor development, which are responsible for the poor outcomes of cancer immunotherapy. Theoretically, cancer cell membranes can serve as sources of neoantigens for the formulation of vaccines, though this effect appears to be insufficient. By virtue of the cell membranes isolated from the *in vitro* primed immune cells, immunotherapy would benefit from the elevated expression of immune-associated chemokines on membranes, the nanoscale size and the non-living nature of PNs to overcome immunosuppression barriers. Wang's group [553] coated the cell membranes extracted from ovarian cancer cell lysate-primed DCs, which preserved the antigen-presentation components (such as MHC, CD86, and CD40) on their surface, onto the interleukin-2 (IL-2)-loaded PLGA nanoparticles for mimicking DC's antigen-presenting ability to stimulate T cells for therapeutic and prophylactic effects against cancers. With the presence of certain proteins (*e.g.*, RANKL or DNAM-1), NK cell membranes, which were coated on the PNs capable of photodynamic therapy (PDT), could induce pro-inflammatory M1-macrophage polarization to reverse intratumoral immunosuppression microenvironment, and serve as an immune inducer to stimulate the immune response caused by PDT-induced immunogenic cell death for activating APCs (Figure 42) [554].

Expanding the application scope of cell membranes is a hot topic at presence. For instance, the binding and recognition toward the pathogens are key tasks of certain cells, such as macrophages, leukocytes [555]. RBC membranes were identified with the ability to absorb exotoxin to relieve bacterial infection [539,556]. The biomembranes were thus used to coat PNs for the applications including antibacterial

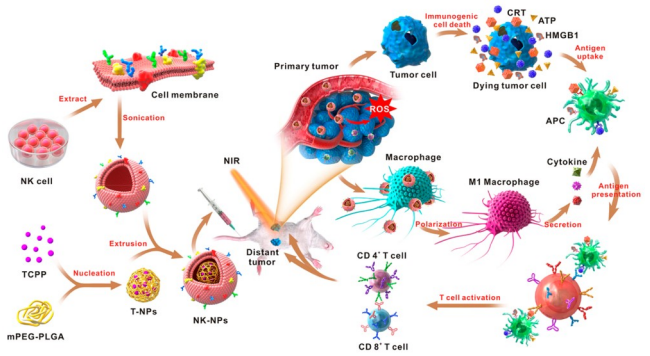


Figure 42 Schematic illustration of NK cell-membranes-cloaked nanoparticles for PDT-enhanced cell-membrane immunotherapy. Extracted NK cell membranes were coated onto photosensitizer TCPP-loaded polymeric nanoparticles by extrusion. NK cell membrane enabled the NK-NPs to elicit pro-inflammatory M1-macrophage polarization in tumor for generating cell-membrane immunotherapy. NK-NPs could elicit dying tumor cells to generate DAMPs (CRT exposure, ATP secretion, and HMGB1 release) through PDT-induced immunogenic cell death (ICD) for enhancing the NK cell-membrane immunotherapy effect. Specifically, immunogenic PDT enhanced NK cell-membranes immunotherapy, which significantly improved the infiltration of effector T cells ($CD4^+$ T cells and $CD8^+$ T cells) in tumors for the highly efficient inhibition of both primary tumors and abscopal tumors [554] (color online).

vaccines, endotoxin removal and inflammation reduction. Besides, the beta cell membrane coated on nanofiber scaffolds was shown to promote the growth of other beta cells, due to cell-to-cell interactions for their survival [557].

Via physical, chemical and biological techniques, artificial engineering of cell membranes provides room to advance the development of the biomembrane coating nanotechnology. To preserve the membrane's biological activity, direct chemical modification of cell membranes is not a preferable option. The hybrid coating with multiple membranes from different source cells enables the combination of their individual biofunctions present on PNs surface. For instance, fusing bacterial membrane with the cancer cell membrane could provide the combined biofunctions as cancerous antigens and natural adjuvants, forming a cancer-targeting immunotherapeutic formulation [558]. In an attempt to deal with choroidal neovascularization involved in blinding diseases, the retinal endotheliocyte membrane coating provided homotypic targeting capability to the vascular endothelial growth factor while the fused RBC membranes enabled the escape from phagocytosis by macrophages [559]. Free of chemistry in membrane modification, the lipid-insert-membrane approaches are usually used *via* the spontaneous insert of a lipid linked with functional groups into the cell membranes. For instance, PNs were coated with RBC membranes to avoid immune clearance, while the targeting function was provided by inserting DSPE-PEG2000-T (T represents functional groups) lipids into RBC membranes [560]. Biological approaches show strong potency in cell membrane modification. Metabolic glycoengineering technique and bioorthogonal reaction are combined to introduce functional moieties on cell membranes to artificially create new ligand-receptor recognition between cell membrane and the targeted cells (Figure 43) [561]. By engineering neural stem cells (NSCs) with the surfacial over-expression of targeting CXCR4 through lentiviral transduction, the ischemic brain-targeted delivery efficiency of the NSC membrane coated PNs was further increased [562].

