Biomaterials Science

REVIEW

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Cite this: *Biomater. Sci.*, 2019, **7**, 4848

Recent progress of glycopolymer synthesis for biomedical applications

Irawan Pramudya and Hoyong Chung *

Received 29th August 2019,
Accepted 7th October 2019

DOI: 10.1039/c9bm01385g

rsc.li/biomaterials-science

Glycopolymers are an important class of biomaterials which include carbohydrate moieties in their polymer structure. In addition to biological research on the interactions of glycopolymers with lectin-carbonate, glycopolymers have recently been used as a new synthetic biomaterial for direct therapeutic methods, medical adhesives, and biosensors. Thus, a comprehensive understanding of new advances in glycopolymer research is essential for the next level of biomaterial studies. This review article highlights commonly used glycopolymer synthesis methods and biomedical applications thereof. Glycopolymers can be synthesized by modern polymerization methods that can control the molecular weight, molecular weight distribution, chemical functionality, and polymer architecture. The polymerizations include free radical polymerization, atom transfer radical polymerization, reversible addition–fragmentation chain-transfer polymerization, and nitroxide-mediated polymerization. Because the carbohydrate–lectin interactions with glycopolymers are involved in many biological processes, carbohydrates containing glycopolymers are used in (1) fundamental studies to understand the specificity and strength of biological binding, (2) controllable interactions to prevent microorganism adhesion to human cells, (3) large scale bulk adhesives for medical applications, (4) biocompatible therapeutic nanoparticles, (5) direct drug delivery vehicles, and (6) precise quantitative measurement of biosensor materials that can detect physiological signals.

1. Introduction

Synthetic polymers containing carbohydrate pendants, commonly referred to as glycopolymers, have attracted the attention of many scientists due to their significance in biological processes. Carbohydrates contain three major components including monosaccharides, oligosaccharides, and polysaccharides. A synthetic glycopolymer generally possesses a monosaccharide and/or oligosaccharide pendant group in a repeating unit. The chemical study of carbohydrates, natural saccharides, was first published by Emil Fischer in 1884.[1,2] The cyclic structure of natural carbohydrates which can be seen in maltose, sucrose, lactose, and cellobiose was elucidated in 1930s by Haworth and colleagues.[3] Soon after, the macromolecular structures of saccharides and polysaccharides were discovered. Two conventional applications of polysaccharides are found in food (*e.g.*, molasses, starch, and glycogen)[4] and structural materials (*e.g.*, cellulose, collagen, fiber, and chitin).[5–7] In modern science research, carbohydrates play an important role in understanding and controlling various biological processes. For instance, heparin (Fig. 1a), a sulfated polysaccharide (glycosaminoglycan), interferes with the blood clotting process in the human body by inhibiting thrombin activation during the coagulation cascades.[8] Other polysaccharide examples such as hyaluronan (Fig. 1b) and chondroitin sulfate (Fig. 1c) possess anti-inflammatory properties.[9]

Recent advances in carbohydrate research has led to a new division of biology, glycobiology.[10] Glycobiology significantly increases the understanding of sophisticated interactions of carbohydrates for biomedical applications,[11,12] especially in selective and controlled recognition events.[13] Accurate recognition is essential for cell interactions[13] including fertilization,[14,15] embryogenesis,[16,17] cell migration,[18] organ formation,[19] bacterial/viral infection,[20] inflammation,[21] and cancer metastasis.[22] Precise and efficient synthesis of carbohydrates must be developed in order to fully comprehend and utilize these important cell interactions. Synthesis of carbohydrates has been a pivotal point that has resulted in crucial progress in biomedical fields such as carbohydrate-based vaccines,[23] drug carrier and delivery systems,[24,25] tissue scaffold engineering,[26,27] and HIV treatment.[28]

The specific binding interactions of a glycopolymer with carbohydrate-binding proteins (lectins)[29–31] result in cell agglutination such as hemagglutination.[32] Linear glycopolymers offer enhanced binding affinity to lectins due to the

Department of Chemical and Biomedical Engineering, Florida State University, 2525 Pottsdamer Street, Building A, Suite A131, Tallahassee, Florida, 32310, USA. E-mail: hchung@fsu.edu

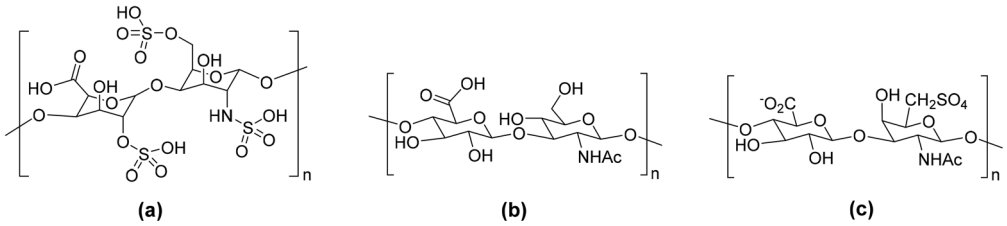

Fig. 1 Structures of polysaccharide examples: (a) heparin, (b) hyaluronan, and (c) chondroitin sulfate.

multivalent binding sites compared to a single carbohydrate unit. This holds true as long as the functionalization of the carbohydrate moieties does not impede the recognition process.[32] In addition, linear synthetic glycopolymers are the most studied class of glycopolymers due to the simplicity of their synthesis.[33] Whitesides and co-workers have elucidated that optimum binding is achieved when the distance between two glucose pendants on a polymer is equivalent to the distance between the binding sites of the lectin.[34] Likewise, linear glycopolymers exhibit generally acceptable biorecognition capability. However, the application of a regular linear glycopolymer is limited due to its insufficient binding affinity to lectins compared to that of other polymer architectures. The poor binding affinity arises from unwanted clustering which occurs often due to hydrogen bonds between hydroxyl groups of carbohydrate pendants.[35] Therefore, the fields of study that require high levels of recognition, including biosensing and drug delivery, do not commonly use linear glycopolymers.

The advanced non-linear glycopolymer architecture (*e.g.*, micelles of amphiphilic polymers, dendrimers, and nano-particle cored star-shape polymers) provides more surface area for binding between the polymer's carbohydrate and lectins.[32] In addition, new synthetic methods that enable the formation of well-defined glycopolymer chemical structures can precisely control the binding site distance that can customize the related applications. Hence, more sophisticated structures, which are non-linear and have well-defined architectures like that of glycopolymers, have gained high interest in recent glycopolymer studies.

2. Polymerization methods to prepare glycopolymers

Due to significant scientific and practical potential of glycopolymers, various architectures of glycopolymers have been prepared. Modern polymerization techniques used in preparing glycopoymers are discussed in this section.

2.1. Glycopolymer synthesis *via* conventional free radical polymerization (FRP)

Conventional free radical polymerization (FRP) has been the most commonly used polymerization technique to synthesize glycopolymers. Typical advantages of conventional FRP include well-established experimental methods, ample commercially available initiators, moderate tolerance to impurities, and a broad range of reaction conditions in terms of solvents and temperatures.[13,32] Glycomonomers are mainly synthesized by glycosylation (a chemical reaction between carbohydrates and other molecules) of vinyl compounds. A carbohydrate containing vinyl monomers may possess additional functionalities on a pendant group.[36]

Hořejší *et al.* reported an initial example of monomer synthesis and polymerization of glucoside acrylates *via* conventional FRP (Fig. 2a).[37] The conventional FRP of glucoside acrylates was conducted in water using an ammonium persulfate initiator and a tetramethylethylenediamine (TMEDA) catalyst (Fig. 2b).[37] The synthesized glycopolymer exhibits similar characteristics to natural polysaccharides in terms of lectin binding.[37]

Coupling of oligosaccharides with *p*-vinylbenzylamine was reported by Kobayashi *et al.*[38] Fig. 3a displays the oxidation of lactose in the presence of a hypoiodite to form a lactone. The oxidized lactone was subsequently reacted with *p*-vinylbenzylamine (Fig. 3b) by refluxing in methanol yielding a vinyl benzyl containing monomer as shown in Fig. 3b and c. This glycosylation step showed high yield without protection of hydroxyl groups on carbohydrates.[38] The glycomonomer was then polymerized *via* conventional FRP with an azobisisobutyronitrile (AIBN) initiator and potassium persulfate ($K_2S_2O_8$) (Fig. 3c). The prepared glycopolymer showed interactions with concanavalin A (Con A) which is a commonly used commercially available plant-origin lectin.

Roy *et al.* reported the synthesis of a 4-acrylamidophenyl β-lactoside monomer from lactose as shown in Fig. 4.[39] Acetyl protection of hydroxyl groups was required for the glycosylation during monomer synthesis. The protected, brominated carbohydrate was then reacted with a phenolic compound to yield a corresponding vinyl monomer as a result of a substitution reaction (Fig. 4a). The prepared 4-acrylamidophenyl β-lactoside monomer was then copolymerized with acrylamide by utilizing ammonium persulfate as an initiator and TMEDA as a catalyst at 90 °C (Fig. 4b).[39] The binding capability of poly (acrylamidophenyl β-lactoside) was tested with three different lectins: *A. hypogaea* (peanut) lectin, *Ricinus communis* (castor bean) agglutinin, and wheat germ agglutinin (WGA). Lectins from peanuts and castor beans showed precipitate formation, whereas wheat germ lectin did not show any interaction with the glycopolymer, hence, demonstrating the selective glycopolymer–lectin interactions.[39]

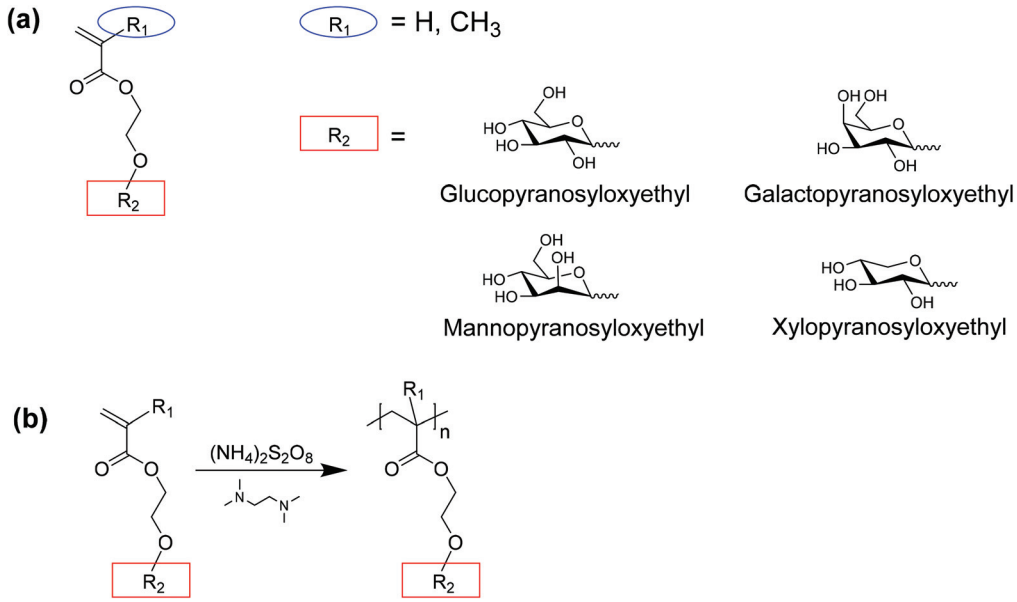

Fig. 2 (a) Glucoside acrylate monomer, and (b) free radical polymerization (FRP) of a linear glycopolymer using ammonium persulfate as the initiator and tetramethylethylenediamine (TMEDA) as the catalyst.[37]

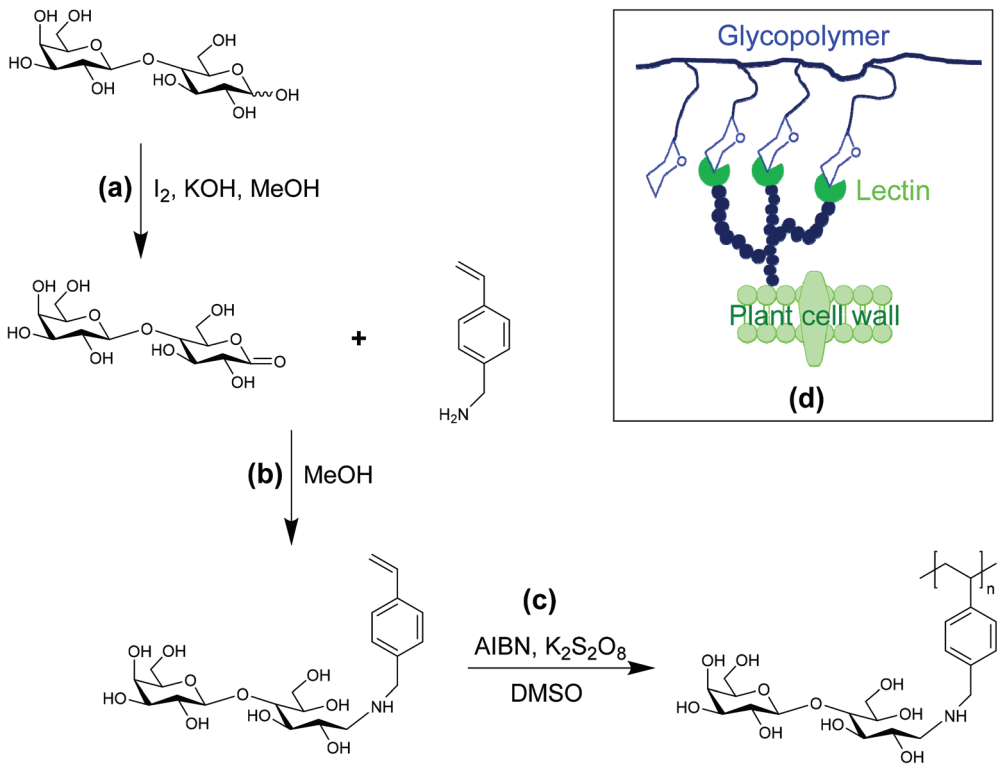

Fig. 3 (a) Oxidation of lactose to lactone, (b) glycosylation of lactone with *p*-vinylbenzylamine, (c) FRP of lactose-substituted polystyrene, and (d) interaction between the glycopolymer and concanavalin A (Con A), a commonly used commercially available plant-origin lectin.[38]

Fig. 5 displays other glycopolymers that are prepared from carbohydrates containing vinyl monomers through conventional FRP. As previously stated, FRP has been widely used in glycopolymer synthesis. However, conventional FRP has disadvantages including poor molecular weight control which leads to high molecular weight distribution (polydispersity index, PDI > 2.0) and poor control on polymer terminals.[13]

