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Glycopolymer-Based Nanoparticles: Synthesis and Application

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Synthetic glycopolymers with pendent sugar moieties are able to interact with lectins as multivalent ligand in a similar manner to natural glycoproteins. Nanoparticles (NPs), due to the small size and high surface/volume ratio, leads to very different properties compared with bulk-matter, and NPs have shown great potential in nanomedicine and other biological applications. NPs with glycopolymers on the surface are one of the desirable bio-active particles and an important material to investigate. This review focuses on the synthesis of various glycopolymer-based nanoparticles via different approaches such as self-assembly and preparing glycopolymer-conjugated inorganic NPs, and their different applications.

1. Introduction

Sugars are the foundation of all life and glycocalyx on cell surface play an irreplaceable role in a variety of cellular events, including proliferation, recognition, intercellular communication and immunoregulation. Cell surface glycosylation is believed to be as important to understanding life as is the genetic code, yet our understanding of the information is rudimentary.[1] The deep understanding of their biological interactions has triggered a strong development in the preparation of synthetic glycopolymers with pendent sugar moieties, which are able to interact with lectin as multivalent ligand in a similar manner to natural glycoproteins, with quite a few thorough reviews covering the synthesis of glycopolymers and their interaction with lectins.[2-5] Nanoparticles, due to the small size and high surface/volume ratio, leading to very different properties compared with bulk-matter, and NPs have shown great potential in nanomedicine and other biological applications. NPs with glycopolymers on the surface are one of the desirable bio-active particles and an important material to investigate. In addition, recent research found both by experimental and theoretical studies that particle shape has obvious effects on nanoparticles-cells interaction. To better understand the interaction between glycopolymer-coated NPs and protein/cells and to promote the application of glyco-nanoparticles, a variety of approaches have been used to fabricate NPs with glycopolymer in the corona with different shape and size. It should be noted that there is an extensive literature on NPs containing functional simple carbohydrates or oligosaccharides. Here we will focus on the synthetic glycopolymer-based nanoparticles. The different approaches for fabricating glycopolymer-based nanoparticles will first be summerizd, and then we will discuss about the applications of glycopolymer-based nanoparticles.

2. Synthesis of glycopolymer-based nanoparticles via self-assembly

Self-assembly of block copolymers has been widely used as one promising bottom-up strategies for fabricating a variety of functional nanomaterials, where block copolymers self-assemble into diverse morphologies in solution (micelles, vesicles and so on) with size ranging from tens to hundreds of nanometers. A variety of glycopolymers were reported to self-assemble into different nanoparticles in solution.

2.1 Amphiphilic Block Copolymers

In solution, amphiphilic block copolymers have been shown to assemble into a variety of structures such as micelles, worm-like structures, and polymeric vesicles (polymersomes). Amphiphilic block copolymers have also shown great potential as drug delivery systems as these amphiphilic structures are capable of encapsulating bioactive molecules or drugs. Amphiphilic block copolymers with carbohydrate functionalities are most widely used for fabricating glycopolymer-based nanoparticles via self-assembly in aqueous media. For example, block copolymers, PS-*b*-PGEA were synthesized by Li and co-workers, and different morphologies of aggregates, such as micelle-like spheres, vesicles and tubules were observed by varying copolymer compositions, with diameters ranging from 100 nm to 2 mm.[6]

2.1.1 Glycopolymer-based micelles

Spherical nanoparticles are the morphology most commonly obtained. The sizes of the spherical micelles are normally below 100 nm, however, particles bigger than 200 nm were obtained in many cases, possibly due to the aggregation of single micelles caused by the hydrogen-bonds between hydrophilic shells. Kataoka and coworkers reported a one-pot synthesis of PEG-PLA block copolymers having glucose and galactose groups at the PEG chain end, micelles with a diameter of ~40 nm were formed for the polymers in water.[7] Using PCL as the hydrophobic block, biodegradable, amphiphilic block glycopolymers were obtained and micelles of 20-125 nm were formed,[8] with the observation of some bigger aggregates (400 nm).[9] Other examples include using hydrophobic block of polycarbonate (PC),[10] poly(n-butyl acrylate) (PBA),[11, 12] poly(*tert*-butyl acrylate) (PtBA),[13] poly(D,L-

lactide) (PLA),[14] poly(propylene oxide) (PPO) and/or by sequential monomer addition of other methacrylic monomers such as 2-(diethylamino) ethyl methacrylate (DEA), 2-(diisopropylamino) ethyl methacrylate (DPA), or glycerol monomethacrylate (GMA),[15-17] poly(3-hexylthiophene) (P_3HT).[18] In another example, Guo and coworkers prepared triple stimuli (temperature/pH/photo)-responsive amphiphilic glycopolymer [P(DMAEMA-*co*-MAIpGP)-*b*-PMAZO], deprotection afforded the target diblock copolymers P(DMAEMA-*co*-MAGP)-*b*-PMAZO and the copolymers form micelles in solution.[19]

In addition to the widely used *di*- or *tri*- block copolymers, tree-like oligosaccharides-grafted-polypeptides were prepared by Bonduelle and coworkers using Huisgen 1,3-dipolar cycloaddition between poly(γ-benzyl-*L*-glutamate)-*block*-poly(propargylglycine) and two different oligosaccharides, dextran or hyaluronan. Small assemblies with sizes below 50 nm and low polydispersity were formed by direct solubilizing these glycopeptides in water.[20] Luo *et al.* prepared "coil-comb-coil" triblock glycopolymer PMAIpGlc-*b*-P(HEMA-*g*-PCL)-*b*-PNIPAM, the glycopolymers self-assembled into spherical micelles with P(HEMA-*g*-PCL) blocks as hydrophobic cores and PMAGlc and PNIPAM blocks as hydrophilic shells in aqueous solution, and the micellar size was dependent on temperature (Fig. 1).[21]