The coating with cell membranes offers a platform technology to arm PNs with biological complex functions on the surface in a facile way. Future advance in this field relies on the clarification of cellular membrane-membrane interaction mechanisms, the discovery of more membrane biofunctions and the understanding about the role of biomembrane-PN interactions in biomedical applications.

7.3 Microorganism-based biomedical polymers for cancer therapy

By virtue of their special targeting, immune evoking, easy functionalization and natural therapeutic features, the unprecedented tumor treatment ability of living microorganisms (including bacteria, fungi, viruses, and microalgae) as well as their natural components have been highlighted recently [563,564]. In particular, in order to vastly reinforce the microbes-based therapeutic platforms, many functional materials, especially the available biomedical polymers are

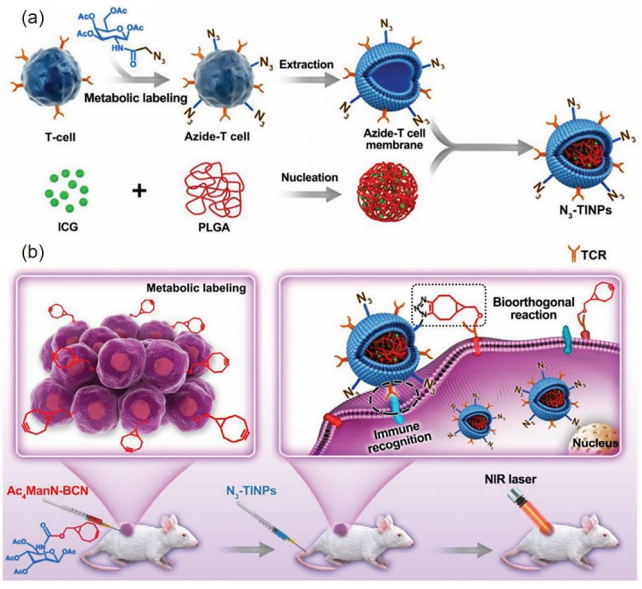


Figure 43 Schematic illustration of N_3-labeled T cell membrane-biomimetic nanoparticles with dual-targeting mechanism for highly efficient photothermal therapy. (a) Synthesis of N_3-TINPs. Extracting N_3-labeling T cell membranes were coated on prepared ICG-PLGA polymeric cores by extrusion to form N_3-TINPs. (b) Tumor cells carrying the BCN group *via* natural glycometabolic labeling by pretreatment with Ac4ManN-BCN. N_3-TINPs could target tumor through immune recognition of T cell membrane and bioorthogonal reaction between BCN and N_3 groups, and effectively eliminate mouse tumors through ICG-mediated photothermal effects [561] (color online).

employed to integrate with therapeutic microbes and their components to construct living microbes-involved therapeutic formula by multiple integration methods, including physical assembling, chemical conjugation, and biological recombinant expression [565,566]. Besides, the microbial components containing proteins, peptides, polysaccharides and lipids can also serve as life-derived natural biomedical polymers used for establishment of potent therapeutic nanomedicines [567,568]. Encouraged by the enhanced therapeutic outcomes of cancers in a lot of literatures, the active therapeutic agents based on life-unit involved polymers (LIPs) provided a new paradigm in cancer treatment (Figure 44).