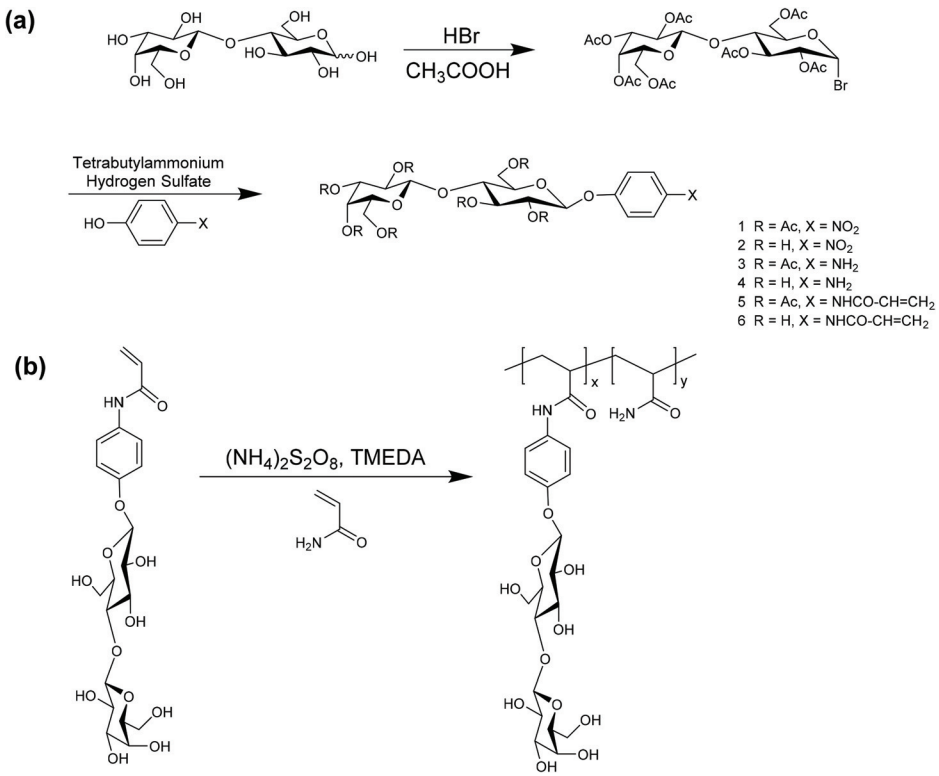

Fig. 4 (a) Modification of lactose to 4-acrylamidophenyl β-lactoside to prepare monomers, and (b) copolymerization of 4-acrylamidophenyl β-lactoside and acrylamide *via* FRP to synthesize poly(acrylamide-*co*-acrylamidophenyl β-lactoside).[39]

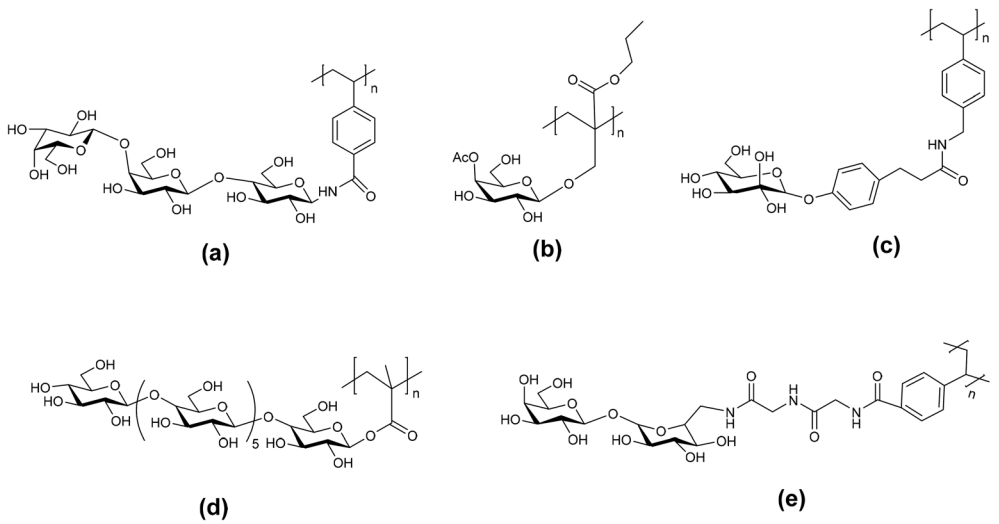

Fig. 5 (a) Poly(*p*-vinylbenzamido-β-4′-galactosyllactose),[40] (b) poly(ethyl α-(β-D-galactosyloxymethyl)acrylate),[41] (c) poly[*p*-(2-(*N*-(*p*-vinylbenzyl) carbamoyl)ethyl)phenyl α-D-mannopyranoside],[42] (d) poly(*O*-methacryloyl maltoheptaoside),[43] and (e) poly[(galacto-trehalose)acrylate].[44]

2.2. Glycopolymer synthesis *via* controlled radical polymerization (CRP)

Atom transfer radical polymerization (ATRP). ATRP is a type of controlled radical polymerization (CRP) that allows precise control of molecular weight distribution, functional terminals, molecular weights, and polymer architecture. Typical ATRP can be performed in the presence of a transition metal catalyst complex and an alkyl halide initiator for polymerization of polar group containing vinyl monomers.[45] Copper metal complexes have been most commonly used; however, diverse metal complexes, such as Ru, Fe, Mo, and Os, have also been previously reported as transition metal catalyst complexes.[46] With reference to glycopolymers, ATRP has two key advantages over

FRP. ATRP can be carried out without protection of hydroxyl groups in the glycomonomer due to ATRP's excellent functional group tolerance.[47] ATRP also allows for more control over molecular weight which leads to narrow molecular distribution. Another important feature of ATRP is the halide polymer terminal which can be used for further post-polymerization modifications.[47]

Makoto *et al.* reported an amphiphilic block glycopolymer, poly(2-(α-D-mannopyranosyloxy) ethyl methacrylate)-*b*-poly(L-lactide) (PManEMA-*b*-PLLA), which is synthesized by ATRP.[48] Two polymers, PLLA and PManEMA, were synthesized separately *via* ring opening polymerization (ROP) and ATRP as shown in Fig. 6a and b, respectively. By selecting an azide containing an ATRP initiator, azide terminal PManEMA was prepared (Fig. 6b). Next, the two prepared polymers were coupled by a copper-catalyzed click reaction to produce a block copolymer (Fig. 6).[48]

Fig. 7 demonstrates surface initiated ATRP of a glycomonomer. The target surface was treated with plasma followed by the introduction of an amine on the surface (Fig. 7b, left). The covalently linked amine on the surface was used to integrate the alkyl halide ATRP initiator. A similar surface modification was performed for gold electrodes as shown in Fig. 7a and b in the right side schematic. After the successful introduction of alkyl halides on the surface, a separately prepared glycomonomer, *N*-acetylglucosamine (GlcNAc), was polymerized by ATRP.[49,50] In particular, Fig. 7a illustrates the application of an advanced biosensor platform that studies the

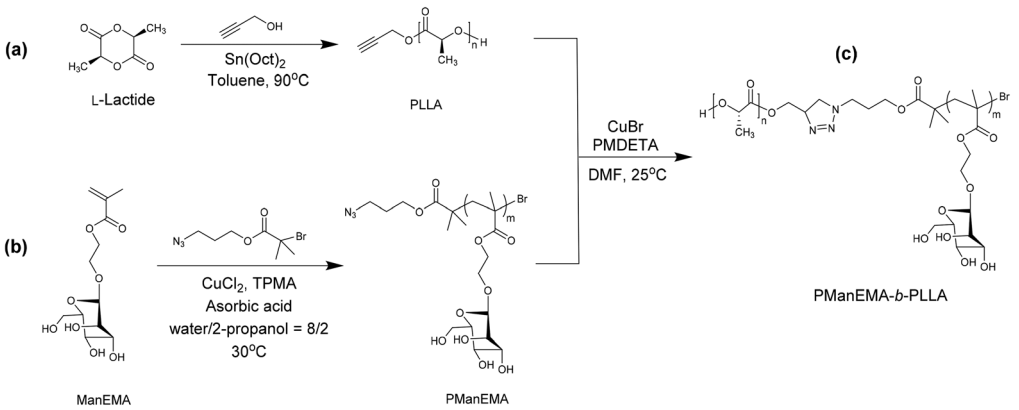

Fig. 6 Synthesis of the block glycopolymer poly(2-(α-D-mannopyranosyloxy) ethyl methacrylate)-*b*-poly(L-lactide) (PManEMA-*b*-PLLA); (a) synthesis of PLLA *via* ROP and (b) ATRP of ManEMA, and (c) PManEMA-*b*-PLLA *via* click chemistry.[48]

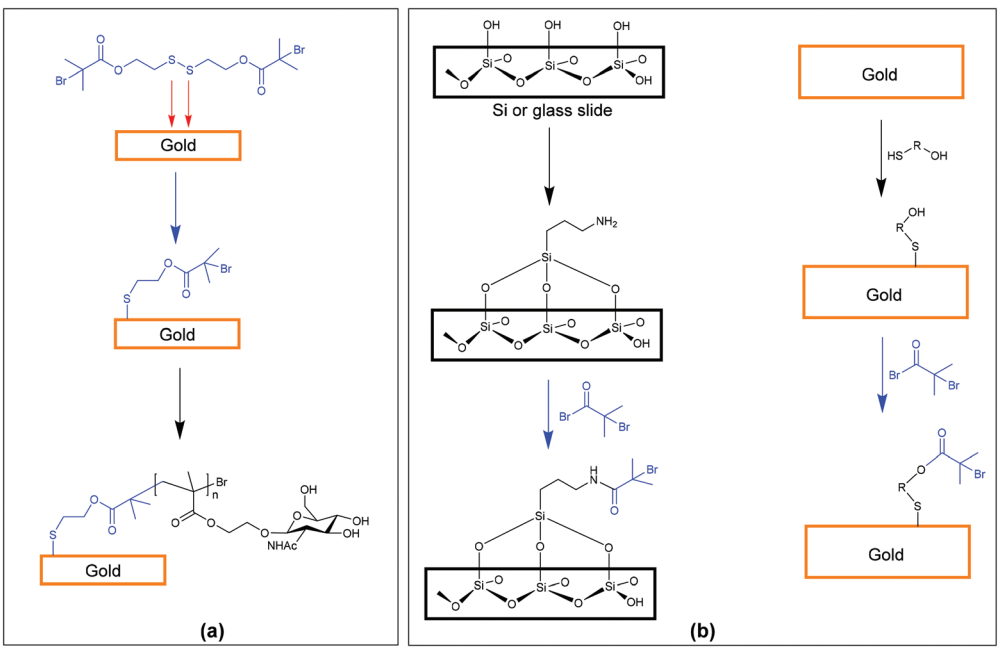

Fig. 7 (a) Surface-initiated ATRP of an *N*-acetylglucosamine (GlcNAc) monomer on plasma-treated gold electrodes,[49] and (b) initiator deposition on both substrate surfaces.[50]

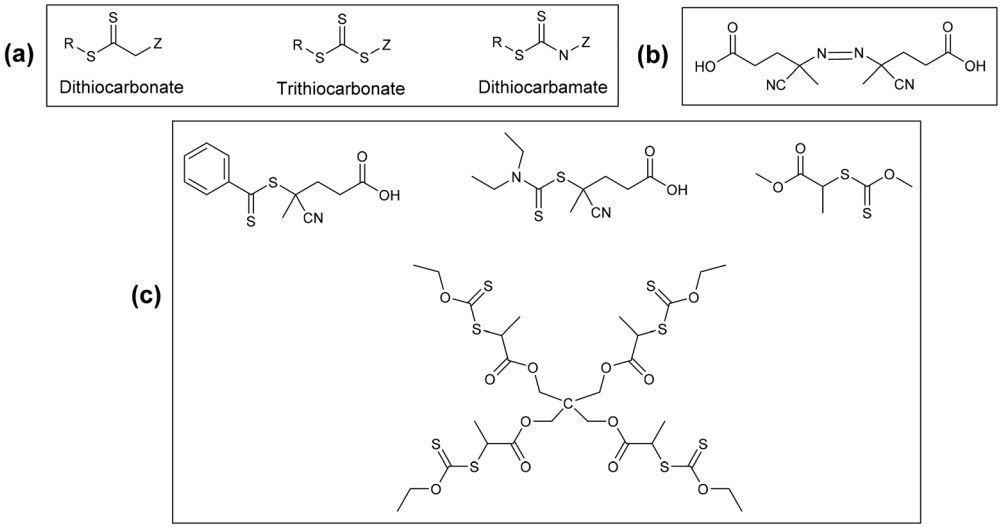

Fig. 8 (a) Generalized chemical structures of commonly used chain transfer agents (CTA) in RAFT,[47] (b) an example of a radical initiator, 4,4′-Azobis (4-cyanovaleric acid), and (c) representative examples of CTAs for glycopolymer synthesis *via* RAFT.[53,54]

influence of glycopolymer graft lengths on lectin–glycan binding.[49]

Reversible addition–fragmentation chain-transfer polymerization (RAFT). RAFT is another efficient CRP method which was first reported in 1998 by Tang *et al.* at Commonwealth Scientific and Industrial Research Organization (CSIRO).[51] Unlike ATRP, RAFT does not require a transition metal to mediate the polymerization. RAFT requires a chain transfer agent (CTA) (Fig. 8a and c) that enables reversible deactivation of propagating radicals by degeneration of chain transfer. RAFT also requires a radical initiator such as AIBN. Commonly used CTAs of RAFT include dithioesters, trithiocarbonates, xanthates, and dithiocarbamates, shown in Fig. 8c.[52]

Well-defined poly(acryloyl glucosamine) (PAGA) with a low PDI ($1.1 \leq \text{PDI} \leq 1.3$) was prepared by RAFT in aqueous media without hydroxyl protection on the glycomonomers (Fig. 9).[54] The PAGA was then extended with a second monomer, *N*-isopropyl acrylamide (NIPAM), to form a block copolymer, PAGA-*b*-PNIPAM, as shown in Fig. 9a.[54] Additionally, as shown in Fig. 9b, a 3-armed glycopolymer was also synthesized with the same monomer using a trifunctional RAFT CTA.[54]

RAFT can also be used to perform the graft-from copolymerization (surface initiated polymerization) method so that the polymer can modify a target surface. Herein, the graft-from copolymerization means that a monomer can be polymerized from the initiating sites on the backbone polymer which results in a high density of polymer grafts on the backbone polymer (or a surface).[55] By using a similar surface modification and following RAFT, Fig. 10 illustrates the graft-from copolymerization of the glycopolymer, poly(acryloyl glucosamine) (PAGA), on a CTA integrated silicon wafer using RAFT polymerization *via* a Z-group approach.[56]

Nitroxide-mediated polymerization (NMP). NMP employs nitroxides or their associated alkylated derivatives, such as alkoxyamines as an initiator.[57] The use of NMP for polymerization of glycopolymers is not common, because other modern CRP techniques, such as ATRP and RAFT, are much more convenient to conduct and well-studied in general. In this section, we discussed a few examples of glycopolymer preparation *via* NMP.

In 1998, Fukuda *et al.* synthesized the first glycopolymer *via* NMP from protected and unprotected monomers, to form poly (*N*-(*p*-vinylbenzyl)-[*O*-β-D-galactopyranosyl-(1 → 4)]-D-gluconamide), shown in Fig. 11.[58] The acetyl protected glycomonomer displayed higher control during polymerization than an unprotected glycomonomer.

Additionally, a well-defined glycopolymer, poly(2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactosyloxy)ethyl methacrylate-*co*-styrene) (poly(AcGalEMA-*co*-S)), was successfully prepared by NMP using *N*-*tert*-butyl-*N*-(1-diethylphosphono-2,2-dimethylpropyl) (BlocBuilder™) as the NMP agent (Fig. 12).[59] The introduction of a hydrophobic styrene block on the glycopolymer produced an amphiphilic polymer which could undergo self-assembly into micelles.[59] It is also proven that the polymerization conditions and deacetylation (deprotection) of poly(AcGalEMA-*co*-S) did not have a negative effect on the biofunctionality of the copolymer when it was tested with a lectin, peanut agglutinin (PNA).[59]

2.3. Glycopolymer synthesis *via* post-polymerization modification

Besides direct polymerization of carbohydrate containing monomers, glycopolymers have also been synthesized through a post-polymerization modification technique.[60–66] The post-polymerization modification can convert a polymer to possess a broad range of side-chain functionalities *via* modification reactions.[67] In particular, the post-polymerization modification is an efficient method to prepare functional polymers that cannot be directly polymerized from monomers due to poor functional group tolerance of the polymerization.