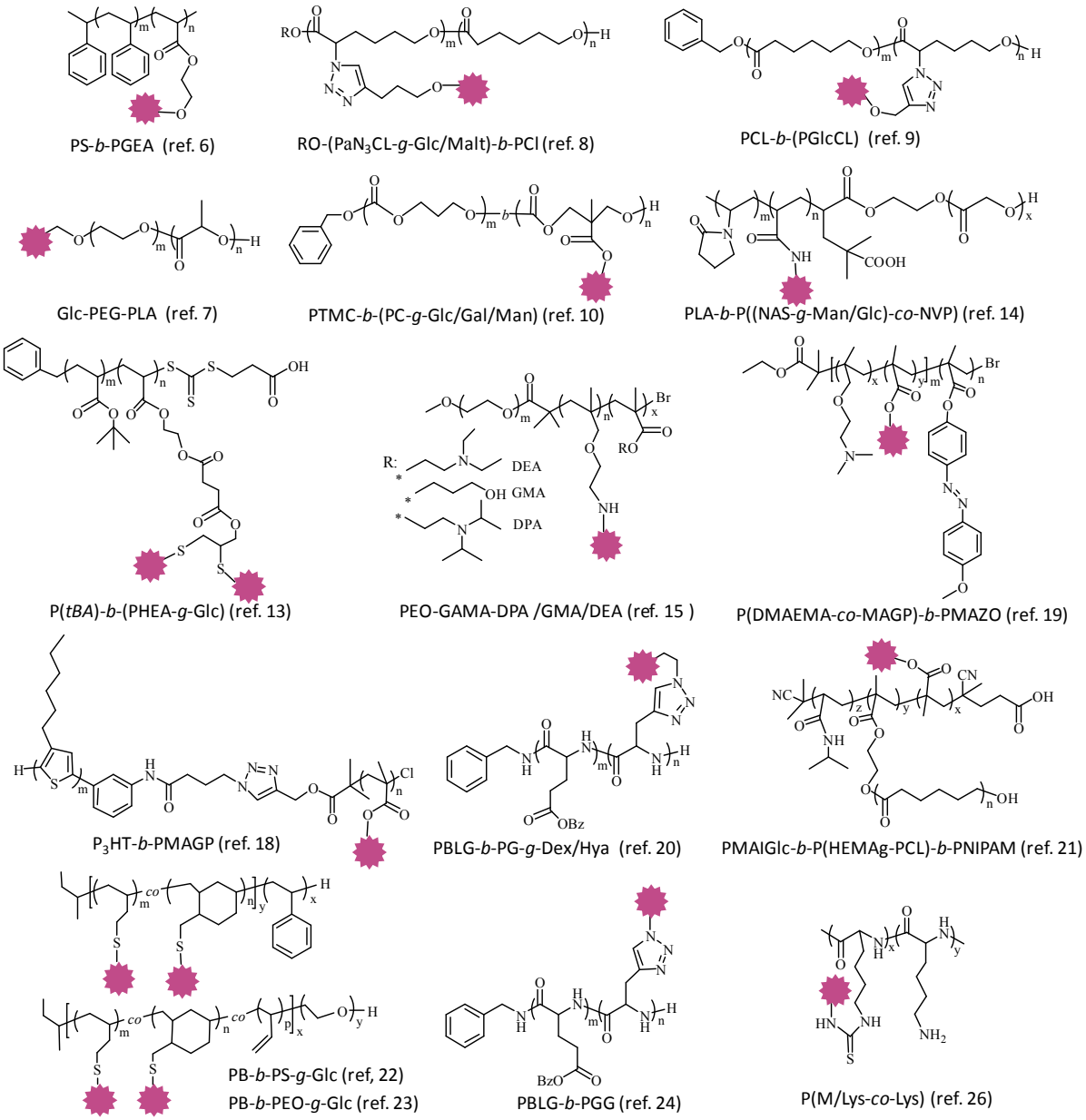

Fig. 1 Amphiphilic block glycopolymers used in the preparation of nanoparticles via self-assembly (:sugar)

2.1.2 Glycopolymer-based vesicles and non-spherical NPs

The morphology of nanoparticles can play a very important role for the interaction between nanoparticles and cells. Besides spherical micelles, other morphologies were obtained via the self-assembly of block glycopolymers in water, and the morphology can be tuned by changing polymer structure, composition, solvent type and other factors. Among the different self-assembled glyco-

nanoparticles, polymeric vesicle mimicking of glycocalyx (PV-Gx) are even attractive, due to the similar size, appropriate density, flexibility etc. Schlaad and co-workers reported that glucose-grafted polybutadiene-block-polystyrene (17 wt % glucose) self-assembled into vesicles in both organic (250 nm) and aqueous media (120 nm),[22] and the direct dissolution of glycosylated polybutadiene-poly(ethylene oxide) block copolymers formed vesicles or membranes (230-310 nm or 500-570 nm).[23] Amphiphilic glycopeptides PBLG-*b*-poly(galactosylated propargylglycine) (PBLG-*b*-PGG) copolymers were prepared by Lecommandoux and co-workers, these copolymers self-assembled into wormlike micelles or polymersomes (<100 nm) by varying copolymer composition and self-assembly protocol. The order of adding solvent (DMSO in water or water in DMSO) have shown clear effect on the morphology of nanoparticles obtained.[24]

Stenzel *et al.* presented a one-pot technology to generate different self-assembled glycopolymer-based nanoparticles. Poly(NIPAAm-*co*-TlaAm) was used to react with various amines (n-propylamine, n-hexylamine, and n-dodecylamine), to liberate the corresponding thiol, which consequently reacted *in situ* with 2-bromoethyl-2',3',4',6'-tetra-*O*-acetyl-α-D-mannopyranoside. While the n-propylamine-derived amphiphiles mainly led to micelles (30 nm), the n-hexylamine adducts gave rise to larger vesicles (200-600 nm), a further increase of the hydrophobicity (n-dodecylamine adducts) led to large particles of around 1 μm (Fig. 2).[25] Li and coworkers prepared a mannose-modified polylysine amphiphilic diblock copolymer P(M/Lys-*co*-Lys), which is capable of self-assembling into a variety of structures (spherical micelles, vesicles or rod-like micelles) by simply changing the pH of the solution and adding SDS to the solution.[26]

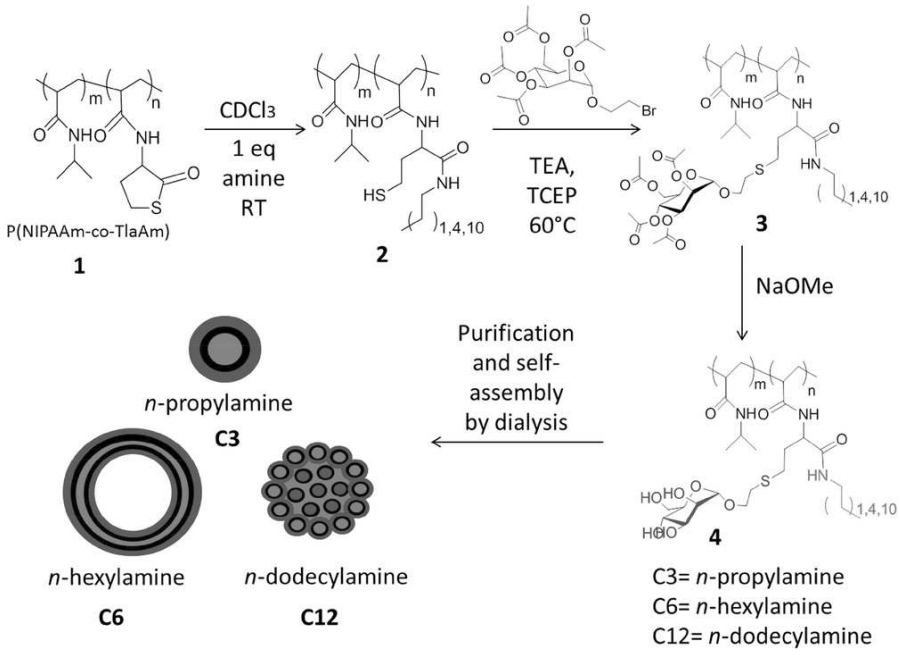

Fig. 2 Glycopolymer-based nanoparticles synthesized via aminolysis and nucleophilic substitution of thiolactone-containing polyacryl-amides. Reprinted with permission from ref. 25. Copyright (2014) Wiley VCH.

In addition to the traditional approach of making self-assembled nanoparticles by dissolving amphiphilic polymers in poor solvents, other approaches have also been reported. For example, based on the protection-deprotection chemistry of carbohydrate, Chen and coworkers prepared glyco-inside nanostructures with a new self-assembly strategy. They found that deacetylation of a series of block copolymers of PS-*b*-PManAc (PS, polystyrene block; PManAc, "sugar block" with acetylated α-mannopyranoside side groups) in THF resulted in glyco-inside structures with PS as the soluble shell and glycopolymer as the solidified state, *i.e.* the wall of vesicles or core of micelles depending on the weight ratio of the glyco-part. They also found that homogeneous Au nanoparticles were generated within the layer of the glyco-block from $AuCl_4^-$ without any additional reducing reagents or energy input (Fig. 3a).[27]

In another example, Ladmiral and Armes prepared a range of galactose-functionalized diblock copolymer nano-objects (nanospheres, worm-like micelles or vesicles) in concentrated aqueous solution via the polymerization-induced self-assembly (PISA) approach (Fig. 3b).[28] Compared to traditional self-assembly strategies, which only allow the formation of block copolymer nano-objects in relatively dilute solution (<1%), PISA formulations based on RAFT polymerization enables well defined block copolymer nano-objects to be prepared directly at high concentrations without recourse to any postpolymerization processing.[26, 29]

