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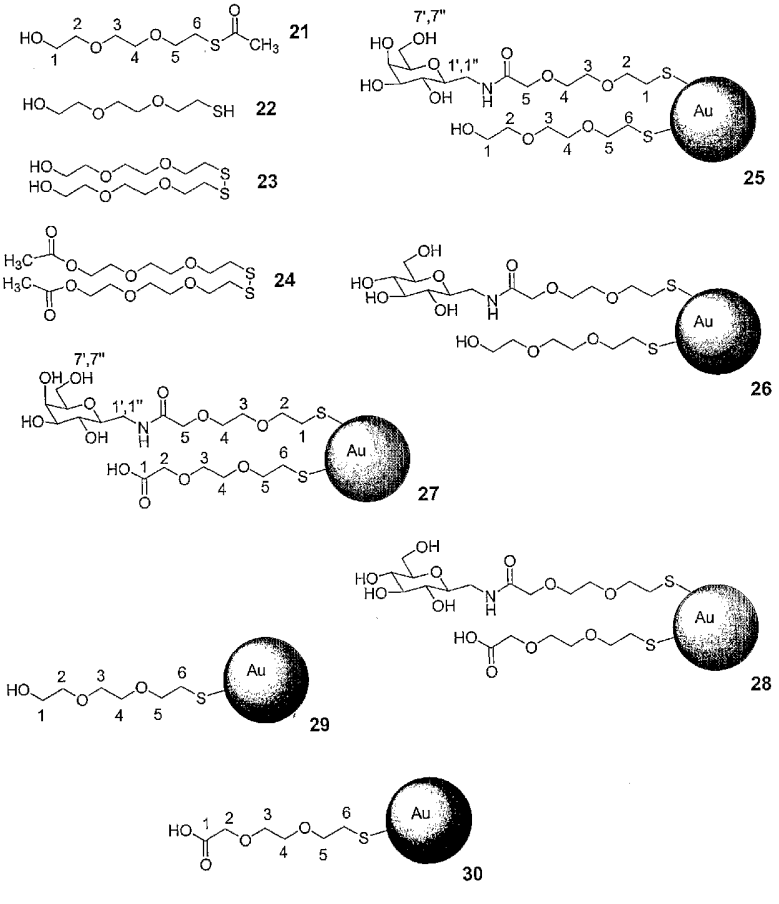

(57) Abstract: Nanoparticles having a gold or gold alloy core portion and a surface of attached ligands, and optionally having attached co-ligand groups are provided. The attached ligands can be a variety of saccharide or oligosaccharide components, at least a portion of which are *C*-glycosides.

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PREPARATION AND USE OF GOLD GLYCONANOPARTICLES

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/475,836, filed June 3, 2003, the teaching of which is incorporated herein by reference in its entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with assistance provided by NSF-CHE0210807. The government may have rights in certain aspects of the invention.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] Recently, the fundamental and molecular level understanding of adhesion processes involving viral recognition of host cells has been undertaken by a number of research groups. The results of those efforts has provided significant guidance to the development of novel materials for use in diagnostic assays, as well as therapeutic treatments.

[0005] Often viral adhesion and infection are mediated through polyvalent interactions involving viral proteins and cellular receptors (*see,* (a) Choi, S. K.; Mammen, M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1997,** *119*, 4103-4111. (b) Sigal, G.B.; Mammen, M.; Dahmann, G.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996,** *118(16)*, 3789-3800. (c) Stoiber, H.; Schneider, R.; Janatova, J.; Dierich, M.P. *Immunobiology* **1995,** *193(1)*, 98-113). In comparison to monovalent interactions, much less is understood about the molecular basis of polyvalent interactions (*see,* Mammen, M.; Choi, S. K.; Whitesides, G. M. *Angew. Chem. Int. Ed.* **1998,** *37*, 2754-2794). However, recent developments in nanotechnology and bioimaging allow additional studies focusing on these important protein-ligand interactions

systematically and at a molecular level. Of particular interest are investigations that target the HIV virus and interactions that are important in its adhesion to cellular hosts.

[0006] The HIV virus gains entry into host cells through a cascade of events mediated by the viral glycoproteins gp120 and gp41 (*see,* (a) Allan, J. S.; Coligan, J. E.; Barin, F.; McLane, M. F.; Sodroski, J. G.; Rosen, C. A.; Haseltine, W. A.; Lee, T. H.; Essex, M. *Science* **1985**, *228*, 1091-1094; (b) Barin, F.; McLane, M. F.; Allan, J. S.; Lee, T. H.; Groopman, J. E.; Essex, M. *Science* **1985**, *228*, 1094-1096; and (c) McKeating, J. A.; Willey, R. L. *Aids* **1989**, *3*, S35-S41). Together these two glycoproteins are presented in trimeric form on the viral surface. *See,* (a) Chan, D.C.; Kim, P. S. *Cell* **1998**, *93*, 681-684. (b) Eckert, D. M.; Kim, P. S. *Ann. Rev. Biochem.* **2001**, *70*, 777-810. HIV is known to infect host cells expressing both a critical domain protein called CD4 and chemokine co-receptors. *See,* Littman, D. R. *Cell* **1998**, *93*, 677-680 and references therein. T-lymphocytes and macrophages are the primary targets of HIV infection and the process is initiated by interactions between gp120, CD4, and the chemokine co-receptor. These interactions lead to conformational changes in gp120, which subsequently unmask a hydrophobic region of gp41 that is capable of inserting into the host cell membrane.

