Supporting Information

1. Experimetal Procedures

1.1 Materials

Water was distilled and deionized at 18 MΩ resistance (Gelante Pure Water, Shijiazhuang, China). G2.0-G5.0 PAMAM, D-galactose, lactose, N-acetylgalactosamine (GalNAc), wheat germ agglutinin (WGA) and concanavalin A(ConA) were obtained from Aldrich (Milwaukee, WI). D-N-acetylglucosamine, D-mannose, hydrazine hydrate, 1, 2-ethylenediamine, methyl acrylate, and methanol were from Alfa Aesar (Ward Hill, MA). Dulbecco's phosphate buffered saline (DPBS) and cell culture reagents were purchased from Invitrogen (Carlsbad, CA), and CellTiter 96® AQueous One Solution Cell Proliferation Assay (MTS) systems from Promega (Madison, WI).The suppliers of other chemicals, biological reagents and equipment are specified below.

1.2 Synthesis of glycodendrimers

Synthesis of PAMAM-HYD G0.5 and G1.5 PAMAM dendrimers bearing methyl ester groups on the surface were synthesized through repetitive reactions of ethylene diamine with methyl acrylate using a method described in the literature. (Tomalia, D. A. *Tetrahedron* **2003**, *59*, 3799) Higher generation PAMAM dendrimers, G2.5 to G4.5 were obtained using purchased G2.0 to G4.0 PAMAMs as starting materials via one-step reactions with methyl acrylate, respectively.

To generate hydrazides on the PAMAM surface, half generation PAMAMs (G0.5-G4.5) were dissolved in ethanol at a concentration of 5 mg/ml.[25] Hydrazine hydrate (10 fold molar excess of PAMAM methyl esters) was slowly added and the reaction was maintained under reflux at 55^{o}C for 24 h. The solvent and hydrazine were removed under reduced pressure at 65^{o}C, using a rotary evaporator. To further purify the PAMAM-HYD, the solution was dialyzed for 3 d against deionized water, using cellulose membranes (Union Carbide Corp., NY) with proper molecular weight cutoff (MWCO 500 for G0.5 and G1.5 and MWCO 1000 for G2.5-G4.5 PAMAM-HYDs). Whitish solid products were collected and stored under 4^{o}C for future use.

Conjugation of saccharides to PAMAM-HYD To conjugate saccharides to the dendrimer scaffolds, PAMAM-HYD was dissolved in pH5.0 sodium phosphate buffer (5 mg/ml), and a selected saccharide (in 10 fold excess of the hydrazide groups) were added. The solution was stirred for 24 h at 50^{o}C. To remove unbound saccharides and purify the final products, solutions containing crude products were subjected to dialysis against deionized water for 3 d using the MWCO 1000 dialysis membrane. The final glycoPAMAM conjugates were collected after lyophilization.

To vary the glycosylation level in Lac-PAMAM, lactose was reacted with G4.5 PAMAM-HYD in four more ratios, with the lactose saccharides in 0.25, 0.5, 1 and 2 molar folds of the hydrazide groups. The glycodendrimer products were collected as described above. The synthesis for each conjugates was performed for 3-5 times.

1.3 Chemical analysis of PAMAM-HYD and glycodendrimers

PAMAM-HYD and glycodendrimer products (10 mg) were dissolved in 5.5 ml D_2O, and ^{1}HNMR experiments were performed with 400 MHz NMR equipment (ARX400, Bruker, Switzerland).

