

CARBOHYDRATE-BASED NANOSCIENCE: METALLO-GLYCODENDRIMERS AND QUANTUM DOTS AS MULTIVALENT PROBES

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ABSTRACT

Rapid progress in nanoscience and its potential applications have spurred observers to predict that nanotechnology will be the foremost science of the 21st century. Nanomaterials are beginning to have a major impact on research across the material and life sciences. While wide varieties of nanomaterials have been prepared with proteins, DNA, lipids and polymers, serious limitations arise with the neo-glycoconjugates due to the ambiguous structures and lack of well-defined carbohydrates. This chapter highlights the contribution of glyconanomaterials to biological, biochemical and biophysical studies. Particular focus will be placed on metallo-glycodendrimers and glyconanoparticles.

INTRODUCTION

Naturally occurring carbohydrates and oligosaccharides as well as glycoconjugates such as glycoproteins or glycolipids are present on the surface of nearly every cell within living systems [1]. These carbohydrates are known to have crucial roles in biological events as recognition sites between cells. They can trigger various phenomena such as cell growth, inflammatory responses or viral infections. In particular, the recognition phenomena between pathogens and host cells are thought to proceed *via* specific carbohydrate-protein interactions [2]. In comparison to the field of DNA/RNA (genomics) and proteins (proteomics), the understanding of the role of oligosaccharides/carbohydrates (glycomics) is very limited. While DNA-DNA and protein-protein interactions are well-studied and largely known, carbohydrate-carbohydrate and carbohydrate-protein interactions are poorly understood [1, 3]. The difficulties associated with studying carbohydrates are mainly a consequence of weak carbohydrate-protein interactions, the time-consuming synthesis and purification of oligosaccharides. In general, the interaction between a protein and a monosaccharide is weak with a dissociation constant (K_d) typically in the range of 10^{-4} — 10^{-6} M compared with 10^{-6} — 10^{-9} M antigen-antibodies interactions [4]. Multivalent presentation strongly enhances the binding to receptors on the cognate cells via polyvalent interactions, forming oligosaccharide structures of carbohydrate-protein receptors.

There is a clear need to develop new multivalent probes decorated with carbohydrates in order to investigate the information encoded by carbohydrates and biochemical events involving them. Such knowledge can open up novel platforms for a vast range of pharmaceutical, medical or biomedical commercial applications such as for imaging, targeted drug delivery, vaccine development and clinical diagnostics.

NANOPARTICLES AS MULTIVALENT PROBES

Nanoparticles are attractive multivalent systems: they exhibit unique pharmacokinetics (*e.g.* minimal renal filtration), very high surface to volume ratios, variation of material properties without change in chemical composition (*e.g.* quantum dot emission varies with size), they can exploit biological trafficking pathways (*e.g.* receptor-mediated endocytosis), and they have the potential for multi-functionality (*i.e.* both diagnostic and therapeutic) [5]. Multi-functional nanoparticles typically contain a particle ‘core’ and multiple surface moieties that can each endow the platform with distinct functionalities.

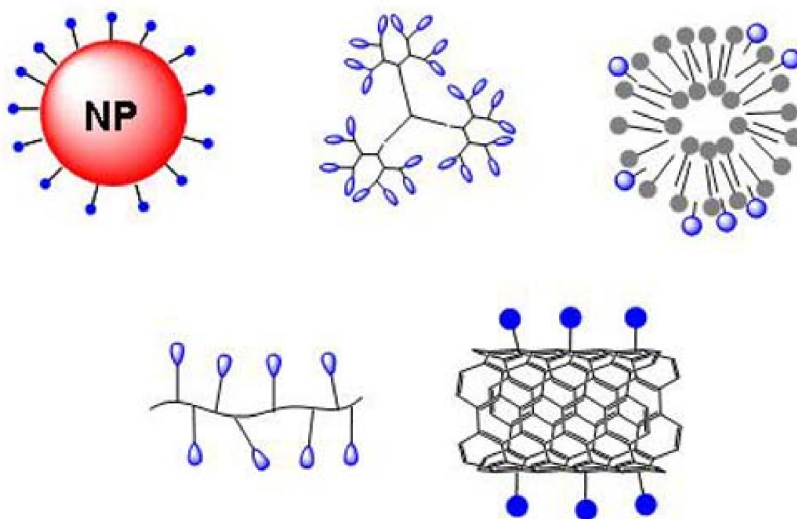


Figure 1. Selected multivalent carbohydrate probes: Top row from left to right, glyconanoparticle, glycodendrimer, glyco-functionalized liposome. Bottom row from left to right: glycopolymers and glyco-carbon nanotubes.

Many multifunctional nanoparticle ‘cores’ have been explored including dendrimers, liposomes, gold, iron oxide, quantum dots, carbon nanotubes and degradable polymers (Fig. 1) [6]. Multivalent nanoparticles present several advantages over free carbohydrates. They offer the potential to improve targeting by combining lower affinity carbohydrates on the particle surface to increase the binding avidity over what can be achieved with a single carbohydrate. In addition, nanoparticles provide modularity whereby different glycan sequences or other compounds can be combined to customize therapy or show selectivity of targeting. Multivalency also provides additional sites for conjugation of polymers that improve nanoparticle pharmacokinetics (*e.g.* PEG). Finally, a multivalent surface offers multiple binding sites that increase the therapeutic ‘payload’ and carry combinations of therapeutics.

The initial forays of our group into this area employed metallo-glycodendrimers. Subsequently, we focused on the applications of quantum dots as a multivalent probe. Currently, many other systems are under evaluation.

MULTIVALENT PROBES: SUPRAMOLECULAR METALLO-GLYCODENDRIMERS

Multivalency is of fundamental importance for carbohydrate-protein interactions. Several methods have been developed to study those molecular interactions. However, multivalency, ligand placement, folding, and active adjustment of ligand positioning are topics that need to be addressed for the generation of polyvalent systems. Self-assembly processes are promis-

ing methods for the formation of such dendrimers, where electrostatic forces, hydrogen bonding, metal coordination and other non-covalent interactions control the assembly of the dendron [7]. Our laboratory initially explored the relevance of self-assembly processes to synthesize tunable fluorescent glycodendrimers. An amide derivative of 8-hydroxyquinoline confined glycodendrons was synthesized and coordinated with transition and lanthanide metal complexes upon self-assembly to obtain high nuclear glycodendrimers (Fig. 2).