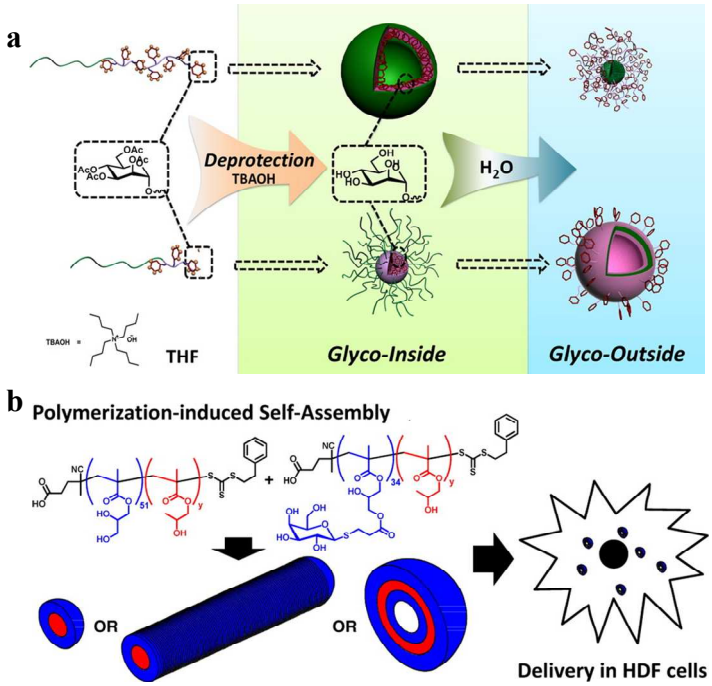

Fig. 3 a) Deprotection-induced micellization process and the inversion of the glyco-inside vesicles to glyco-outside micelles (ref. 27); b) Polymerization-induced self-assembly of galactose-functionalized diblock copolymers (ref. 28). Reprinted with permission. Copyright 2014 and 2013 American Chemical Society.

2.2 Other amphiphilic glycopolymers

2.2.1 Hydrophilic glycopolymer conjugated with hydrophobic small molecules

Other than typical block copolymers, hydrophobic small molecules linked with hydrophilic glycopolymers also self-assemble into nanoparticles. Using tetra(*p*-phenylene) as the hydrophobic rod chain end of PEG where sugar was on the other chain end, vesicles (210 nm) and highly regular spherical micelles (10 nm) were observed for the glypolymers with different PEG chain length.[30] And the amphiphilic rod-coil molecules consisting of tetra(*p*-phenylene) or di[tetra(*p*-phenylene)] as a rod segment and α-D-mannopyranoside-fuctionalized oligo(ethylene oxide)s as a coil segment self-assemble into a variety of structures such as vesicles (40 nm), spherical micelles (20 nm) and cylindrical micelles (20 nm) by varying polymer structure and compostion.[31] Similarly, hydrophobic porphyrin in the middle of the glycopolymer chain could also self-assemble into nanoparticles with potential applications in targeted photodynamic therapy.[32]

2.2.2 Amphiphilic statistical or gradient glycopolymers

Not only block copolymers, amphiphilic statistical copolymers were also prepared for generating nanoparticles. Zhang and Li synthesized glucose-responsive glycopolymers consisting a phenylboronic acid-functionalized monomer (AAPBA) and a glucosamine-carrying monomer (MAGA) using free-radical polymerization. Nanoparticles of 120-200 nm were generated via the nanoprecipitation method.[33] Amphiphilic glycopolymer poly(2-lactobionamidoethyl methacrylate-random-3-acrylamidophenylboronic acid) (P(LAMA-*r*-AAPBA) could assemble into nanoparticles of 280-360 nm.[34] Random copolymer of BODIPYMA and 2-*O*-methacryloyloxyethyl-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside) (AcGEMA) were synthesized by ATRP, and the polymers assembled into 210-250 nm spherical micelles.[35]

Lu *et al.* reported an efficient methodology to synthesize gradient glycopolymers combining concurrent enzymatic monomer transformation and reversible addition-fragmentation chain transfer (RAFT) polymerization. Glycopolymers with different sequential structures (statistical, gradient and block glycopolymers) were prepared, and the glycopolymers with gradient and block structures showed high affinities towards the RCA_{120} lectin receptor compared with the other structural counterpart.[36]

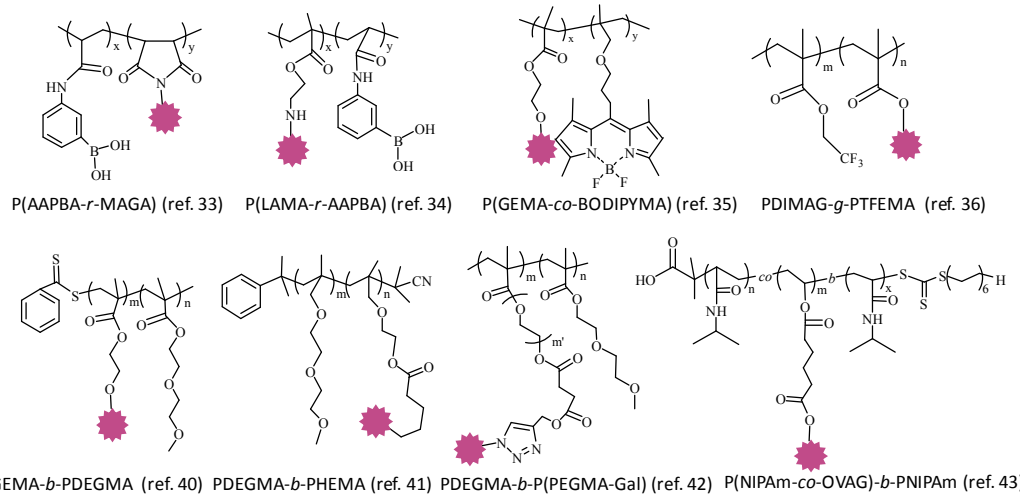

Fig. 4 Random, gradient and double hydrophilic glycopolymers used in the preparation of nanoparticles via self-assembly (:sugar)

2.2.3 Amphiphilic homopolymer

Homopolymers whose repeating unit consists of both hydrophilic and hydrophobic moieties can also be used to form self-assembled NPs. Amphiphilic homoglycopolypeptide was prepared by a combination of NCA polymerization and "click chemistry", and the amphiphilic polypeptide self-assembled in water to form multimicellar clusters with diameters between 250 and 300 nm (Fig. 5a).[37] Dan *et al.* prepared pH responsive aggregation of amphiphilic acrylate based homoglycopolymers. At acidic conditions, swollen multi-micellar aggregates were formed, and at basic conditions more compact particles were found, which further co-assembled to generate either garland type or fractal-aggregates (Fig. 5b).[38] In another example, a glycomonomer, 1,2:3,4-di-*O*-isopropylidene-6-*O*-(2'-formyl-4'-vinylphenyl)-D-galactopyranose (IVDG) was synthesized, and removal of protective isopropylidene groups from the sugar residue in polyIVDG yielded amphiphilic homopolymer which can self-assembled into micelles with size in the 80-205 nm range in aqueous solution.[39]

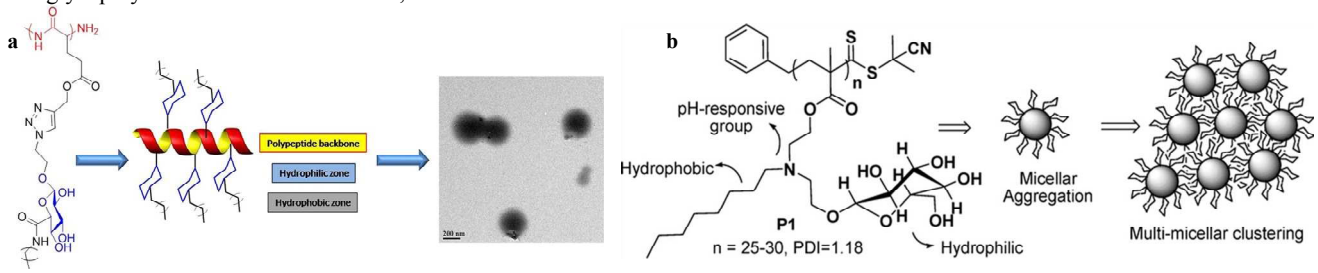

Fig. 5 Synthesis of nanoparticles via self-assembly of a) amphiphilic homoglycopolypeptides. Reprinted with permission from ref. 37. Copyright (2013) American Chemical Society; b) pH-responsive amphiphilic glycol-homopolymer. Readapted with permission from ref. 38. Copyright (2012) Wiley VCH.

