

Cite this: *Chem. Sci.*, 2025, 16, 22805

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 31st July 2025
Accepted 10th November 2025

DOI: 10.1039/d5sc05780a

rsc.li/chemical-science

Multivalently engineered glyco-nanoplatfoms for targeted therapy and diagnostics

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Glyco-nanoplatfoms have emerged as powerful nanosystems that exploit glycan–lectin interactions for targeted therapy, diagnostics, and immunomodulation. By presenting glycans in multivalent architectures, glyco-nanoplatfoms enhance binding affinity and specificity toward glycan-recognizing receptors on mammalian and bacterial cells. This perspective highlights recent advances in the design and synthesis of glyco-nanoplatfoms across four key classes, including glyco-gold nanoparticles, glycopolymer-based nanoplatfoms, glyco-functionalized quantum dots, and glycan-based magnetic nanocomposites. Through diverse synthetic strategies, structurally distinct glyco-nanoplatfoms have been developed with improved binding affinities, stability, and biodistribution. Moreover, we further discuss their diverse biomedical applications in both mammalian and bacterial cells, ranging from targeted cancer therapy and biosensing to immunomodulation and antimicrobial treatment. Finally, we outline key challenges and provide an outlook on further directions in this field, aiming to unlock the therapeutic potential of the glyco-code.

1 Introduction

Carbohydrates are ubiquitous and functionally diverse biomolecules whose precise spatial arrangement and

composition encode a rich layer of biological information, referred to as the “glyco-code”.^{1,2} Beyond their role as essential nutrients, these glycans mediate a wide range of cellular communication and recognition. Through interactions with carbohydrate-binding proteins such as lectins, they regulate numerous pathophysiological processes, including cell differentiation, pathogen invasion, cancer progression, and immune dysfunction, positioning the glyco-code as a valuable blueprint for decoding disease mechanisms and advancing therapeutic innovation.^{3,4} While glycan–lectin interactions are typically highly selective, their intrinsic monovalent affinities are

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relatively weak, often falling in the mM to μM range.⁵ To overcome this limitation, nature employs a compensated strategy by presenting multiple glycan copies in the carbohydrate epitopes to enable multivalent engagement with several receptor sites.⁶ This cooperative binding markedly enhances overall affinity and often improves specificity. Although the underlying molecular mechanisms of multivalent interactions remain incompletely understood, it is widely believed that clustering, rebinding, and chelation processes may act in concert to strengthen glycan–protein interactions.⁵

Building on this principle, glyco-nanoplatfoms have been developed as powerful systems that can present glycans in a multivalent arrangement with different architectures, to enhance binding affinities to target biological receptors.⁷ Various glycan-functionalized nanostructures have been explored in targeted cancer therapies,^{8,9} immunomodulation,^{10,11} biosensing,^{12,13} and antimicrobial strategies (Fig. 1).¹¹ These investigations have deepened our insights into the

primary factors that govern carbohydrate–lectin interactions. Beyond the degree of multivalency, factors such as glycan type, conjugating linker, and the size and morphology of glyco-nanoplatfoms have been shown to play critical roles in modulating glycan–lectin interactions both *in vitro* and *in vivo*. Moreover, the dynamic adsorption of proteins onto nano-carriers, known as the protein corona, has been shown to markedly influence *in vivo* performance of glyco-nanoplatfoms, including biodistribution and targeting accuracy.¹⁴ Regulating the composition of the protein corona presents a valuable approach to improving the selectivity and therapeutic efficacy of glyco-nanoplatfoms in biomedical applications.¹⁵ In this perspective, we summarize recent progress in the synthesis of different types of glyco-nanoplatfoms and discuss their applications in both mammalian and bacterial cells, including targeted cancer therapy, biosensing, immunomodulation, and antimicrobial treatment. These advances will push forward glyco-nanoplatfoms as next-generation tools for clinical treatments.



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2 Classes of glyco-nanoplatfoms

Inspired by the intriguing advantages of glyco-decorated nanoplatfoms, diverse glyco-nanosystems have been developed to probe carbohydrate–protein and carbohydrate–carbohydrate interactions. In general, four principal classes of glyco-nanoplatfoms dominate the field, including glyco-gold NPs (glyco-AuNPs), glycopolymer-based nanoplatfoms, glyco-functionalized quantum dots (glycodots), and glycan-based magnetic nanocomposites. Nonetheless, clinical translation remains hindered by synthetic complexity, scalability constraints, and inconsistent efficacy,^{16,17} prompting continued refinement and optimization of glyco-nanoplatfom design and fabrication. This section summarizes recent advances in their preparation to guide the development of more efficient glyco-



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Fig. 1 Glyco-nanoparticles enable diverse biological applications via specific carbohydrate-lectin interactions, including targeted cancer therapy, biosensing, immunomodulation, and antimicrobial strategies. In cancer therapy, glyco-nanoparticles enter tumor cells via receptor-mediated endocytosis and release payloads such as prodrugs, proteins, or DNA/RNAs to induce cell death. Light-responsive agents further support photothermal (PTT) or photodynamic (PDT) therapy, either alone or in combination with chemo- or immunotherapies. For biosensing applications, glyco-nanoparticles enable the detection of cancer cells or pathogens by different techniques, depending on the nanomaterial composition, including glycodots-based multicolor detection, magnetic resonance imaging (MRI) using magnetic nanocomposites, surface-enhanced Raman spectroscopy (SERS) via metallic nanostructures, as well as fluorescence/near-infrared imaging, colorimetric aggregation, and electrochemical sensing. For immunomodulation, they activate dendritic cells or repolarize anti-inflammatory M2 macrophages into pro-inflammatory M1 phenotypes, reshaping the immune microenvironment to enhance T cell-mediated clearance of tumor cells or bacteria. In antimicrobial strategies, glyco-nanoparticles recognize bacterial surface lectins or enter cells via ATP-dependent ABC transporter commonly reported in glyco-based gold nanoparticles. Combined therapies, such as PTT coupled with antimicrobial agents, disrupt bacterial membranes, compromise cell integrity, and promote intracellular drug delivery. Moreover, quorum-sensing interference suppresses biofilm formation and virulence factor expression by mimicking inducers or blocking quorum-sensing receptors.

nanoparticles. Table 1 illustrates various glyco-nanoparticles with their biological applications or improved system features.

2.1 Glyco-gold nanoparticles

For decades, gold nanoparticles (AuNPs) have attracted substantial interest for biomedical applications due to their desirable features,¹⁸ such as chemical inertness, stability, unique nanoscale optical/electronic properties, and readily tunable morphology.^{19,20} Harnessing these attributes, AuNPs have been explored extensively as potential therapeutic and diagnostic platforms in cancer diseases,²¹ immunomodulation,²² and bacterial infections.²³ Though they possess these distinctive advantages, AuNPs still perform suboptimally *in vivo*.²⁴

Specifically, once recognized as exogenous molecules, AuNPs trigger the immune system and are rapidly removed from the bloodstream, which causes poor biodistribution and shortened circulation time. To overcome these limitations, surface glyco-functionalization offers a practical strategy. By displaying glycans, glyco-AuNPs appear more "self-like" to the host immune system. The resulting increase in immune tolerance can enhance the biocompatibility and prolong circulation of glyco-AuNPs,²⁵ thereby improving the target delivery efficiency.