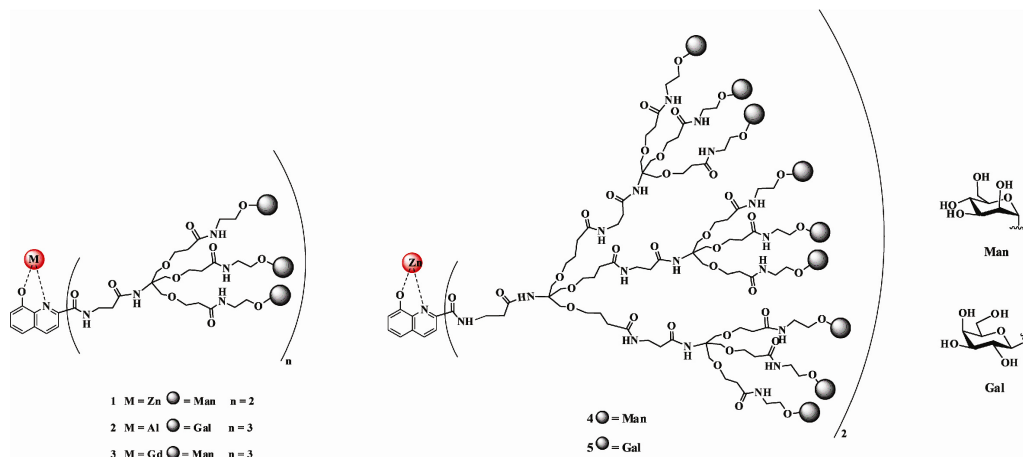


Figure 2. Glycodendrimers produced by self assembly.

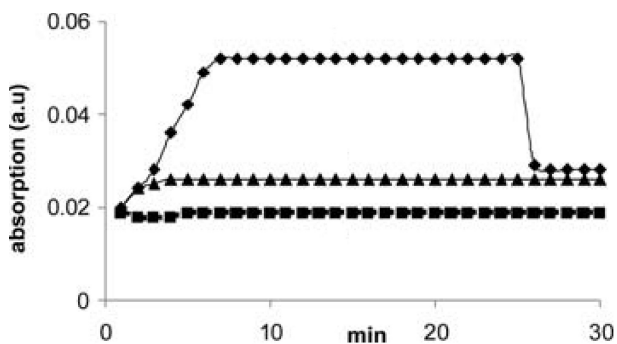


Figure 3. Turbidity analysis: absorption change of compound 1 (■), 5 (▲) and 4 (◆) at 500 nm on addition of ConA (1 mg ml^{-1}). Mannose (100 mM) was added to 4 after 25 min.

Complex formation was confirmed by various spectroscopic methods. Zn(II) and Al(III) complexes showed strong fluorescent intensities at 532 and 528 nm respectively and the quantum yields were approximately six to seven times higher than that of the dendrons. However, fluorescence of Gd(III) complexes were observed at 501 nm with almost the same quantum yield of the dendron due to weak HOMO-LUMO energy transfer of the Gd(III)

metal ions. Finally, we have shown that high sugar density is essential for the lectin binding using a turbidity assay. The interaction of metallo-glycodendrimers with Concanavalin A (ConA) as a lectin showed high mannose sugar density depended turbidity (Fig. 3).

MULTIVALENT PROBES: Ru(II)-GLYCODENDRIMERS

Inspired by the tunable and non-bleaching fluorescent nature of the metallo-glycodendrimers, we synthesized a series of Ru(II)-glycodendrimers and applied them to carbohydrate research. The Ru(II) core is most attractive for its octahedral core symmetry and robustness. Ru(II) complexes exhibit a low excited triple metal-to-ligand charge-transfer ($^3\text{MLCT}$) state and room temperature with $^3\text{MLCT}$ lifetimes of up to 1 μs . High emission quantum yields and strong oxidizing and reducing capabilities are important properties of these complexes [8, 9].

Ru(II)-glycodendrimers are composed of three major portions: the inner shell, dendron branches and an outer shell (Fig. 4A). A Ru(II)(bipy) $_3$ metal complex is used as an inner core material to provide optical and electrochemical signal to the dendrimers and to control the geometry of the complex branched dendron that typically originates from a 4,4'-bipyridyl ligand of the inner core. Different branches result in different dendrimer generations. Finally, the outer shell is constituted with different carbohydrate moieties (Fig. 4B).