2.3 Double-hydrophilic and responsive block copolymers

Preparing nanoparticles based on amphiphilic polymers often require organic solvent to dissolve polymers before self-assembling in water, and these solvents might be difficult to remove completely. Double-hydrophilic block copolymers, often incorporating a responsive block, can be easily dissolved in water and form nanoparticles upon stimuli. Poly(diethyleneglycol methacrylate) (PDEGMA) and poly(*N*-isopropylacrylamide) (PNIPAm) are the two most widely used responsive hydrophilic blocks for preparing double-hydrophilic glycopolymers that can self-assemble into nanoparticles in water upon heating. Alexander *et al.* prepared block copolymers with highly hydrophilic poly(2-glucosyloxyethyl methacrylate) (PGEMA) as one block and PDEGMA as the second block by using controlled free-radical techniques, the block copolymers assembled into vesicles (251 and 500 nm at 20 °C and 182 and 300 nm at 37 °C), as a mimic of natural cells with their associated glycocalyx.[40] Copolymer containing the sugar block and PDEGMA block was synthesized by Stenzel and coworkers via RAFT and thiol-ene reaction to obtain thermo-responsive micelles.[41, 42] Thermoresponsive double hydrophilic block glycopolymer poly(*N*-isopropylacrylamide-*co*-6-*O*-vinyladipoyl-D-glucose)-*b*-poly(*N*-isopropylacrylamide) (P(NIPAm-*co*-OVAG)-*b*-PNIPAm) was prepared and the block glycopolymer was able to self-assemble into regularly spherical micelles with sizes of about 20 nm in aqueous solutions.[43] Aqueous SET-LRP has been applied for the synthesis of the double hydrophilic, thermoresponsive diblock glycopolymers PManA-*b*-PDEGEEA by Haddleton and coworkers, the thermoresponsive glycopolymers self-assembled into nanoparticles with glycopolymer corona above their LCST (Fig. 6).[44]

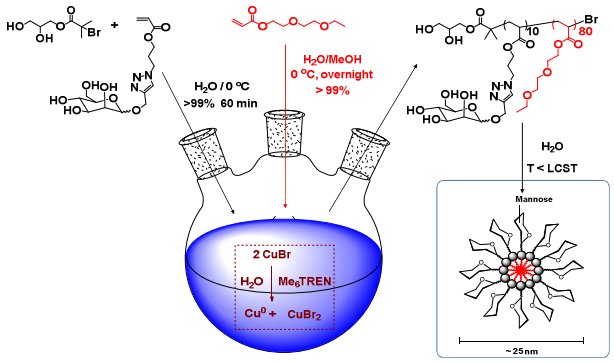

Fig. 6 Synthesis and aggregation of double hydrophilic diblock glycopolymers via aqueous SET-LRP. Reprinted with permission from ref. 44. Copyright (2014) American Chemical Society.

3 Synthesis of glycopolymer/inorganic hybrid nanoparticles

Sugar-coated inorganic nanoparticles (such as gold, iron oxide or semiconductor) with defined glycopolymers on the surface are another category of glyconanoparticles (GNPs) attracting the attention of researchers. These type of glyconanoparticles combine the multivalent presentation of carbohydrates (glycoclusters) with the special chemico-physical properties of the nano-sized inorganic core. The possibility of attaching different types of carbohydrates or modifying the core to obtain glyconanoparticles with magnetic or fluorescence properties makes this multivalent glyco-scaffold suitable for carrying out studies on carbohydrate-mediated interactions and applications in molecular imaging. In addition, inorganic NPs with different shapes can be synthesized easily and precisely. Gold glyconanoparticles, semiconductor glyco-quantum dots and magnetic glyconanoparticles are the three major types of glyconanoparticles prepared.

3.1 Gold/glycopolymer nanoparticles

With the development of nanotechnology, gold nanoparticles can not only be coated with different carbohydrates, and nanotechnologies also allow the preparation of GNPs with varying percentage of different carbohydrates. Multifunctional glyconanoparticles incorporating not only carbohydrates but also peptides, lipids, DNA, RNA or fluorescent molecules can also be prepared allowing us to effectively create highly complex GNPs as "artificial glycocalix". Control the size and shape of the gold core can be modified to obtain glyconanoparticles with semiconductor and magnetic properties (multimodal GNPs) to broaden the application of biotechnoiogy. Several excellent reviews focused on the preparation and characterization of glyco-gold NPs,[45, 46] and thus, this category will not be discussed here. In this section, we will focus more on recent publications regarding the synthesis of glycopolymer-based gold NPs.

Since Brust *et al*.[47] reported that a thiol ligand strongly binds gold and protect the metallic core by a covalent Au-S bond, synthesis of polymer protected GNPs became easy, and the majority of gold-based glyconanoparticles have been prepared by this method. For example, Yoshiko Miura prepared poly(AcMan-*r*-AAm) glycopolymers (poly(acrylamidophenyl α-mannose-*co*-acrylamide)) using RAFT polymerization, the polymer terminal group was reduced to a thiol, and the resulting polymers were mixed with an aqueous dispersion of AuNPs to prepare glycopolymer-substituted gold nanoparticles. The mannose density was adjusted, and the colloidal stability of the polymer-coated gold nanoparticles is found to be dependent on the mannose density.[48]

Other than spherical gold NPs, gold nanorods (GNRs) are attractive for their highly efficient absorption in the NIR region and numerous applications such as photothermal therapy and two photo fluorescence imaging, it is also an attractive model for investing interactions between cell and non-spherical nanoparticles. Glycopolymer-coated gold nanorods were prepared in a well-controlled manner by Chen and coworkers via a copper(0)-catalyzed one-pot reaction combining living radical polymerisation and "click chemistry". The room temperature Cu(0)-catalyzed strategy provides an easy and efficient approach to make well-defined glycopolymers with thiol-terminal functionality, which can be easily modified onto gold nanorods via Au-S bonds and the glycopolymer substituted GNRs showed strong, specific molecular recognition abilities with lectin (PNA) (Fig. 7).[49]

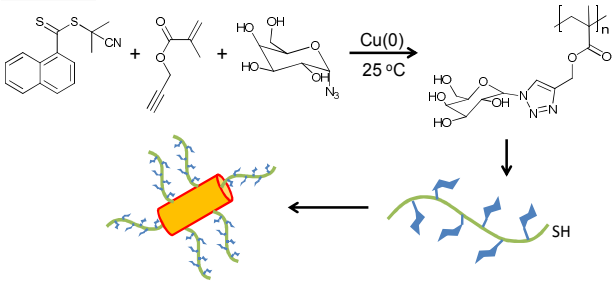

Fig. 7 Synthesis of glycopolymer-coated gold nanorods. Reproduced from ref. 49 with permission from RSC. Copyright 2014.

Instead of attaching glycopolymers to preformed gold nanoparticles, glycopolymer decorated gold nanoparticles can be formed *in situ*. In a report by Davis and Cameron, well-defined glycopolymers which have Tn-antigen glycan were prepared via RAFT polymerization. Sodium borohydride was then used to reduce simultaneously $HAuCl_4$ to Au^0 and the dithioester end groups of the RAFT polymers to thiol, forming the Tn-antigen glycan gold nanoparticles *in situ*.[50] Another type of gold-based glyco-nanoparticles are glycopolymer gold conjugates synthesized from gold salt, and these conjugates normally show high cytotoxicity toward cancer cells. Stenzel *et al.* prepared an amphiphilic block copolymer with the $AuPEt_3$ complexed to the thiol units of the pendent sugar to fabricate a micelllar system containing pendant auranofin-like groups in the core. RAFT polymerization was used to prepare a block copolymer of 2-hydroxyethyl acrylate (HEA) and glucose derivatives, after complexation with $AuPEt_3Cl$, the conjugates can self-assemble into a core-shell structure micelles in an aqueous environment with a mean diameter of approximately 75 nm. The glyconanoparticles had a high anti-proliferative effect against OVCAR-3 human ovarian carcinoma cells.[51] Narain and coworkers synthesized random glycopolymer (p(GAPMAm-*st*-APMAn)) via RAFT polymerisation, the amine groups on the polymer were then modified to generate dithiocarbamate (DTC)-functionalized glycopolymers, the obtainied glycopolymers were further reacted with gold salt to yield gold(I) phosphine derivatives. These gold nanoparticles displayed higher accumulation and cytotoxicity in cancer cells under hypoxic

conditions in comparison to the normoxic conditions.[52] It was noted that the glycopolymer gold(I) conjugates showed a significantly higher degree of inhibition of cell proliferation and its activity efficiency was dependent on the solubility and molecular weight of the copolymers. In addition, gold(I) triphenyl phosphine was attached to glycopolymers decorated gold nanoparticles to prepare a new class of gold-based anticancer drugs, which were found to be more toxic than standard chemotherapeutic reagents such as cisplatin.[53]