Carbohydrate-functionalized AuNPs have attracted growing interest due to their promising applications in biomedical nanotechnology.^{26,27} The primary approach for anchoring carbohydrates onto AuNPs involves covalent attachment through bond formation with the metal surface, most



Table 1 Summary of diverse glyco-nanoplatform types and their associated biological applications or improved system features

Glyco-nanoplatform types	Applications/improved features	Ref.		
Glyco-gold nanoparticles (glyco-AuNPs)	Ultra-small thiolated glyco-AuNPs by <i>in situ</i> reduction	Modeling cell surface interactions to study carbohydrate self-recognition	29	
	Glucose-based ultra-small AuNPs	First preparation of glyco-AuNPs Drug delivery of ciprofloxacin against <i>Plasmodium falciparum</i> (<i>P. falciparum</i>)	31	
	Ultra-small thiolated glyco-AuNPs	First photo-induced microfluidic strategy for reproducibility and precise control over particle size and morphology	34	
	Mannose-stabilized AuNPs by post ligand exchange	Rapid, quantitative colorimetric detection of lectin	36	
	Glycosaminoglycan-anchored AuNPs	Stem cell neural differentiation	38	
	Glyco thiolate-capped AuNPs	Cytotoxicity in peripheral blood mononuclear cells (PBMCs) and A549 cancer cells	39	
	<i>N</i> -Acetylneuraminic acid-functionalized AuNPs	Detection and capture of SARS-CoV-2	40	
	Liposomal hyaluronic acid (HA)-AuNPs	Surface-enhanced Raman spectroscopy (SERS) imaging for tumor visualization and surgical guidance	41	
	Star-shaped glycopeptide-capped glyco-AuNPs	Enhanced immune response for glyco-vaccine development	42	
	Spherical mannose- or sialic acid-functionalized AuNPs	Functional polarization of liver macrophages Highly reproducible <i>via</i> a microfluidic strategy	44	
	Glycopolymer-based nanoplatforms	Amphiphilic PMAG- <i>b</i> -P(Lys- <i>co</i> -Phe) self-assembled spherical glycopolymer-based nanoplatforms	Drug delivery of paclitaxel against A549 and MCF-7 cancer cells	8
		Linear or branched oligomannose-functionalized amphiphilic Janus glycodendrimers self-assembled glycodendrimersomes	Simulation of cell membrane for probing glycan-lectin interactions	51
		Amphiphilic Janus glycopeptide dendrimers self-assembled glycopolymer nanoplatforms with diverse structures	Lectin-guided, pH-responsive drug delivery system with immunotherapeutic potential	52
Glycopolymer nanocarriers <i>via</i> co-assembly of hydrophobic PBA- <i>m</i> PEG- <i>t</i> -PCL and mannoside- <i>b</i> -PCL		Mannose-guided nanocarriers for MDA-MB-231 breast cancer cell targeting with high drug payload	53	
Zwitterionic guanidiniocarbonyl pyrrole (GCP)-lactose folded glyco-nanoplatforms		Lactose-guided, pH-responsive nanocarriers for liver tumor targeting	54	
Cationic dihexadecyldimethylammonium bromide (DHDAB) and mannose-mimetic polymer co-assembled glyco-nanoplatforms		Cationic glycopolymer nanocarriers for nucleic acid delivery and cancer vaccine immunotherapy	55	
Dextran-hydroxypropyl methacrylate (HPMA) UV-triggered glyco-nanoplatforms		Photo-controlled self-assembly of dextran-stabilized nanostructures with tunable morphology	56	
Glyco-inside enzyme-responsive glyco-nanoplatforms		Controlled antigen release activated by lysosomal lipase	58	
Polymerization-induced self-assembled (PISA) glyco-nanoplatforms with internal galactose		First combination of glyco-inside strategy with reversible addition-fragmentation chain transfer (RAFT) mediate PISA for tunable glycopolymer nanoassemblies	59	



Table 1 (Contd.)

Glyco-nanopatform types	Applications/improved features	Ref.	
Glyco-functionalized quantum dots	Lactose-containing glycopolymer-grafted nanosystems	Selective bacterial capture and water disinfection	60
	Glucose- or <i>N</i> -acetylglucosamine-based glycopolymer-grafted silica NPs	Tumor metastasis inhibition <i>via</i> anti-adhesion by glyco-nanopatforms mimicking natural glycosaminoglycans	61
	Aminoxy thiol and phosphorylcholine-modified Cd-based glycodots	<i>In vivo</i> live near-infrared fluorescence imaging (NIR-FI) revealing the role of terminal sialic acids in blood circulation and biodistribution	66
	Glucose-coated CdSe/ZnS glycodots containing specific sulfonamide inhibitor	Targeted imaging of carbonic anhydrase IX-overexpressing cancer cells <i>via</i> sulfonamide inhibitor	65
Glycan-based magnetic nanocomposites	α -1,2-Manno-biose-coated CdSe/CdS glycodots	Shape-dependent multivalent lectin recognition in bacteria	68
	Glucose-coated CuInS ₂ glycodots	Cd-free glycodots with dual visible and NIR fluorescence for biocompatible imaging	67
	Lactose-coated carbon dots	Fluorescent glyco-nanoprobes for selective lectin targeting and cellular imaging	70
	α -2,6-Sialyllactose-decorated carbon dots	Multivalent Siglec-targeting glycodots for selective binding and cytotoxicity induction in B cells	71
	Physically blended chitosan-coated magnetic nanoparticles (MNPs)	Enzyme immobilization and efficient galactooligosaccharide (GOS) production	78
	Graft-polymerized chitosan-coated MNPs	pH-responsive MNPs for high-efficiency paclitaxel delivery and cancer chemotherapy	80
	Dextran-coated superparamagnetic iron oxide (SPIO)	Magnetic resonance imaging (MRI)	82
	Cross-linked iron oxide nanoparticles (CLIO)	Diagnostic magnetic resonance, targeted MRI, positron emission tomography (PET) imaging, and photodynamic therapy	84
	Starch-coated magnetic nanocrystals	Effective purification of recombinant proteins bearing the maltose-binding motif	85
	Co-precipitated chitosan-HA magnetic nanocarriers	pH-responsive doxorubicin (DOX) nanocarriers with high encapsulation efficiency and antitumor activity against MDA-MB-231 and MCF-7 cancer cells	86
Hydrothermally synthesized chitosan-coated MNPs	Ultrasensitive tuberculosis diagnosis <i>via</i> capturing acid-fast bacilli (AFB) from sputum	72 and 87	
	Rapid <i>Escherichia coli</i> (<i>E. coli</i>) capture from leafy greens		
	Ionically cross-linked hydrogel beads between alginate and mixed magnetic cellulose nanocrystals	Ionic hydrogel system for magnetically guided, controlled delivery of anti-inflammatory drug, ibuprofen	88
	Magnetic hydrogel nanoclusters integrated by alginate and hydrophobic MNPs	Both MRI and photoacoustic imaging	81
Chitosan-sodium tripolyphosphate (NaTPP) ionically cross-linked magnetic nanogels	Cationic magnetic hydrogels for enhanced cancer cell uptake <i>via</i> electrostatic interaction	89	
	Magnetic hydrogels stabilized by internally cross-linked HA	Tissue-regenerative hydrogels enabling cell adhesion, angiogenesis, and controlled degradation	90



Table 1 (Contd.)