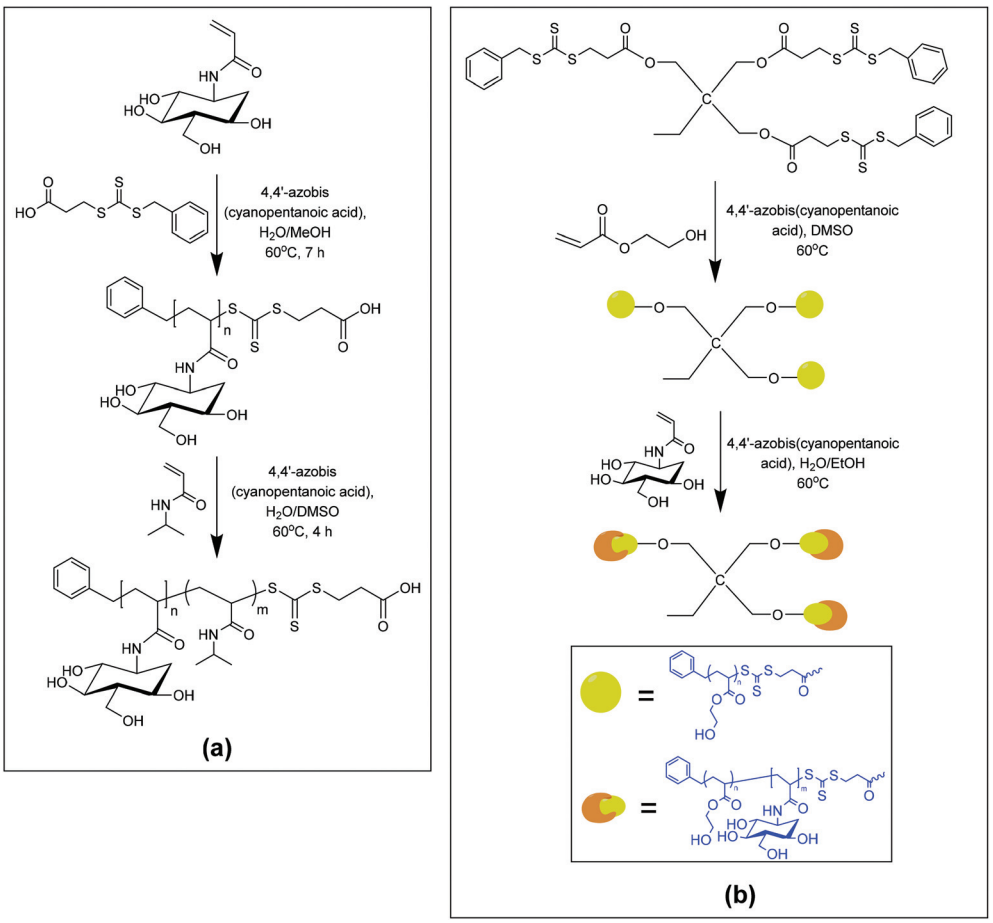

Fig. 9 RAFT polymerizations of (a) a linear glycopolymer PAGA-*b*-PNIPAM and (b) a non-linear 3-armed glycopolymer.[54]

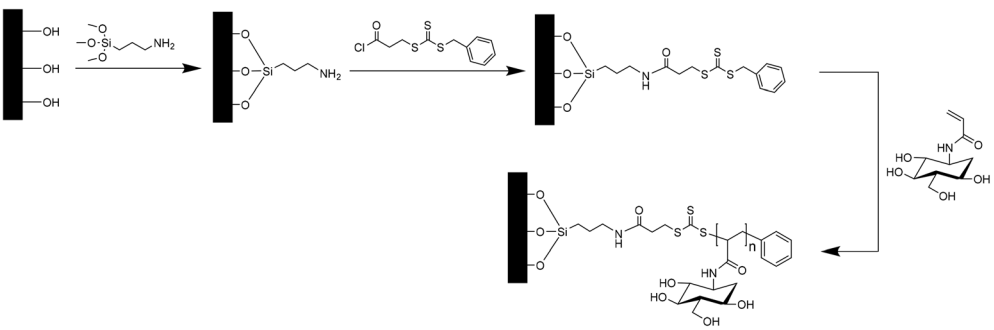

Fig. 10 Synthesis of poly(acryloyl glucosamine) (PAGA) grafts on a silicon wafer surface using RAFT *via* the Z-group approach.[54]

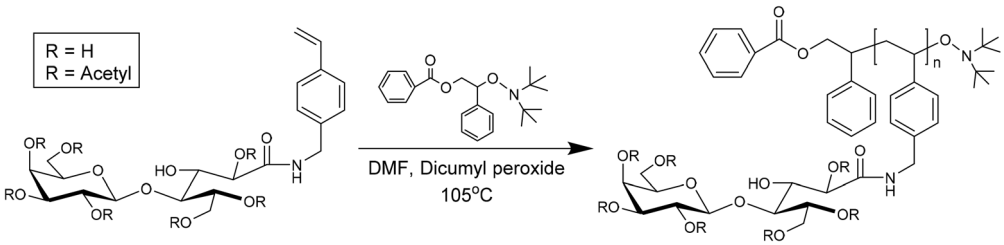

Fig. 11 Synthesis of protected (and unprotected) poly(*N*-(*p*-vinylbenzyl)-[*O*-β-D-galactopyranosyl-(1 → 4)]-D-gluconamide) *via* NMP.[58]

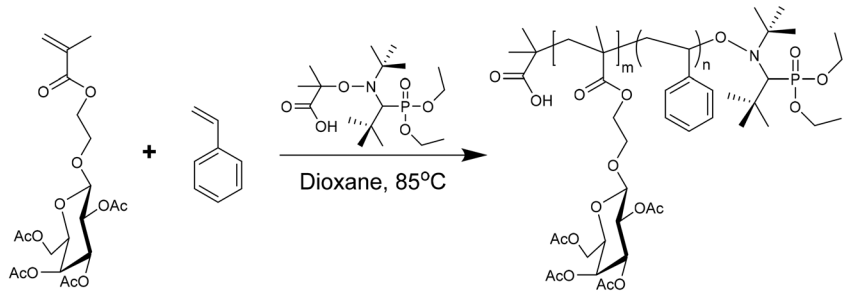

Fig. 12 Synthesis of a glycopolymer poly(2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactosyloxy)ethyl methacrylate-*co*-styrene) (poly(AcGalEMA-*co*-S)) *via* NMP.[59]

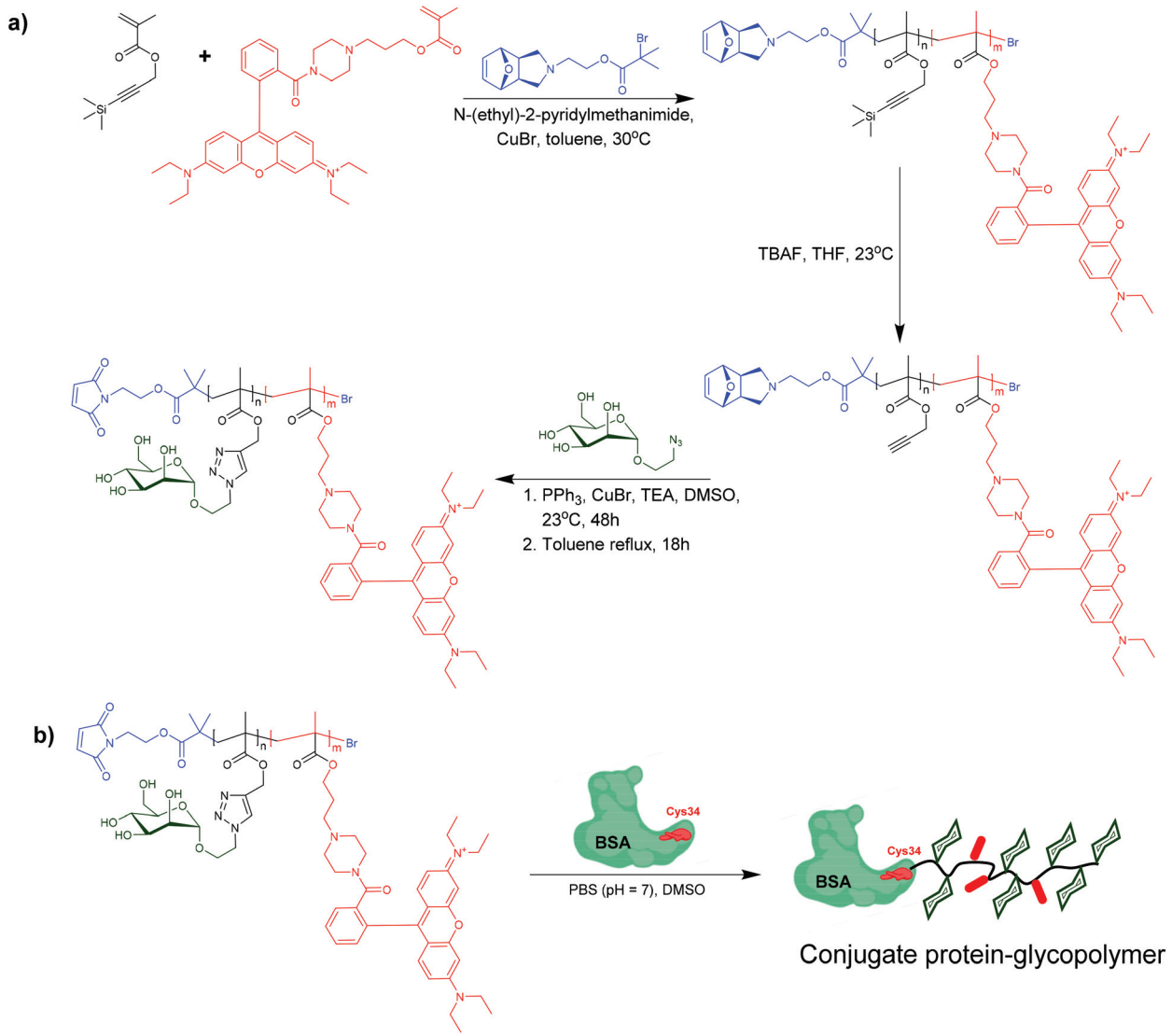

Fig. 13 Synthesis of (a) an α-mannopyranoside-containing glycopolymer *via* post-polymerization modification using copper catalyzed click chemistry, and (b) facile and selective formation of protein–glycopolymer conjugates through maleimide and cys34 protein of BSA.[60]

Post-polymerization modification through azide–alkyne "click chemistry". An α-mannopyranoside-containing glycopolymer was prepared by the post-polymerization modification approach *via* copper-catalyzed azide–alkyne cycloaddition (Fig. 13a).[60] The maleimide-terminated glycopolymer is selectively bound to the cysteine (Cys34) protein of bovine serum albumin (BSA) (Fig. 13b). The conjugate of protein–glycopolymer offers an easy pathway of defined biological molecules

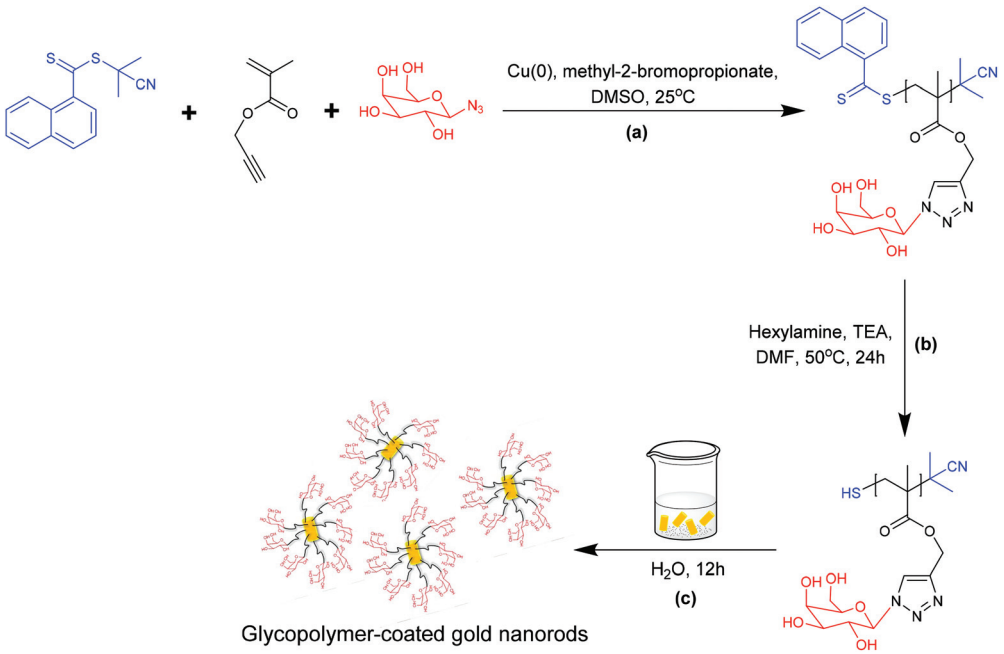

Fig. 14 (a) One pot reaction combining RAFT polymerization and "click chemistry", (b) post-polymerization reduction to form thiol-terminated glycopolymer and (c) glycopolymer-coated gold nanorods.[62]

which is promising in the development of a new generation of therapeutic agents.[60]

Chen and coworkers reported a one pot synthesis, which involves RAFT polymerization and "click reaction" simultaneously, of a glycopolymer (Fig. 14a). The glycopolymer was then reduced to form a thiol-terminated glycopolymer (Fig. 14b) which was subsequently grafted on the surface of gold nanorods by taking advantage of Au–S interactions (Fig. 14c).[62] The glycopolymer-coated gold nanorods showed robust and selective recognition with lectin. There was no evidence that the triazole moiety caused a negative impact on the lectin-binding property.[62]

Glycopolymers can also be prepared by ring opening of the glycidyl functional group followed by copper-catalyzed azide–alkyne cycloaddition. Jiang *et al.* successfully synthesized various glucose pendant containing polymers which self-assembled in an aqueous solution with polystyrene (PS) as the inert hydrophobic core and a glycopolymer (PR) as the shell.[63] The synthesis consisted of multi-step reactions (Fig. 15a). The first step was RAFT to create an amphiphilic block copolymer, polystyrene-*block*-poly(glycidyl methacrylate), followed by its reduction to form a thiol chain terminal for attachment of fluorescein isothiocyanate (FITC). An azide-containing glycopolymer was prepared by simultaneous ring opening of the glycidyl group and azide substitution. The azide of the synthesized polymer underwent copper-catalyzed azide–alkyne cycloaddition with alkynated-glucose molecules to form the desired block copolymer (Fig. 15a).[63] In an aqueous solution, the glycopolymer self-assembled with a diameter of 34–36 nm as shown in Fig. 15b. The self-assembled glycopolymers were observed at macrophages both *in vitro* and *in vivo*. Based upon this behavior, the new glycopolymer is expected to be used in targeting therapeutic applications.[63]