Accompanying the transcendent features of microorganisms on anticancer treatment, some inevitable drawbacks (*e.g.*, intrinsic microbial immunogenicity, easy immune clearance, and indiscriminate cell damage) seriously limited the progress on construction of microorganisms-based tumor therapeutic formula. In order to solve the dilemma in elevating the tumor therapeutic efficacy and concurrently weakening the intrinsic defects, artificial strategies have been duly adopted to remold the objective microorganisms by employing various available functional materials [569]. Specially, biomedical polymers represent the most suitable materials due to their good biocompatibility and easy modification [570]. For example, by hierarchically encapsulating the microbes with functional polymers through self-cross-linking and self-polymerization, the highly cytoprotective capability can be obtained to against external aggressors, which are also beneficial to accelerate microorganisms-based disease therapy [571,572]. It was reported that, when coating the synthetic nanoparticles originated from the self-assembling of cationic polymers and plasmid DNA onto live attenuated bacteria surface, bacteria can effectively escape phagosomes and enhance the gastric acid tolerance after oral administration due to the protective effect of the coated nanoparticle layer, therefore significantly facilitate penetration of bacteria into blood circulation and promote cancer immunotherapy [573]. Except for the simple cytoprotection and transport promotion, some prebiotic polymers can also serve as the important metabolism substances of deliverable probiotic microbes to produce therapeutic ingredients, which will further promote microorganisms-based tumor therapy. For instance, by the host-guest interaction strategy, Zhang *et al.* [574] utilized prebiotics of dextran (Dex) to encapsulate the probiotics of C. butyricum spores and load chemotherapeutic drugs. It was found that spores-Dex can selectively target to colon tumor lesions after oral administration and dextran was subsequently metabolized by germinal spores to produce anti-cancer short chain fatty acids (SCFAs). More importantly, the richness of SCFA-producing commensal bacteria in gut can be improved by spores-Dex, which also significantly enhanced the overall abundance and diversity of the gut commensal bacteria. Leveraging these effects, drug-loaded spores-Dex significantly inhibited tumor growth without causing obvious adverse effects in established mouse colon cancer models (Figure 45a, b). This strategy constructed a typical paradigm for safe and effective treatment of gastrointestinal cancer through organically integrating prebiotics and probiotics to globally modulate gut microbiota. Similarly, by chemically conjugating chemotherapeutic drugs-loaded dextran nanoparticles with the targeted phages of pro-tumoral *Fusobacterium nucleatum* (*F. nucleatum*), after oral administration, the growth of *F. nucleatum* was obviously inhibited and the treatment result of chemotherapy on colorectal cancer was significantly augmented owing to the global modulation of gut microbiota [575]. Except for modification of individual microbe, the encapsulation of multiple microorganisms using biomedical polymers was also explored for disease treatment [576]. For example, to solve the difficulties in delivery of active phages to the deep lung, hollow PLGA polymeric microspheres were synthesized to load lytic phages and keep phage activity. By dry powder inhalation, *Pseudomonas aeruginosa* (*P. aeruginosa*)-caused lung infections and infection-related cystic fibrosis can be finally reduced [577]. In another example, Zhang *et al.* [578] encapsulated microbial cocktail (*Escherichia*, *Bacillus*, *Enterobacter*) into calcium alginate microspheres coated with a polydopamine layer which is selectively permeable of small-molecule nitrogenous wastes for orally delivering. Considering the ability of encapsulated bacteria to convert various types of nitrogenous wastes into

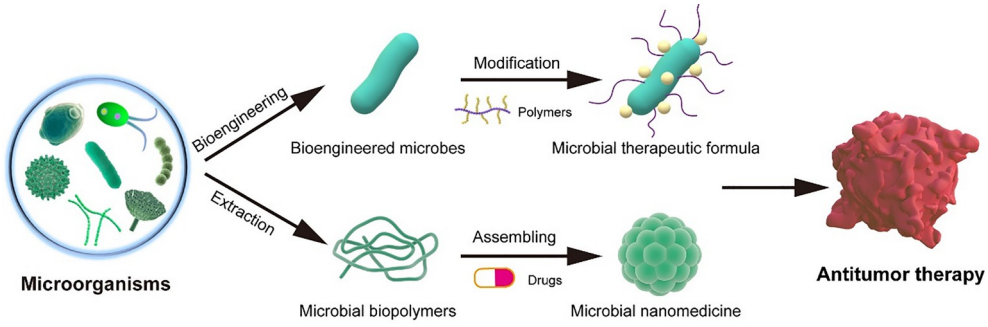


Figure 44 Schematic illustration of microorganisms-based biomedical polymers for antitumor application (color online).