Glyco-nanoplatform types	Applications/improved features	Ref.
Monosaccharide-conjugated iron oxide nanoclusters	Cell subtype differentiation by multivalent glycan-lectin recognition	91
HA-conjugated magnetic nanoplatforms integrated with indocyanine green (ICG)	Dual-modal MRI/NIR-FI for HA-mediated cancer targeting	73
Sialyl Lewis ^x -conjugated magnetic nanoparticles	Targeted imaging of inflamed endothelium by Sialyl Lewis ^x -selectin interaction	92
Glucosamine-conjugated MNPs by glutaraldehyde linkage	Selective glycoprotein concanavalin A (conA) detection and magnetic isolation through glucose-ConA interaction	93
Noncovalently glyco-coated MNPs	Magnetically guided <i>E. coli</i> capture and swarming modulation for biofilm research	79

commonly *via* Au-S linkages.²⁸ Construction of glyco-AuNPs typically relies on neoglycoconjugates bearing thiol-terminated linkers or their disulfides. These conjugates are introduced either by (1) *in situ* reduction of gold salts in the presence of thiolated glycoconjugates or (2) post ligand exchange, where thiolated glycoconjugates replace existing surface ligands on preformed nanoparticle cores. In 2001, Penadés *et al.* first described the preparation of glyco-AuNPs by the landmark Brust-Schiffrin two-phase protocol for the synthesis of thiol-derivatized AuNPs.²⁹ In particular, the method utilized tetraoctylammonium bromide (TOAB) as a phase transfer reagent and sodium borohydride (NaBH₄) as a strong reducing agent (Fig. 2a). Following the immediate addition of the capping thiolated glycoconjugates, this method provides ultra-small glyco-AuNPs with core diameters typically of 1–3 nm. By this method, different ultra-small glyco-AuNPs were achieved by employing various thiol derivatives.³⁰ Despite the success of this strategy, the resulting glyco-AuNPs often exhibited broad size distribution and low yield, primarily due to an increased tendency to aggregate. In addition, the use of strong reducing agents may degrade sensitive thiolated ligands, compromising the stability and functionality of glyco-AuNPs. Recently, alternative protocols have been attempted to synthesize AuNPs without relying on NaBH₄ as a reducing agent. Seeberger *et al.* developed a streamlined method for preparing monodisperse glucose-conjugated ultra-small AuNPs (Fig. 2b).³¹ In particular, they utilized the 1-thiogluco-6-phosphate as both a stabilizing and reducing agent, eliminating the need for an additional reducing agent. By fine-tuning the ratio of HAuCl₄ and 1-thio-β-D-glucose sodium, uniform glucose-AuNPs rapidly formed within seconds, though other glyco-derivatives were not involved in this method. Moreover, Jiang *et al.* reported the preparation of ultra-small AuNPs by mixing HAuCl₄ solution with 4,6-diamino-2-pyrimidinethiol (DAPT) in ethanol at 70 °C for 24 h.³² Similarly, Liu *et al.* obtained AuNPs ranging from 2.4–6.1 nm by

stirring a mixture of HAuCl₄ and thiol-ligands at 95 °C for 18 h, with particle size controlled by the ligand-to-gold ratio.³³ However, both protocols require elevated temperatures and long reaction times. To address these challenges, Polito *et al.* developed a photo-induced microfluidic strategy for the synthesis of different ultra-small glyco-AuNPs (Fig. 2c),³⁴ offering precise control over particle size, morphology, and reproducibility. The one-pot method enables the formation of ultra-small glyco-AuNPs at room temperature within 2 h by flowing the HAuCl₄ and thiol-glycoconjugates through a UV-irradiated microfluidic reactor, without extra reducing agents. Importantly, under UV light, the solvent undergoes photodecomposition, generating hydroxyl radicals and solvated electrons that serve as active reductants in the formation of ultra-small glyco-AuNPs.^{34,35}

The other common strategy for constructing glyco-AuNPs with thiolated carbohydrates is post ligand exchange, where thiol-terminated glycoconjugates are introduced onto preformed AuNP cores. This approach was initially reported by Russell *et al.*,³⁶ who prepared mannose-stabilized AuNPs using the classical method developed by Turkevich *et al.*,³⁷ with sodium citrate serving as both the reducing and stabilizing agent (Fig. 3a). In this method, preheated solutions of HAuCl₄ and sodium citrate were rapidly mixed and stirred at 85 °C for 2.5 h. Thiolated glycans were subsequently added, and the solution was left at room temperature for 24–48 h or boiled for 1–2 min to enable partial displacement of the surface-bound citrate ions, leading to the formation of Au-S bonds and self-assembly of glyco-AuNPs.^{38–41} These anisotropic glyco-AuNPs exhibit strong surface plasmon resonance (SPR) signals, enabling their applications in surface-enhanced Raman spectroscopy (SERS), biosensing, and photothermal therapy. To further enhance their SPR properties and improve carbohydrate-protein binding efficiencies, star-shaped AuNPs have been developed. Typically, they are synthesized through



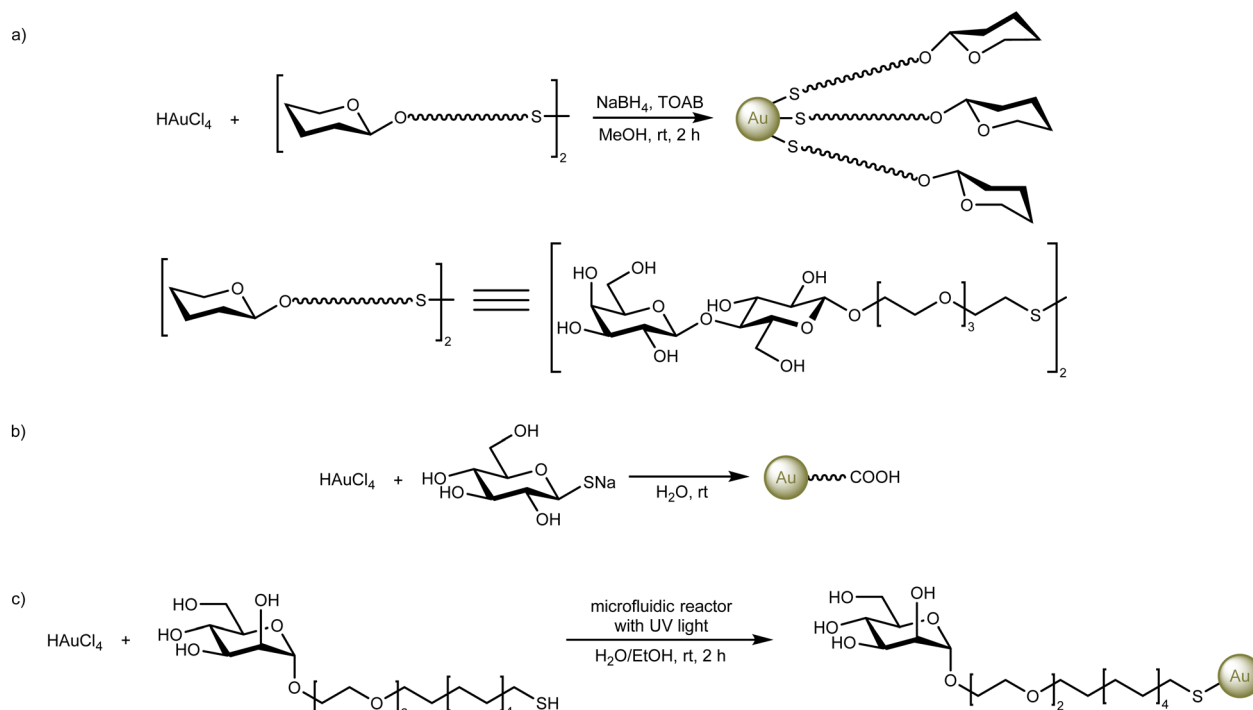
In situ reduction of gold salts in the presence of thiolated glycoconjugates