Post-polymerization modification through thiol–ene "click chemistry". In addition to the frequently used "click chemistry", copper-catalyzed azide–alkyne cycloaddition and thiol–ene reactions have also been widely reported as a post-polymerization modification to prepare functional glycopolymers.[61,65,66] The thiol–ene reaction is a highly efficient reaction and has high tolerance against various functional groups. Moreover, the coupling reaction occurs under metal-free conditions, which is an attractive feature for biomedical applications.[68] Finally, the sulfide linkage (thioether linkage, R–S–R′) in a protein-sulfide-oligosaccharide has been reported to have high flexibility.[69]

Stenzel *et al.* have synthesized a block copolymer containing a glucose pendant *via* thiol–ene click chemistry (Fig. 16).[61] The polymer showed a unique thermo-responsive behavior with a lower critical solution temperature (LCST) of 29 °C.[61] This route opens a new non-toxic (metal-free) pathway of developing a sophisticated glycosylated macromolecular architecture which can be beneficial for advancing targeted drug delivery systems.[61]

Microarray technology plays an important role in inspecting carbohydrate–protein interactions due to the large number of glucose-pendants generated with variability in the size and composition.[70,71] Microarrays using an inject fabrication technique from well-defined glycopolymers achieved by post-polymerization modification of poly(allyl glycidyl ether) (PAGE) has been reported.[66] The fabrication technique produced a highly dense and broad range of glucose epitopes in a

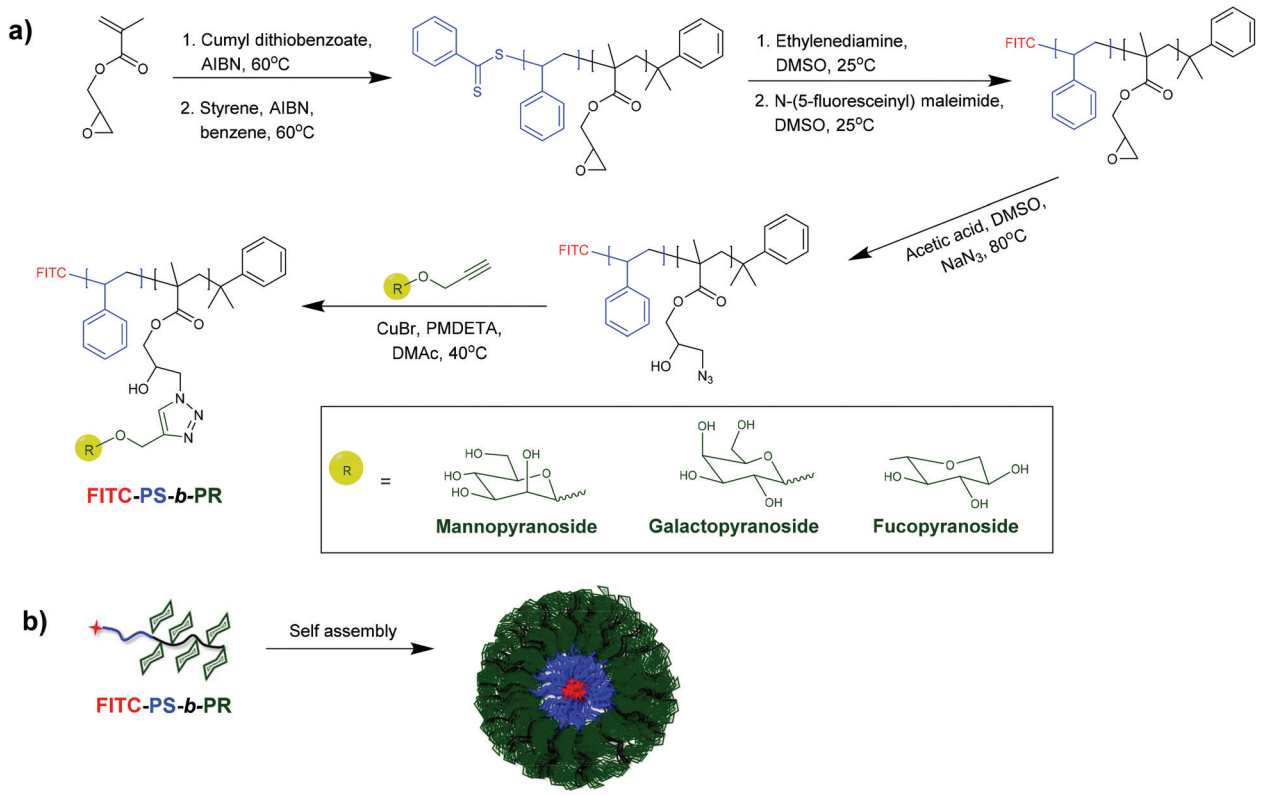

Fig. 15 (a) Synthesis of fluorescent-labelled amphiphilic glycopolymers, FITC-PS-*b*-PR, and (b) self-assembly of a glycopolymer containing a block copolymer in an aqueous solution.[63]

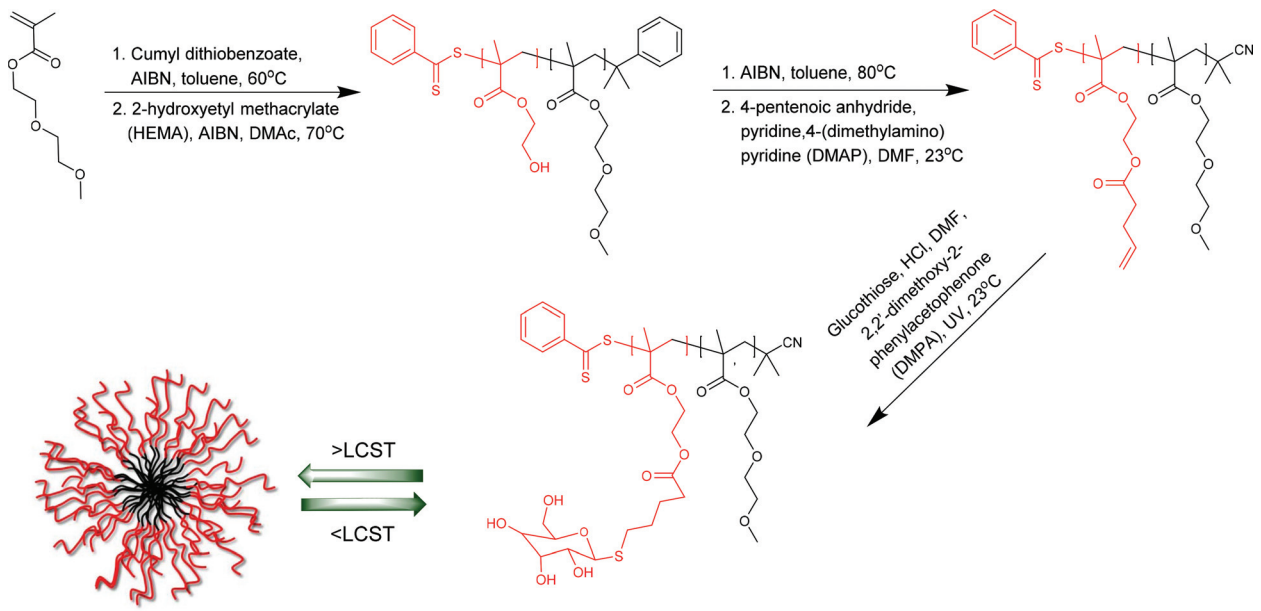

Fig. 16 Synthesis of poly(di(ethylene glycol) methyl ether methacrylate)-*block*-poly(2-hydroxyethyl methacrylate) and post-polymerization modification of the thermo-responsive glycopolymer *via* thiol–ene "click chemistry".[61]

rapid manner on a single glass chip.[66] In this work, PAGE was used as a main structure which is suitable for various post-polymerization reactions through pendant alkene moieties. Additionally, the poly(ethylene glycol) backbone of PAGE shows high hydrophilicity that enables the introduction of highly dense glucose-pendants on a polymer backbone.[66,72,73]

A surface modification of the glass surface (substrate) with isocyanate was performed to allow covalent immobilization of

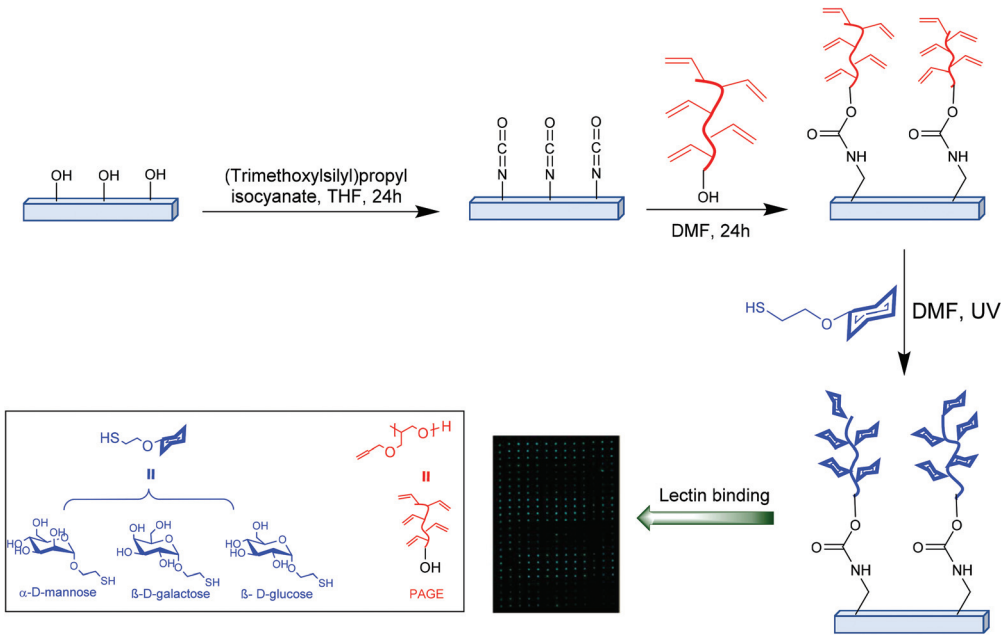

Fig. 17 Preparation of a glycopolymer-microarray utilizing thiol–ene "click reaction" for high-throughput analysis of carbohydrate–lectin binding properties.[66] Reproduced with permission from ref. 66, copyright [2017], [American Chemical Society].

PAGE on the substrate. The surface was further modified by the thiol–ene reaction with thiolated-glucose molecules, such as α-D-mannose, β-D-galactose, and β-D-glucose (Fig. 17).[66] This microarray was used for investigating selective glucose binding to lectin using the fluorescence technique. The high-throughput analysis is essential for elaboration of cell-surface interactions, adhesion mechanisms, and multivalent inhibitor development.[66]

Another example of thiol–ene "click chemistry" in glycopolymer synthesis has been reported by Maynard *et al.*[65] A copolymer, poly(5,6-benzo-2-methylene-1,3-dioxepane-*co*-but-3-enyl methacrylate) [poly(BMDO-*co*-bMA)], was first prepared by RAFT with a trithiocarbonate CTA. The protected thiolated-trehalose underwent the thiol–ene reaction to yield poly(BMDO-*co*-bMA) followed by deprotection of the side chain of the glycopolymer, poly(BMDO-*co*-bMA-trehalose) (Fig. 18).[65]

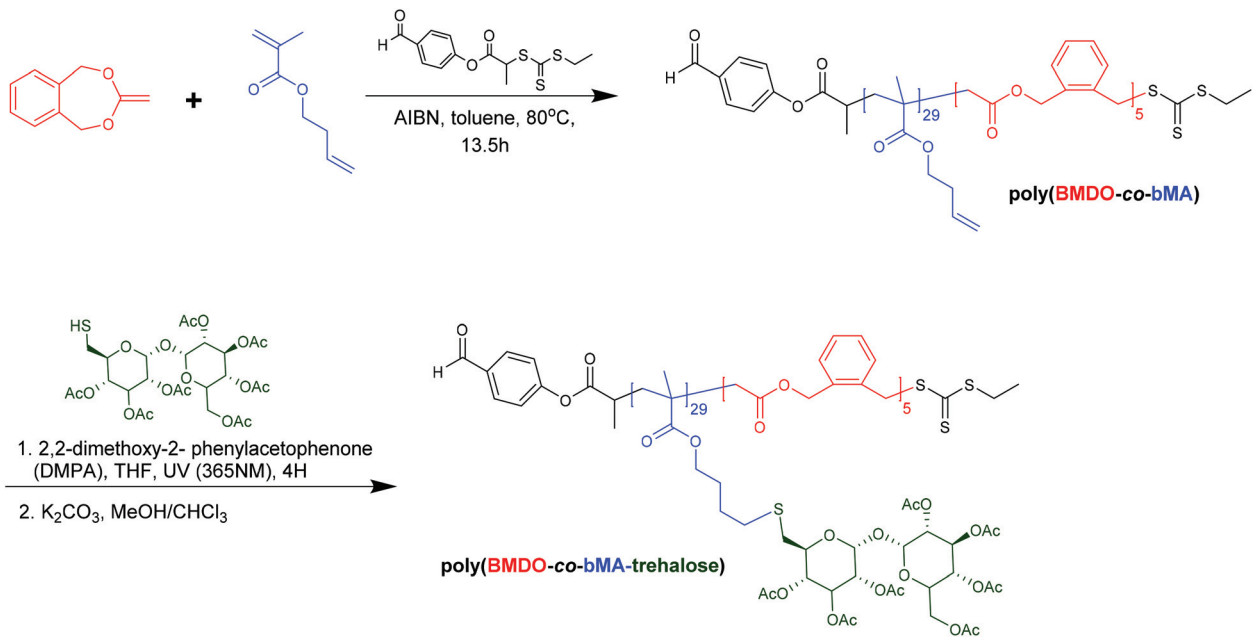

Fig. 18 Preparation of a degradable trehalose-side chain glycopolymer, poly(BMDO-*co*-bMA-trehalose), *via* RAFT polymerization followed by thiol–ene "click" reaction.

3. Applications of glycopolymers

3.1. Fundamental study of carbohydrate–lectin interactions

The carbohydrate–lectin interaction is the most studied field of application for synthetic glycopolymers. By definition, lectins are proteins that bind to carbohydrates with high affinity and specificity.[74] Because glycopolymers are synthetic polymers that contain carbohydrate pendants, they are known to have the ability to mimic natural polysaccharides during biological recognition events[75–80] due to their binding affinity to lectins (Fig. 19).