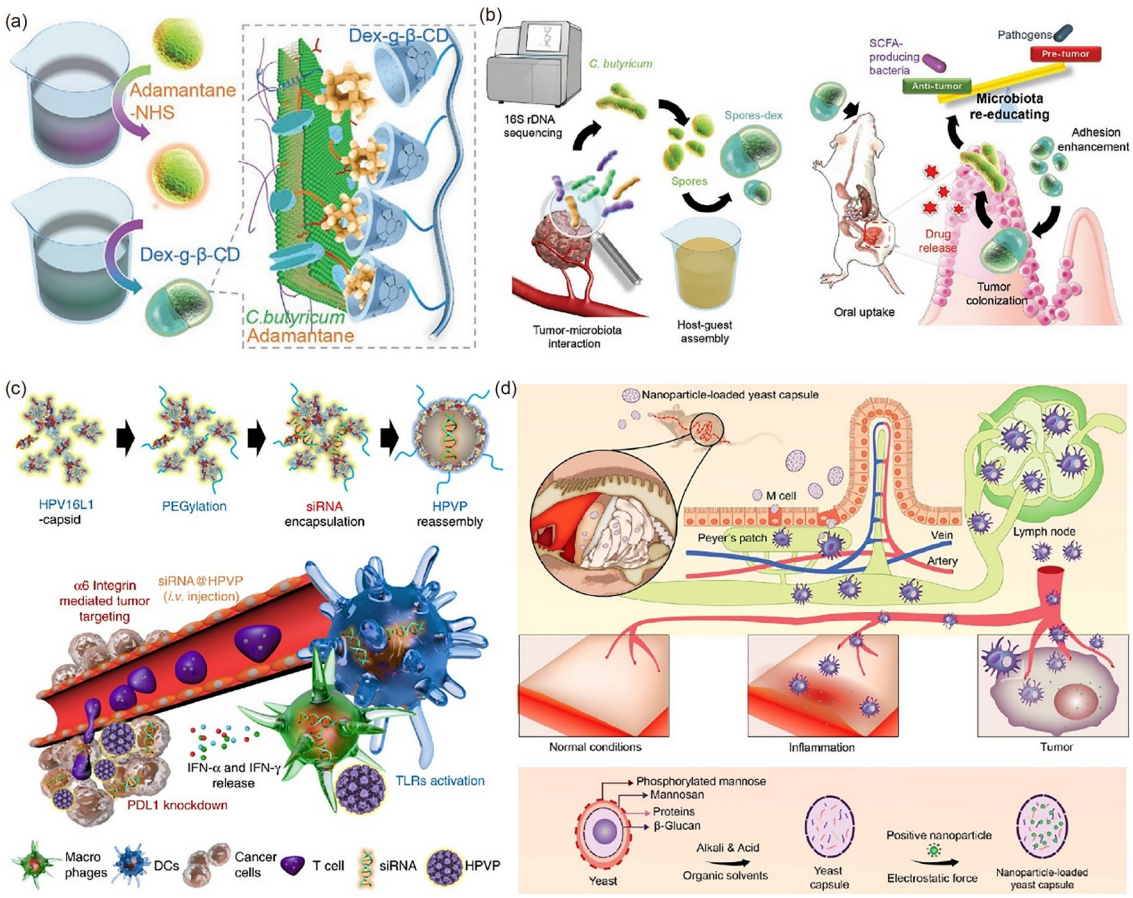


Figure 45 (a) Schematic illustration of the integration of prebiotics with probiotics *via* host-guest interaction [574]; (b) schematic illustration of the encapsulation of probiotics by prebiotics to modulate gut microbiota and inhibit colorectal cancer [574]; (c) schematic illustration of the construction and therapeutic process of the siRNA@HPVP system [581]; (d) schematic illustration of YC-guided oral transportation of nanoparticles to diseased sites distant from the gastrointestinal tract [582] (color online).

amino acid *via* the cascaded bacterial metabolism, the fabricated bacterial micro-ecosystem prominently reduced urea and creatinine concentrations in blood without causing any adverse effects in multiple kidney failure model of animals. In view of the superior properties of this ingenious bacterial micro-ecosystem, the concept about cascaded bacterial metabolism could be extended to antitumor application by integrating multiple microorganisms with multifunctional biomedical polymers.