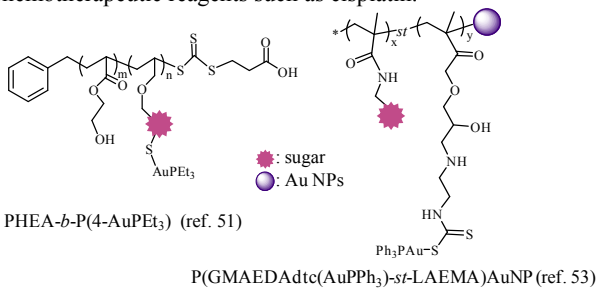

Fig. 8 Glycopolymer/gold complexes of PHEA-*b*-P(4-AuPEt$_3$) (ref. 51) and P(GMAEDAdtc(AuPPh$_3$)-*st*-LAEMA)AuNP (ref. 53).

3.2 Iron oxide/glycopolymer nanoparticles

Biofunctional magnetic and semiconductor nanoparticles are versatile platforms suitable for targeted imaging, thermal therapy, drug delivery, and cell labelling.[54, 55] It is obvious that the carbohydrate coating of magnetic NPs can contribute to improving the biocompatibility and the targeting properties of nanomaterials for biomedical applications. Phosphonic acid groups are commonly used to achor glycopolymers to iron oxide nanoparticle (IONP) surfaces. Quite often, a phosphonate functional initiator can be used to prepare glycopolymers and the phosphonic esters are de-protected to afford glycopolymers with phosphonic acid groups that can be attached to IONP surface via P-O-Fe bonds. For example, Haddleton and coworkers reported a facile one-pot synthesis of diblock PEG glycopolymers using a combination of Cu(0) mediated living radical polymerization and click chemistry to attach three different carbohydrates, α-D-mannose, α-D-glucose and β-D-glucose, to iron oxide nanoparticle surfaces.[56]

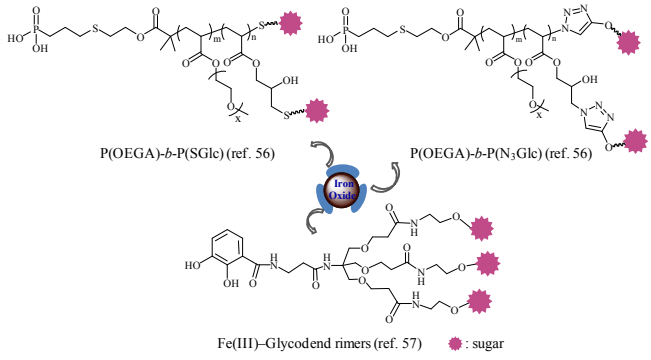

Fig. 9 Phosphonic acid terminal glycopolymers, P(OEGA)-*b*-P(SGlc) (ref. 56), P(OEGA)-*b*-P(N$_3$Glc) (ref. 56) and catechol confined glycodendrons (ref. 57) for preparing iron oxide/glycopolymer NPs.

Catechol chemistry is another useful tool to combine an inorganic magnetic core with a bioactive organic coating. Catechol confined glycodendrons were used as biomimetic siderophores to bind Fe(III) by a self-assembly process (refluxing stoichiometric amounts of glycodendrons with ferric chloride in methanol), the obtained Fe(III)-glycodendrimers can interact with concanavalin A lectin and a specific *E. coli* strain, inducing iron mediated growth promotion.[57] Li *et al.* used a biomimetic coating strategy to modify the iron oxide surface by introducing vinyl groups through catecholic chemistry. DMA, a dopamine derivative with vinyl functionality was used for iron oxide surface modification. The vinyl groups introduced by DMA would then react with thiol-terminal glycopolymers (PMAG) via thiol-ene chemistry, therefore anchoring glycopolymers on the surface(Fig. 10).[58]

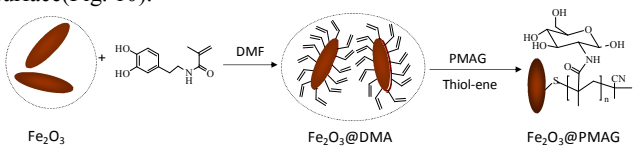

Fig. 10 Synthesis of PMAG decorated iron oxide nanoparticles via a combination of catechol and thiol-ene chemistry (ref. 58). Reproduced from ref. 49 with permission from RSC. Copyright 2014.

Instead of attaching glycopolymers to preformed INPs, iron oxide nanoparticles can be prepared and stabilized by coprecipitation of ferrous and ferric salts solution and biocompatible molecules such as dextran or oleic acid. Other biomolecules can be further attached to the protected nanoparticle by covalent or electrostatic coupling. For example, magnetite nanoparticles were prepared by coprecipitating ferric chloride and ferrous sulfate under amonium hydroxide condition in the presence of dextran. Dextran coats the external surface of the nanoparticles forming a stable colloidal suspension. Folic acid (FA) can be further conjugated to the Dextran-coated INPs to improve the signal enhancement for the detection of the inflammatory site of arthritis, as potential MRI contrast agents for diagnosis and treatment of rheumatoid arthritis.[59]

Similarly, Dextran coating can be further modified with epichlorohydrin, followed by ammonia treatment to introduce amine groups. The amine functionalized magnetic glyconanoparticles can be further modified with other biological molecules, such as sialic acid (NP-Sia)[60] or hyaluronan (HA-NP).[61] NP-Sia allowed easy detection of *β*-amyloid both *in vitro* and *ex vivo* by magnetic resonance imaging, highlighting the potential of these nanoparticles for detection and imaging of *β*-amyloid. In another example, silica encapsulated iron oxide nanospheres with a particle size of 58 nm and a shell thickness of 22 nm were prepared and transformed into double-bond-bearing spheres by condensation of MPTS onto the surface of the particles. Thiol-ene chemistry was then used to graft a glycol-copolymer consisting of 6-*O*-methacryloylgalactopyranose (MAGal) and 4-(pyrenyl) butyl methacrylate (PyMA) onto the magnetic silica particles, leading to the formation of galactose-displaying core-shell nanospheres exhibiting both fluorescent and magnetic properties.[62]

3.3 Quantum dots/glycopolymer nanoparticles

Compared with conventional fluorescent dyes, quantum dots (QDs) have several advantages, QDs have size-tuneable light emission, bright luminescence and long emission stability. Since their quantum size effects are understood, fundamental and applied research on these systems has become increasingly popular. One of the most interesting applications is the use of QDs as luminescent labels for biological systems, but for any

application in this area, the QDs must be water soluble, biocompatible and should emit in the near-infrared region. Conjugating QD with hydrophilic polymers can greatly improve its solubility and stability in water. Carbohydrates are attractive molecules due to their hydrophilicity and specific recognition properties. Sugars can be attached to the QDs surface via thiol-based ligands addition and ligand exchange, electrostatic interaction, alkyne-azide click chemistry, EDC/NHS coupling and streptavidin-biotin binding, etc. The chemistry used for preparing glyco-QDs were discussed in detail in the book chapter *Glyco-Functionalized Quantum Dots* by Weingart and Sun.[63] It should be noted that most reported glyco-QDs are covered with simple carbohydrates or oligosaccharide. For example, Rotello and coworkers prepared glucose-functionalized QDs, and insulin or 2-deoxyglucose (2-DG) was used to modulate the cellular uptake by controlling the GLUT4 level on the membrane of C2C12 muscle cells. Results show that the cellular uptake of Glc-QDs can be modulated up to almost two-fold under insulin stimulation while be down-regulated in the presence of 2-DG, demonstrating the use of secondary regulators to control cellular uptake of NPs.[64] Galan and coworkers prepared a series of glycan-coated QDs. The QDs were first modified with carboxylic acid groups by ligand exchange and then different glycosylamines were attached to the acid capped QDs via EDC coupling. Results showed that glycan density mostly impacts on cell toxicity, whereas glycan type affects the cell uptake and intracellular localization. Moreover, lactose as a "Trojan Horse" for bi-functionalized QDs cell transport, can help intracellular delivery of non-internalizable glycan moieties and largely avoid the endosomal/lysosomal degradative pathway (Fig. 11a).[65]