1.4 Characterization of glycoPAMAM-lectin interactions

Turbidity Assay To analyze whether the glycodendrimer products can interact with their cognate lectin receptors in a specific multivalent way, a turbidity assay was performed.[8,26] In a typical assay, the lectin was dissolved at 1 mg/ml in PBS buffer (pH 6.8), and then diluted to a concentration of 55.5 μM. A stock solution of the selected glycoPAMAM was prepared (0.5 mM GlcNAc-PAMAM or 5 mM mannose-PAMAM per saccharide residue). To perform turbidity measurements, 135 μL of lectin solutions were first dispensed to a 96 micro-well plate. 15 μL of glycoPAMAMsolutions were added and mixed with lectin rapidly by pipetting for 3 s. The solution was then placed in the spectrometer (SpectraMax M2e, Molecular Devices, USA), and absorbance at 490nm was recorded every 8 s for 10 min. The rate of lectin and glycoPAMAM aggregation was determined by the initial steepest portion of the kinetic absorbance curve.

1.5 Cellular binding and cytotoxicity studies

HepG2 cells were seeded in 96-well plates at a density of 1.5×10^4 cells per well and allowed to attach to surface and grow for 24 h at 37 °C with 5% CO_2. To investigate cellular uptake of glycodendrimers, dendritic materials were labeled with a fluorescein dye. Briefly, NHS-fluorescein (0.1 mg/ml) and dendrimer solutions (4 mg/ml) were mixed at 2:1 molar ratio and reacted for 3 h. The labeled dendrimers were diluted in DMEM to a concentration of 1.6 μM, and 500 μL aliquots were added to each well plated with HepG2 cells. After 24 h incubation, the medium was removed, and the cells were washed with DPBS and detached by trypsin treatment. After centrifugation at 1000 rpm for 5 min, cells were collected and re-suspended in 500 μL DPBS. Flow cytometry was conducted by FASCalibur (Becton, Dickinson and Company, NJ). For fluorescence microscopy, cells were visually examined and imaged captured by an IX71 fluorescence microscope (Olympus, Japan). Representative results from one of five independent experiments were shown in Figure 3.

To study the cell viability upon the treatment of different glycodendrimers, a selected material was diluted in DMEM containing 5% FBS to prescribed concentrations (0-60 μM) and incubated with cells. After 24 h, the cell culture medium in each sample well was replaced by a solution containing 100 μl of fresh DMEM mixed with 20 μl of MTS reagent. After 1 h incubation, the light absorbance at 490 nm was recorded for each sample by a SpectraMax M2 microplate reader (SpectraMax M2, Molecular Devices, CA).

1.6 Data analysis and statistics

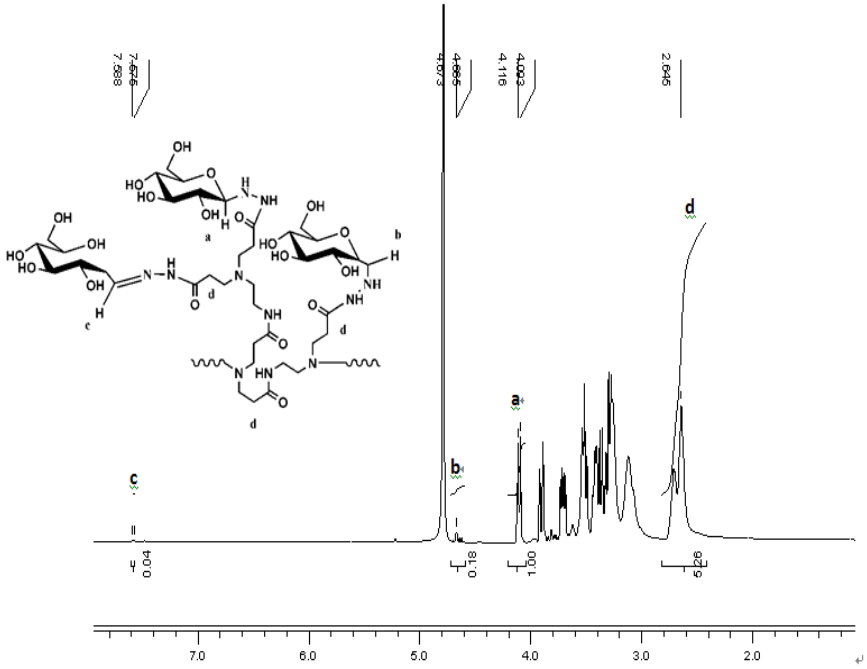
Quantitative results were presented as means ± standard error of measurements (S.E.M.). Statistical comparisons were performed by one way analysis of variance (ANOVA) followed by the Newman-Keuls tests to compare selected data pairs using SigmaStat 3.5. The level of significance was set at <0.05.