[0007] One approach to successful therapy is to block an early step in the viral entry process, for example, blocking initial gp120 interactions with cellular receptors that play an important role in sexual transmission of HIV. Galactosyl ceramide (GalCer) is a glycosphingolipid (GSL) expressed on mucosal membrane cells that do not express CD4. Several studies have shown that an alternative pathway of HIV infection occurs in these CD4- cells through gp120 interactions with GalCer (*see,* (a) Yahi, N.; Baghdiguian, S.; Moreau, H.; Fantini, J. *J. Virol.* **1992**, *66*, 4848-4854; (b) Harouse, J. M.; Kunsch, C.; Hartle, H. T.; Laughlin, M. A.; Hoxie, J. A.; Wigdahl, B.; Gonzalez-Scarano, F. *J. Virol.* **1989**, *63*, 2527-2533; (c) Harouse, J. M.; Bhat, S.; Spitalnik, S. L.; Laughlin, M.; Stefano, K.; Silberberg, D. H.; Gonzalez-Scarano, F. *Science* **1991**, *253*, 320-323; (d) McAlarney, T.; Apostolski, S.; Lederman, S.; Latov, N. *J. Neurosci. Res.* **1994**, *37*, 453-460; (e) Brogi, A.; Presentini, R.; Solazzo, D.; Piomboni, P.; Constantino-Ceccarini, E. *AIDS Res. Hum. Retroviruses* **1996**, *12*, 483-489; and (f) Brogi, A.; Presentini, R.; Piomboni, P.; Collodel, G.; Strazza, M.; Solazzo, D.; Costantino-Ceccarini, E. *J. Submicrosc. Cyt. Pathol.* **1995**, *27*, 565-571). McReynolds, et al. have shown that gp120 (recombinant gp120 is used in most studies) recognizes several different GSLs in addition to GalCer including naturally occurring GlcCer, and LacCer and even non-natural analogs such as MelCer, and CelCer (**Figure 1,** *see,*

McReynolds, K. D.; Hadd, M. J.; Gervay-Hague; J. *Bioconjugate Chem.* **1999**, *10*, 1021-1031; and McReynolds, K. D.; Bhat, A.; Conboy, J. C.; Saavedra, S. S.; Gervay-Hague; J. *Biorganic & Medicinal Chemistry* **2002**, *10*, 625-637). More recently, it has been shown that *C*-glycoside analogs of GalCer are recognized by rgp120 and the relatively complex sphingosine sidechain can be replaced with simpler lipids without diminished activity. *See,* for example, Gu, Y.; LaBell, R Y..; O'Brien, D. F.; Saavedra, S. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 2320-2322, corrigenda: Gu, Y.; LaBell, R. Y.; O'Brien, D. F.; Saavedra, S. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 2947; Bertozzi, C. R. ; Cook, D. G.; Kobertz, W. R.; Gonzalez-Scarano, F.; Bednarski, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 10639-10641; Faroux-Corlay, B.; Clary, L.; Gadras, C.; Hammache, D.; Greiner, J.; Santaella, C.; Aubertin, A.-M.; Vierling, P.; Fantini, J. *Carbohydr. Res.* **2000**, *327*, 223-260; and Rico-Lattes, I.; Garrigues, J.-C.; Perez, E.; Andre-Barres, C.; Madelaine-Duuich, C.; Lattes, A.; Linas, M.-D.; Aubertin, A.-M. *New J. Chem.* **1995**, *19*, 341.

[0008] Over the last decade, several multivalent model systems with both low and high valencies (i.e. dendrimers, soluble and immobilized polymers, and self-assembled monolayers) have been developed and applied to the study of carbohydrate-protein and carbohydrate-carbohydrate interactions. *See,* (a) Conboy, J. C.; McReynolds, K. D.; Gervay-Hague, J.; Saavedra .S. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 2882-2884; (b) Conboy, J. C.; McReynolds, K. D.; Gervay-Hague, J.; Saavedra. S. S. *J. Am. Chem. Soc.* **2002**, *124*, 968-977; and Houseman, B. T.; Mrksich, M. *Topics in Curr. Chem.* **2002**, *218*, 1-44 and references therein. More recently, the advantages of using carbohydrate-functionalized gold nanoparticles have been demonstrated ((a) de la Fuente, J. M.; Barrientos, A. G.; Rojas, T. C., Rojo, J.; Cañada, J.; Fernández, A.; Penadés ,S. *Angew. Chem. Int. Ed.* **2001**, *40*, 2257-2261; (b) Penadés, S.; Rojo, J.; Martín-Lomas, M. PCT WO 02/32404 A2; and (c) Hernáiz, M. J.; de la Fuente, J.; Barrientos, A. G.; Penadés, S. *Angew. Chem. Int. Ed.* **2002**, 41, 1554-57). While the scaffolds are relatively easy to assemble and particle size can often be tuned depending upon reaction conditions, (*see,* Hosteler, M. J.; Wingate, J. E.; Zhong, C.-J.; Harris; J. E., Vachet, R. W.; Clark, M. R.; Londono, J. D.; Green, S. J.; Stokes, J. J.; Wignall, G. D.; Glish, G. L.; Porter, M. D.; Evans, N. D.; Murray, R. W. *Langmuir* **1998**, *14,* 17-30) the reported nanoparticles contain linkages that are susceptible to enzymatic degradation, generally via hydrolysis.