Fig. 2 Synthesis of glyco-AuNPs through *in situ* reduction of gold salts. (a) Synthesis of glyco-AuNPs by conventional NaBH_4 reduction; (b) synthesis of glyco-AuNPs using 1-thioglucose as both reducing and stabilizing agent; (c) photo-induced microfluidic synthesis of glyco-AuNPs.

Post ligand exchange



Fig. 3 Synthesis of glyco-AuNPs through post ligand exchange. (a) Synthesis of glyco-AuNPs by conventional post ligand exchange, with sodium citrate serving as both reducing and stabilizing agent; (b) two-step synthesis of star-shaped glyco-AuNPs: seed generation using sodium citrate, followed by shape growth under ascorbic acid and sodium nitrate; (c) one-step, seedless synthesis of spherical glyco-AuNPs with high reproducibility using a microfluidic platform.



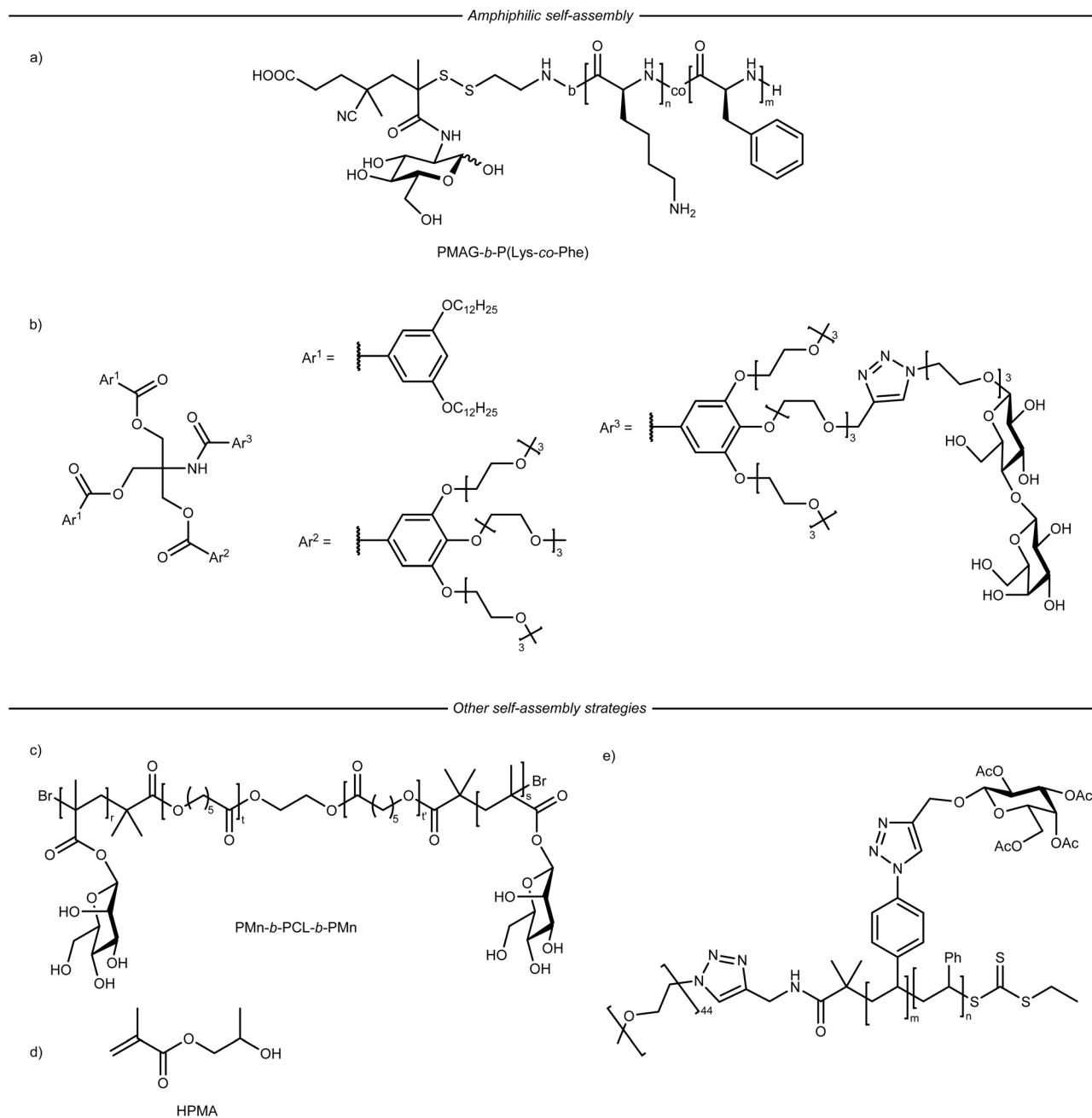


Fig. 4 Representative glycopolymer structures employed in the formation of glycopolymer-based nanoplatfoms *via* self-assembly. (a) Structure of amphiphilic PMAG-*b*-P(Lys-co-Phe) copolymer forming spherical glycopolymer-based nanoplatfoms; (b) structure of amphiphilic Janus glycodendrimers bearing sequence-defined oligomannose for the formation of glycodendrimersomes; (c) structure of mannose-mimicking ABA-type triblock copolymer (PMn-*b*-PCL-*b*-PMn), which electrostatically co-assembles with dihexadecyldimethylammonium bromide (DHDAB); (d) structure of hydroxypropyl methacrylate (HPMA) grafted onto dextran backbone, enabling UV-induced self-assembly into nanostructures; (e) representative glycopolymer structure applied in the "glyco-side" strategy.

polymers but also provided a sharp and switchable pH-response mechanism for controlled drug release that is distinct from conventional acid-labile linker cleavage. Owing to the presence of lactose moieties, the resulting glycopolymer-based nanoplatfoms exhibited potential for targeted delivery to HepG2 liver cancer cells. Separately, Chakravarty *et al.* constructed glycopolymeric nanoplatfoms by co-assembling a mannose-mimicking ABA-type triblock copolymer (PMn-*b*-PCL-*b*-PMn) with the cationic surfactant dihexadecyldimethylammonium

bromide (DHDAB) (Fig. 4c).⁵⁵ The electrostatically driven co-assembly resulted in stable, well-defined positively charged nanoplatfoms capable of encapsulating nucleic acids, which not only protected nucleic acids from enzymatic degradation but also promoted dendritic cell uptake and activation through electrostatic interactions with negatively charged membranes, supporting their potential as vaccine carriers for cancer immunotherapy. In addition to attaching sugar monomers onto different polymers, Six *et al.* first utilized the reversible addition-