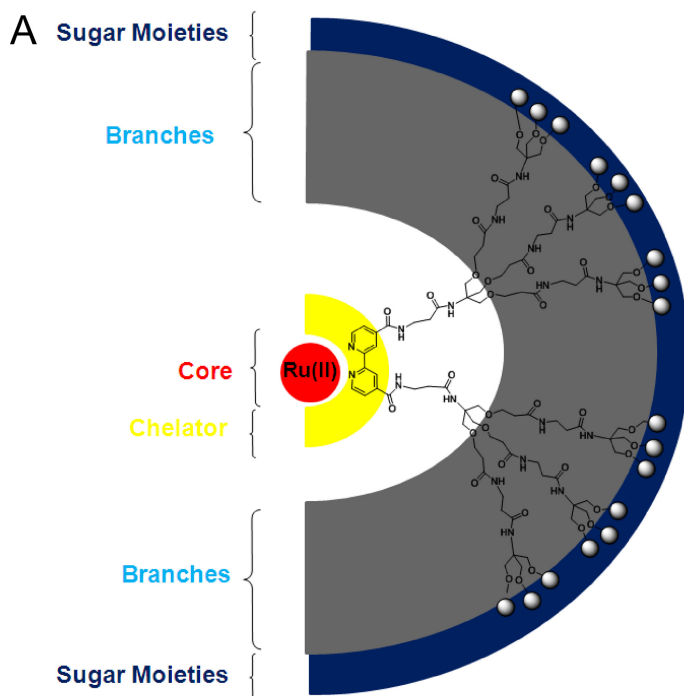


Figure 4. (A) Schematic representation of Ru(II)-glycodendrimer

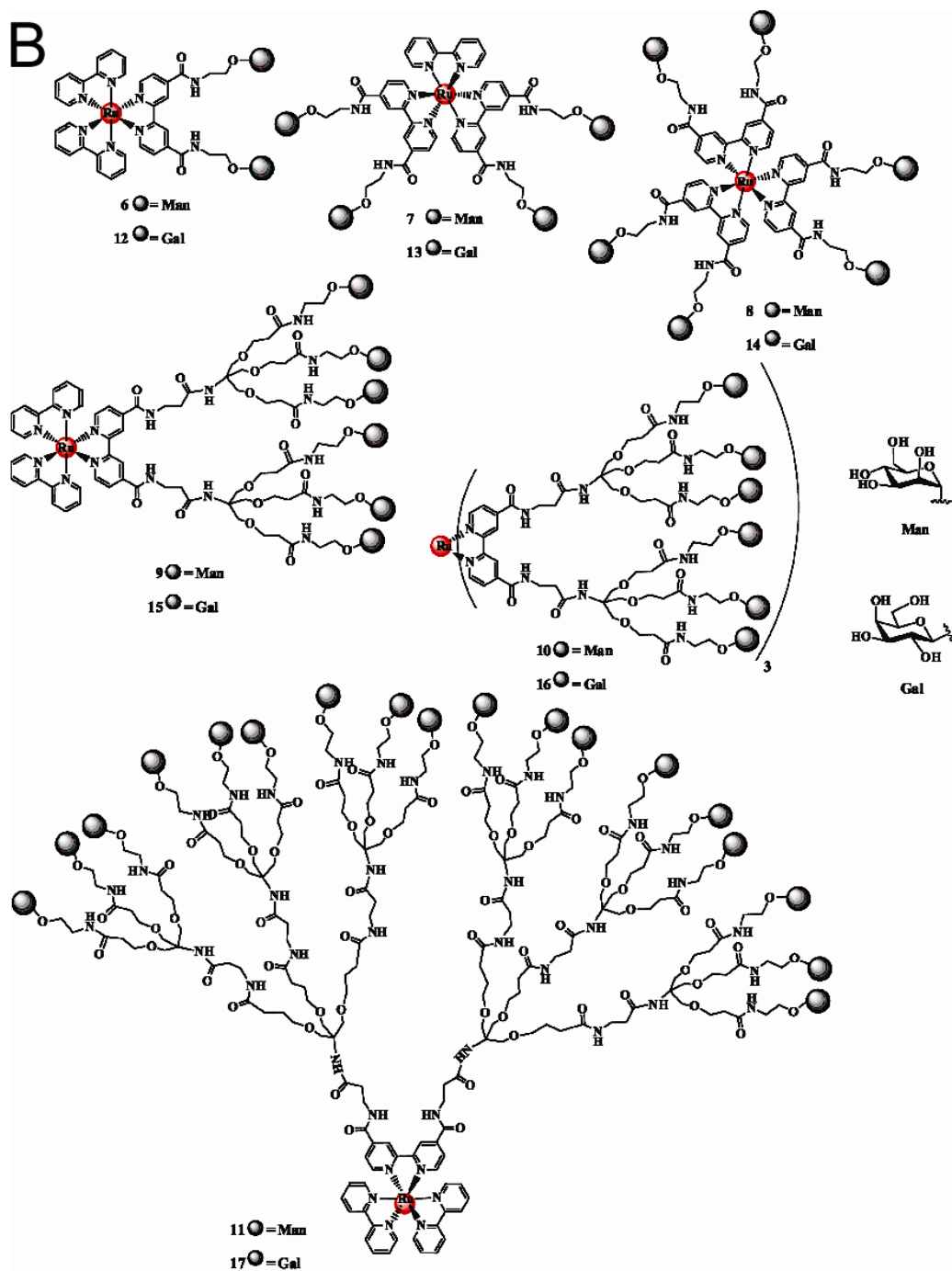
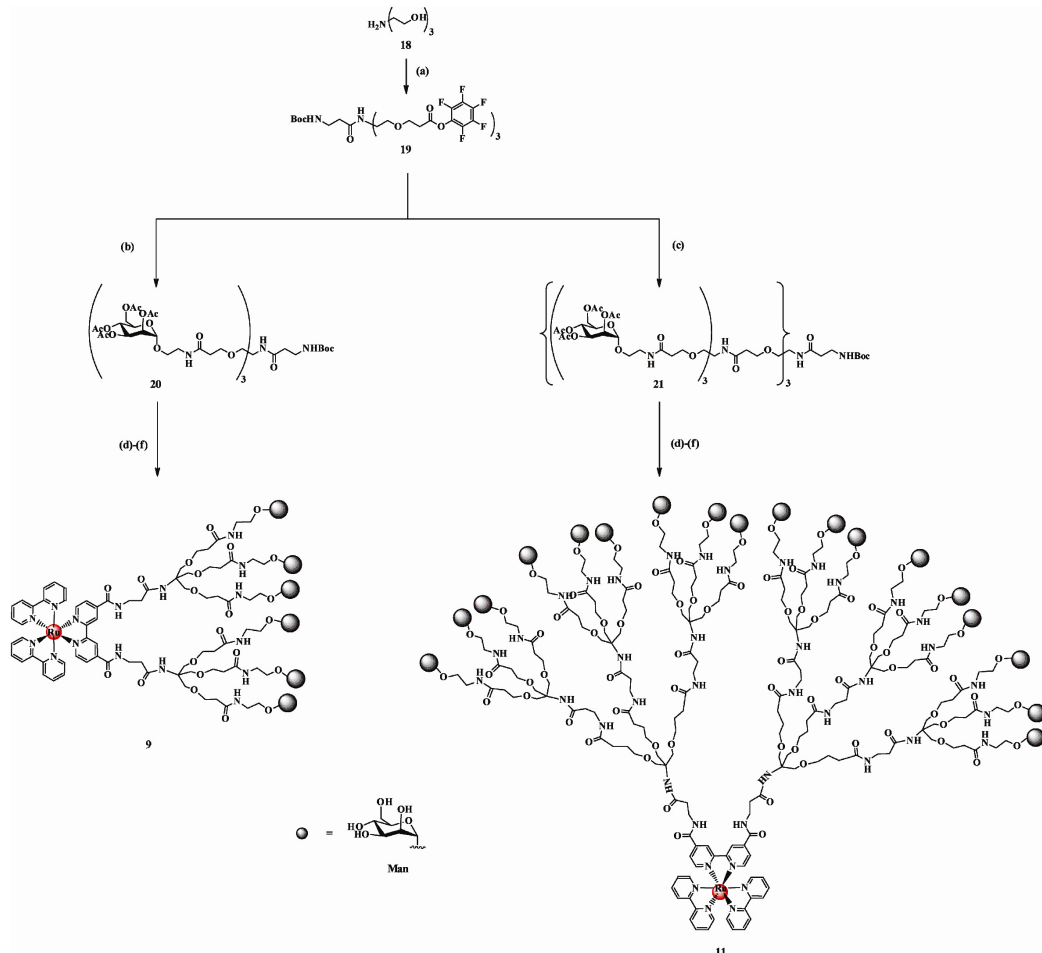


Figure 4. (B) Structures of Ru(II)-glycodendrimers 6-17.