Concanavalin A or Con A is the most widely used plant lectin found in *Canavalia ensiformis* and is commonly known as jack bean. Con A has been used to study multivalent binding of glycopolymers that contain mannose and glucose pendants.[61] Another lectin from the plant legume family is PNA which is extracted from *Arachis hypogaea*. PNA specifically binds to galactose pendants on glycopolymers.[61] Additionally, WGA from *Triticum vulgare* is also commonly used to study lectin binding to glycopolymers. WGA binds selectively to *N*-acetylglucosamine and *N*-acetylneuraminic acid (a sialic acid).[31] Unlike plant lectins, animal lectins are more complex structurally, and they can be generally classified into five main types: C-type, I-type, P-type, S-type (galectins) lectins, and pentraxins according to their structural features.[31] Animal lectins are crucial to biological functions such as recognition of molecules within the immune system, regulation of cellular growth, cell–cell interactions, and extracellular molecular bridging.[32] Because of the selective binding affinity of Con A to glucose molecules, Con A is very crucial for the investigation of carbohydrate–protein interactions that occur on the cell surface.[32,61]

Unique interactions (lock-and-key metaphors) between a monosaccharide and lectin are normally weak. The simplest strategy to enhance overall binding strength is to increase the number of binding sites.[81] Because glycopolymers contain many carbohydrate pendants, the study of lectin binding affinity to glycopolymers is an important field to research for further biological applications. Kiessling and co-workers reported a 7-oxanorbornene pendant which consists of linear glycopolymers that are prepared by ring opening metathesis polymerization (ROMP). The glycopolymer was investigated by utilizing agglutination inhibition assay with regard to its multivalent effects on Con A binding efficiency.[82] In this report, it was revealed that the density of saccharides is an important control factor for carbohydrate–lectin interactions. By decreasing the density of carbohydrate pendants on an aliphatic backbone, the binding activity of a glycopolymer towards bulky Con A increased due to less steric hindrance (Fig. 20).[83]

Generally, glycopolymers enable enhanced binding activity compared to a single glucose ligand due to an increase in available binding sites. Therefore, optimum distance-dependent binding can be achieved if the distance between two carbohydrates is equivalent to the distance between two binding sites on a lectin.[34] For the optimum distance-dependent binding, the glycopolymer must be flexible. If the glycopolymer is stiff, the exact binding does not occur.[34] Other parameters of efficient lectin–glycopolymer binding are molecular weights and spacers between the glucose pendant and the polymer backbone. Kiessling *et al.* discovered that an increase in the molecular weight of the glycopolymer leads to an increase in the binding capability to Con A.[84] Additionally, flexible spacers between glucose pendants and the polymer backbone enhance multivalent binding because the distance between binding sites can be adequately adjusted for an optimal binding.[85]

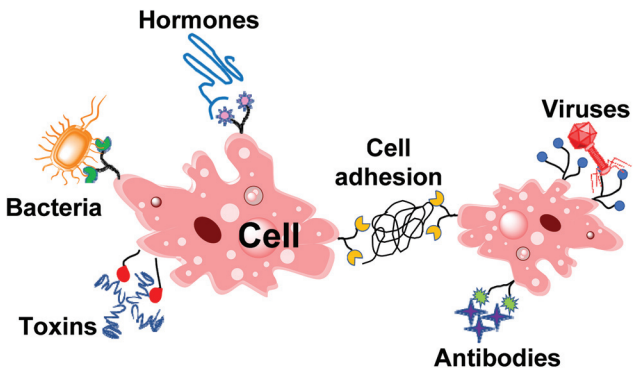

Fig. 19 Illustration of various biological recognition processes that use lectin's high and specific affinity for carbohydrates; examples include affinities in bacteria, toxins, hormones, antibodies, viruses, and cell–cell adhesion.[75–80] The figure is imaginary to describe multiple affinities in a single illustration, not real.

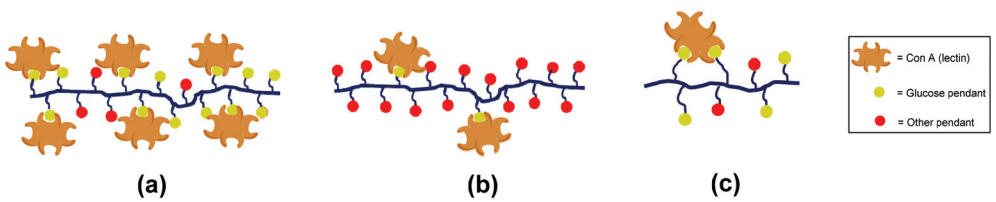

Fig. 20 Illustration of Con A binding on multivalent ligands. (a) High density carbohydrate pendants shown in the high density glycopolymer which allows many receptors to attach to a single molecule. However, the attachment is limited by the steric hindrance which results in unused molecules. (b) Low density carbohydrate pendants; the low density glycopolymer allows fewer total receptors per molecule. The space between carbohydrates on the glycopolymer is too large to bind efficiently.[83] (c) Optimum binding activity occurs when the distance between two glucose pendants is equivalent to the distance between two binding sites of a lectin.[34]

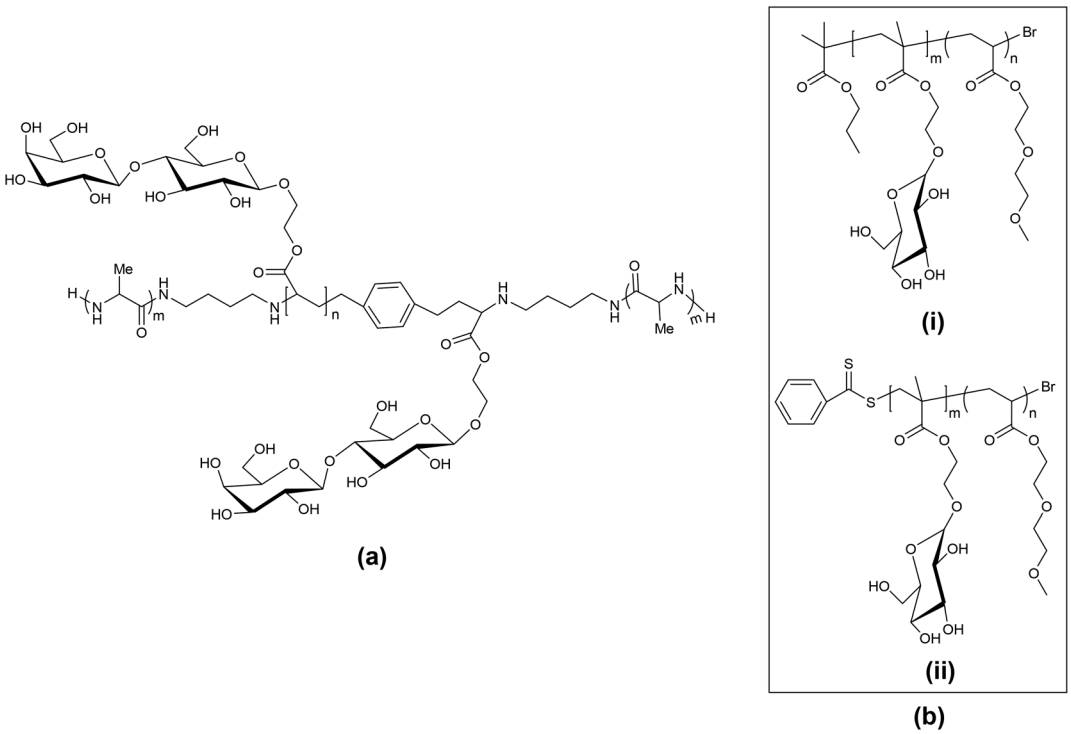

Fig. 21 (a) Poly[(L-alanine)-*b*-poly(2-acryloyloxyethyllactoside)-*b*-poly(L-alanine)] which exhibits a micelle-like structure in solution,[88] and (b) poly [(2-glucosyloxyethyl methacrylate)-*b*-poly(diethyleneglycolmethacrylate)], which exhibits a vesicle-like structure in solution. These glycopolymers are prepared by ATRP and RAFT.[89]

In addition to the linear homoglycopolymer, more complex architectures of glycopolymers have been reported. Fig. 21 shows an example of an amphiphilic block copolymer possessing a hydrophilic glycopolymer block and a hydrophobic polymer block. The amphiphilic feature allows for structural diversities such as micelles,[59,86–88] vesicles,[86,87] helices, and worm-like aggregates.[87] The non-linear polymer architecture results in an increase of the surface area of glycopolymers, thus enhancing the lectin–glycopolymer binding probability.[32]

Glycopolymers have also been integrated with metallic and organic nanoparticles prior to the glycopolymer–lectin interaction. Chen *et al.* reported two synthetic approaches for producing glucose modified nanoparticles.[90] Fig. 22a shows the introduction of monosaccharides on a nanoparticle *via* click-chemistry. The second example is surface initiated ATRP, conducted to have glycopolymers on a nanoparticle (Fig. 22b).[90] Both modified nanoparticles show efficient recognition to Con A lectin (Fig. 22c).[90]

3.2. Carbohydrate to cell, bacteria, and virus interactions

Based on the strong and specific affinity of carbohydrates to lectins, the interactions of glycopolymers with lectin containing cells and microorganisms (bacteria and viruses) have been studied. The study of the glycopolymer interactions has led to a precise understanding of the infection mechanisms of microorganisms to the host. The first stage of infection is physical attachment of microorganisms on a cell.[34] For example, the influenza virus attaches to the surface of a bronchial epithelial cell as illustrated in Fig. 23.[76,91] The influenza virus membrane contains a highly dense (2–4 per 100 nm^2) glycoprotein, *i.e.* hemagglutinin.[76,92] Its counterpart, the bronchial epithelial cell membrane, consists of densely (50–200 nm^{-2}) packed glycoprotein with an *N*-acetylneuraminic acid (sialic acid) terminal sugar. Multiple attachments of hemagglutinin-sialic acid initiate the infection of cells.[76] Therefore, precise control of microorganism–human cell interactions can be important in decreasing the susceptibility of human cells to infectious diseases.

Hardy *et al.* reported that glycopolymer functionalized spider silk mimics enhance cell adhesion.[77] Alkyne-capped-poly(-6-*O*-methacryloyl-D-galactopyranose) (PMAGal) was synthesized *via* ATRP (Fig. 24a).[77] The engineered spider silk (eADF4(C16)), in Fig. 24b, was modified with alkyne-capped-PMAGal at various degrees of polymerization (degree of polymerization = 31, 64, and 97). A fibroblast cell line (M-MSV-BALB/3T3, mouse embryo fibroblast) was used to study cell adhesion. Based on this study, functionalization of spider silk substrates with PMAGal enhances the attachment of fibroblasts on the substrates (cell surface area of 310–390 μm^2) compared to unmodified spider silk substrates (cell surface area of 210 μm^2) (Fig. 24c).[77]

Lees *et al.* reported that the interaction between a virus and the glycoprotein of cells can be suppressed by three approaches: (i) utilizing a ligand to compete with sialic acid on the cell wall so that the hemagglutinin binding sites on the virion are sterically blocked, (ii) modification of sialic acid

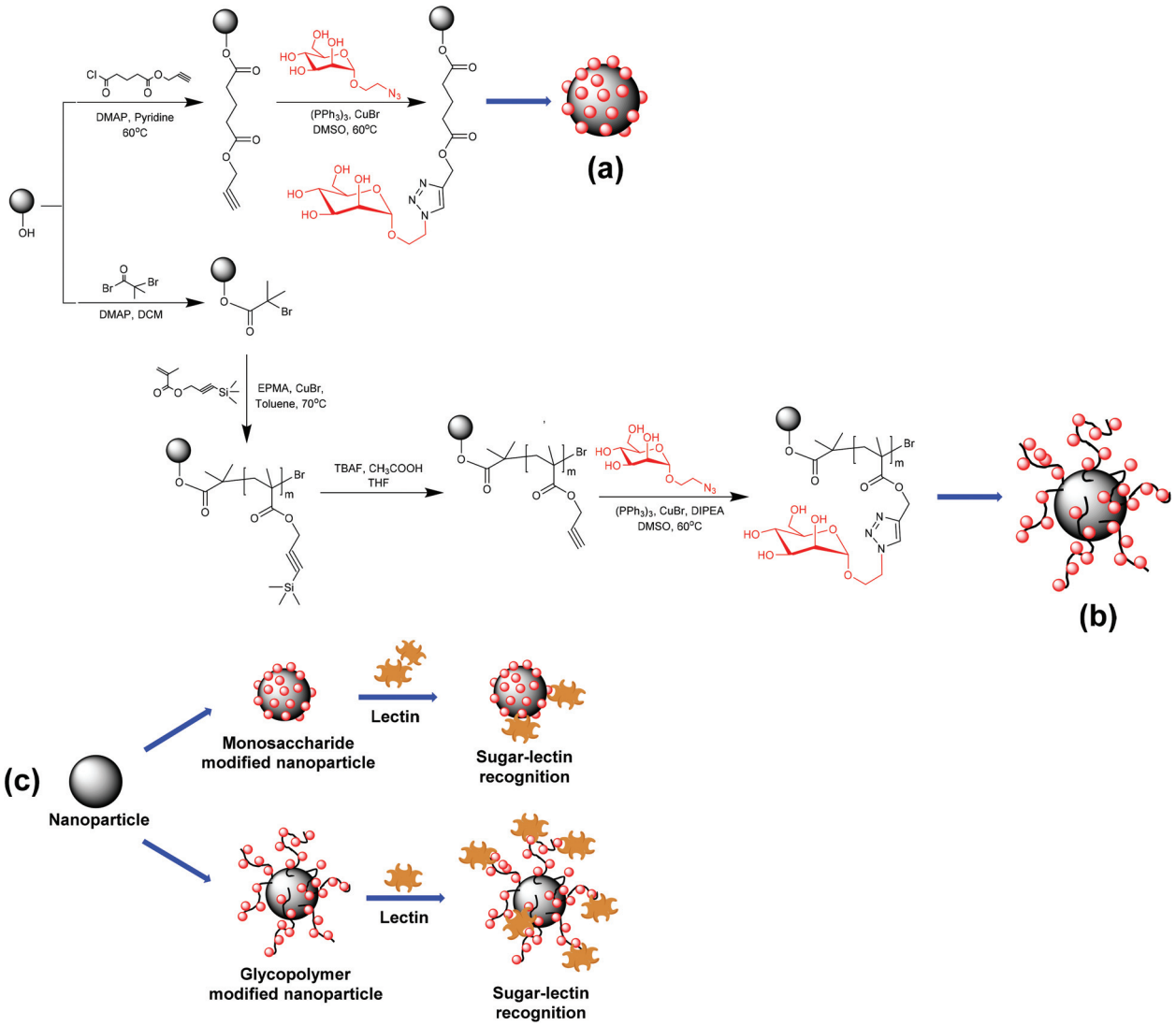

Fig. 22 (a) A monosaccharide-modified nanoparticle *via* click-chemistry, (b) a glycopolymer-modified nanoparticle *via* ATRP, and (c) sugar-lectin recognition on the modified nanoparticles.[90]

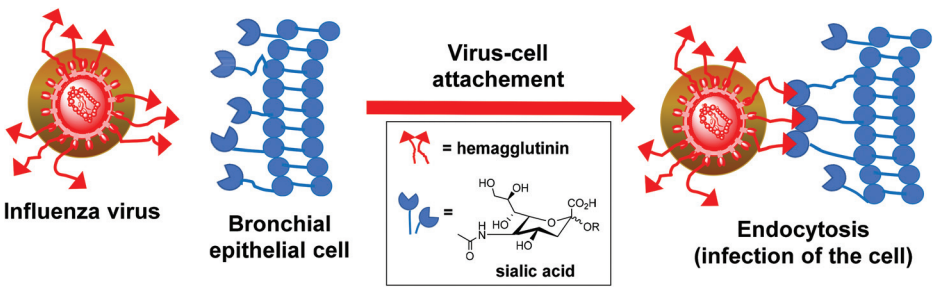

Fig. 23 Attachment of influenza virus to a bronchial epithelial cell *via* the interaction of hemagglutinin of the virus with sialic acid on the cell;[76,91] the described bronchial epithelial cell is a simplified figure showing a part of the outer surface of the cell.

groups so that the cell binding sites are not accessible for the hemagglutinin of the virus, and (iii) blocking hemagglutinin of the virus which only allows them to access the sialic acid on a cell.[76] However, blocking all sialic acid moieties of the cells is impractical due to the possibility of interference with normal cell functions. In this work, a copolymer, poly(acrylamide-*co*-*O*-glycoside) (Fig. 25a), was investigated to understand the function of hemagglutinin inhibition through cell