Table S1. NMR peaks of anomeric glycoside protons in G2 glycoPAMAMs

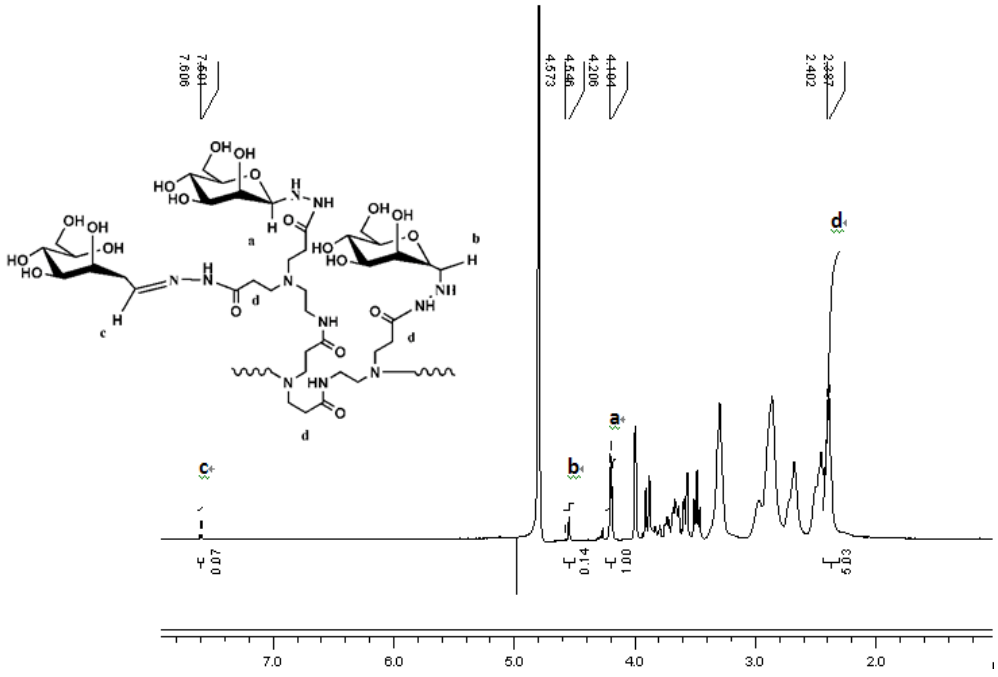
Saccharide	α-H (d)	β-H (d)	cyclic-H (d)
Glu	4.665，4.673	4.116，4.093	7.575，7.588
Man	4.546，4.573	4.194，4.206	7.591，7.606
Gal	4.667，4.680	4.030，4.008	7.626，7.636
GlcNAc	4.686，4.698	4.234，4.210	7.556，7.568
Lac	4.649，4.669	4.125，4.102	7.710，7.723