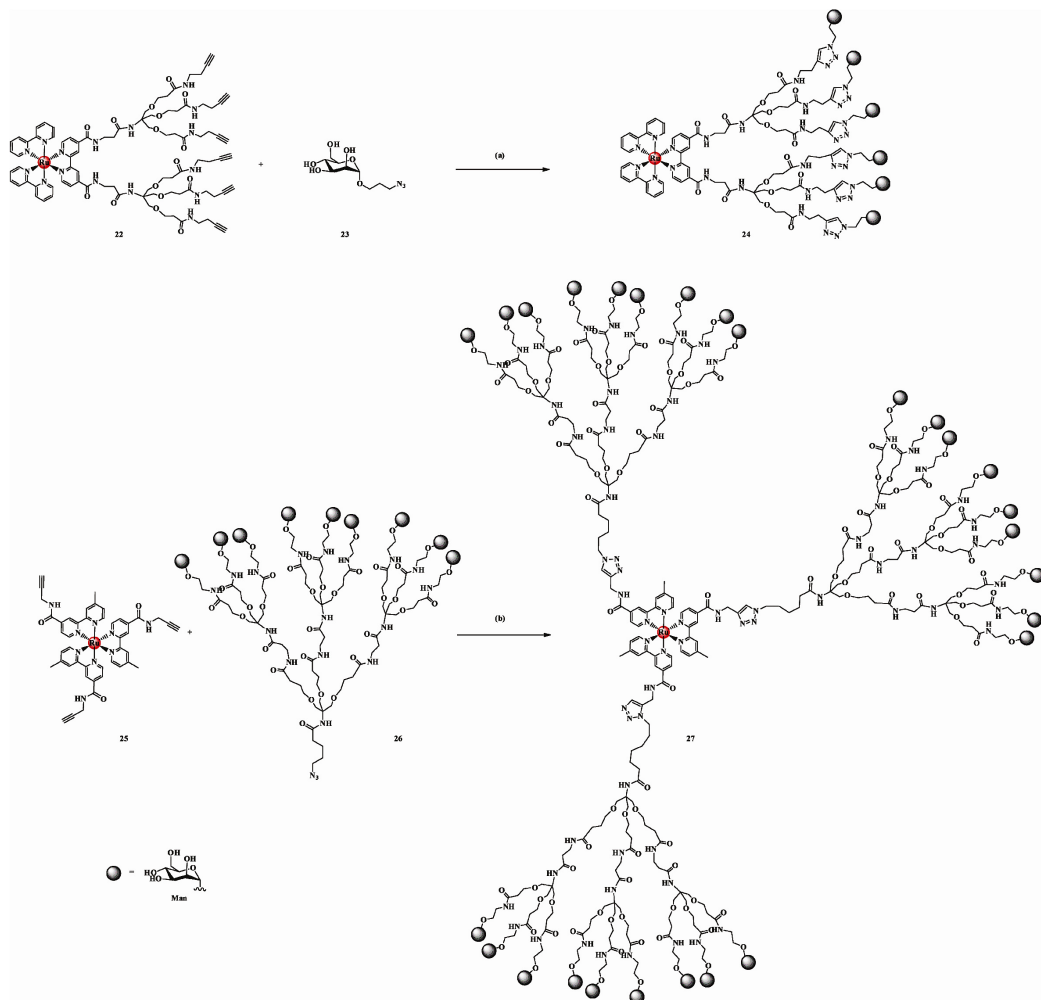
SYNTHESIS OF Ru(II)-GLYCODENDRIMERS

The synthesis of Ru(II)-glycodendrimers relied on by using convergent method, where the core and dendrons were prepared separately and then united in the final step. Glycodendrons were prepared starting from tris-HCl **18**, following acrylonitril addition, later treatment with conc. HCl in ethanol to yield tri-ester. Hydrolysis of triester, followed by coupling with pentafluorophenol afforded activated ester **19**. Pentafluorophenol ester was further reacted with peracetylated sugars that contain an anomeric 2-aminoethoxy linker to yield the final dendrons (**20** or **21**). Then, sugars were coupled with bipyridine derivatives and before the reaction with *cis*-Ru(bipy)₂Cl₂ resulted in complexes **9** and **11** respectively (Scheme 1).



Scheme 1. Synthesis of Ru(II)-dendrimers **9** and **11**. (a) Acrylonitril/NaOH; Conc. HCl/EtOH; *N*-Boc- β -Ala/DIC/HOBT/DCM; PFP-OH/DIC/HOBT/DCM; (b) 2-aminoethyl- α -D-peracetylated mannopyranoside/DCM; (c) TFA/**20**/DCM; (d) 2,2'-bipyridine 4,4'-dicarboxylic acyl chloride, DCM, TEA; (e) *cis*-Ru(bipy)₂Cl₂, EtOH; (f) NaOMe, MeOH.

We also devised a rapid and effective synthesis of Ru(II)-glycodendrimers bearing varying number of carbohydrates via Cu(I)-catalyzed [3+2] cycloaddition. Here, carbohydrate-dendrimers containing an azido-linker and Ru(II)-acetylene complexes were prepared separately. Subsequent Huisgen-[3+2] cycloaddition, followed by the removal of protecting groups on carbohydrate moieties provided access to the desired complexes in a straightforward and modular fashion (Scheme 2).



Scheme 2. Synthesis of Ru(II) complexes via Cu(I)-catalyzed [3+2] cycloaddition: **(a)** CuSO₄/ascorbic acid/THF:H₂O (1:1). **(b)** CuSO₄/ascorbic acid/THF:H₂O (1:1).

EFFECT OF CARBOHYDRATE DENSITY ON A Ru(II)-GLYCODENDRIMER PROBE

After synthesizing Ru(II)-glycodendrimers with different carbohydrate moieties, we investigated how the carbohydrate density and bulk affected the photophysical properties and lectin binding affinity of these molecules in water. It is known that many fluorophores are quenched by water and the association with the dendritic structure might exhibit a shielding effect to reduce the quenching and increase of the quantum efficiency. As expected, the quantum yields of complexes **10** and **11** were approximately twice higher than those of the complexes **6-9**.

Table 1. Quantum yields of complexes **6-11**.

Entry	6	7	8	9	10	11
Quantum Yield	0.061	0.06	0.064	0.072	0.102	0.112

Ru(II) complexes are known to display long range energy and electron transfer processes. The rate of electron transfer in complexes **9-11** was investigated using photoinduced electron transfer (PET) between photo excited Ru(II)-templates and methyl viologen dication (MV^{2+}) as quencher. Complexes **9** to **11** showed almost an order of magnitude difference in quenching constant (K_q) and a decrease in life time. These results indicate that a high degree of carbohydrate density around the ruthenium core allows for efficient encapsulation and modification of the core properties.

Table 2. Photophysical data of Ru(II)-glycodendrimers. Quantum yield and life time were measured by excited complex **9-11** at $\lambda_{max} = 450$ nm and emission at $\lambda_{max} = 645$ nm.