[0009] What is needed in the art are new compositions to facilitate the study of cell recognition and adhesion processes, that are useful in systems comprising the complete

panoply of enzymes present in vivo. Additionally, compositions are needed that can be used in therapeutic applications in which enzymatic degradation contributes to reduced half-life and which can be finely tuned to provide ionic charge characteristics to facilitate uptake and distribution. Surprisingly, the present invention provides such compounds and compositions.

BRIEF SUMMARY OF THE INVENTION

[0010] The present invention provides a variety of nanoparticles having a core portion and a surface of attached ligands, and optionally having attached co-ligand groups. The core portion comprises gold or a gold alloy and the attached ligands can be a variety of saccharide or oligosaccharide components, at least a portion of which are *C*-glycosides.

[0011] In a related aspect of the invention, methods are provided for treating diseases dependent on glycoprotein recognition. In these methods, a subject in need of treatment is administered a therapeutically effective amount of a composition comprising nanoparticles having a core portion and attached ligands, and optionally having attached co-ligands, wherein the core portion comprises gold or a gold alloy, and the attached ligands are the same or different, at least a portion of the attached ligands being *C*-glycosides that are capable of disrupting glycoprotein recognition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **Figure 1** illustrates the structures of alternate Gp120 receptors including galactosyl ceramide (GalCer) and other glycosphingolipids.

[0013] **Figure 2** provides a TEM image of Gal-Au (**17**, in (a)) and Glc-Au (**18**, in (b)). A drop of a solution of colloidal Au nanoparticles in nanopure water was deposited onto a silicon-coated copper grid and left to dry completely.

[0014] **Figure 3** provides an AFM topograph of the Gal-Au (**17**) nanoparticles in (a) and a cursor profile along a selected line showing three particles with diameters of 2.0 nm, 1.6 nm and 2.1 nm, in (b).

[0015] **Figure 4** provides the UV/Vis spectra of the Au nanoparticles.

[0016] **Figure 5** provides an illustration of the competitive BNAA competitive assay employed to characterize the activity of the Au nanoparticles. Biotinylated GalCer is immobilized through interactions with NeutrAvidin™ and HRP-rgp120 is introduced. In the

next step, HRP-rgp120 is competed off by the introduction of an alternate ligand. The extent to which the ligand is able to compete can be measured by comparing absorbance data from competition wells relative to bGalCer wells where no external ligand was introduced.

[0017] **Figure 6** is a bar graph illustrating the results for the BNAA competition assay described in Example 4. Assay data is provided for disulfides **14**, **15**, and **16**; Au nanoparticles **17**, **18**, and **19**; and bGalCer **20** shown as endpoint readings at 415 nm after 20 min. As control, data for **20** correspond to maximal absorbance (no exposure to ligands in competition step).

[0018] **Figure 7** illustrates the structures of the linking groups and mixed glyconanoparticles prepared according to Example 5.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

[0019] The terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

[0020] The term "therapeutically effective amount" refers to that amount of the compound being administered sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the condition or disorder being treated.

[0021] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the subject recipient thereof.

[0022] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

General

[0023] As progress is made in the understanding of biological processes that lead to diseases, the need for alternative therapeutic agents to regulate these processes increases. In

particular, it has now been discovered that many processes involve polyvalent interactions in cellular recognition. Recently, several multivalent model systems having low and/or high valencies (*i.e.*, dendrimers, soluble and immobilized polymers, and self-assembled monolayers) have been developed and applied to the study of carbohydrate-protein and carbohydrate-carbohydrate interactions. Even more recently, the advantages of using carbohydrate-functionalized gold nanoparticles have been demonstrated.

[0024] Alternative nanoparticle compositions and methods are needed, and are provided herein, in which the polyvalent presentations are made with stable linkages. Additionally, the nanoparticles are preferably prepared by methods that allow the introduction of multiple ligands or co-ligands.

Description of the Embodiments

Compounds and compositions

[0025] In view of the above, the present invention provides in one aspect, nanoparticles comprising a core portion and attached ligands, and optionally having attached co-ligands, wherein said core portion comprises gold or a gold alloy, and said attached ligands are the same or different, at least a portion of said attached ligands being C-glycosides.

[0026] Turning first to the core portion of the nanoparticles, the core will generally comprise gold, a gold alloy, or silica (*i.e.*, SiO_2). Suitable gold alloys include those made with silver, copper, iron, platinum, palladium and combinations thereof, particularly, silver and copper as well as silver, copper and palladium combinations. In certain preferred embodiments, the core portion is at least 80% gold, more preferably at least 95% gold, and still more preferably at least 99% gold. In certain other preferred embodiments, the core of larger nanoparticles (*e.g.*, greater than about 50 nm) comprises silica. Suitable silica core portions for use in the present invention include those that are commercially available from Nissan Chemical Industries under the name Snowtex and those that are made according to methods known in the art, such as those described in Stober *et al.*, *J. Colloid and Interface Science*, 26:62-69 (1968). In additional preferred embodiments, the silica core portion is coated with gold or a gold alloy according to methods known in the art, such as those described in Pham *et al.*, *Langmuir*, 18:4915-4920 (2002); Westcott *et al.*, *Langmuir*, 14:5396-5401 (1998); and Oldenburg *et al.*, *Chemical Physics Letters*, 288:243-247 (1998). For example, a 100 nm silica core portion can be coated with a 10 nm to 20 nm layer of gold or gold alloy. In other embodiments of the present invention, the mean diameter of the core