Figure S1. NMR spectra of G2 GlycoPAMAMs

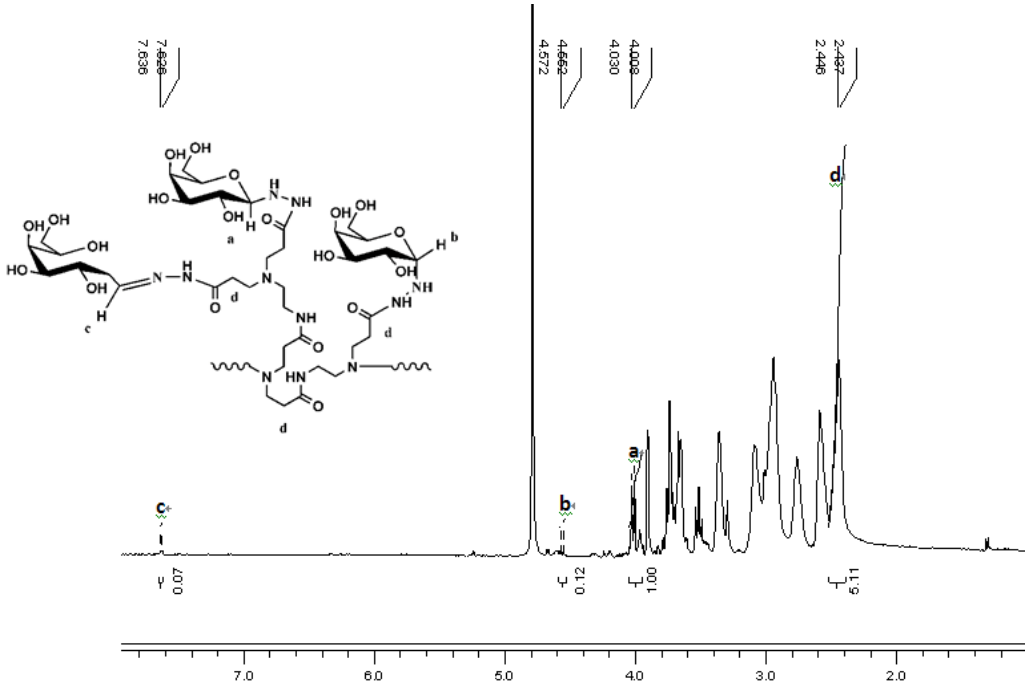
(A) G2 Glu-PAMAM



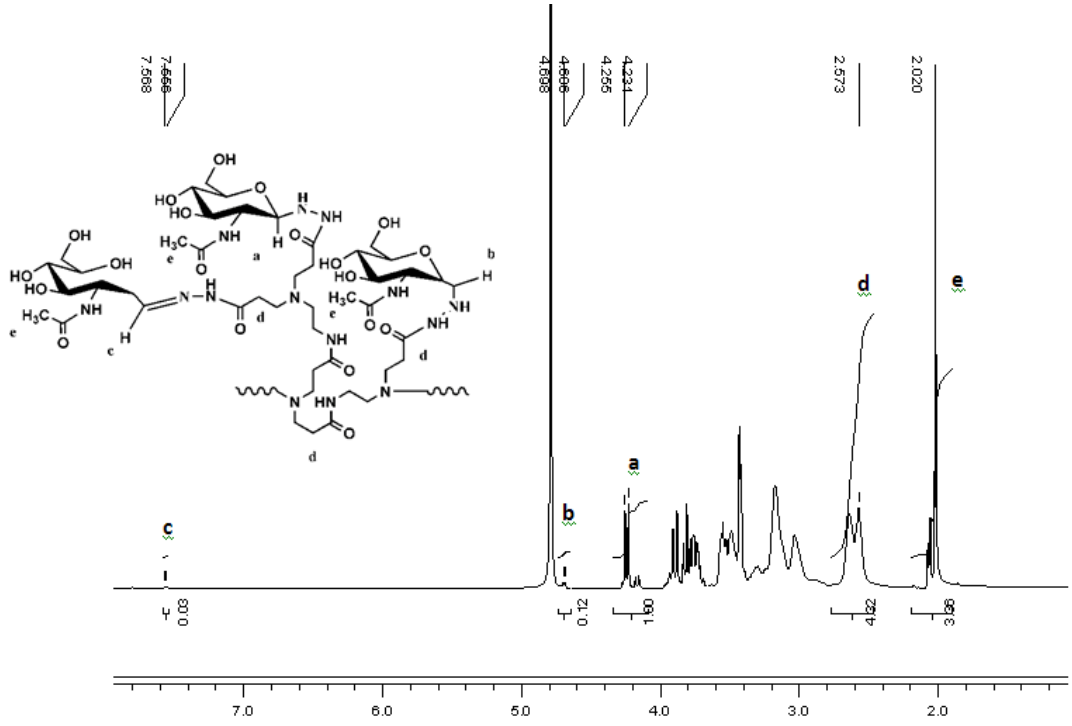
(B) G2 Man-PAMAM



(C) G2 Gal-PAMAM