Entry	λ_{max} [nm]	k_q [$M^{-1}\cdot s^{-1}$]	τ_o [μs]	I_o
9	645	$9.8\cdot 10^8$	0.61	0.072
10	648	$1.8\cdot 10^8$	1.31	0.102
11	648	$1.1\cdot 10^8$	1.26	0.112
Ru(bipy) ₃	613	$2.5\cdot 10^9$	0.54	0.062

To evaluate the rate of energy transfer by **9-11**, we studied the formation of molecular oxygen in the singlet state upon photoexcitation of the ruthenium tris(bipyridine) complex. Tetramethyl piperidine (TEMP) was used as a trap for singlet oxygen to form a stable species (TEMPO) easily detected by EPR (see eq. 1) [9]. Continuous irradiation of Ru-complexes **9-11** in the presence of TEMP yielded a nitroxide triplet in the EPR spectrum. The rate of appearance of the TEMPO signal decreases from **9** to **11**, in support of the notion that carbohydrate encapsulation of the Ru(II)-template stops effective energy transfer to dissolved oxygen (Fig. 5).

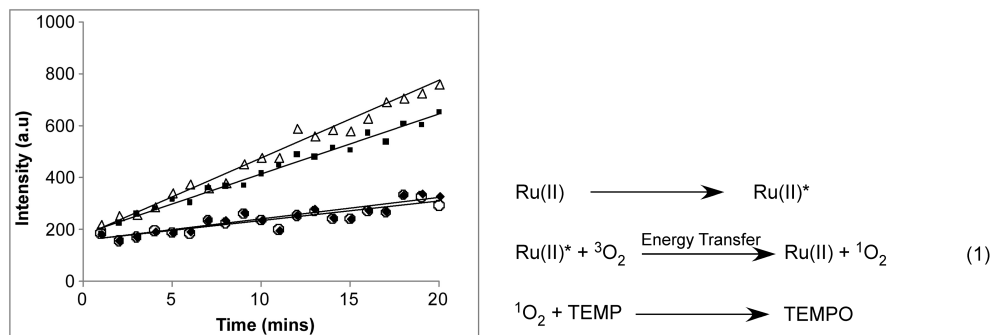


Figure 5. Kinetic profile of singlet oxygen formation upon irradiation of complexes **9** (■), **10** (◆), **11** (○) and Ru(bipy)₃ (△).

A PHOTOINDUCED ELECTRON TRANSFER BASED LECTIN SENSOR

After determining the photophysical properties of Ru(II)-glycodendrimers, we explored the donor/acceptor concept of complexes **9-11**/BBV²⁺ interactions in lectin sensing process. Two lectins that recognize mannose were selected, ConA and galanthus nivalis agglutinin (GNA). Using a donor/acceptor mixture of complex **1** and BBV, a spontaneous gain in fluorescence was observed upon the addition of 75 nM of ConA and a further slow increase in the signal at 200 – 1000 nM was observed. In contrast, for 0 to 100 nM of ConA, complexes **10** and **11** displayed more modest gains in fluorescence compared to complex **9**, but a steady and linear increase upon the addition of 100 – 600 nM. Similar experiments with the higher valency lectin GNA were performed. The detection limits for the Ru-complexes were calculated based on these results (Table 3). Complex **9** is noticeably more sensitive than other sensors described in the literature[10].

Table 3. Detection limit of lectins using different Ru-mannose dendrimers

Compound	ConA [nM]	GNA [nM]
9	23 ± 3	25 ± 4
10	340 ± 12	328 ± 9
11	347 ± 14	331 ± 12

OPTICAL LECTIN SENSOR

Ru(II) complexes are very also known as strong optical probes. To capitalize on this property, we developed a microarray based on direct carbohydrate-protein interaction read-out. ConA lectin was immobilized on a microarray prior to incubation with complexes **9**, **11**, **15** and **17**. Upon fluorescence scanning of the rinsed slides, strong fluorescent signals were observed on slides that were incubated with mannose complexes **9** and **11**. Using dendrimers **9** and **11** that contain six and eighteen mannoses respectively, ConA was detected at 0.125 mg/ml (620 nM).

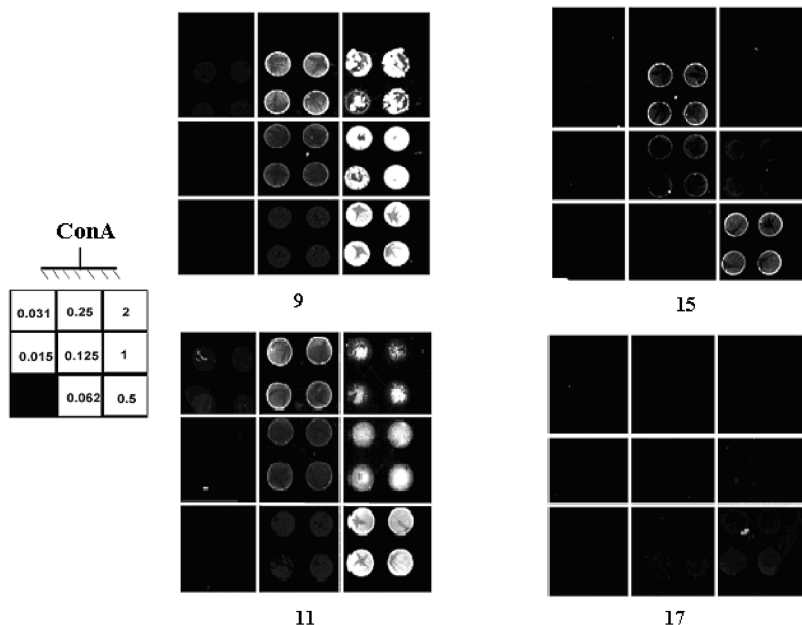


Figure 6. Incubation of Ru(II) dendrimers (**9**, **11**, **15** and **17**) with protein microarrays that contain different concentrations (mg/mL) of the lectin ConA (excitation at 480 nm).

ELECTROCHEMICAL LECTIN SENSOR

After establishing that Ru(II) glycodendrimers are useful tools to detect visually lectin-carbohydrate interactions, we utilized the redox properties of Ru(II) core to develop an electrochemical biosensor. ConA lectin was immobilized on a self-assembled monolayer on a gold surface prior to incubation of these surfaces with Ru(II)-complexes **9** and **11**. Following incubation, the chip was transferred to an electrochemical cell containing phosphate buffer. The scanning potential of 100 mV/s in the region of 1.0–1.4 V showed a peak at 1.62 μ A. Repeated measurements at different time intervals revealed that maximal ConA/Ru(II)-complex interactions were reached after 240 min incubation (Fig. 7). Interestingly, incubation of complex **11** carrying 18 mannoses with ConA monolayers showed a very weak signal in the region of 1.0–1.4 V. An optimum current at 4.1 nA was obtained after 180 min incubation. Based on these findings, complex **9** was better suited for electrochemical sensing than the more complex dendrimer **11**. After establishing that the lectin-glycodendrimer interactions can be measured electrochemically, we determined the detection limit. Different concentrations of ConA were immobilized on gold substrates and treated with 0.5 mM of **9** prior to recording square-wave voltammetric (SWV) signals. At 2.5 nM the detection limit for **9** is comparable to other sensors [10].