portion ranges from about 0.2 nm to about 150 nm so that the overall nanoparticle size has a mean particle diameter of from about 0.25 nm to about 160 nm, preferably from about 0.5 nm to 100 nm, more preferably from about 0.5 nm to about 5.0 nm, and still more preferably from about 1.0 nm to about 3.0 nm. In certain instances, the mean diameter of the core portion is that which is comparable to the binding partner for the nanoparticle ligands. For example, the glycoprotein gp120 has a size of about 2.5 nm and preferably binds to gold nanoparticles having a mean diameter of about 2.5 ± 0.5 nm.

[0027] Attached to the core portion of the nanoparticles is a linking group or spacer, generally having from 6 to 50 main chain atoms selected from the group consisting of S, O, N and C (hydrogen atoms will typically fill the remaining valences). In preferred embodiments, the spacer is selected to impart a variety of characteristics to the nanoparticle, such as increased stability, water solubility and circulation half-life. For example, the spacer is generally selected to reduce degradation or removal of the ligand from the core portion by being stable to hydrolytic processes (both enzymatic and chemolytic) under physiological conditions. Additionally, certain linking groups or spacers will have attached functional groups that operate to increase solubility (*e.g.*, hydroxy, amino or ammonium groups). The linking group or spacer portions are preferably of sufficient length to permit the ligand, or ligands, in the completed nanoparticle to interact freely with a target. Generally, the spacer or linking group has a core- or surface-attaching portion and a longer chain portion. The surface attaching portion is that part of the linking group which is directly attached to the core (*e.g.*, Au). Preferred attaching portions are thiols that are produced just prior to reaction with a gold or gold alloy core. The longer chain portions are typically alkanes, alkenes, glycols (*e.g.*, ethylene glycol oligomers containing multiple monomer units), alcohols, amines, polyamines (*e.g.*, spermine, spermidine and polymeric derivatives thereof) or combinations thereof. Preferably, the linking group will be a polyethyleneglycol group which is at least a di or tri-ethyleneglycol. As noted above, the longer chain portion can be selected based upon its hydrophilic/hydrophobic properties to improve presentation of the ligands to certain receptors or proteins. Methods of forming ether, carbamate or amine linkages are known to those of skill in the art and particular reagents and references can be found in such texts as March, Advanced Organic Chemistry, 4th Ed., Wiley-Interscience, New York, N.Y, 1992, incorporated herein by reference.

[0028] Attached to the distal portion of the linking group is a ligand or mixture of ligands that can be the same or different, with at least a portion of the attached ligands being *C*-

glycosides. The preparation of *C*-glycosides are known to those of skill in the art and exemplary processes are provided in detail below (*see,* Examples and Scheme 1). *C*-glycosides can be used as ligands as monosaccharides, disaccharides, oligo- or polysaccharides. Preferred *C*-glycosides are selected from *C*-α or β, D or L, glycobiosyl alkylamines (*e.g.,* meliobiosyl, lactobiosyl, and cellobiosyl); and longer oligosaccharides containing any combination of carbohydrate linkages involving C, N, O and S and combinations thereof. Particularly preferred *C*-glycosides are selected from *C*-(β-D-glycopyranosyl)methylamines and *C*-(β-D-galactopyranosyl)methylamines. As used herein, the term "glycoconjugate" refers to a conjugate between a *C*-glycoside ligand and a linking group.

[0029] The ligands are generally present on the surface of the core portion in an amount that optimizes binding with the target and reduces steric crowding of the ligands with one another. Preferably, the core portion has from 10 to 500 attached ligands, more preferably from 20 to 200 attached ligands, and still more preferably from 50 to 150 attached ligands. In some embodiments, the nanoparticles will further comprise attached co-ligands. As used herein, the term "co-ligands" refers to a moiety that facilitates ligand binding to a target by providing an environment that is conducive to such binding. The co-ligands can be positively charged, negatively charged, or neutral. For example, a co-ligand will, in some embodiments, be a functional group that is positively charged at physiological pH and promotes solubility in physiological systems. In other embodiments, the co-ligand can provide a co-factor that facilitates target-ligand binding. In still other embodiments, the co-ligand can be a targeting agent. A variety of targeting agents are useful in the nanoparticles described herein. Typically, the targeting agents are attached to the core portion in the same manner as described for the ligands, although in some instances, the linkages can be less robust than those used for the ligands. The targeting agents themselves can be any element that makes it possible to direct the binding of a ligand on the nanoparticle to a particular site. The targeting agent can be an extracellular targeting agent, which allows, for example, a nanoparticle to be directed towards certain types of cells or certain desired tissues (tumor cells, liver cells, hematopoietic cells, and the like).