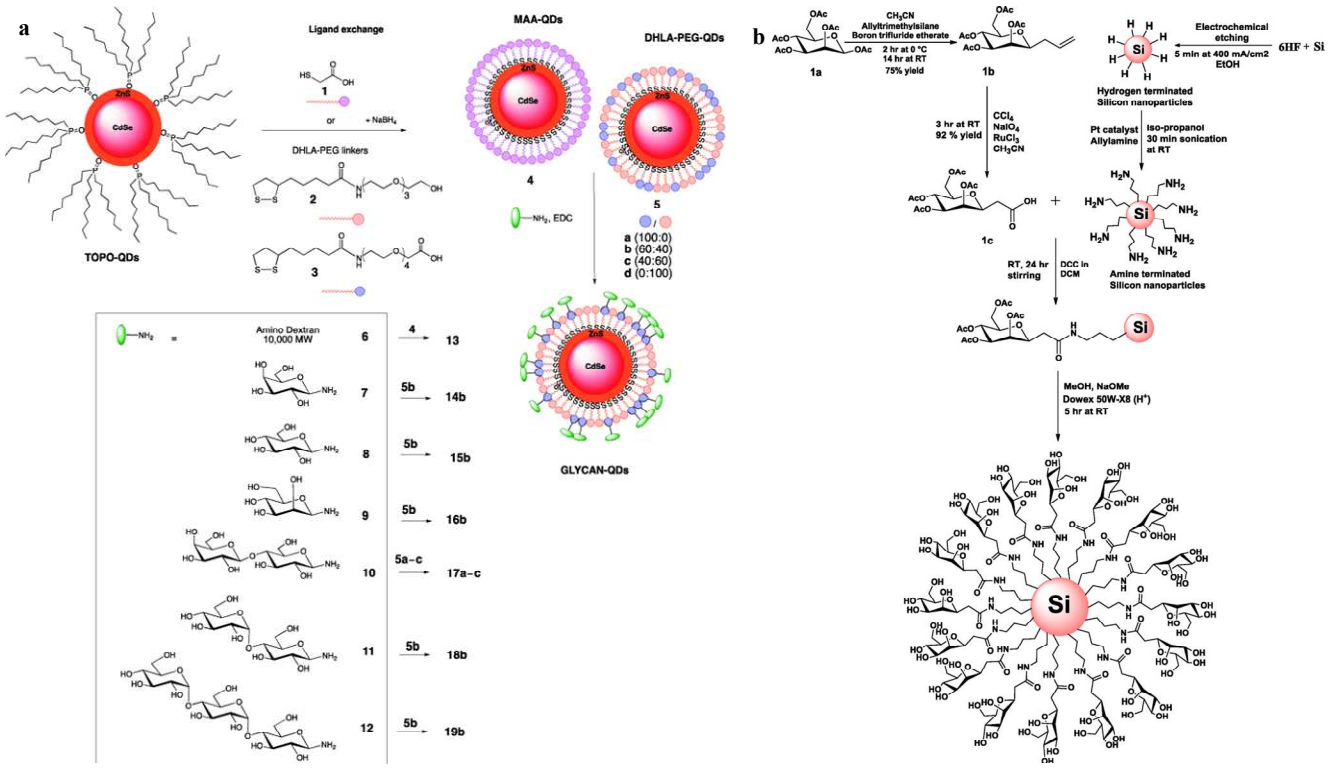

Fig. 11 Prepation of a) glyco-QD (Reprinted with permission from ref. 65. Copyright (2014) Wiley VCH); b) D-Mannose capped SiNPs (Reprinted with permission from ref. 66. Copyright (2013) American Chemical Society).

In order to suppress the cytotoxicity of cadmium ions, non-metallic materials that can also produce a quantum dot, such as silicon is an attractive choice. Chao and coworkers reported the synthesis of stable and brightly luminescent D-Mannose (Man) capped silicon nanoparticles (SiNPs) by amine terminated SiNPs and D-mannopyranoside acid, the prepared NPs presented high photoluminescence emission quantum yield, and the biochemical activity of Man-capped SiNPs was tested with ConA (Fig. 11b).[66]

Glycopolymer-based multivalent carbohydrates can facilitate high binding affinity and specificity, however only a few examples of the glycopolymer/QD conjugates were reported. Rosenzweig and coworkers prepared CdSe-ZnS quantum dots protected with carboxymethyldextran and polylysine through electrostatic attraction, this is the first example of QDs protected with polysaccharides,[67] then a set of multifunctional glyco-QDs were prepared, including lactose,[68] trisaccharide antigen Lewis X (Le^x) and phosphorylcholine ligands (PC)[69] on the shell and displaying a variety of glycans. Sun *et al.* was the first to report QDs protected with synthetic biotin-terminal glycopolymers. By using CdSe-ZnS QDs functionalized with streptavidin, the biotin functionalized glycopolymer bound to QDs creating a layer with multivalent carbohydrate labeling, demonstrating the potential of these multivalent carbohydrates in imaging and biocapture applications.[70] Narain and coworkers prepared functionalized QDs capped with both biotin and carbohydrates moieties via two approaches. The carboxyl-capped QDs was modified with biotin and carbohydrate molecules bearing amine groups. Alternatively, the QD surface was modified directly with biotinylated glycopolymers bearing biotin, amine, and carbohydrate as pendent moieties (Fig. 12).[71]

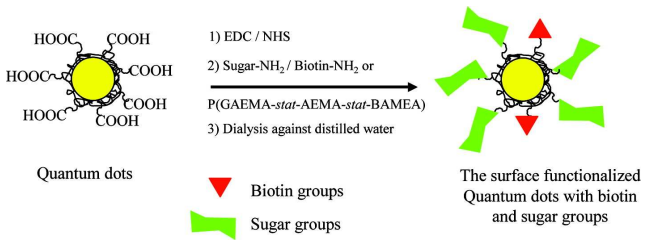

Fig. 12 Fabrication of biotin and sugar/glycopolymer functionalized QDs. Reprinted with permission from ref. 71. Copyright (2009) American Chemical Society.

4. Application of glyconanoparticles

Although glyco-science encompasses a broad range of topics including energy and materials, the area of human health is the major focus. A variety of glycopolymer-based nanoparticles were synthesized and used as models to investigate carbohydrate-protein/cell interactions, as drug-delivery vehicles, vaccine candidates and imaging probes, etc. Below are a summary of their applications.