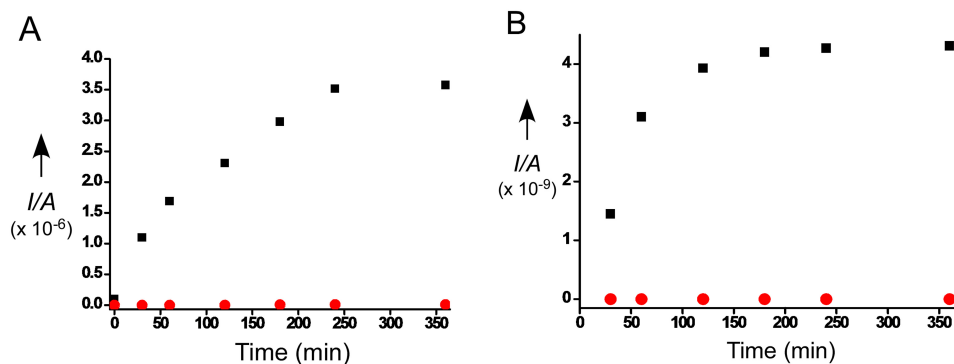


Figure 7. Square-wave voltammetric measurements at 1.14 V following incubation of (A) complexes **9** (■) and **15** (●) with ConA-functionalized surfaces for six hours; (B) complexes **11** (■) and **17** (●) with ConA-functionalized surfaces for six hours.

Table 4. Detection limits of ConA by different sensory systems

Methods	Detection Limits [nM]	References
Optical detection by Ru(II)-carbohydrate coated dendrimers and BBV by photoinduced electron transfer process	28 ± 3	[9a]
Optical detection by ConA microarray with Ru(II)-carbohydrate dendrimers	620	[9b]
Electrochemical detection by immobilizing ConA-Ru(II) dendrimers	2.5 ± 0.12	[9b]

REUSABLE SUGAR SENSOR

We have also developed a sugar sensor based on displacement of Ru(II)-glycodendrimer from the lectin-functionalized gold chips to allow for the detection of sugars that are bound by the lectin. ConA-functionalized gold chips containing **9** were immersed into solutions containing varying concentrations of D-glucose, D-mannose, α -D-man-(1→6)man, D-galactose, D-maltose or PIM glycans before SWV signals for Ru(II) were recorded. The current decreased in a concentration-dependent manner, indicating that the redox-active complex **9** is replaced in a competitive manner by the preferentially-binding carbohydrate. The detection limit for glucose (7 μ M) compares favorably with the detection limits for other methods that are also in the micromolar range (Fig. 8) [11]. Similarly, other sugars resulted in different mode of current signal quenching and showed different detection limits (Table 5). Rapid quenching can be interpreted as a simultaneous displacement of weakly bound complex **9** from immobilized ConA and high affinity of the sugar for the lectin.

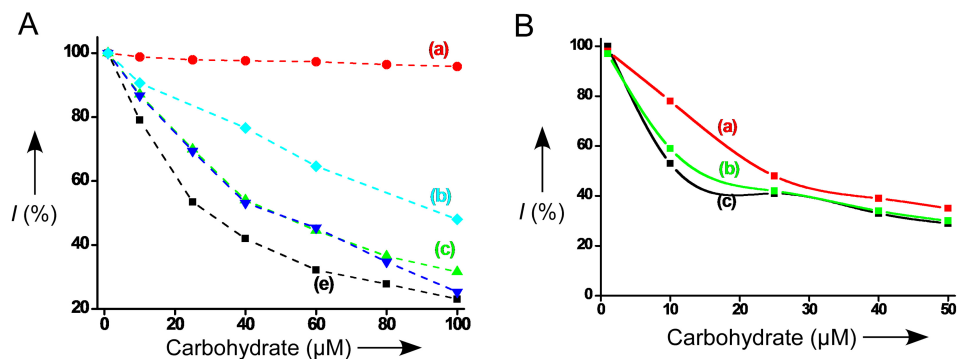


Figure 8. Response of square-wave voltammetric signals to increasing concentrations of (A) (a) D-galactose (●) (b) D-glucose (◆) (c) D-maltose (▲) (d) D-mannose (▲) and (e) D-mannose(1–6)man (■); (B) (a) PIM3 (■); (b) Tri-mannose (■); (c) PIM4 (■).

Table 5. Detection limits of different free sugars by electrochemical ConA/Ru(II)-glycodendrimer method.

Methods	Detection limits (μM)
D-glucose	7 ± 0.12
D-mannose	3 ± 0.11
D-maltose	3 ± 0.06
D-galactose	–
D-mannose(1–6)man	1.4 ± 0.12
PIM3	1.4 ± 0.11
Tri-mannose	0.61 ± 0.07
PIM4	0.61 ± 0.11

Primary level clinical diagnostic kits are expected to reset for repeated measurements. A gold chip exposed to 100 μM D-glucose solution was incubated with boronic acid substituted Merrifield resin to displace any sugar attached to the immobilized ConA. Incubation with complex **9** regenerated the surface for the next measurement. To verify the quality of the readings after regenerating the electrochemical detector, the chip was exposed to solutions containing 40 and 80 μM D-glucose. The platform was regenerated ten times using this re-iterative process (Fig. 9). The SWV signal decreases over the first six cycles and then remains constant for the last four regeneration cycles. Deactivation or effective hosting of glucose by ConA may be responsible for the observed decrease in the electrochemical signal after each cycle.

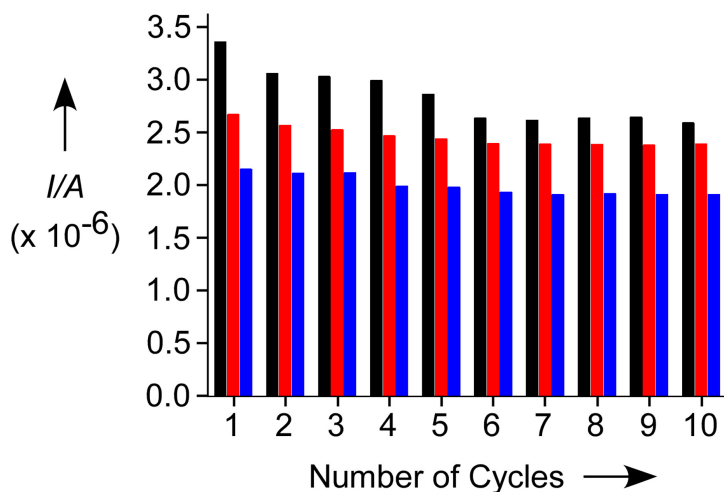


Figure 9. Maximum current signal upon regeneration of the ConA/9 glucose detector: Complex 9 on gold substrate (black), addition of 40 μ M of D-glucose (red), addition of 80 μ M of D-glucose (blue).