[0030] In one group of embodiments, the targeting agent can be a fusogenic peptide (*e.g.,* gp41) for preventing cellular infection or a host cell fusogenic peptide for promoting cellular transfections, favoring the passage of the nanoparticle across membranes. The targeting agent can also be a cell receptor ligand for a receptor that is present at the surface of the cell

type, such as, for example, a carbohydrate, transferrin or insulin. Other targeting agents useful in the context of the invention, include peptides, hormones, vitamins, cytokines, oligonucleotides, lipids or sequences or fractions derived from these elements and which allow specific binding with their corresponding receptors. Preferably, the targeting agents are sugars and/or peptides such as antibodies or antibody fragments, cell receptor ligands or fragments thereof, receptors or receptor fragments, and the like. More preferably, the targeting agents are ligands of growth factor receptors, of cytokine receptors, or of cell lectin receptors or of adhesion protein receptors. The targeting agent can also be an antibody Fab fragment which makes it possible to target the Fc fragment receptor of immunoglobulins.

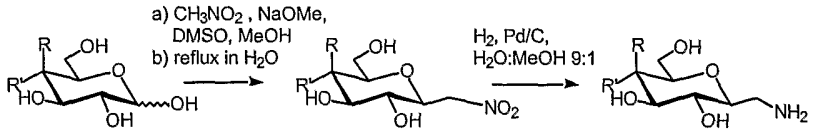
[0031] In certain instances, all of the linking groups attached to the core portion have a ligand attached thereto, *e.g.,* only glycoconjugates are attached to the core portion. In certain other instances, a mixture of linking groups with attached ligands and linking groups without attached ligands, *e.g.,* a mixture of glycoconjugates and linking groups, are attached to the core portion. Suitable ratios of the linking groups with attached ligands to the linking groups without attached ligands include, without limitation, ratios of from about 3:1 to about 1:3.

Preparation of Nanoparticles

[0032] Preparation of the nanoparticles of the present invention can be carried out using a variety of techniques known to the skilled synthetic chemist. In general, preparation of the nanoparticles begins with preparation of a suitable ligand having an attached linking group which terminates in a functional group or protected functional group suitable (after removal of the protecting group) for attachment to the core portion. At least a portion of the ligands used in the present invention are *C*-glycosides, selected for their stability in in vivo systems. The preparation of *C*-glycosides can be accomplished by a variety of methods. Schemes 1-4, below, illustrate and describe one method for *C*-glycoside preparation, followed by construction of a heterobifunctional linking group (Scheme 2), attachment of the linking group to the *C*-glycoside (Scheme 3) to form a thiolated *C*-glycoside, or disulfide dimer of the *C*-glycoside, and synthesis of the functionalized gold nanoparticles (Scheme 4). While specific reagents and conditions are provided in the schemes below, one of skill in the art will appreciate that alternative reagents and conditions can also be employed to prepare the desired nanoparticles.

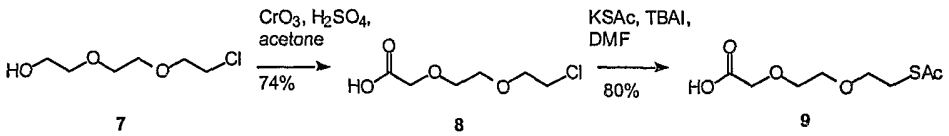
[0033] Turning first to Scheme 1, preparation of the *C*-glycosides was accomplished upon reaction of the appropriate carbohydrate (**1** or **2**) with nitromethane under basic conditions to

provide cyclic derivatives favoring the β-pyranosylglycosides with the bulky nitromethyl group in the equatorial position. *See,* Sowden, J. C.; Oftedahl, M. L. *J. Org. Chem.* **1961**, *26*, 1974-1977; and Kopf, J.; Topf, C.; Köll, P. *Carbohydr. Res.* **1989**, *186*, 1-28. Following an improved preparation method, *C*-(β-D-galactopyranosyl)- and *C*-(β-D-glucopyranosyl)nitromethanes (**3**) and (**4**) were obtained in yields of 50 and 53%, respectively. Hydrogenation over palladium/charcoal afforded *C*-(β-D-galactopyranosyl)- and *C*-(β-D-glucopyranosyl)methylamines (**5**) and (**6**) in virtually quantitative yields (Scheme 1). *See,* for example, procedures provided in the examples below, and in Sowden, J. C.; Bowers, C. H.; Lloyd, K. O. *J. Org Chem.* **1964**, *29*, 130-132; Hough, L.; Shute, S. H. *J. Chem. Soc.* **1962**, 4633-4637; Sowden, J. C.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1946**, *68*, 1511-1513; Petrus, L.; Bystricky, S.; Sticzay, T.; Bilik, V. *Chem. Zvesti* **1982**, *36*, 103-110.; Petrus, L.; Mihalov, V.; *Collect. Czech. Chem. Commun.* **1983**, 48, 1867-1871; Coxon, B.; Fletcher, H. G. *J. Am. Chem. Soc.* **1964**, *86*, 922-926; BeMiller, J. N.; Yadav, M. P.; Kalabokis, V. N.; Myers, R. W. *Carbohydr. Res.* **1990**, *200*, 111-126; Coxon, B.; and Fletcher, H. G. *J. Am. Chem. Soc.* **1963**, *85*, 2637-2642.