4.1 Bio-mimetic model

Polyvalent carbohydrate-protein interactions play a key role in bio- and pathological processes, and these carbohydrate-binding proteins include enzymes, plant, bacterial and mammalian lectins, toxins, or antibodies. There are detailed reviews about the glycopolymer-lectin interactions.[3, 4, 72] Glycopolymer-based nanoparticles, especially those prepared via self-assembly are often used as models to investigate their interactions with lectins. The binding ability of glycopolymer/nanoparticles can be analyzed via lectin immobilized column,[73] light-scattering measurements,[28,41,74,] fluorescence quenching assay,[21] precipitation assay,[13] enzyme-linked lectin assay (ELLA),[14] QCM,[36] and most commonly turbidimetric assay,[9, 14, 38, 75,] considering variations such as temperature,[41,42] polymer molecular weight,[76] composition,[12,21,36] and structure[13,43]. For example, Luo *et al.* found that for copolymer PMAG-*b*-P(HEMA-*g*-PCL)-*b*-PNIPAm, depending on the length of PNIPAm either steric hindrance or entropy enhancement was greater than the other, leading to different lectin binding abilities.[21] Kuma *et al.* prepared glycopolymers which can led to micelles with a dendritic glycopolymer surface and a linear glycopolymer brush structure, respectively. The turbidity assay and the precipitation assay found that lectins (ConA) more efficiently bind to the dendritic structure.[13] Chen and coworkers investigated the influence of the macromolecule architecture, *i.e.*, block, statistical, and gradient copolymers, on the self-assembly and binding behavior toward RCA120 . The block and gradient structures exhibited superior lectin-binding capability than statistical via experimental procedures, and both the self-assembly and binding mechanisms were further studied using simulations. Simulation results highlight the important influence of the hairy structure of micelles on protein binding, which can be attributed to the unique molecular architectures of the block and gradient copolymers (Fig. 13).[36]

Miura and coworkers prepared glycopolymer-substituted gold nanoparticles. By varying the copolymer preparation and the glycopolymer-polyacrylamide mixture, the mannose density was adjusted and they found that surface distribution of sugars can be used to control aggregation properties of AuNPs through molecular recognition. In addition, the glycopolymer-substituted AuNPs were applied for the detection of mannose-protein interactions using an immunochromatographic assay whereas higher sugar contents resulted in more sensitive detection.[48]

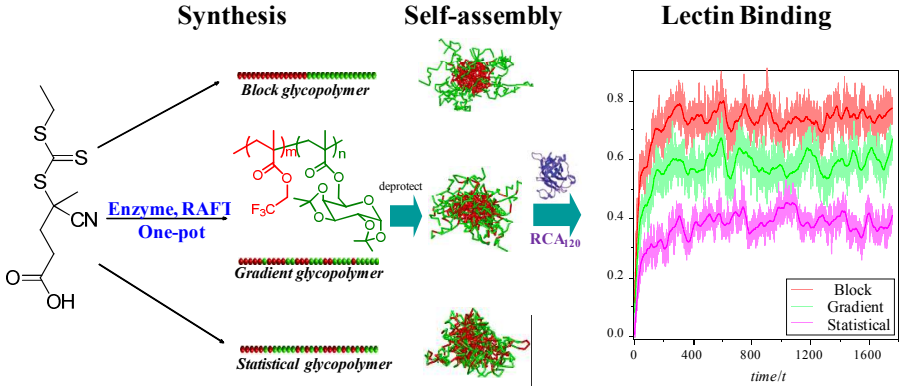

Fig.13 Synthesis and lecin-binding of block, statistical, and gradient glycopolymers. Reprinted with permission from ref. 36. Copyright (2014) American Chemical Society.

Carbohydrates are involved in different cellular recognition events, and sugar are recognized as the face of cells. Glycopolymer-based nanoparticles are appealing models to investigate cell-related interactions. For example, Ladmiral *et al.* synthesized a range of galactosylated nano-objects and their biocompatibility and cellular uptake behaviors have been studied on HDF cells.[28] Alexander and coworkers prepared glycopolymer-based vesicles with glucose functionality as a mimic of eukaryotic cell surfaces and their interaction with *E. coli* showed that it is possible to change interactions from bulk aggregation to individual associations, indicating that not only affinity can be optimized but information transfer between cells and vesicles might be achieved by proper design.[77] To investigate the impact of density of carbohydrate and especially shape on the interaction of glycopolymer-based nanoparticles and cells, Li *et al.* synthesized glycopolymer-coated iron oxide nanoparticles of different shapes (spindle and cubic-like) by catecholic and thiol-ene chemistry. The glyco-nanoparticles with variable shapes are stable in serum and exhibit shape dependent cell uptake behaviors as well as enhanced activity toward specific lectins (Fig. 14).[58]

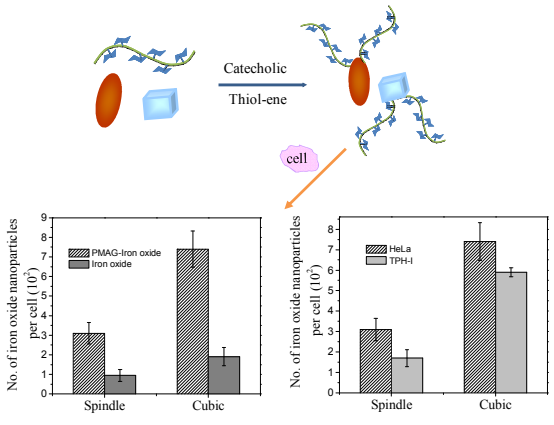

Fig.14 Glycopolymer-coated iron oxide nanoparticles and the effect of shape of the nanoparticles on cellular uptake. Adapted from ref. 58 with permission from RSC. Copyright 2014.

4.2 Therapy and imaging

The importance of carbohydrate/glycans in immunity has been widely recognized, and cell surface glycans/glycan-binding proteins are found to contribute to all stages of cancer progression and metastasis, therefore another major application of glycopolymer-based nanoparticles is in the area of therapy.

Glycans are commonly used by microbes and viruses to bind host cells, vaccines for infectious diseases recognize glycans present on the disease-causing organisms. The first glycan-containing vaccines were reported in 1929.[78] After that, more and more glycan-based vaccine have been reported. For example, Penadés[79] and Barchi[80] prepared synthetic carbohydrate-vaccines based on gold nanoparticles coated with TetraPn/Glc/OVA(323-339) or MUC4 glycopeptides/C3d/hydroxyl-linker. Under the hypothesis that presenting glycans in a "multicopy-multivalent" manner might produce a nanoparticle with a surface that mimics much more closely the surface of cancer cells and thus produce an effective synthetic vaccine. Davis and collaborators prepared glycopolymer-based gold nanoparticles which can generate strong and long-lasting production of antibodies that are selective to the Tn-antigen glycan and cross-reactive toward mucin proteins displaying Tn, which show a simple and modular approach toward synthetic anticancer vaccines (Fig. 15).[50]

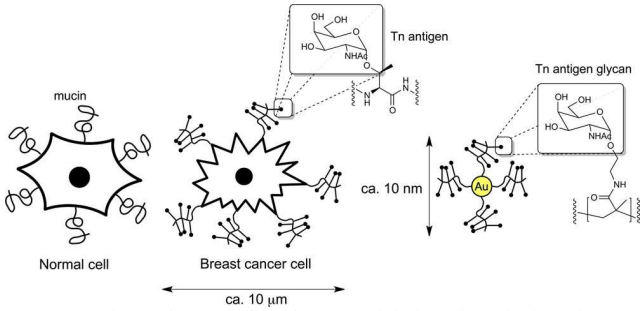

Fig. 15 Glycopolymer and gold nanoparticle-based synthetic anticancer vaccines. Reprinted with permission from ref. 50. Copyright (2013) American Chemical Society.