Microorganisms-derived polymeric components (*e.g.*, bacterial surface layer protein and biopolymers, virus-like particles (VLPs), fungi-related polysaccharides) also displayed superior properties in biomedical application due to their high stability, intrinsic bioaffinity, easy extraction and modification, and higher biosecurity [567,579]. For example, fusing with cell membrane-coated nanomedicine, bacterial surface layer proteins can obviously potentiate the immune response to the antigens [580]. Particularly, due to their immunogenicity and self-assembling ability, proteins derived from viruses have been widely researched in biomedical applications, which can be applied as general platforms for cancer vaccines and antitumor drug delivery. For example, Zhang *et al.* [581] constructed an anticancer vaccine by encapsulating the tailored siRNA into commercial VLPs of HPV (siRNA@HPVP) to enhance the tumor therapeutic efficacy of ICB-based immunotherapy. Through knocking down the transcription of Cd274, the encapsulated siRNA can downregulate the expression of the tumor-specific programmed cell death ligand 1 (PD-L1). VLPs can also induce innate immunity through activating the type 1 interferon pathway. Combining the two effects, *in vivo* experiments demonstrated that the immune response rate was significantly elevated when cooperating with ICB antibody-based immunotherapy in various genetically modified breast cancer models (Figure 45c). This VLPs-based immunotherapeutic platform proposed a universal strategy for optimizing current ICB immunotherapy. Additionally, owing to the inner layer of the yeast cell wall is mainly composed of β-glucan, yeast cells (YCs) can be specially recognized and transcytosed by intestinal microfold cells (M cells) and sequentially endocytosed by macrophages and transported to adjacent lymphoid nodes, and finally delivered to remote

diseased sites of inflammation or tumors. The special transepithelial transport pathway can preferentially guide the delivery of YCs-based theranostic systems into the desired disease nidus, which revealed that YCs can be constructed into universal drug delivery platform for oral administration (Figure 45d) [582]. ECM components of microorganisms like bacterial cellulose and bacterial curli fibers, which can be further bioengineered to functionalize with evolvable functionalities such as self-healing and disease therapy, also have been widely developed for biomedical applications [583,584]. For instance, engineered living materials can be fabricated by genetically engineering *Escherichia coli* Nissle 1917 (EcN) with amyloid protein domain of trefoil factors (TFFs) to create curli nanofiber matrices associated with the abilities of mucosal healing and immunomodulation, which can improve *in situ* intestinal barrier function and epithelial restitution in a dextran sodium sulfate (DSS)-induced colitis in mice [585]. This work revealed the development of *in situ* generation of therapeutic protein matrices from probiotic bacteria for effective disease treatment. Besides, the growing bacterial cellulose matrix can also be utilized to fabricate functional bacterial cellulose-based living materials by co-culturing with other engineered microorganisms for exogenous stimulus-responsive biosensing and bio-catalysis [586]. These strategies can also be extended to antitumoral probiotic delivery for microbiota modulation and colon cancer therapy.

Because some of their special features are perfectly adaptive to treat tumors, the preponderant microorganisms as well as their derived polymers are being emergently exploited as antitumor formulations or antitumor nanomedicines [587,588]. In view of its highly intelligent property and effective therapeutic potential, this emerging strategy has reformed the landscape of tumor therapeutics. Encouraged by the united advantages of available microorganisms and functions-tailored biomedical polymers, LIPs are proposed flourishing prospects in the future antitumor research.

7.4 Biomedical polymers for cell-mediated cancer therapy

As of now, therapeutic approaches mediated by cells that mainly belong to the native and adaptive immune systems have been developed for treating cancers [589,590]. Cell therapy has achieved significant progress; however, challenges remain to demonstrate their clinical treatment efficacy and acceptable toxicity [591]. At the same time, these cells can also serve as carriers to deliver anticancer drugs to tumors with high specificity and efficiency; however, cellular carriers face issues associated with efficiency and safety [592,593]. Therefore, polymeric carriers loaded with bioactive drugs have been developed to enhance cells' viability, functionality, and sustainability [594]. Also, polymeric materials are used to encapsulate drugs before attaching drugs to cellular carriers to improve spatiotemporal precision in tumor-targeted drug delivery and controlled release. To realize these two goals, researchers have employed polymeric materials to prepare hydrogels, microneedles, and micro/nanoparticles to cooperate with cells.