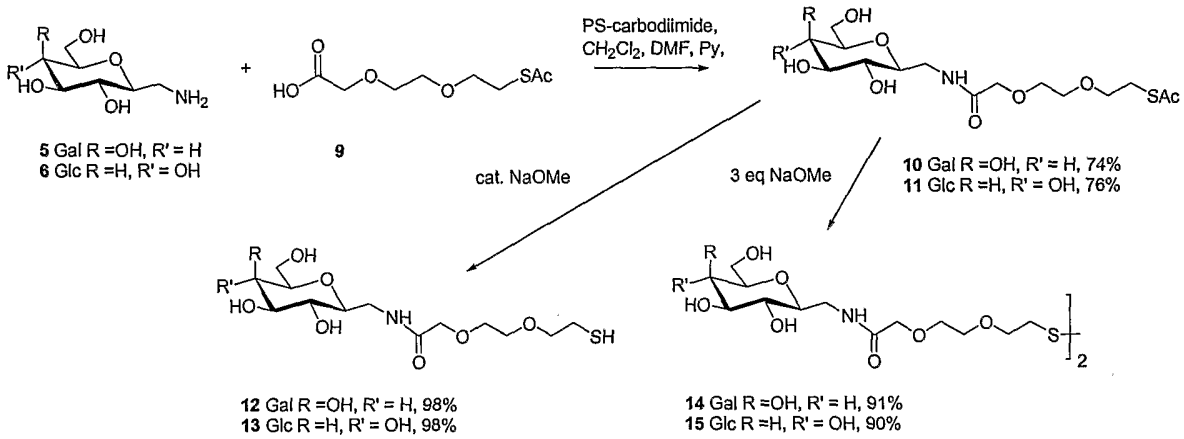
Scheme 1. Synthesis of *β-C*-Glycoside Amines

[0034] In preparation of the thio-functionalized hydrophilic spacer, commercially available [2-(2-chloroethoxy)ethoxy]ethanol (**7**) underwent Jones oxidation yielding the carboxylic acid **8**. *See,* LaBell, R. Y.; Jacobsen, N. E.; Gervay-Hague, J.; O'Brien, D. F *Bioconjugate Chem.* **2002**, *13*, 143-149. Conversion of **8** to [2-(2-thioacetylethoxy)ethoxy]acetic acid (**9**) was accomplished in 80% yield by the action of potassium thioacetate in the presence of TBAI (Scheme 2).



Scheme 2. Synthesis of Thiol-functionalized Linker

[0035] The final step in the glycoconjugate synthesis was amide bond formation between thiolated linker (**9**) and *C*-(β-D-glycopyranosyl)methylamines (**5**) and (**6**) as head group carbohydrates. Activation of the carboxylic acid functionality with PS-carbodiimide followed by addition of amino methyl glycosides (**5**) or (**6**) produced the desired thiolated glycoconjugates (**10**) and (**11**) in isolated yields of 74-76% (Scheme 3).

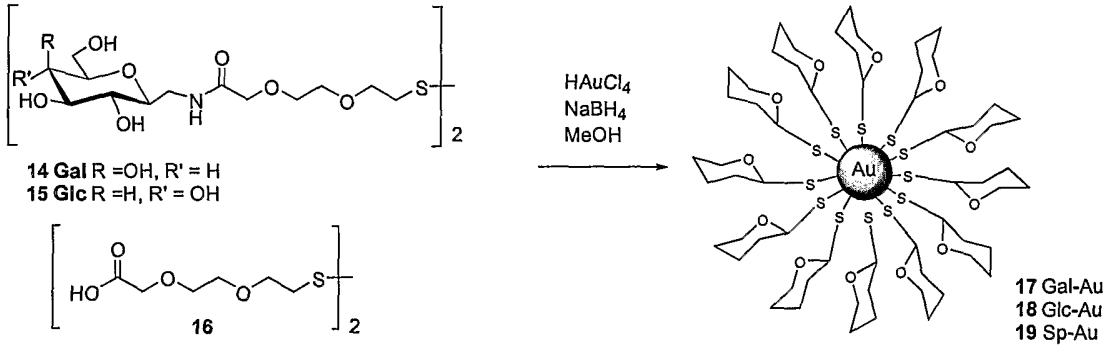


Scheme 3. Synthesis of Thiolated *C*-Glycosides

[0036] Treatment of (**10**) and (**11**) with catalytic amounts of sodium methoxide in methanol for 30 minutes afforded the corresponding thio-functionalized glycoconjugates (**12**) and (**13**), while longer reaction times (10-18 h) in the presence of air and an excess of sodium methoxide (3 eq) resulted almost exclusively in the formation of the corresponding disulfide derivatives (**14**) and (**15**). Oxidation was easily detected by ^{1}H and ^{13}C NMR, where the signals for the methylene groups next to the thiol functionality in (**12**) or (**13**) were found at ca. 2.7 ppm (ca. 23.7 ppm), whereas these signals are shifted downfield to ca. 2.9 ppm (ca. 38.6 ppm) in the case of the disulfide species (**14**) or (**15**).

Synthesis of the Functionalized Au Nanoparticles

[0037] In the formation of functionalized Au nanoparticles, a methanolic solution of the disulfide derivatives (**14, 15, 16**) was combined with an aqueous solution of $HAuCl_4$ in a molar ratio of 3:1 and an excess of $NaBH_4$ (22 eq.) as reducing agent was added in small portions (Scheme 4). The precipitated functionalized Au nanoparticles, Gal-Au (**17**), Glc-Au (**18**), and carboxy-functionalized Sp-Au (**19**) were purified by centrifugal filtration and obtained as dark-brown powders after lyophilization in 88%, 93%, 91% yields, respectively. These materials were repeatedly dried and redissolved in water without visible aggregation or loss of solubility.