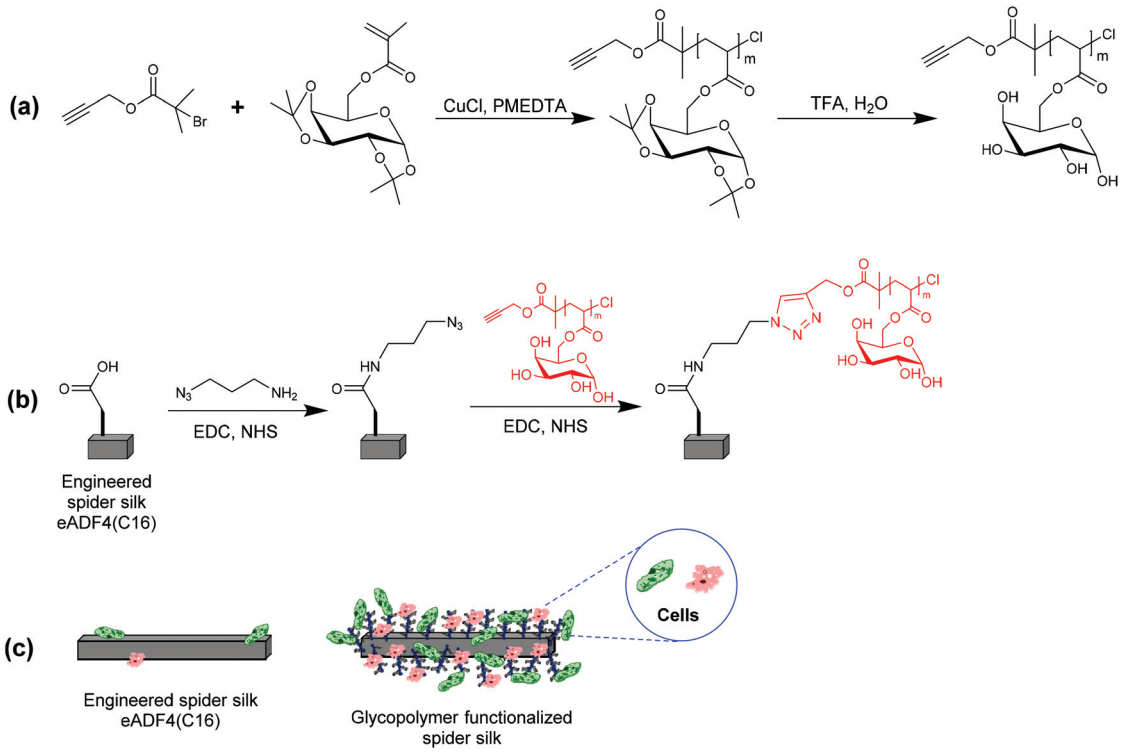

Fig. 24 (a) Synthesis of alkyne-capped PMAGal *via* ATRP, (b) PMAGal surface-functionalized spider silk eADF4(C16) *via* click chemistry, and (c) cell attachment comparison between spider silk (control) and glycopolymer-modified spider silk.[77]

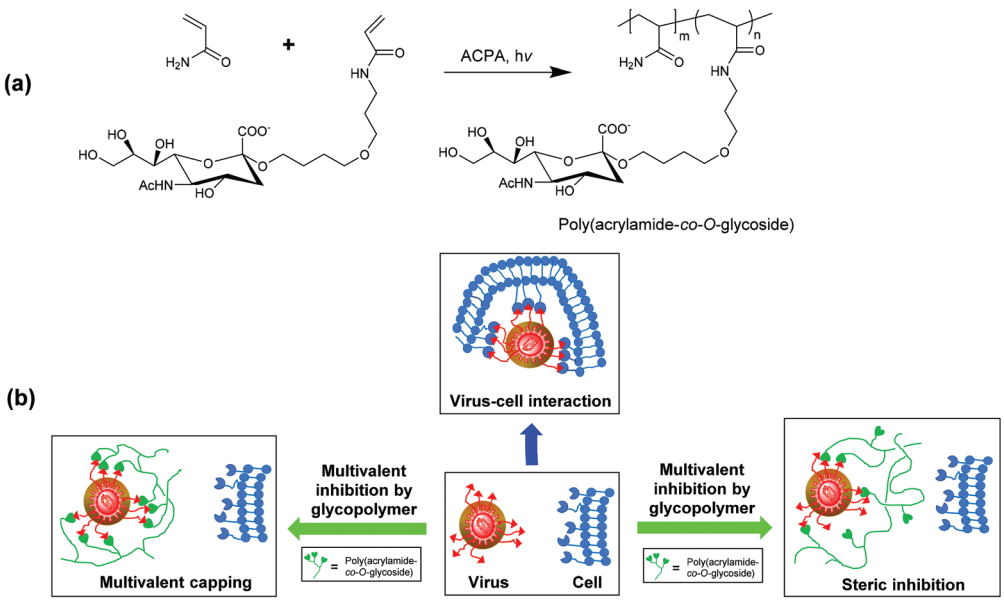

Fig. 25 (a) Synthesis of poly(acrylamide-*co*-*O*-glycoside), and (b) multivalent inhibition of hemagglutinin of virion by the glycopolymer.[76]

binding site blocking *via* capping and/or steric inhibition (Fig. 25b).[76]

Glycopolymers can be an anti-bacterial-adhesion agent. Similar to that of a viral infection, bacterial adhesion to a cell is the initial stage of a bacterial infection. For instance, an overgrown population of *Escherichia coli* (*E. coli*) causes many infections such as urinary tract and bladder infections, meningitis, and bowel diseases which often require antibiotic treatment. *E. coli* carries hair-like organelles, type 1 piliated fimbriae, on its cell wall.[93] The type 1 pili contain a fibrillar short-tip structure bearing FimG and FimH adhesion which is responsible for binding to mannose units of oligosaccharides.[93] A *n*-heptyl

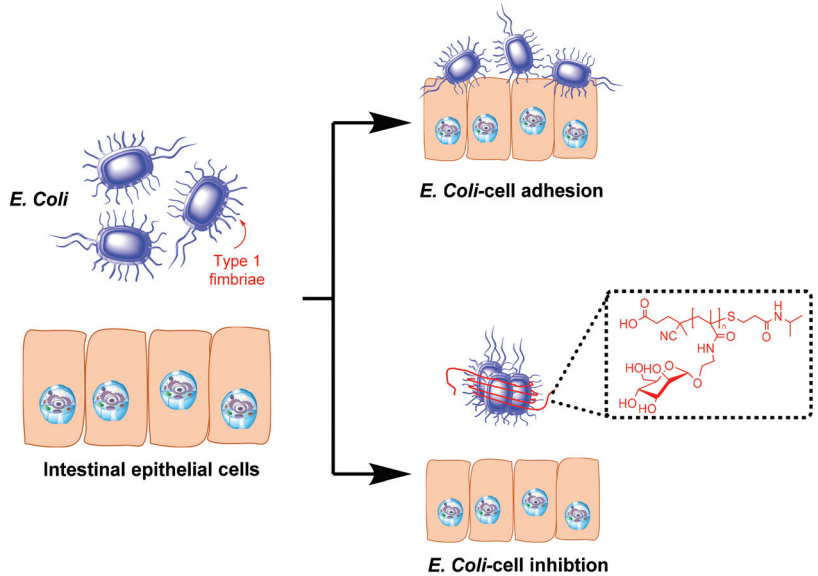

Fig. 26 Principle of an *n*-heptyl α-D-mannose (HM)-based glycopolymer as an anti-bacterial-adhesion agent against *E. coli* bacteria.[79]

α-D-mannose (HM)-based glycopolymer was studied as a FimH adhesion inhibitor to reduce a virulence factor of *E. coli* (Fig. 26).[79] Based on an *in vitro* study, the HM-based glycopolymer showed inhibition of *E. coli* adhesion to intestinal epithelial cells at a low density of mannose in the glycopolymer.[79]

In a relatively new study, glycopolymers have also been reported to play a crucial role in immunology.[63,94] In particular, cancer immunotherapy uses the immune system to eliminate cancer cells. This process is designed to allow immune cells attacking target cancer cells specifically.[95,96] Jiang *et al.* developed an artificial glycocalyx based on self-assembled glyco-nanoparticles (glyco-NPs) which is discussed in Fig. 15.[63] Herein, glycocalyx is a highly dense carbohydrate-coating on the surface of cells.[97,98] The glyco-NPs were able to reverse the immunosuppressive phenotype which impairs the antitumor immune response.[63] Then, the enhanced immune-function of the macrophage can enable tumor immunotherapy. The reversal of the immunosuppressive phenotype is controlled by macrophage polarization, which is caused by the synthesized glycopolymer.[63,99]

As an additional example of anti-cancer immunotherapy, two synthetic glycopolymers, poly(*N*-methacryloylglucosamine) (pMAG) and poly(*N*-methacryloylmannosamine) (pMAM), have been used to create engineered tumor cell membranes as shown in Fig. 27.[94] In this example, tumor cell membranes were engineered with pMAG and pMAM. pMAG and pMAM function as binding sites allowing selective recognition to macrophage lectins, such as a mannose receptor (MR), and complement receptor three (CR3). The binding, between pMAG-MR and pMAM-CR3, triggers immune responses which lead to elimination of the tumor cells (Fig. 27).[94,100] These examples of glycopolymer application in immunology would offer strong potential in the development of immunotherapy for cancer treament.

3.3. Glycopolymer-based adhesives and materials

In previous sections, direct biological interactions of glycopolymers have been described to demonstrate various applications. Glycopolymers have also been recently reported to be utilized in tissue adhesives, sealants[101] and pressure sensitive adhesives which exhibit mechanically elastomeric behavior.[102,103] The advantages of glycopolymer-based adhesive materials include their abundance and sustainability of the natural resources.[103]

The glycopolymer, poly(6-methacryloyl-α-D-galactopyranose) (polyMG), has been introduced into collagen to form an interpenetrated polymer network hydrogel.[101] The hydrogel was prepared by photo-crosslinking of MG with poly(ethylene glycol) diacrylate in the presence of a photo-initiator, Irgacure-2959. Herein, the crosslinking and polymerization occur simultaneously with collagen (Fig. 28).[101] The hydrogel was used in corneal application due to its exceptional transparency which resembles that of human cornea.[101]

For the corneal substitute application, the mechanical properties of the hydrogel are very important. By introducing a small amount of MG to collagen (MG to collagen of 1 : 16, 1 : 8, 1 : 4, 1 : 2), the tensile strength of the hydrogel increased significantly from 520 kPa (pure collagen) to 530 kPa (ratio of 1 : 16), 540 kPa (ratio of 1 : 8), and 570 kPa (ratio of 1 : 4), and peaking at 720 kPa (ratio of 1 : 2).[101] However, at a ratio of 1 : 1 (MG to collagen), the tensile strength started decreasing presumably due to over-crosslinking between MG and collagen in the hydrogel.[101] Additionally, the modulus of the hydrogel containing MG also shows a similar trend to tensile strength, which was higher with the introduction of MG to the collagen (1200 kPa, 1230 kPa, and 1300 kPa for 1 : 8, 1 : 4, and 1 : 2 ratios of MG to collagen) compared with the pure collagen modulus at 700 kPa.[101] No significant change of

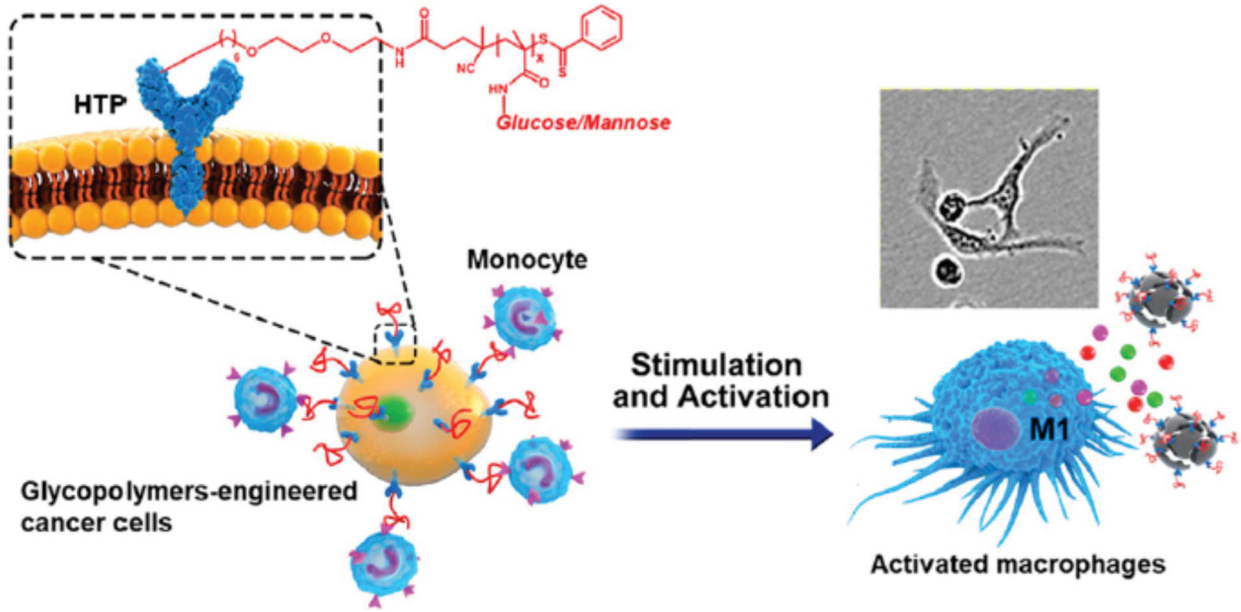

Fig. 27 Glycopolymers for cancer immunotherapy: glycopolymer-bound tumor cells enhance tumor cell recognition of macrophages to trigger immune response against tumor cells.[94] Reproduced with permission from ref. 94, copyright [2019], [American Chemical Society].