Hydrogels based on polymers are widely explored in cancer therapy because of porous networks, swelling capability, suitable mechanical strength, mild gelation conditions, and high biocompatibility [595,596]. In cell-based immune therapy, immune cells, including T cells, nature killer (NK) cells, dendritic cells (DCs), and chimeric antigen receptor (CAR) T-cells, could be loaded into environmental-sensitive smart hydrogels [597]. These types of smart hydrogels have significant advantages in improving cells' viability and ameliorating tumor microenvironment, therefore substantially strengthening the immune response against tumors [598]. Hyaluronic acid is a linear and non-sulfated glycosaminoglycan composed of repeated disaccharides of *N*-acetylglucosamine and glucuronic acid. HA is non-immunogenic, hydrophilic, biodegradable, and structure tunable, so it functions as a widely used polymer for preparing hydrogels [599]. For instance, an HA hydrogel was created to accommodate CAR T cells into the tumor cavity of mice after resection and allowed the gradual release of cells to enhance the antitumor activity (Figure 46) [600]. The HA hydrogel also allowed the simultaneous loading of other bioactive drugs, including interleukin-15 preloaded in nanoparticulate particles and antibody against programmed death-ligand 1 (PD-L1) that was conjugated to platelets. The release of these cargos reversed the immunosuppressive microenvironment and supported the cell function, thus inhibiting the tumor metastasis and recurrence. In addition, GFOGER-modified alginate hydrogel implant [345], an injectable polyisocyanopeptides hydrogel [601], and a T-cell stimulating cytokine-loaded PEG-chitosan hydrogel [602], have been developed to increase T cell penetration capability, improve T cells' sustainability and proliferation capability, and eventually achieve a high anticancer activity.

Polymeric microneedle (MN) array patch is another sort of biomedical platform for cell delivery in cancer therapy [603]. MN can pierce the stratum corneum minimally invasively and painlessly and transfer the cargos directly to the dermis [604]. MN array patch has various advantages, including easy preparation and manipulation of structure, avoidance of the first-pass effect of the absorbed drug, and easy retrieval [605,606]. PLGA is a biodegradable and biocompatible polyester that has drawn wide attention in biomedical applications [607]. When hydrolysis is in the body, PLGA degrades into lactic acid and glycolic acid, both are natural metabolites without toxicity [608]. Also, PLGA has sufficiently high mechanical strength, making the microneedles

capable of inserting into the tissues. PLGA is thus suitable for preparing MN array patches. A PLGA porous MN array patch accommodating CAR T cells was developed for cancer treatment (Figure 47). The researchers incorporated micrometer-sized pores in the body of MNs by etching $CaCO_3$ microparticles that were pre-embedded in the MN. This patch allowed evenly seeding of CAR T cells when it was implanted toward a tumor or within the surgical tumor resection [609]. Also, this MN patch can retain CAR T cells in the pores and protect them from scratches during insertion into tumors. After seeding the CAR T cells in the tumor sites using microneedle patches, the CAR T cells exhibited high proliferation and anticancer activity in subcutaneous WM115 and orthotopic pancreatic tumor models. This porous patch could adapt to accommodate other cell types for treating various diseases.

Microparticles and nanoparticles, which are widely used carriers in the field of cancer treatment, can also be applied for cellular therapy [610]. In cell-mediated anticancer therapy, particulate drugs, including chemotherapeutic or immunomodulating drugs, could be attached to or internalized by cells for improving their pharmacokinetics and targeting capability to specific organs. Thus, the drug-loaded particles can selectively accumulate in the tumor or specific sites, significantly promoting treatment efficacy and reducing the systemic off-target toxicity [611]. Chemotherapeutic drugs

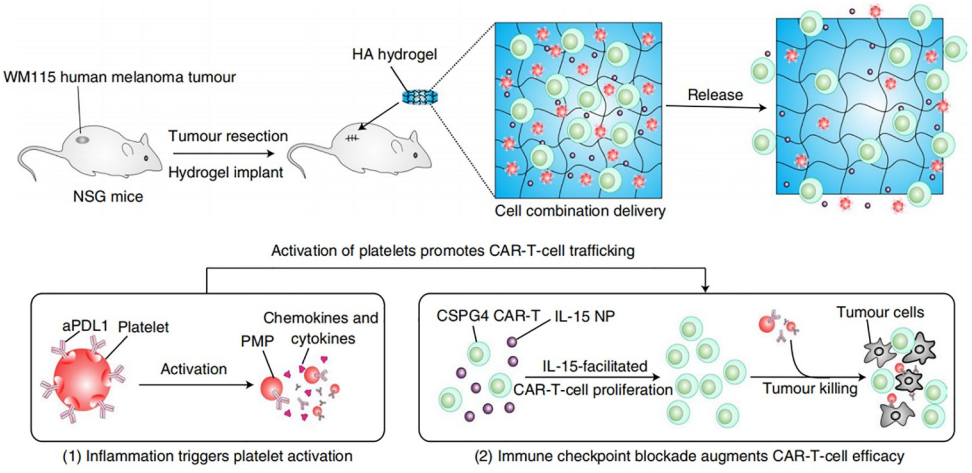


Figure 46 A hydrogel for delivering CAR T cells. The hydrogel was prepared from cross-linked HA and loaded with CAR T cells, IL-15-loaded PLGA NPs, and aPD-L1 [600] (color online).