Nanoparticles prepared via self-assembly of amphiphilic copolymers are quite often used as delivery vehicles to load drugs such as doxorubicin (DOX) [8,10] and insulin [29,81,82,83]. For example, Shi and coworkers synthesized a biodegradable and biocompatible block copolymer poly(ethylene glycol)-*b*-poly(aspartic acid-co-aspartamidophenylboronic acid) PEG-*b*-P(Asp-*co*-AspPBA) and PAsp-based glycopolymer poly(aspartic acid-*co*-aspartglucosamine) P(Asp-*co*-AGA), the formed complex micelles showed notable glucose-responsiveness under physiological conditions and offered self-regulated insulin delivery in response to physiological glucose level (Fig. 16a).[83] In another example, an efficient one-pot reaction generated novel glycopolymer-porphyrin conjugate, where hydrophobic and photosensitive porphyrin was in the middle of the glycopolymer chain, and the conjugate then self-assembled into nanoparticles with potential applications in targeted photodynamic therapy (Fig. 16b).[32] Gold(I) complex auranofin has been used to treat rheumatoid arthritis and more recently against several tumour cell lines. Stenzel and coworkers prepared glycopolymers bearing thiosugar units that can be efficiently converted to polymeric Au(I) complexes. The micelles formed from the block copolymers displayed higher activity against OVCAR-3 cells than its small molecule analogue, offering a promising alternative delivery mechanism which may overcome the stability and toxicity issues faced by discrete Au(I) based chemotherapeutics.[51] In another example, polymeric DTC derivatives and their gold conjugates prepared by Narain and coworkers showed higher accumulation as well as cytotoxicity to cancer cells under hypoxic conditions in comparison to the normoxic ones, and hypoxic MCF-7 cells showed significant sensitivity toward the low molecular weight (10 kDa) glycopolymer-Au(I) complexes.[52] They further attached gold(I) triphenyl phosphine to glycopolymers decorated gold nanoparticles to prepare a new class of gold-based anticancer drugs, which are found to be more toxic than standard chemotherapeutic reagents such as cisplatin.[53]

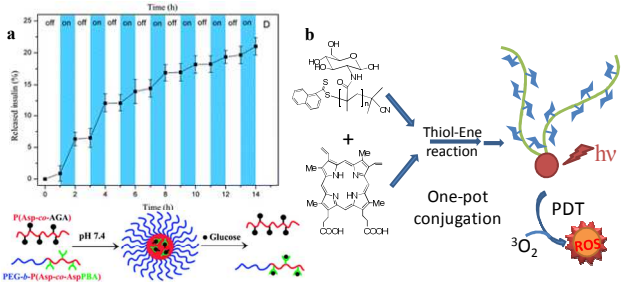

Fig. 16 a) Glucose-responsive glycopolymer-based micelles for insulin delivery (Adapted from ref. 83 with permission from RSC. Copyright 2013); b) Fabrication of protoporphyrin-glycopolymer conjugate for photodynamic therapy (Adapted with permission from ref. 32. Copyright (2014) Wiley VCH).

Fluorescent probes in targeted imaging and early detection of tumor cells are useful for disease and cancer therapy. Glycopolymers may bring desired features such as good stability, high specificity and efficiency for tumor cells, therefore glycopolymer-based fluorescent probes are attractive imaging candidates. These glycopolymer-decorated imaging probes include complex molecules of glycopolymers and organic fluorophore, magnetic metal nanoparticles, nanoclusters and quantum dots. For example, incorporation of 4,4-difluoro-4-bora-3a,4a-diazas-indacene (BODIPY) into a glycopolymer endows the polymer with fluorescence property, which can be used as a fluorescent probe for detection of asialoglycoprotein (ASGP) on liver cells, and with its potential application for fluorescent imaging in living cells.[35] Basuki *et al.* prepared mannose functionalized IONPs, (IONP@P(OEGA)-*b*-P(N_3Man)), which exhibited high transverse relaxivity when measured in MRI. And a significant change in relaxation was observed after binding to

the lectin Con A, with a response proportional to the lectin concentration, indicating that the specific binding of lectin to nanoparticle surfaces can be quantitatively detected using MRI, showing significant promise for future diagnostic applications.[56]

By grafting a glycocopolymer consisting of 6-*O*-methacryloylgalactopyranose (MAGal) and 4-(pyrenyl)butyl methacrylate (PyMA) onto magnetic silica particles, Pfaff *et al.* prepared galactose-displaying core-shell nanospheres exhibiting both fluorescent and magnetic properties. Incorporation of the galactose-containing polymers were found to induce the internalization of the fluorescent particles by mammalian cells such as A549 cells, with a particular tendency for targeting the cells' nucleus. The synthesized particles showed potential in both fluorescence and magnetic resonance imaging (Fig. 17b).[62] Lu *et al.* reported that random copolymer of 2-(methacrylamido) glucopyranose (MAG) and methacrylic acid (MAA) could be used as templates to prepare the glycopolymer-functionalized Ag nanoclusters through microwave irradiation, and the nanoclusters showed efficient binding ability toward K562 cells and inhibited the cell viability in a dose dependent manner (Fig. 17a).[84] Narain and coworkers prepared quantum dots (QDs) modified with biotinylated glycopolymers, the surface modified QDs showed excellent water solubility, colloidal stability and showed an enhancement in biocompatibility as compared to that of the original QDs.[71]

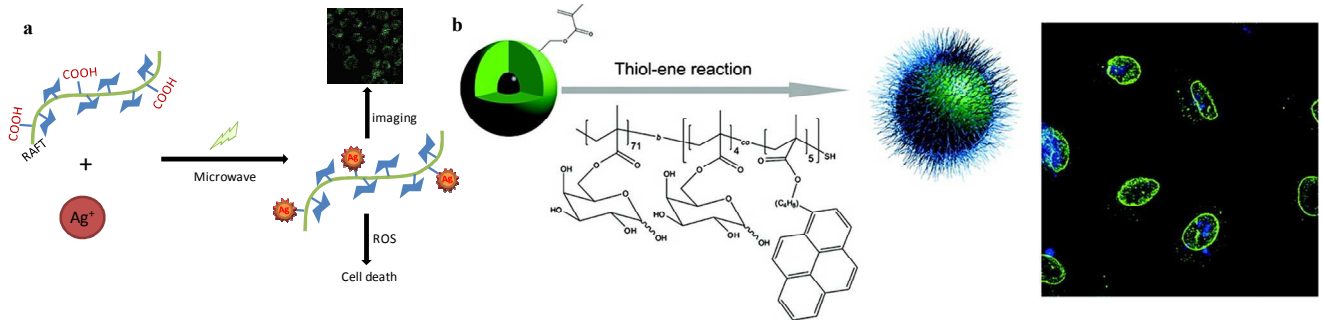

Fig. 17 a) Synthesis of glycopolymer-functionalized silver nanoclusters (Adapted with permission from ref. 84. Copyright (2014) Wiley VCH); b) Synthesis of fluorescent, magnetic glycopolymer-grafted nanoparticles and intranuclear optical imaging (Adapted with permission from ref. 62. Copyright (2011) American Chemical Society).

5. Conclusions

In this review, we have provided an in-depth discussion about the synthesis of various glycopolymer-based nanoparticles (NPs). The synthesis of these NPs have been generally documented into two main categories: (a) synthesis of glycopolymer-based nanoparticles via self-assembly; (b) synthesis of glycopolymer/inorganic hybrid nanoparticles. For those synthesized via self-assembly, a variety of polymers can be used, including amphiphilic block copolymers, hydrophilic glycopolymers linked with hydrophobic small molecules, amphiphilic statistical or gradient copolymers, amphiphilic homopolymers, double-hydrophilic block copolymers, etc. Spherical nanoparticles are commonly obtained, and by tuning polymer composition and other parameters, non-spherical NPs such as rod-like or vesicles can be obtained. For the synthesis of glycopolymer/inorganic hybrid nanoparticles, it is advantageous that these type of glyconanoparticles combine the multivalent presentation of carbohydrates from glycopolymers with the special chemico-physical properties of the nano-sized inorganic core. A variety of inorganic NPs such as gold, iron oxide and quantum dots can be used to fabricate novel conjugated glycopolymeric nanoparticles with defined variable shapes and new properties. We also provide a brief discussion about the applications of these glycopolymer-based nanoparticles. Due to the importance of carbohydrates in biology as noted that sugar is essential to understand the language of life, most applications of the glycopolymer-based nanoparticles are health related. They were used as models to investigate carbohydrate-protein/cell interactions, as drug-delivery vehicles, vaccine candidates and imaging probes, etc. It should be noted that glycopolymer-based nanoparticles are most commonly used as models or demonstrating concepts. More not only in numbers but also in-depth applications are expected, as compared to oligosaccharide-based nanoparticles, glycopolymer-based nanoparticles facilitate high binding affinity and specificity due to their multivalent display of carbohydrates and hairy structures. We believe that the emergence of more efficient polymeric synthetic methods such as one-pot and multi-component reactions that greatly simplifies fabrication of carbohydrate-based materials, will contribute more to the progress of glycoscience.

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TOC

This review focuses on the different approaches to synthesisze glycopolymer-based nanoparticles and their various applications.