Scheme 4. Synthesis of Functionalized Gold nanoparticles.

Pharmaceutical compositions

[0038] In related aspects, the present invention provides pharmaceutical compositions comprising the nanoparticles described above in admixture with a pharmaceutically acceptable carrier or excipient. The compositions are suitable for pharmaceutical or diagnostic use.

[0039] In one embodiment, the invention provides the subject nanoparticles combined with a pharmaceutically acceptable excipient such as sterile saline or other medium, water, gelatin, an oil, etc. to form pharmaceutically acceptable compositions. The compositions can be administered alone or in combination with another convenient carrier, diluent, etc. and such administration may be provided in single or multiple dosages. Useful carriers include solid, semi-solid or liquid media including water and non-toxic organic solvents.

[0040] The compositions can be provided in any convenient form, including tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, suppositories, etc. As such, the compositions, in pharmaceutically acceptable dosage units or in bulk, may be incorporated into a wide variety of containers. For example, dosage units may be included in a variety of containers including capsules, pills, *etc.*

Methods of Use

[0041] In yet another aspect, the present invention provides methods for the use of the foregoing nanoparticles and compositions. In particular, the invention provides methods for treating diseases dependent on glycoprotein recognition. The methods typically involve administering to a patient an effective formulation of one or more of the subject nanoparticles.

[0042] In one group of embodiments, the invention provides methods of using the subject nanoparticles and compositions to treat disease or provide medicinal prophylaxis to individuals who possess a compromised immune system or are expected to suffer immunosuppressed conditions, such as patients prior to undergoing immunosuppressive therapy in connection with organ transplantation or anticancer chemotherapy. These methods generally involve administering to the host an effective amount of the subject compounds or pharmaceutically acceptable compositions.

[0043] In other embodiments, the nanoparticles of the present invention are advantageously combined and/or used in combination with other antiviral agents useful in the treatment and/or prevention of the viral infections described herein. For example, the nanoparticles may be advantageously combined and/or used in combination with agents useful in the treatment and/or prevention of conditions often associated with the viral infections described herein, such as anti-HIV agents (described below), immunostimulatory agents (*e.g.*, vaccines) or immunosuppressive agents (*e.g.*, cyclosporin, FK-506 and rapamycin). In many instances, administration of the subject compounds or compositions in conjunction with these alternative agents enhances the efficacy of such agents. Accordingly, in some instances, the present nanoparticles, when combined or administered in combination with other antiviral or immunosuppressive agents, can be used in dosages which are less than the expected amounts when used alone, or less than the calculated amounts for combination therapy.

[0044] Suitable agents for combination therapy include those that are currently commercially available and those that are in development or will be developed. While antiviral agents may be particularly suitable for the treatment or prevention of a particular viral disorder(s), practitioners skilled in the art understand that such agents frequently are useful in treating a range of viral-related disorders. Exemplary agents useful in the treatment of certain viral infections include acyclovir, cidofovir, ganciclovir, immunoglobulin and foscarnet. Other promising antiviral agents include the nucleoside/nucleotide analogs valaciclovir, valganciclovir, adefovir, dipivoxil and lobucavir; the antisense agents fomivirsen, GEM 132 (Hybridon), ISIS 13312 (ISIS); and other therapies like benzimidavir and sevirumab.

[0045] Exemplary anti-HIV agents include nucleoside analog reverse transcriptase inhibitors such as zidovudine (AZT), didanosine (ddI), zalcitabine (ddC, dideoxycytidine), stavudine (d4T), lamivudine (3TC), abacavir (1592U89), emtricitabine (FTC, Triangle

Pharmaceuticals), BCH-10652 (BioChem Pharma) and the related nucleotide analogs (*e.g.*, PMPA (Gilead Sciences)); non-nucleoside reverse transcriptase inhibitors such as nevirapine (NVP), delavirdine (DLV), efavirenz (DMP-266), emivirine (MKC-442), AG1549 (Agouron Pharmaceuticals; PNU142721 (Pharmacia),calanolide-A (Sarawak MediChem Pharmaceuticals); protease inhibitors such as saquinavir (SQV), ritonavir (RTV), indinavir (IDV), nelfinavir (NFV) saquinavir (SQV), amprenavir (APV), 232,632 (Bristol-Myers Squibb), tipranavir, DMP-450 (Triangle Pharmaceuticals), and lopinavir; immune stimulators such as interleukin 2 (Chiron), Reticulose® (Advance Viral Research Corporation), Multikine® (Cel-Sci Corporation), and HIV-1 immunogen (Immune Response Corporation). Other anti-HIV agents that may be used in combination with the compounds and compositions of the present invention include HIV integrase inhibitors (*e.g.*, AR-177 (Aronex Pharmaceuticals)), fusion inhibitors (*e.g.*, T-20 (Roche)) and antisense drugs (*e.g.*, HGTV43 (Enzo Therapeutics)).

[0046] The nanoparticles and compositions of the present invention may also be advantageously used as antiviral prophylactic treatment in combination with immunosuppressive protocols such as bone-marrow destruction (either by radiation or chemotherapy).