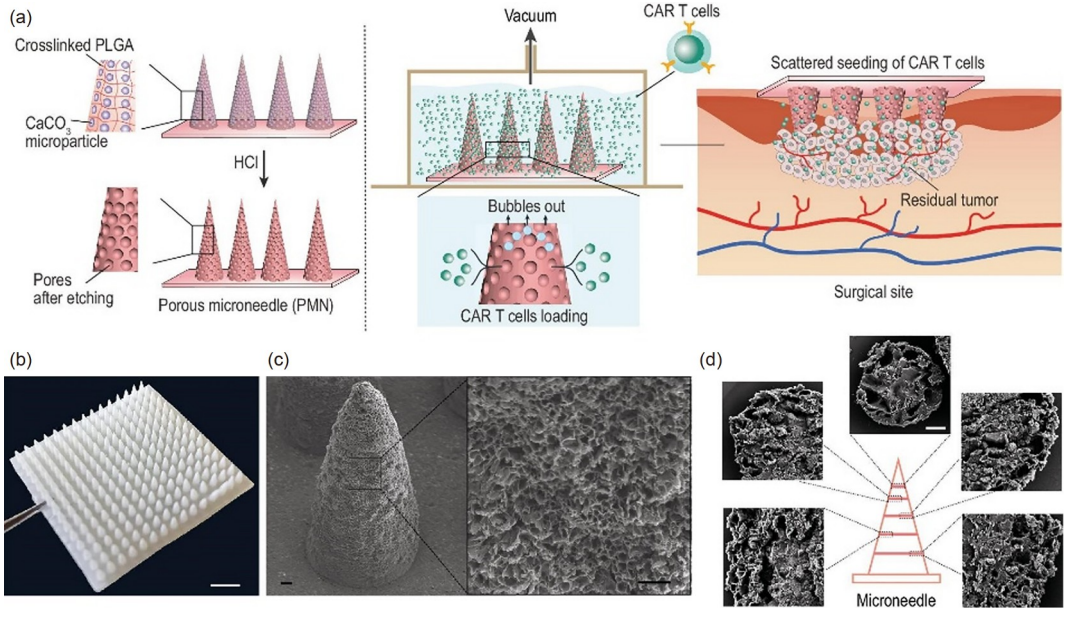


Figure 47 Preparation and characterization of CAR T cell-loaded porous microneedle patch [609]. (a) Scheme of the preparation of porous microneedles and the loading of cells into the microneedle patch. The microneedle patch could be applied toward a tumor *via* transdermal delivery of CAR T cells. (b) MN patch's picture. Scale bar: 2 mm. (c) A typical SEM image of MN showing the porous structure. (d) Typical SEM images of the cross section of MN (color online).

delivered by cells can directly exert a cancer cell-killing effect. In one study, positively-charged polymer-coated nanoparticles were able to adsorb to erythrocytes more tightly than neutral or negatively-charged particles. A 75-fold increase in accumulation of the chitosan-coated nanoparticles in lungs after they hitchhiked RBCs as the carriers. Then, doxorubicin, which was preloaded in chitosan-coated nanoparticles (100 nm), was utilized to treat B16-F1 metastasized tumor, and a 3-fold decrease of metastasized tumors was validated [612].

Drugs for immunomodulating tumor microenvironment, attracting immune cells, or enhancing cellular physiological function can also be loaded into nanoparticles. Based on an erythrocyte-driven immune targeting process, nanoparticles on erythrocytes can selectively accumulate in the spleen to achieve a robust immune response [613]. Thus, ovalbumin was conjugated to polystyrene nanoparticles that were further attached to erythrocytes for spleen-targeted antigen delivery, thus robustly inducing an adaptive immune response. Also, a polyelectrolyte multilayer particle prepared from PLGA and poly(vinyl alcohol) was prepared to deliver interferon-γ (IFN-γ) directly to the macrophage that it attached to. The particles had a disk-like shape, which could prevent the endocytosis of drug backpack by the macrophage carrier. This system has shown the capability to polarize tumor-associated macrophages (M2 type) to the M1 phenotype, therefore switching the tumor microenvironment toward a proinflammatory state and promoting anticancer immune response to suppress metastasis and inhibit tumor growth [614]. Chemokine-loaded PLGA nanoparticles have also been attached to erythrocytes for lung-targeted drug delivery [615]. Immunotherapeutic CXCL10-loaded PLGA nanoparticles were detached from erythrocytes to the capillaries in the lungs because of shear stress, therefore establishing a gradient of CXCL10 to attract immune effector cells to migrate toward the lungs and activate anticancer adaptive immunity. This strategy could be specifically employed to enhance lung cancer treatment efficacy. As a special type of cell, bacteria could also be used for delivering polymeric nanodrugs for treating cancers. Polyethylenimine, a generally used gene vector, is a highly-positively charged polymer. In one study, salmonella was used as a carrier to deliver PEI/DNA complex to M-cells to activate T cells that are specific for vascular endothelial growth factor receptors (VEGFR)-positive cells [573]. Because VEGFR is critical for tumoral angiogenesis, the immune response against these cells destructed tumor vascular network, blocked the nutrient and oxygen supply, and thus inhibited tumor growth.