(D) G2 GlcNAc-PAMAM



(E) G2 Lac-PAMAM

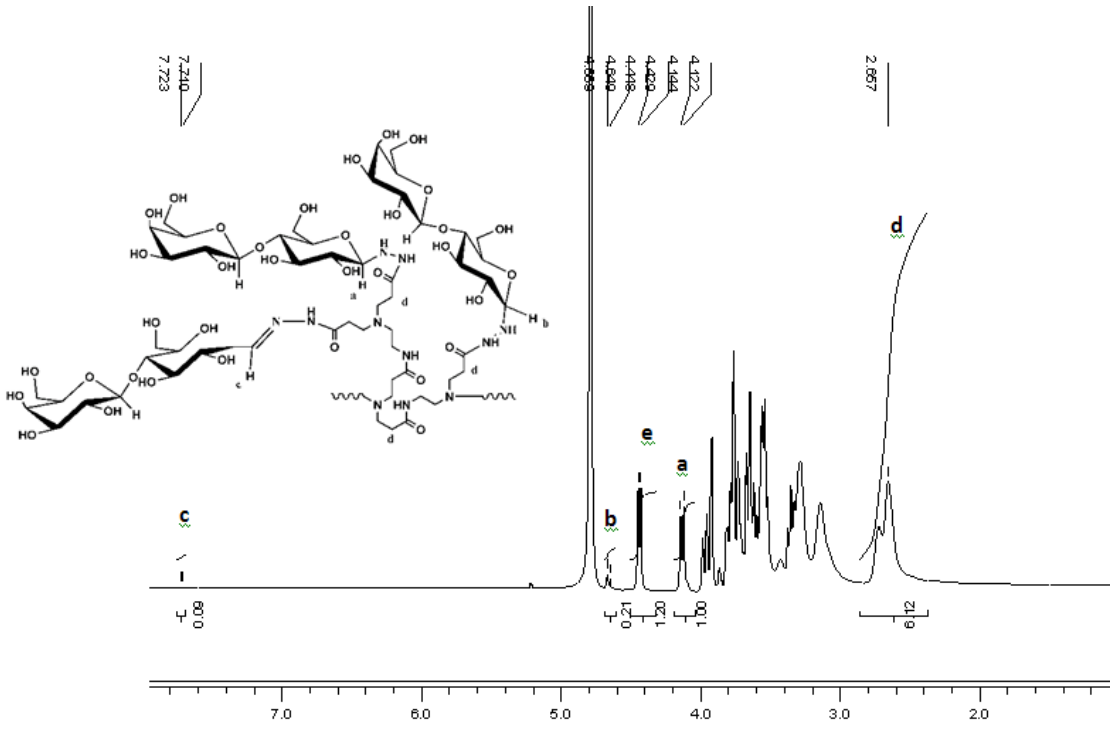


Figure S2 NMR Spectra of G5 Lac-PAMAM of varied modification levels （Lac5-, Lac20- and Lac35-PAMAM）