Fig. 5 Representative glycopolymer structures for the formation of glycopolymer-based nanoplateforms by grafting glycopolymers onto nanosystems. (a) Structure of lactose-containing glycopolymers grafted onto core nanoplateforms; (b) structure of glucose-derived glycopolymers grafted onto silica nanoplateforms. Conjugating moieties are highlighted in blue.

terminal sialic acid residues in extending the circulation time and biodistribution of glycodots *in vivo*.⁶⁶ Building on the similar concept of a mixed-ligand surface, Richichi *et al.* designed a multifunctional glycodot platform based on CdSe/ZnS QDs using a dual-ligand coating (Fig. 6a).⁶⁵ A glucose-attached ligand served as a stabilizing agent to prevent aggregation in biological fluids, while the other, containing a specific sulfonamide inhibitor, conferred active targeting of the cancer biomarker carbonic anhydrase IX (CA IX). The resulting glycodots demonstrated selective binding of bladder cancer cells overexpressing CA IX, with no binding observed in control cells lacking the protein. This work highlights the unique integration of colloidal stability and specific molecular recognition with the superior optical properties of QDs, yielding a robust nanoprobe for targeted cancer imaging. Advancing beyond the dual-ligand,

spherical QD design, Guo *et al.* recently introduced a structurally refined glycodot by employing elongated CdSe/CdS QDs coated with a single ligand presenting α -1,2-manno-biose (DiMan) to investigate how glycodot's shape affects multivalent lectin–glycan interactions.⁶⁸ Using two structurally similar tetrameric lectins, DC-SIGN and DC-SIGNR as models, they demonstrated that scaffold curvature dictates distinct binding modes. This work highlights glycodots as mechanistic probes for shape-selective lectin recognition and guides the rational design of glyco-nanoplateforms for targeting multivalent lectins. Despite their promising optical properties, Cd-based QDs pose significant cytotoxicity risks due to the release of heavy metal Cd²⁺ ions under physiological conditions, which limits their biomedical applicability. This concern has prompted growing interest in developing Cd-free glycodots with reduced toxicity.

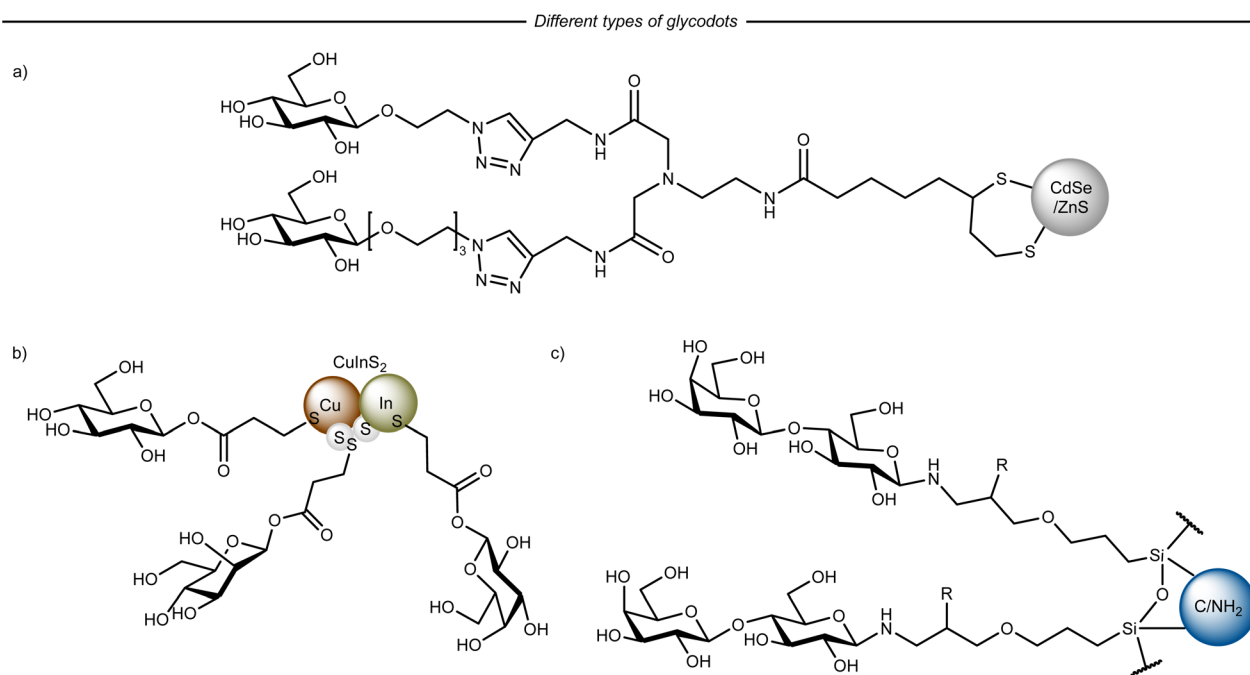


Fig. 6 Representative structures of different types of glycodots. (a) Structure of a glycodot based on conventional CdSe/ZnS quantum dots (QDs) coating with glucose-derived ligand; (b) structure of glyco-CuInS₂ QDs free of heavy metals; (c) structure of lactose-derived carbon dots (CDs).





Fig. 7 Representative glyco-based magnetic nanocomposites in which polysaccharides act as structural scaffolds. (a) Synthesis of chitosan-based magnetic nanosystems by the blending method; (b) synthesis of starch-based magnetic nanocrystals with uniform particle distribution by *in situ* co-precipitation; (c) synthesis of glyco-based magnetic hydrogels with negatively charged alginate by ionic gelation.

30–40 nm dextran-coated superparamagnetic iron oxide (SPIO) by co-precipitating iron salts in an alkaline solution with dextran. Subsequent periodate oxidation and reductive amination enabled conjugation of *Staphylococcus aureus* (*S. aureus*) protein A, facilitating efficient immunolabelling and magnetic separation of antibody-tagged cells using simple permanent magnets. The dextran-coated SPIO has been proved by the U.S. FDA as an MRI contrast agent, especially for hepatic imaging. However, their rapid clearance by the liver and spleen limits their utility for targeted applications. To address this, Weisleder and co-workers⁸³ developed monocrystalline iron-oxide NPs (MION), yielding 4–5 nm single-crystal cores with reproducible colloidal and magnetic properties for target specific MRI. Nevertheless, the noncovalent association between the iron core and dextran shell rendered the structure susceptible to dissociation under physiological conditions. Therefore, the MIONs were further modified by cross-linking the dextran shell with epichlorohydrin (cross-linked iron oxide nanoparticles, CLIO), followed by surface animation to finally give CLIO-NH₂.⁸⁴ This cross-linked formulation significantly improved *in vivo* stability and introduced abundant reactive amine groups, enabling efficient conjugation of targeting ligands and fluorophores for robust and multimodal imaging applications. Moreover, the co-precipitation strategy has been extended to a variety of polysaccharide systems. For instance, Frank *et al.*⁸⁵ employed a co-precipitation method to prepare starch-coated magnetic iron oxide nanocrystals with an average size of 11.5 nm and a narrow distribution (Fig. 7b). In this system, starch functioned not only as a stabilizer but also as a template, promoting uniform particle distribution and enabling effective affinity purification of several recombinant proteins bearing the