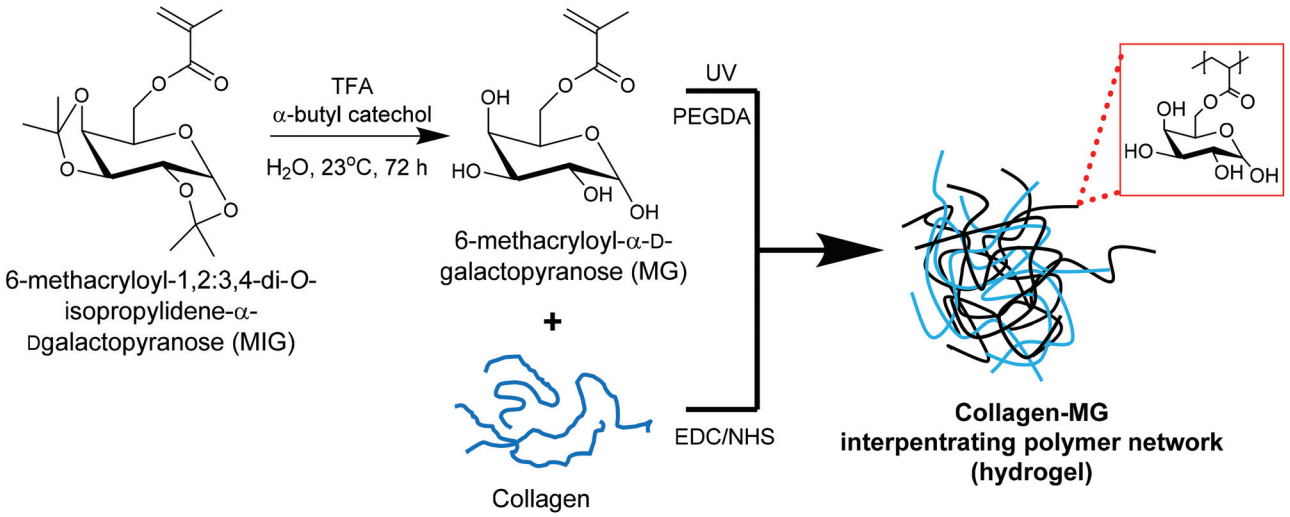

Fig. 28 Synthesis of a collagen-poly(6-methacryloyl-α-D-galactopyranose) (polyMG) interpenetrating polymer network for hydrogel application.[101]

elongation at break (±35–53%) was reported when MG was introduced to collagen which is close to the value of human corneal tissue, 45–75% elongation at break.[101,104] *In vitro* testing also revealed that the corneal epithelial cell count favored the glycopolymer hydrogel over the pure collagen hydrogel. In addition to the excellent optical and biological properties, the synthesized glycopolymer hydrogel prevents bacterial adhesion.[101]

In 2015, Pokeržnik and Krajnc used a glucose-based surfmer (surfactant and monomer) and butyl polyglucoside maleic acid ester (BGMAH) to prepare a poly(*n*-butyl acrylate) (PnBA) copolymer *via* emulsion polymerization. Due to the –COOH and C=C bonds in the chemical structure (Fig. 29a), BGMAH behaves as not only an anionic surfactant but also a vinyl monomer.[103] Various amounts of BGMAH in an acrylate-based pressure sensitive adhesive were investigated. Increasing the amount of BMGAH up to 25% did not change the elastic moduli (G') of the polymer. The higher percentage of BMGAH in the copolymer showed higher adhesion properties (Fig. 29b).[103]

An important design principle of thermoplastic elastomers is an ABA-type triblock copolymer that contains both soft/rubbery segment (B block) and glassy segment (A block) in ABA-type triblock copolymers. The two glassy segments A allow

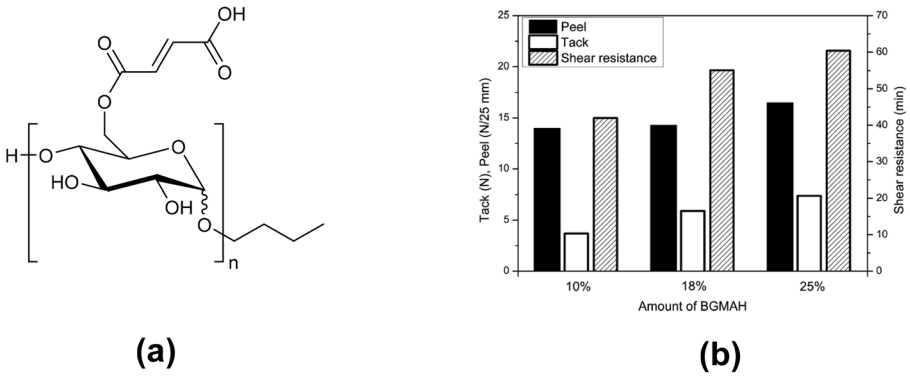

Fig. 29 (a) Butyl polyglucoside maleic acid ester (BGMAH) structure, and (b) the effect of the amount of BGMAH in the copolymer on peel and tack strength.[103] Reproduced with permission from ref. 103, copyright [2015], [Elsevier].

the entire polymer to resist the flow resulting in elastomeric properties.[105] To achieve this elastomeric behavior, Nasiri and Reineke developed an ABA-type triblock copolymer. In the new triblock copolymer, poly(glucose-6-acrylate-1,2,3,4-tetraacetate), PGATA is the outer glassy segment A, and PnBA is the soft/rubbery middle segment B (Fig. 30a).[102] The triblock copolymer, containing 14% GATA, was mixed with a 30% weight of tackifier. The mixture exhibited a 2.31 N m^{-2} peel adhesion strength[102] which is comparable to those of many commercial pressure sensitive adhesives such as duct tape, electrical tape, and paper tape (peel adhesion strength range of 1.9–4.2 N m^{-2}).[106]

Due to the importance of glycopolymers in biological processes, a study of glycopolymers as a bulk tissue adhesive is a new and attractive field to be explored. The glycopolymer is an excellent candidate as a tissue adhesive base material because

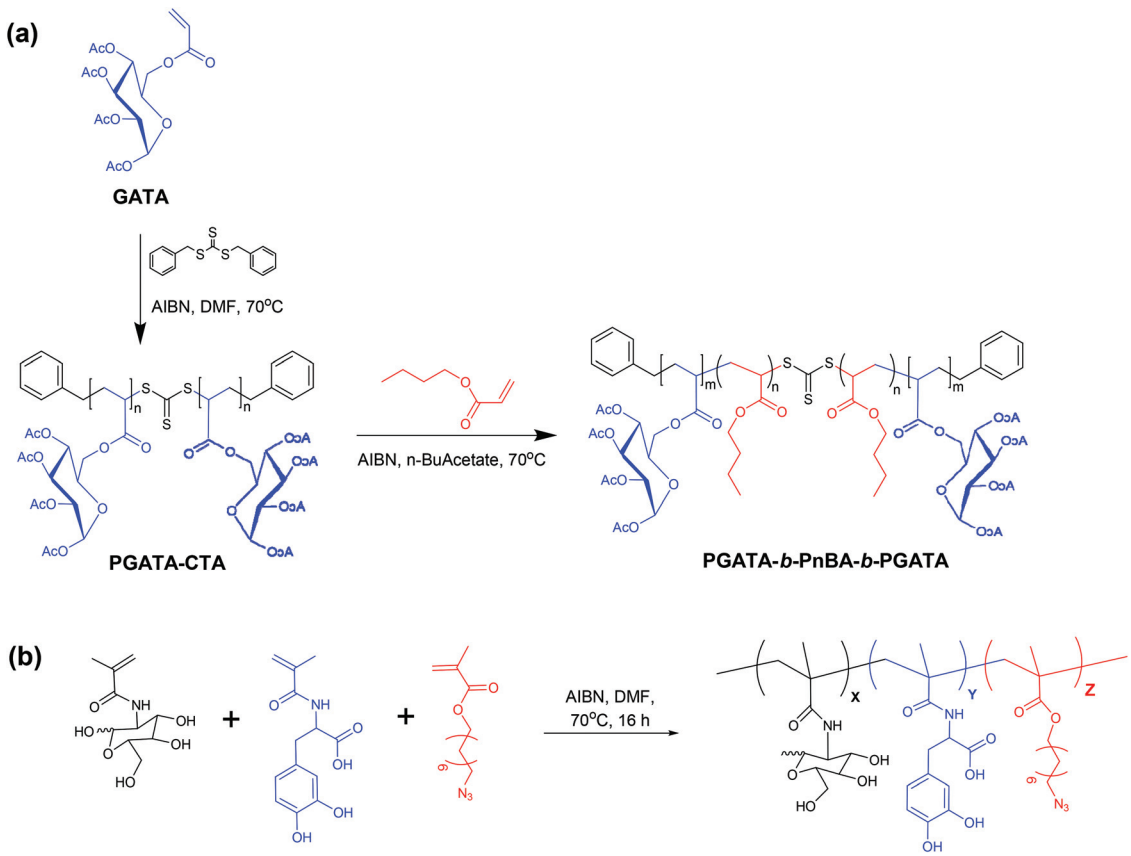

Fig. 30 (a) Synthesis of an ABA triblock copolymer, poly(GATA-*b*-nBA-*b*-GATA), *via* RAFT,[102] and (b) synthesis of a controllable terpolymer bioadhesive, poly(MG-*co*-MDOPA-*co*-AOM).[113]

of its high water compatibility and high flexibility as a hydrogel. During the adhesive bond formation, the polymer should be flexible for easy access to the substrate surface, meaning that the adhesive polymer should wet the substrate surface quickly. Therefore, high flexibility is essential for high quality adhesives.[107–111]

In addition, water compatibility in biomedical applications is always important because the human body contains 60% water and most of the human body is wet, except for the outer skin.[112] However, the glycopolymer has not been studied for tissue adhesive applications in spite of suitable properties as a tissue adhesive. An initial example of glycopolymer-based adhesive includes the spider silk protein ((eADF4(C16))) containing a glycopolymer. This new glycopolymer-based material shows improved cell (BALB/3T3 mouse fibroblasts) adhesion compared to non-glycopolymer samples.[77]

Recently, we have developed a glucosamine pendant containing glycopolymer-based tissue adhesive that shows strong and controllable bulk adhesion (not cell adhesion) between large biological surfaces. The new glycopolymer adhesive, poly (2-methacrylamido glucopyranose-*co*-*N*-methacryloyl-3,4-dihydroxyl-L-phenylalanine-*co*-8-azidooctyl methacrylate) [poly(MG-*co*-MDOPA-*co*-AOM)], was prepared by free radical polymerization of three methacrylate monomers (a hydrophilic glycopolymer segment, a mussel-inspired catechol segment, and a crosslinking azide segment) as shown in Fig. 30b.[113] Even without crosslinking, the new terpolymer adhesive demonstrated 20-fold higher adhesion strength (115 kPa) compared to a commercial rubber cement (5.8 kPa). The bulk adhesion properties of the terpolymer were enhanced by covalent bond forming crosslinking *via* strain-promoted azide–alkyne cycloaddition (SPAAC).[113]

3.4. Glycopolymer nanoparticles

Glucose-coated nanoparticles (glyco-nanoparticles, GNPs) integrate multivalent glycopolymers on a nano-size inorganic core, such as iron oxide,[114,115] silver,[116] and gold.[117,118] The GNPs have advanced molecular imaging technology significantly.[119] The most significant challenge is the synthesis of well-defined nanoparticles that possess high density of multifunctional polymers on their surfaces.[120–124] The well-defined glycopolymer nanoparticle is particularly important for a cell targeted treatment.

Gold nanoparticles have been used in many biomedical applications including fluorescent materials, cell imaging, and radiolabeling substrates due to their inertness, photo-stability, simplicity of preparation and facile conjugation with biological molecules.[117,118] However, there are still multiple challenges that involve the stability of nanoparticle materials under physiological conditions, poor permeability to various biological membranes, rapid renal elimination, and insufficient target cell recognition.[125] There has been a lot of effort made to overcome these limitations by designing and synthesizing new glycopolymers for nanoparticles. Glycopolymer functionalized gold nanoparticles, which form a core–shell architecture, have been reported by Yilmaz *et al.* The glycopolymer was prepared by RAFT polymerization of mannose-methacrylic acid (Fig. 31).[126]

GNPs has also been reported as a photoacoustic imaging agent and photothermal therapy agent of tumors.[127,128] These features are enabled by high-density functional groups on the nano-particle.[121] The glycopolymer for the GNPs was prepared by self-assembly of amphiphilic poly(lactose)-modified perylenediimide (PLAC-PDI) which was synthesized by ATRP (Fig. 32). The selective binding of lactose on GNPs to asialo-

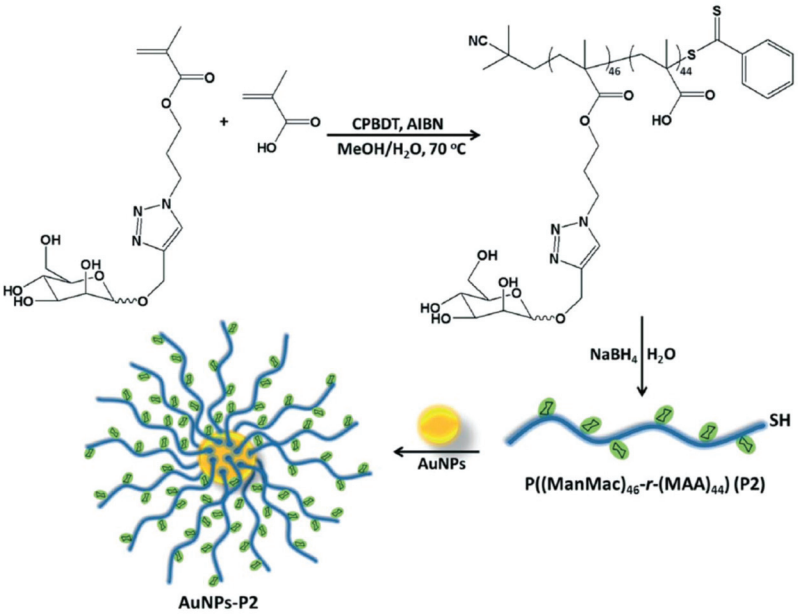

Fig. 31 Glycopolymer-functionalized gold nanoparticles (GNPs) for preparation of pH-sensitive anti-cancer agent delivery. Thiol terminals linked the glycopolymer to the gold nanoparticle surface.[126] Reproduced with permission from ref. 126, copyright [2018], [Royal Society of Chemistry].

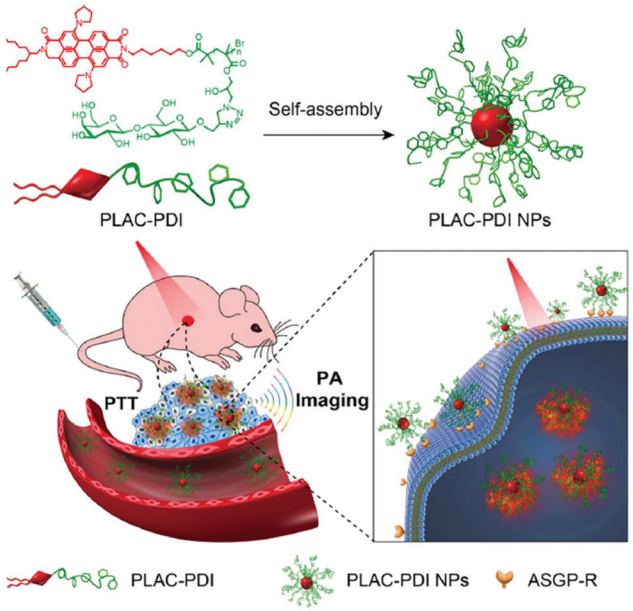

Fig. 32 Preparation of GNPs, poly(lactose)-modified perylenediimide (PLAC-PDI) nanoparticles, for hepatic tumor targeted photoacoustic imaging and photothermal therapy applications.[121] Reproduced with permission from ref. 121, copyright [2017], [American Chemical Society].

glycoprotein receptors at HepG2 cells (human liver cancer cells) enabled the treatment of hepatocellular carcinoma (liver cancer).[129–131] The self-assembling amphiphilic glycopolymer offers high selectivity for a photothermal therapy agent to a hepatic tumor.

Glycopolymers have been incorporated into biologically applicable quantum dots (QDs) which are water soluble and biocompatible, and enable near infrared emission.[132,133] Guo *et al.* developed a polyvalent glycan-quantum dot (Fig. 33) which is an excellent tool used to investigate multivalent protein–glycan interactions *via* multi-modal readout strategies (*e.g.*, Förster resonance energy transfer (FRET), hydrodynamic size measurement, and transmission electron microscopy imaging).[134] The new glycan-quantum dot enables the dissection of a multivalent protein–ligand which leads to inhibition of viral infection at a cellular level.