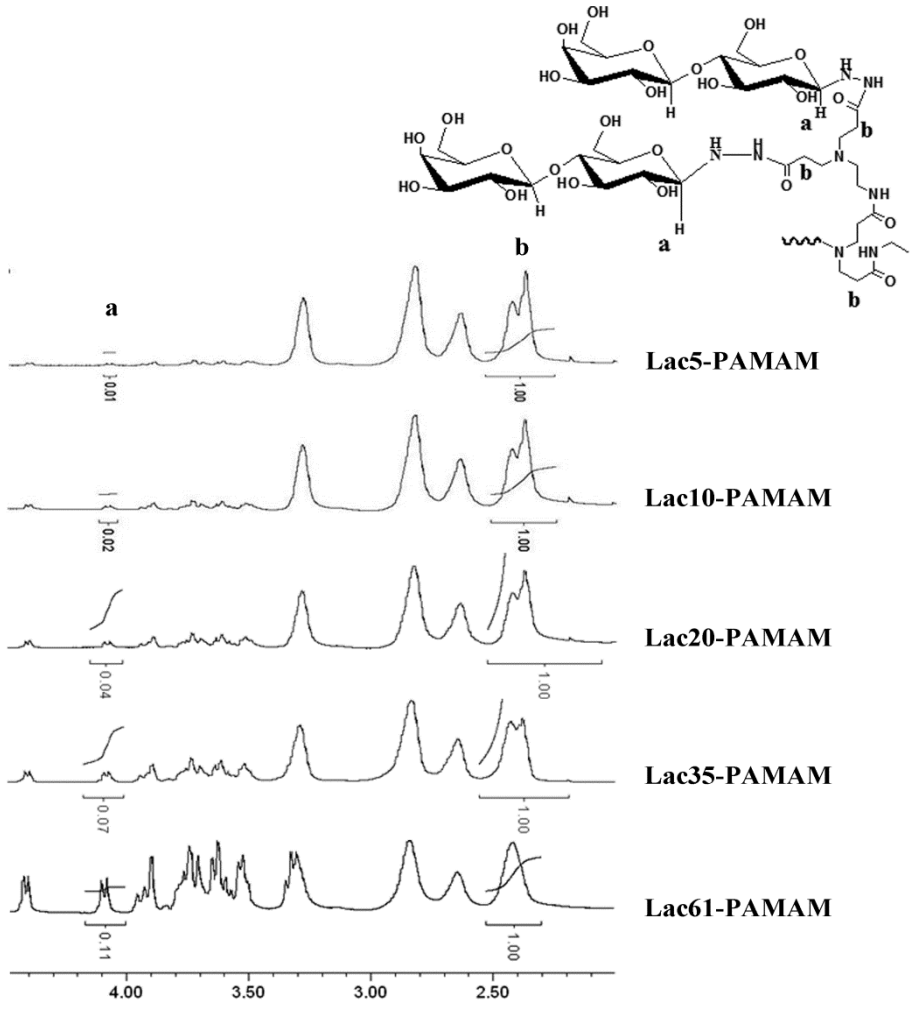
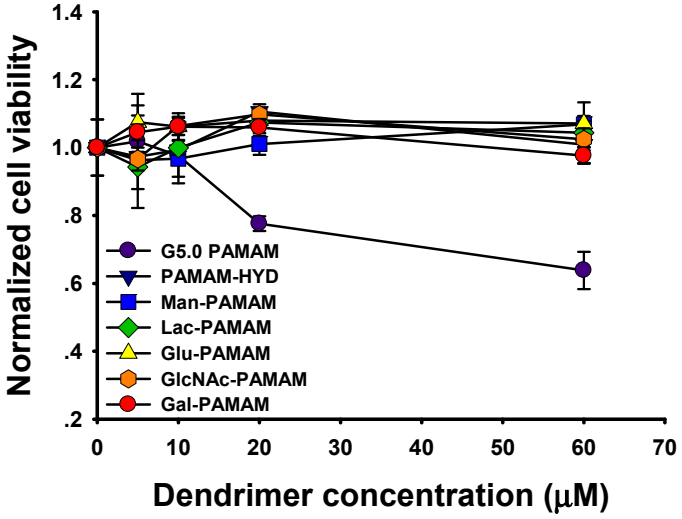


Fig S3. Cell viability of HepG2 cells upon treatment of different glycodendrimers for 24 h.



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