maltose-binding motif. While this system remained confined to sorbent applications, Rezaei *et al.*⁸⁶ adapted the co-precipitation strategy within a blended chitosan-HA matrix, followed by κ -carrageenan cross-linking, to construct multifunctional magnetic nanocarriers. This design achieved a high encapsulation efficiency of 83% and enabled pH-responsive release of DOX, with up to 84% release at pH 5.5, demonstrating potent antitumor activity against both MDA-MB-231 and MCF-7 cancer cells. Moreover, the hydrothermal method has also been employed to facilitate *in situ* magnetite nucleation under controlled high-temperature and high-pressure conditions, simultaneously enabling glycan coupling to form well-defined and stable nanostructures with uniform dispersion and reduced leakage. A notable example is the development of chitosan-based MNPs for capturing acid-fast bacilli (AFB) from sputum, as demonstrated by Alocilja *et al.*⁷² In this system, ferric chloride and sodium acetate were dissolved in ethylene glycol and heated in a sealed Teflon-lined vessel at 200 °C for 15 h, with chitosan added directly during synthesis, to generate the final MNPs with a glycan shell of 10–50 nm. When used in combination with Tween 80 as a dispersant, the glycan-based MNPs improved AFB quantification by up to 445% compared with smear microscopy, offering a rapid, low-cost, and sensitive diagnostic tool for tuberculosis. A similar nanocomposite was later applied to pathogen detection in food matrices by the same group,⁸⁷ which enabled the rapid capture of *E. coli* directly from leafy greens within 60 min, as confirmed by transmission electron microscopy.

A milder and widely adopted technique for synthesizing glycan-based magnetic hydrogels is ionic gelation, which relies on the electrostatic interactions between ionic cross-linking agents and



glycans while encapsulating MNPs. Within such hydrogels, polysaccharides typically serve as stabilizers, enhancing structural integrity and regulating drug release. For instance, Bushra *et al.*⁸⁸ developed magnetic hydrogel beads for model drug delivery by the ionic gelation method. They first mixed magnetic cellulose nanocrystals (*m*-CNCs), an alginate matrix, and an anti-inflammatory drug, ibuprofen. Upon the addition of CaCl₂, the ionic cross-linking was induced between the negatively charged carboxylate group on alginate and Ca²⁺, yielding magnetic hydrogel beads capable of ibuprofen delivery. To address the incorporation of hydrophobic MNPs into hydrogels, Seo *et al.*⁸¹ employed a phase-transfer agent, tetramethylammonium hydroxide (TMAOH), which allowed stable dispersion of hydrophobic MNPs within alginate (Fig. 7c). Subsequent cross-linking with Ca²⁺ generated hydrogel nanoclusters suitable for dual-mode MRI and photoacoustic imaging, overcoming the challenge of stabilizing hydrophobic nanoplatfoms in biological systems. More recently, Dureja *et al.*⁸⁹ introduced a strategic material shift by utilizing chitosan, a positively charged polymer, in combination with sodium tripolyphosphate (NaTPP) as the ionic linker. The gelation occurred *via* electrostatic interactions between the chitosan amine groups and the phosphate groups of the NaTPP. The recruitment of chitosan possesses the MNPs with a positive charge surface, facilitating uptake by cancer cells, which tend to have a negatively charged surface. Furthermore, to extend the stabilizer role of the glycan matrix, HA was first incorporated into magnetic hydrogels owing to its unique roles in tissue regeneration, wound healing, and drug delivery, as reported by Liu *et al.*⁹⁰ HA, as essential polysaccharide found in natural tissues like skin and cartilage, was covalently cross-linked with trace peptide impurities retained from the extraction process *via* 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/*N*-hydroxysuccinimide (EDC/NHS) chemistry to form HA-MNP hydrogels. In this system, HA not only stabilized the hydrogel network but also enabled controlled degradation, supported cell adhesion, and promoted angiogenesis, highlighting their promise for tissue regeneration.

Apart from structural polysaccharides, certain glycans have been post-conjugated onto magnetic nanocomposites to serve as specific targeting ligands *via* glycan-lectin interactions. Among the available conjugation strategies, amide bond formation remains the most commonly employed method for anchoring glycans onto the surface of magnetic composites. For example, Huang *et al.*⁹¹ conjugated various monosaccharides, including mannose, galactose, fucose, and sialic acid, onto iron oxide NPs *via* amide bonds formed between sugar carboxyl groups and surface amines (Fig. 8a). Additionally, alkyne-modified *N*-acetylglucosamine was attached through click chemistry to azide-functionalized MNPs. The resulting clusters of glyco-conjugated MNPs demonstrated the ability to differentiate not only cancer cells from normal cells, but also closely related and metastatic cancer cell subtypes. In their subsequent study,⁷³ HA-conjugated MNPs were prepared through a similar amide bond linkage between HA and aminated MNPs, the latter obtained *via* co-precipitation with dextran and subsequent amination with ammonium hydroxide. Notably, this work marked the first application of HA in MNPs for cancer-targeting imaging through specific HA-lectin interaction. Moreover,

incorporation of indocyanine green (ICG) endowed the system with dual-modal capability, enabling both MRI and NIR-FI for enhanced diagnostic accuracy and sensitivity. In another example, Harms *et al.*⁹² recruited EDC/NHS coupling strategy to form amide bonds by reacting NHS-activated MNPs with amino-functionalized oligosaccharide, Sialyl Lewis^x (SX) (Fig. 8b), a well-established ligand of E- and P-selectin, to yield SX@MNPs. These selectin proteins are expressed on vessel endothelium during inflammation, where they mediate leukocyte recruitment to sites of injury. Importantly, exploiting the SX-selectin interaction, these nanocomposites bound selectively to inflamed endothelium with enhanced multivalent affinity and accumulated in brain vasculature after experimental stroke *in vivo*, highlighting promise for noninvasive detection of endothelial activation. In addition to amide bond conjugation, Basiruddin *et al.*⁹³ recently utilized glutaraldehyde-based coupling (Fig. 8c). In this approach, the dialdehyde glutaraldehyde acts as a linker between the amine groups of glucosamine and pre-synthesized MNP surface, forming imine bonds that were subsequently reduced and stabilized by NaBH₄. The glucose-functionalized MNPs demonstrated specific and selective binding to the glycoprotein concanavalin A (ConA), which has a known affinity for glucose. Upon binding, the magnetic nanocomposites aggregated and were readily separated magnetically, allowing efficient protein detection and isolation. Whereas the previous studies relied on covalent conjugation of glycans to MNP surfaces, alternative non-covalent approaches have also been investigated. Silva *et al.*⁷⁹ reported MNPs coated with carbohydrates like glucose, galactose, sucrose, and maltose *via* chemical adsorption, achieved by mixing with uncoated MNPs and stirred at 70 °C for 20 min (Fig. 8d). While the glycan layers contributed to stabilization and biocompatibility, their key role was in mediating bacterial binding. Binding assays revealed glycan-dependent bacterial association, with glucose- and galactose-coated MNPs preferentially binding *E. coli* and enabling efficient magnetization. Notably, glucose-coated MNPs also modulated *E. coli* swarming formation under a magnetic field, highlighting their potential as low-cost, biocompatible tools to manipulate bacterial communities for biofilm studies and drug evaluation. These diverse approaches offer versatile strategies for conjugating glycans onto MNP surfaces, facilitating the construction of biofunctional magnetic nanoplatfoms with specific targeting capabilities.