In summary, polymers could encapsulate cells and load drugs to improve cell therapeutic function or hitchhiking cells as carriers for spatiotemporal drug delivery and controlled release. However, only limited types of polymers have been used in this field. In the future, polymers with high biocompatibility and stimuli-responsive properties need to be developed to expand their applications in cell-mediated anticancer therapy with clinical impact.

8 Summary and outlooks

At present, biomedical polymers have important applications in precise nanomedicine (therapeutics, diagnostics, and theranostics), tissue engineering, and regenerative medicine due to their irreplaceable features, and a few breakthroughs have been made in the explorations of preclinical and clinical studies. However, the current research is largely conducted at the level of small animals such as mice and rabbits, which is far from the real clinical requirements. For example, most of polymer-based nanomedicines have been demonstrated to specifically deliver drugs to tumors in the tumor-bearing mice for promoting the antitumor efficiency, but the therapeutic outcomes are often poor in human clinical trials. Thus, a major challenge remains in establishing and employing reasonable animal models such as patient-derived xenograft (PDX), even large animal models such as pigs and monkeys, for precisely guiding and indicating clinical translation potentials.

Moreover, the biocompatibility and biodegradability of biomedical polymers are two critical important properties for their task-specific biomedical use. For instance, the polymer-based cardiovascular stents or tissue repair materials need to remain in the human body for a long time, which requires the corresponding polymer to have favorable biocompatibility and would not induce the body's inflammatory responses and immunological stress reactions. Similarly, polymer-based drug delivery systems also need to possess good biocompatibility for reducing *in vivo* side effects and improving applicability. More importantly, from the opinion of clinical translation, the biodegradability of biomedical polymers is beneficial to overcome the potential safety burdens such as metabolic toxicity, long-term toxicity, and immunogenicity. Also, addressing safety issues of biomedical polymers is the safety guarantee and prerequisite for their clinical applications. Therefore, for the concern of long-term potential toxicity, more contents related to the biosafety including immunogenicity, metabolism, genotoxicity, biodistribution, pharmacokinetics, and complete blood test, should be carefully carried out and investigated on animal models with a relatively long time (at least several months and more). Besides, the quality control, reproducibility, and large-scale fabrication are additional challenges that are demanded to be overcome for engineering biomedical polymers. Although these aspects are not considered crucial factors in the clinical research, an elaborate consideration should still be involved in the design of polymers for biomedical use.

In recent years, the burgeoning bioactive polymers have

attracted great attention of researchers because of their special physiological activities and functions. For example, some kinds of microorganisms as well as their derived polymers are being exploited as antitumor formulations or antitumor nanomedicines due to their special features that are perfectly adaptive to treat tumors. However, the less controllability, potential pathogenicity and cytotoxicity of these microorganisms in the body may induce safety hazards, which greatly limits their applications in clinical practices. Others like phages, biomembrane, and natural cells *etc*. may also raise safety concerns around immunogenicity. This is a double-edged sword: the strong immunogenicity brings security risks, which, on the other hand, could provide enormous opportunities for immunotherapy. At present, therapeutic approaches mediated by cells that mainly belong to the native and adaptive immune systems have been developed for treating cancers. For instance, NK cells, DCs, and CAR T cells based immune therapy have been used in clinical and achieved significant progress. However, challenges associated with their clinical treatment efficacy, specificity and acceptable toxicity still need to be studied carefully.

These challenges and overlooked points mean that biomedical polymers have a wide space for exploration in therapeutic medicine delivery, disease detection and diagnosis, biosensing, regenerative medicine, and disease treatment. The up-to-date developments and achievements presented in this review are desired to inspire more successful explorations and clinical translation of intelligent polymers for biomedical applications.

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