3.5. Drug delivery and biosensor

Glycopolymers have been used for drug delivery systems in a wide variety of ways and have been well-reviewed in multiple review papers.[135–137] Thus, the present report will discuss a few selected examples of glycopolymer-based drug delivery systems. A photo-responsive block copolymer, poly(methoxyphenyl azo phenoxy ethyl methacrylate-*b*-β-D-galactopyranosyl ethyl methacrylate) (poly(AzOMA-*b*-βGalEtMa), was synthesized *via* RAFT polymerization (Fig. 34a) for delivery of hydrophobic small molecule drugs.[138] The synthesized amphiphilic polymer, (poly(AzOMA-*b*-βGalEtMa), can undergo self-assembly in an aqueous solution to form micelles (Fig. 34b).[138] Drug mimic, Nile red, loaded glycopolymer micelles showed high cellular uptake in human melanoma A375 cells (Fig. 34c).[138]

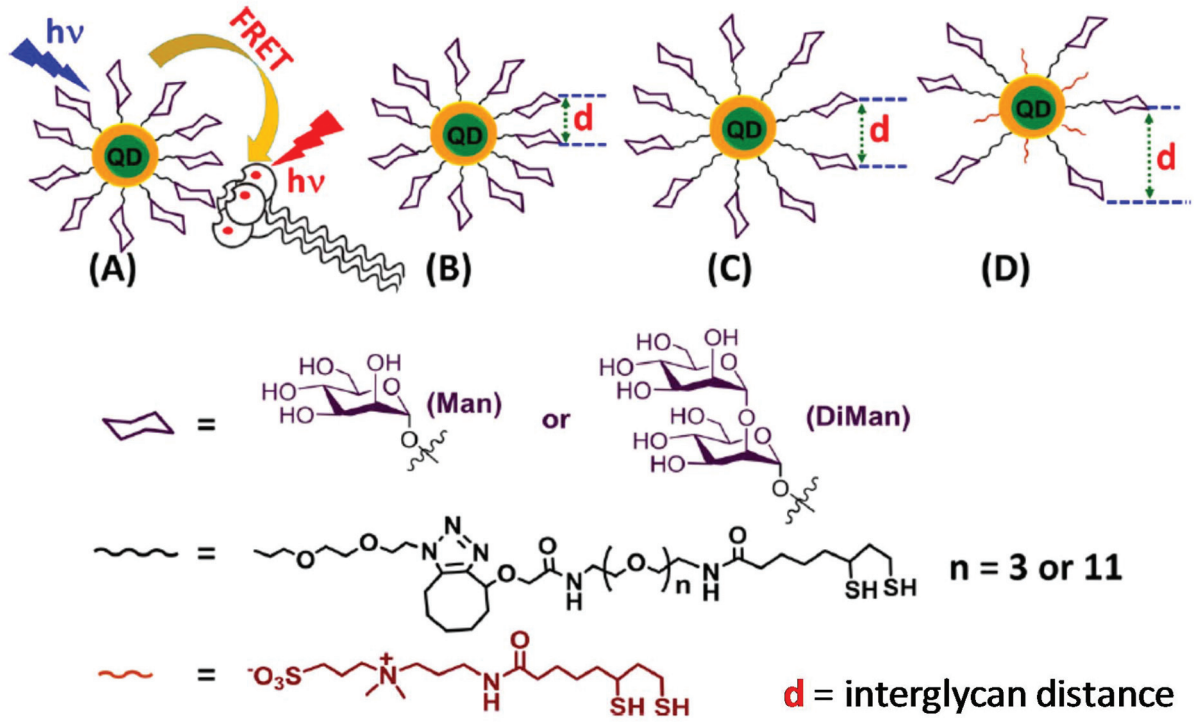

Fig. 33 (A) Polyvalent glycan-quantum dots by QD-sensitized dye FRET mechanism, (B–D) tuning mechanism of QD surface glycan valency and interglycan distance (d) *via* ethylene glycol linker length (*n* = 3 for b, and *n* = 11 for d; d =) and glycan dilution with an inert dihydrolipoic acid-zwitterion spacer ligand.[134] Reproduced with permission from ref. 134, copyright [2017], [American Chemical Society].

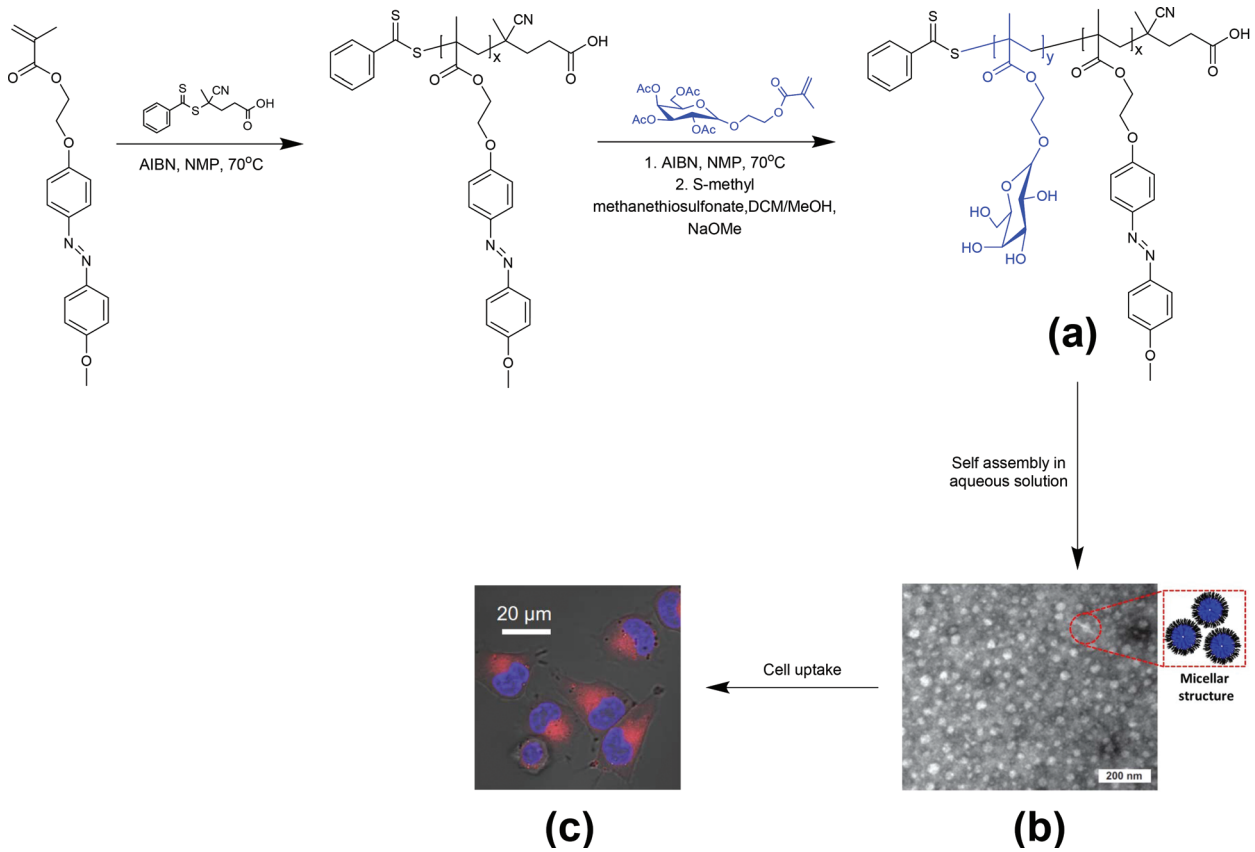

Fig. 34 (a) Synthesis route of photo-responsive block copolymer, poly(AzOMA-*b*-βGalEtMa), *via* RAFT polymerization, (b) micelle formation was observed by TEM, and (c) a confocal image of A375 melanoma cells incubated with a Nile red dye loaded polymer.[138] Reproduced with permission from ref. 138, copyright [2015], [Elsevier].

The safe drug delivery to melanoma cancer cells is most likely due to the structure of the cancer cells which contains galectin-3 receptors. Galectin-3 is known to have strong interactions with galactose, therefore promoting cell uptake by endocytosis.[139]

In diabetes treatment, glycopolymers play an important role due to their selective interaction with lectins. Mees *et al.* introduced the above discussed selective glucose-Con A interaction with glycopolymers. As shown in Fig. 35a, terminal –OH of

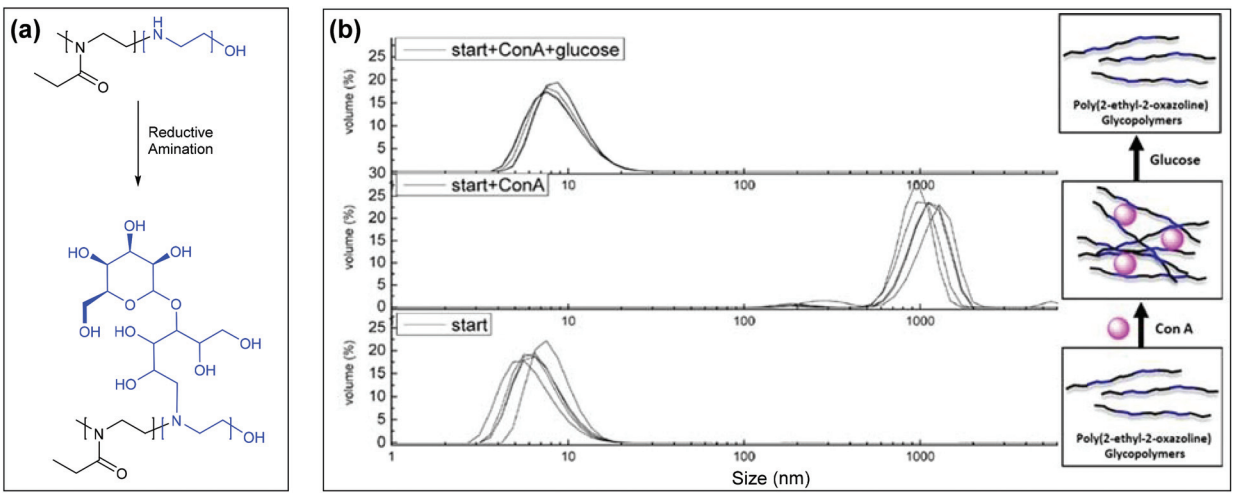

Fig. 35 (a) Synthesis of poly(2-ethyl-2-oxazoline)-based modified glycopolymers, and (b) DLS volume plots of poly(2-ethyl-2-oxazoline)-based modified glycopolymers (glycopolymer only, bottom plot), after introduction of Con A (glycopolymer + Con A, middle plot), and after addition of excess glucose (glycopolymer + Con A + excess glucose, top plot).[140] Reproduced with permission from ref. 140, copyright [2016], [American Chemical Society].

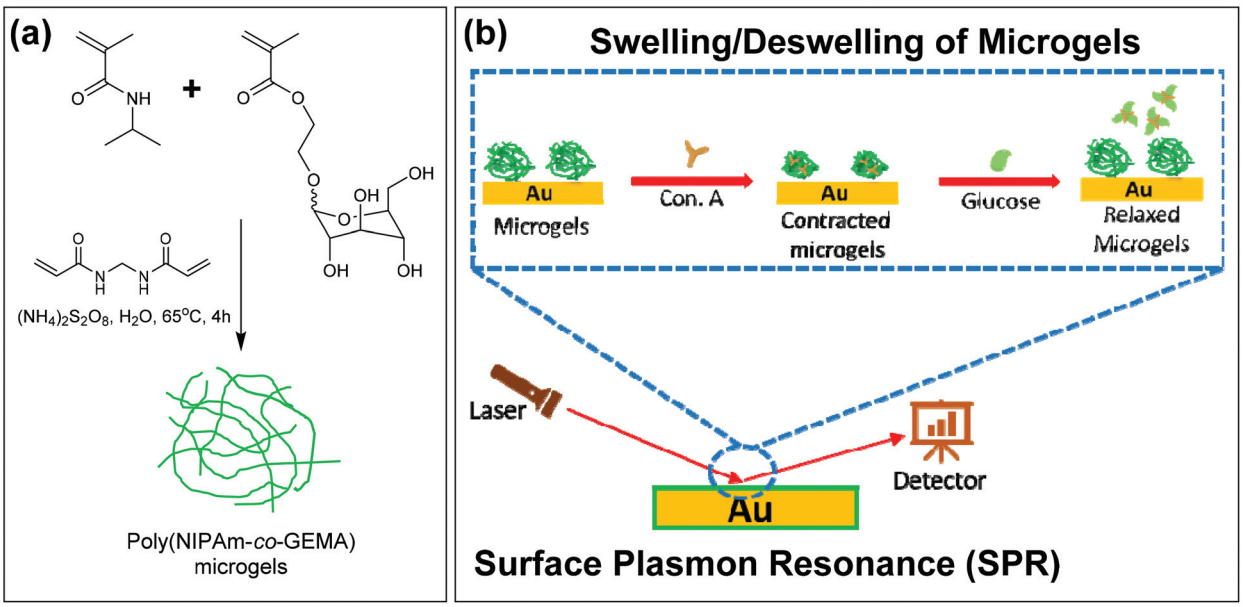

Fig. 36 (a) Synthesis of poly(NIPAm-*co*-GEMA) microgels, and (b) a microgel-based sensing mechanism for glucose detection.[141]

poly(2-ethyl-2-oxazoline) was modified to add a glycopolymer by reductive amination. The copolymer underwent agglutination upon addition of Con A forming a turbid solution (aggregate sizes: 200–1000 nm). After addition of a large excess of glucose, the agglutinated polymers (glycopolymer + Con A) were disrupted and then they formed linear polymers (Fig. 35b).[140]

In a recent study, a glucose sensor, poly(*N*-isopropylacrylamide-*co*-glycosyloxyethyl methacrylate) microgel, was synthesized in the presence of a crosslinker, *N*,*N*′-methylenebisacrylamide (BIS), by free radical polymerization (Fig. 36a).[141] A large number of glucose pendants allows the glycopolymer to have multiple interactions with Con A to form contracted microgels. The contracted microgel immediately expands upon exposure to glucose. By using these phenomena, the concentration of glucose can be quantitatively monitored by surface plasmon resonance (SPR) (Fig. 36b). When the glycopolymer microgels are swollen due to glucose, the SPR's reflected light intensity decreases because of the lowered refractive index of the swollen microgel and *vice versa*.[141]

4. Conclusions

In glycopolymer research, synthesis of a well-defined polymer that includes a variety of multiple polar functionalities is an important first step in biomedical applications. Because of the accuracy of polymerization and the convenience, ATRP and RAFT are two major synthetic tools used to prepare well-defined functional glycopolymers as stated in the recent literature. Furthermore, those synthetic approaches will continue to advance due to the requirement of new chemical functionalities for individualized application. Significant challenges include the synthesis of the more precisely defined glycopolymer molecular structure and the new polar functional group tolerance. Because the main chemical driving forces of carbohydrate–lectin interactions are hydrogen bonding, supramolecular interactions (*e.g.*, van der Waals interactions), and salt bridges, precisely defining the chemical structures of glycopolymers will increase the understanding and control of carbohydrate–lectin interactions. This has resulted in a high demand for various synthetic tools used to prepare 3-dimensional glycopolymer structures. The new 3-dimensional glycopolymers may include helical structured glycopolymers, isotactic/syndiotactic glycopolymers, and crystallized glycopolymers. Finally, the development of new synthetic approaches to combine multiple distinctive properties will direct glycopolymer research in the future. As briefly discussed in the review, a recent example of a multifunctional glycopolymer is [poly(MG-*co*-MDOPA-*co*-AOM)] which can be used for (1) glycopolymer-based tissue adhesives, and (2) selective biological recognition (lectin–glycopolymer interactions).

Conflicts of interest

There are no conflicts to declare.

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