3 Glyco-nanoplatfoms toward mammalian cells

Due to their specific recognition by lectins on cancer and immune cell surfaces, glycans have been widely employed as targeting ligands in delivery systems to direct therapeutic agents to specific cell types or stimulate host immune responses. This glycan-mediated targeting strategy has demonstrated broad utility in glycan-based cancer therapy, biosensing, and immunomodulation.⁹⁴⁻⁹⁸ Several representative carbohydrate-lectin pathways have been extensively explored for biomedical applications.





Fig. 8 Representative glyco-based magnetic nanocomposites with carbohydrates serving as targeting ligands. (a) Synthesis of glyco-grafted magnetic nanoparticles (MNPs) by amide bond formation between carboxylated glycans and aminated MNPs; (b) synthesis of Sialyl Lewis^X-grafted MNPs by EDC/NHS coupling strategy; (c) synthesis of glucose-functionalized MNPs using a glutaraldehyde linker; (d) synthesis of sugar-coated MNPs by chemical adsorption.

In cancer cells, three major glycan–lectin interacting pathways have been widely utilized. First, the glucose transporter (GLUT) family, comprising various isoforms expressed on the cell surface, is frequently overexpressed in a wide range of tumors.^{99,100} These transporters recognize different saccharides, such as glucose, mannose, and fructose (Fig. 9a), facilitating efficient cellular uptake of glycan-conjugated nanosystems and enhancing therapeutic efficacy. Second, the asialoglycoprotein receptor (ASGPR), a liver-specific transmembrane protein upregulated in hepatocellular carcinoma (HCC) cells, selectively binds galactose/lactose and *N*-acetylgalactosamine *via* its Ca^{2+} -dependent carbohydrate recognition domain (Fig. 9b), enabling ligand internalization through ASGPR-mediated endocytosis.^{101–103} Third, CD44, a cell-surface glycoprotein overexpressed in various tumor cells, plays a critical role in cell adhesion and migration.^{104,105} Its high binding affinity for HA has led to the widespread use of HA-functionalized nano-platforms in tumor imaging and drug delivery (Fig. 9c).^{106,107}

Among immune cells, one of the most important lectins is the mannose or galactose receptor, known as CD206, which is highly expressed on tumor-associated macrophages (TAMs) (Fig. 9d), within the tumor microenvironment (TEM).¹⁰⁸ Targeting CD206 has been recognized as a promising strategy to reprogram TEM. The nano-platforms bearing CD206-binding glycans have been shown to induce the repolarization of anti-inflammatory M2 macrophages into pro-inflammatory M1 phenotypes,^{109,110} thereby converting the “cold” tumors into “hot” ones and enhancing antitumor efficiency.

3.1 Glycan-directed cancer therapy

The selective recognition between glycans and overexpressed lectin receptors on cancer cells has been increasingly harnessed to enhance the specificity and efficacy of anticancer therapies. For instance, Pei *et al.* decorated a nanoprodruge system with lactose to achieve ASGPR-mediated targeting, enabling selective cytotoxicity toward HepG2 hepatocellular carcinoma cells while markedly minimizing off-target effects on HL7702 normal liver cells.¹¹¹ Building on this targeting strategy, our group developed a theranostic galactose-modified AuNPs conjugated with a fluorophore and prodrug. The system leveraged galactose-ASGPR interactions, achieving preferential accumulation in HepG2 cells over HeLa and HEK293T cells, confirming ASGPR-dependent cellular selectivity.¹⁰³ Recently, Lai *et al.* synthesized a mannose-functionalized nano-platform, which was efficiently internalized by MDA-MB-231 breast cancer cells *via* mannose receptors, resulting in a significant suppression of tumor cell proliferation.⁵³

3.2 Glycan-based biosensing

Leveraging the specific interactions between carbohydrates and receptors overexpressed on cancer and immune cell surfaces, glyco-decorated nano-platforms have long served as targeting ligands for biosensing applications. Previously, our group developed a novel noncovalent “turn-off/turn-on” biosensor system using fluorescein boronic acid and mannose-modified AuNPs. In this design, fluorescence signal was initially quenched upon interaction with the glyco-AuNPs but restored by the addition of carbohydrate-specific lectin, enabling sensitive biosensing.





Fig. 9 Summary of carbohydrate–lectin interactions in mammalian cells (a–d) and bacterial cells (e and f). (a) Glucose, mannose, and fructose can be recognized and transported by GLUT1; (b) liver specific transmembrane protein, ASGPR, specially binds lactose; (c) CD44, overexpressed in tumor cell surface, binds hyaluronic acid; (d) CD206 in M2 macrophages serves as the mannose or galactose receptor; (e) mannose, glucose, and galactose selectively binds to the lectins on bacterial fimbriae; (f) ATP-dependent ABC transporter on cell membrane enables the transport of maltose into the cytoplasm. TMD: transmembrane domain.

Interestingly, intracellular uptake was observed in Jurkat human T lymphoma cells, highlighting the dual potential of this non-covalent platform for both biosensing and drug delivery.¹² Rather than relying on additional fluorescence, Huang *et al.* recently reported the real-time SERS imaging of breast cancer tissue through the HA-conjugated AuNPs.⁴¹ The installation of the HA ligand significantly enhanced the tumor-targeting efficiency through its specific binding to CD44 receptors. Although the optimized SERS-NPs enabled stable and high-resolution biosensing in tumor tissues, their ability to penetrate dense tumor regions was limited. To address this, Lei *et al.*⁶⁷ developed glyco-CuInS₂ QDs by conjugating different monosaccharides, including galactose, glucose, and mannose, onto the QD surface. *In vitro* imaging revealed excellent membrane-targeting properties of glycodots in HeLa, A549, and MKN-45 cancer cells. Remarkably, their highly negative zeta potential enabled deep penetration into the interior of 3D tumor spheroids. Beyond solid tumors, effective nanocarrier delivery across physiological barriers such as the blood–brain barrier (BBB) remains a major obstacle. Hrubý *et al.* developed glucose-conjugated solid lipid nanoparticles (SLNs) to enhance BBB permeability *via* GLUT1-mediated transport. *In vitro* studies using hCMEC/D3 cells confirmed significantly improved intracellular uptake of glucosylated SLNs compared to unmodified controls,¹¹² underscoring the potential of glucose conjugation for brain-directed drug delivery.