MULTIVALENT PROBES: QUANTUM DOTS

Quantum dots are interesting multivalent tools to probe the glycome. There are different types of quantum dots, such as CdSe, CdS, or CdTe that are only a few nanometers in diameter and exhibit discrete size-dependent energy levels. As the size of the nanocrystal increases, the energy gap between HOMO-LUMO also increases, yielding a size-dependent rainbow of colours. Extensive tunability, from ultraviolet to infrared, can be achieved by varying the size and the composition of QDs, enabling simultaneous examination of multiple molecules and events. For example, small nanocrystals (~2 nm) made of CdSe emit in the range between 495 to 515 nm, whereas larger CdSe nanocrystals (~5 nm) emit between 605 and 630 nm [12].

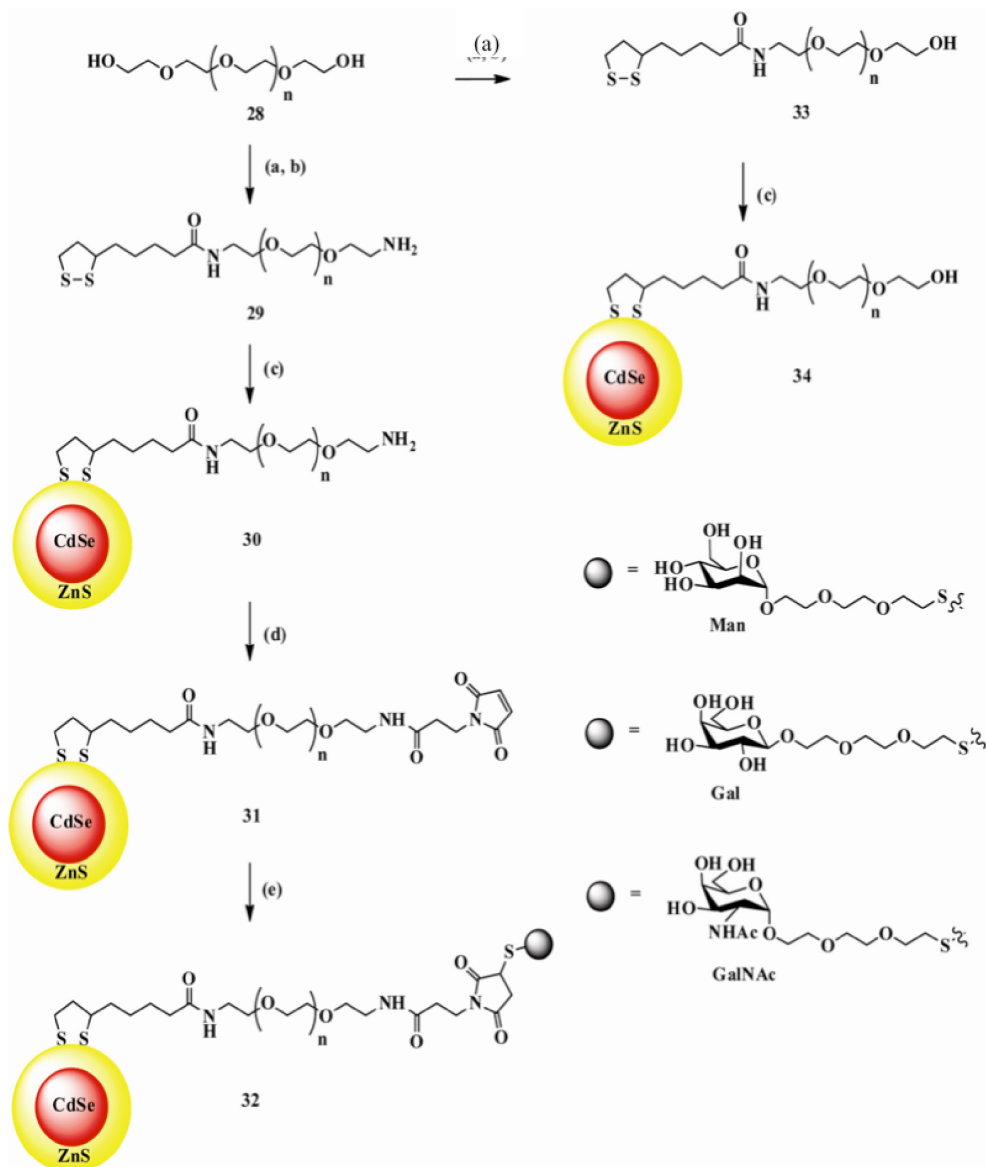
QDs exhibit dramatically different properties when compared to organic fluorophores and fluorescent metal complexes. As illustrated in Table 6, organic and metal complex dyes typically have narrow absorption spectra and MLCT band, which means that they can only be excited within a narrow window of wavelengths. Furthermore, organic and metal complex dyes have broadened asymmetric emission spectra. In contrast, QDs have broad absorption spectra, enabling excitation by a wide range of wavelengths, and their emission spectra are symmetric and narrow. Moreover, QDs show superior quantum yield and multivalency compared to other fluorescent probes, and do not bleach [13].

Table 6. Photophysical properties of organic, metal fluorescent probe and quantum dots.

Optical properties	Organic fluorescent probe	Metal complexes	Quantum dots
Absorption band	Narrow	Narrow	Broad
Emission band	Broad	Broad	Narrow
Band tunability	Not good	Good	Good
Resistant to quenching	Not good	Good	Good
Photochemical stability	Not good	Good	Good
Emitting light intensity	Moderate	Good	High
Fixing ability to analysts	One-to-one	Multiple	Multiple

CARBOHYDRATES CONJUGATED TO QDs

The commercially available QDs are only soluble in nonpolar solvents because of their hydrophobic surface layer. For QDs to be useful probes for examination of biological specimens, the surface must be hydrophilic. Several strategies have been proposed to stabilize QDs in aqueous solutions. The easiest approach is to exchange the hydrophobic surfactant molecules with bifunctional molecules that are hydrophilic on one side and hydrophobic on the other side to bind to the ZnS shell. Most often, thiols (-SH) are used as anchoring groups on the ZnS surface and amine groups are used as the hydrophilic ends. Recently, dithiols such as DL-thioctic acid have been used to prepare PEG linkers **29** and **33**. PEG groups were used to avoid non-specific interaction by the ZnS surface. We used different length PEG linkers and found that PEG₂₀₀₀ is the best model to study carbohydrate interactions. The PEGylated QDs **30** were further treated with 2-*N*-hydroxy succinimide maleimido linker to obtain QD-PEG-maleimido **31**. Finally, the QD-PEG-maleimido was reacted with thio-sugars to obtain final compounds **32**.