3.3 Glycan-driven immunomodulation

Immunotherapy has emerged as a powerful clinical strategy for treating infectious diseases and cancer.^{113–116} Yeh *et al.* identified CD206 as an effective target for cancer immunotherapy.¹¹⁷ By decorating with β -D-galactopyranoside, the glyco-AuNPs selectively

targeted CD206-expressing TAMs in lung cancer. These glyco-AuNPs exhibited enhanced tumor accumulation and, when combined with anti-PD-1 treatment, significantly boosted T cell activation and suppressed tumor growth. To minimize systemic immune activation induced by glycan–lectin engagement, Sita *et al.* recently developed mannose-functionalized AuNPs (Man-AuNPs) that selectively target liver macrophages.²² In a colorectal cancer liver metastasis model, Man-AuNPs reprogrammed tumor-associated macrophages toward a pro-inflammatory phenotype by upregulating related cytokines. Moreover, to enhance cancer immunotherapy by activating dendritic cells (DCs), Hu and co-workers¹¹⁸ first conjugated the DC-targeting ligand, mannose, directly to a model antigen, ovalbumin (OVA), creating a mannose–antigen conjugate (MAN-OVA). In this system, mannose engagement of C-type lectins on DCs promoted receptor-mediated uptake and directed OVA into the MHC class I processing pathway, leading to the subsequent activation of tumor-killing CD8⁺ T cells. Conversely, in a primary biliary cholangitis model, they suppressed inflammatory cytokine expression while promoting anti-inflammatory responses. These dual, context-dependent immunomodulatory effects are likely mediated by mannose-induced metabolic modulation. Man-AuNPs exhibited strong liver tropism and minimal systemic toxicity, offering a promising strategy for localized immunomodulation in both cancer and autoimmune diseases.

Glycan-mediated targeting offers a versatile platform across cancer therapy, biosensing, and immunomodulation. By leveraging the specific interactions between glycans and lectins on cancer and immune cells, glycan-functionalized nanocarriers can improve delivery specificity, enhance diagnostic accuracy, and enable immune reprogramming. These diverse



applications highlight the broad potential of glycan–lectin interactions in advancing targeted biomedical strategies.

4 Glyco-nanoplatfoms toward bacterial cells

Fimbriae on the bacterial surface are decorated with various lectins that enable specific binding to sugars such as mannose, galactose, and fucose (Fig. 9e).^{119–121} These glycan–lectin interactions have been exploited for bacterial targeting in both diagnostic and antimicrobial applications. Additionally, ATP-binding cassette (ABC) transporters located on the bacterial membrane have been leveraged to capture maltose- or maltodextrin-functionalized nanosystems for antibacterial treatments (Fig. 9f).^{23,122}

4.1 Glycan-driven bacterial infection inhibition

Glycan–lectin interactions offer a powerful strategy for selectively targeting drug-resistant pathogenic bacteria. For instance, our group designed galactose-functionalized black phosphorus nanosheets to co-deliver the antibiotic kanamycin and enable photothermal therapy against *Pseudomonas aeruginosa* PAO1 (*P. aeruginosa* PAO1), a Gram-negative, drug-resistant strain.¹²¹ In this system, bacterial capture was mediated through galactose-specific recognition. *In vivo* mouse studies confirmed that the glyco-nanosheets achieved comparable antibacterial activities. Following a similar binding mode, Zhang and co-workers¹²³ developed an acid-responsive polymeric glyco-nanoplatfom to eradicate the drug-resistant *P. aeruginosa* and disrupt its protective biofilm. The dual-targeting NPs were synthesized by self-assembling two acid-degradable block copolymers, functionalized with galactose ligands for LecA lectin binding and guanidine moieties for electrostatic bacterial capture. The photosensitizer Chlorin e6 (Ce6) was encapsulated within the core and released in response to the acidic biofilm microenvironment. Upon 660 nm light irradiation, reactive oxygen species were generated, achieving 95% bacterial killing and >70% biofilm disruption, while minimizing off-target toxicity. Moreover, the ATP-driven ABC transporter was exploited by Yan *et al.* to enhance pathogen localization during bacterial infection inhibition.²³ They engineered D-maltose-capped gold nanoclusters (AuNC-Mal), leveraging the specific recognition of D-maltose by ABC transporters on *P. aeruginosa* PAO1. Upon activation with thiourea (TU), antimicrobial species such as [Au(TU)₂]⁺ and smaller AuNCs were generated, achieving a minimum inhibitory concentration of 1 μg mL⁻¹ and exhibiting 30–60-fold lower *in vitro* cytotoxicity toward mammalian cells.

4.2 Glycan-based bacterial detection

Beyond bacterial eradication, surface lectin interactions have also been harnessed for the detection of drug-resistant bacteria. For instance, Kumar *et al.* reported the synthesis of silver NPs (AgNPs)-loaded gel microspheres functionalized with glucose, mannose, or galactose for simultaneous bacterial detection and inhibition.¹³ The glycan moieties enabled selective binding to bacterial cell walls, while AgNPs formed *in situ* imparted potent antimicrobial activity. Among them, mannose-functionalized

microspheres exhibited the fastest bacterial capture kinetics and effective inhibition against *E. coli* and antibiotic-resistant *S. aureus*. Bacterial detection was visually indicated by microsphere aggregation and a characteristic color change of AgNPs, providing a versatile platform for rapid bacterial sensing. Moreover, the dual-mode mannose-based biosensor was synthesized by Zhou *et al.*¹²⁴ to simultaneously identify mannose-binding bacterial species and quantify their adhesion strength. The sensor featured a gold electrode modified with AuNPs and a self-assembled mannose monolayer, enabling selective capture of bacteria expressing mannose-binding lectins. Leveraging SERS, the platform generated molecular fingerprints, which were analyzed *via* partial least squares discriminant analysis (PLS-DA) for accurate species differentiation. Meanwhile, electrochemical impedance spectroscopy (EIS) quantified binding affinities of the nano-biosensor, revealing significantly stronger adhesion of *Salmonella typhimurium* (*S. typhimurium*) compared to *E. coli* JM109. This integrated strategy overcomes the specificity limitations of conventional glycan sensors, offering both qualitative and quantitative insights from a single device. In addition to aggregation-based and SERS detection strategies, Nazari *et al.*¹²⁵ recently developed a label-free electrochemical biosensor for the rapid, sensitive, and selective detection of *E. coli*. Constructed on a glassy carbon electrode modified with AuNPs, the sensor featured a covalently attached mannose derivative, *p*-carboxyphenylamino mannose (PCAM), which specifically binds the FimH adhesin on *E. coli* type I fimbriae. Upon bacterial binding, the electron transfer to the electrode is impeded, resulting in an increase resistance measured by EIS. The sensor achieved an ultralow detection limit of 2 CFU mL⁻¹ with a broad dynamic range (1.3 × 10¹ to 1.3 × 10⁶ CFU mL⁻¹) and delivered results within 60 min. With excellent selectivity and performance in real samples such as tap water and milk, this cost-effective platform offers a practical tool for on-site microbial monitoring.

These advances underscore the potential of glyco-nanoplatfoms to improve both diagnostic accuracy and therapeutic efficacy in combating antimicrobial resistance. Moving forward, a deeper mechanistic understanding of glycan–lectin interactions may drive the development of programmable nanosystems capable of strain-specific targeting, real-time detection, and potent antimicrobial activity.

5 Summary and outlook

In this perspective, we focused on the recent advances in the preparation of different types of glyco-nanoplatfoms and discussed their potential biomedical application in both mammalian cells and drug-resistant bacteria. Leveraging a wide range of synthetic strategies, glyco-AuNPs, glycopolymer-based nanoplatfoms, glycodots, and glycan-based magnetic nanocomposites have been developed with distinct structural features, enabling enhanced binding affinities, stability, biodistribution, and delivery efficiency. By mimicking naturally multivalent glycan displays, glyco-nanoplatfoms have emerged as versatile platforms that harness the specificity of glycan–



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