Scheme 3. Synthesis of QDs: (a) MsCl, TEA, NaN₃, 12 h; Ph₃P, H₂O, 12 h; (b) Thioctic acid, DIC, NHS, 12 h; (c) NaBH₄, MeOH/H₂O; CdSe/ZnS, EtOH; (d) 4-maleimidopropanoic acid NHS ester, pH 8.5; (e) Man-SH or Gal-SH or GalNH₂-SH, pH 7.5.

IN VIVO AND IN VITRO EXPERIMENTS WITH QDs

Fluorescent probes are widely used in cell biology for probing structure and to locate specific receptors. Owing to their robust optical properties, QDs are ideal probes in this area. Here, we employed HepG2 cells that express asialoglycoprotein receptor (ASGP-R) that bind to galactose glycoproteins. HepG2 cells were cultured in presence of QDs coated with galactose sugars. Flow cytometry (Fig. 10) after 2 h of incubation of the cells with QDs revealed that Gal- capped QDs were taken up by the HepG2 cells preferentially over PEG₂₀₀₀-capped QDs **34**.

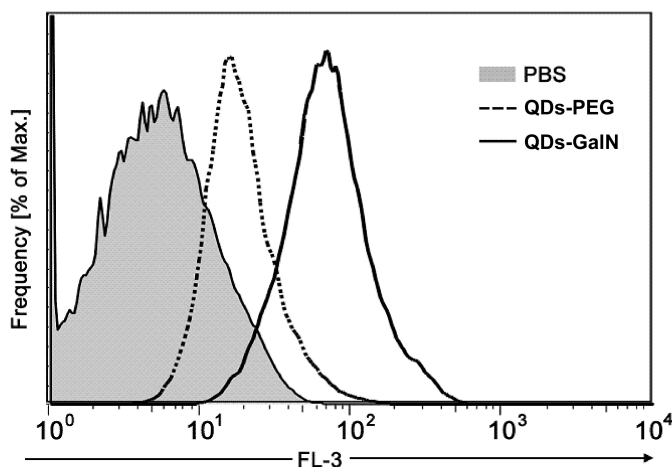


Figure 10. Specific uptake of D-GalN-capped QDs by HepG2 cells. HepG2 cells were incubated overnight with 20 nmol of PEG₂₀₀₀ QDs (dashed line) or 20 nmol of GalN-PEG₂₀₀₀ QDs (solid line). As negative control, PBS was added to the cells.

After demonstrating specific uptake of D-GalN-capped QDs *in vitro* we analyzed specific targeting of the liver *in vivo*. For this purpose, mice received either PEG₂₀₀₀-QDs or QDs capped with D-mannose or D-galactosamine by intravenous (*i.v.*) injection (PBS buffer was injected as a negative control). A low level of unspecific sequestration was observed in the liver 2 h after injection of PEG₂₀₀₀-capped QDs (Fig. 11). In contrast, injection of Man-PEG₂₀₀₀ and also GalN-PEG₂₀₀₀ capped QDs resulted in a high number of QDs sequestering in the liver. This finding suggests binding and/or endocytosis of the QDs mediated by mannose receptor and ASGP-R. ASGP-R is expressed predominantly on hepatocytes, while the mannose receptor is strongly expressed on Kupffer cells and sinusoidal endothelial cells in the liver. This finding indicates that carbohydrate-protein interactions exhibit specificity and may be exploited for targeted drug delivery *in vivo*.

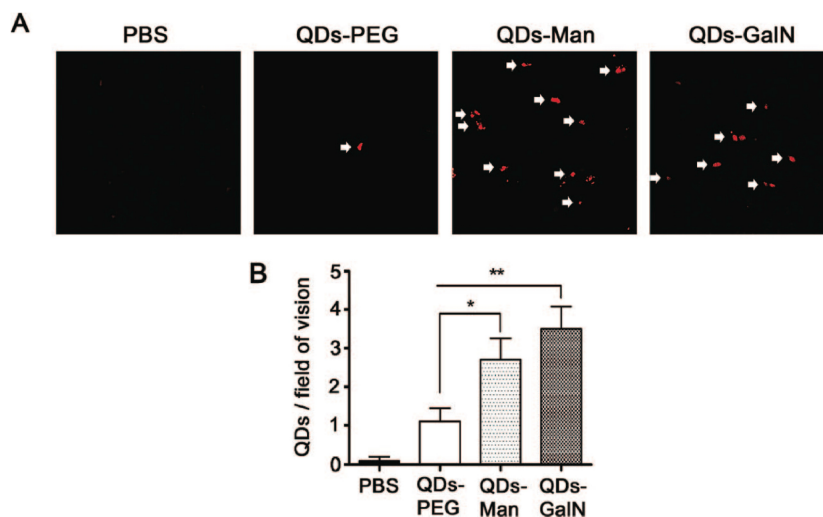


Figure 11. Specific liver sequestration of D-Man and D-GalN capped QDs in liver. **(A)** Paraffin sections of the livers were prepared, and QD sequestration in the liver was visualized by fluorescence microscopy. Arrows indicate QDs sequestered to liver tissue. **(B)** Statistical analysis of QD sequestration in the liver was performed by counting 10 microscopic fields of vision for each mouse. Data are presented as mean (SEM for each group (* $P < 0.05$, ** $P < 0.01$).

CONCLUSION

In conclusion, our laboratory has developed a metallo-glycodendrimer and quantum dots based novel platform to study carbohydrate-protein interactions. The optical and electrochemical signals from $\text{Ru}(\text{bipy})_3$ and CdSe core offers direct readout techniques to image and analyze specific interactions. Additionally, Cu(I)-catalyzed [3+2] cycloaddition and PEGylated sugar conjugation reactions present the opportunity to minimize sugar consumption. The development of sensitive lectin and sugar sensors in optical and electrochemical mode will enable glycobiologists to screen large numbers of carbohydrates that are thought to have important roles in biological systems. Even though impressive applications of quantum dots and metallo-glycodendrimers have been reported, some major drawbacks associated with the biocompatibility and stability of nanoparticles still need to be addressed. Thus, the choice of appropriate nanomaterials for medical applications is still a land of opportunity for material scientists, chemists and glycobiologists.

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