[0047] The compositions and nanoparticles of the invention and the pharmaceutically acceptable salts thereof can be administered in any effective way such as via oral, parenteral or topical routes. Generally, the compounds are administered in dosages ranging from about 2 mg up to about 2,000 mg per day, although variations will necessarily occur depending on the disease target, the patient, and the route of administration. Preferred dosages are administered orally in the range of about 0.05 mg/kg to about 20 mg/kg, more preferably in the range of about 0.05 mg/kg to about 2 mg/kg, most preferably in the range of about 0.05 mg/kg to about 0.2 mg per kg of body weight per day.

EXAMPLES

[0048] All materials were obtained from commercial sources and used without additional purification. Hydrogen tetrachloroaurate (III) hydrate was obtained from Strem Chemicals. All glassware for reactions under anhydrous conditions was flame-dried prior to use. Flash chromatography was performed on Silica Gel Geduran (40-63 μm) from Merck. For TLC, Silica Gel 60 F_{254} plates from Merck were used with detection by UV light and/or charring

with AMC (ammonium molybdate (45 g) and cerium(IV)sulfate (0.9 g) in 10% H_2SO_4 (900 mL).

[0049] ^1H NMR, COSY and HSQC spectra were recorded on Bruker DRX-500 or Bruker DRX-600 spectrometers at 25 °C. ^{13}C NMR spectra were acquired on Varian Mercury-300 MHz or Varian Inova-400 MHz spectrometers. Chemical shifts in ppm were referenced to $CDCl_3$ (7.26 ppm, 77.0 ppm), DMSO-d_6 (2.49 ppm, 39.50 ppm), CD_3OD (3.31 ppm, 49.0 ppm), and for D_2O to HOD (4.85 ppm) or CD_3OD (49.0 ppm) as internal standards. IR data were recorded on a Galaxy series FTIR 3000 instrument at 25 °C. Optical rotations were determined on a Jasco DIP-370 Digital Polarimeter. Bright field transmission electron micrographs were obtained from a Philips CM-12 system operating at 100 keV accelerating voltage. The samples were also viewed under HR-TEM at the National Center of Electron Microscopy and TEM and the results were consistent with those reported below. Mass spectrometry was performed at the University of California, Riverside Mass Spectrometry Facility, Riverside, CA, USA. Elemental analyses were obtained from Desert Analytics Laboratory, Tucson, AZ, USA. TEM experiments were performed by depositing a drop of a solution of the colloidal goldnanoparticles in nanopure water onto a silicon-coated copper grid and allowing the solution to dry completely.

[0050] A home-built scanner with the optical beam deflection configuration was used for atomic force microscopy (AFM) studies. *See,* Liu, G. Y.; Fenter, P.; Chidsey, C. E. D.; Ogletree, D. F.; Evenberger, P.; Salmeron, M. *Chem. Phys.* **1994**, *101,* 4301. The electronic controllers and software are commercially available from RHK Technology, Inc. (Troy, MI). The AFM scanner was calibrated using both mica(0001) and Au(111) surfaces. Sharpened Si_3N_4 microlevers (ThermoMicroscopes) with a force constant of 0.1 N/m were used for AFM imaging. Images were acquired in sec-butanol, and the typical imaging force was 0.1 nN. Nanoparticles were deposited onto atomically flat mica(0001) surfaces which were prepared by freshly cleaving them prior to nanoparticle deposition.

Example 1

[0051] This example illustrates the preparation of precursors used in the preparation of gold glyconanoparticles. Number for the compounds prepared corresponds to the numbering in Schemes 2 and 3, above.

[0052] [2-(2-Acetylsulfanyl-ethoxy)-ethoxy]-acetic acid (9): A mixture of (2-[2-chloroethoxy]ethoxy)acetic acid (1.82 g, 10 mmol, *see,* LaBell, R. Y.; Jacobsen, N. E.; Gervay-Hague, J.; O'Brien, D. F *Bioconjugate Chem.* **2002**, *13*, 143-149) and tetrabutylammonium iodide (400 mg, 1 mmol) in anhydrous DMF (20 mL) was stirred at room temperature as potassium thioacetate (3.4 g, 30 mmol) was added. The reaction was stirred for 18 h, and after completion 1 M HCl (40 mL) and ethyl acetate (100 mL) were added. The organic layer was washed with 1 M HCl (40 mL), and then with satd $NaHCO_3$ (80 mL). The aqueous layer, now containing the product, was washed with CH_2Cl_2 (5 x 100 mL). After acidifying with 1 M HCl, compound (9) was extracted with CH_2Cl_2 (5 x 100 mL), the organic extracts combined, dried and evaporated. Purification by column chromatography (eluent: hexanes/ethyl acetate v/v 1:1) afforded 1.6 g of product (9) (7.2 mmol, 72%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3 H, $SCOCH_3$), 3.02 (app t, 2 H, $J_{5,6}$ = 6.4 Hz, H-6), 3.54 (app t, 2 H, H-5), 3.61, 3.67 (2 m, 4 H, H-3, H-4), 4.01 (s, 2 H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.62 (C-6), 30.41 ($SCOCH_3$), 69.63 (C-5), 69.960, 71.25 (C-3, C-4), 76.12 (C-2), 195.26 ($SCOCH_3$), 199.34 (C-1). FT-IR (film): *ν* 3363 (O=C-O-H str), 2919, 2871 (-CH_2-C=O str, -CH_2- str), 1693 (C=O str), 1126 (C-O, C-C str) cm^{-1}. High-resolution mass spectrum (EI+) calcd. for $C_8H_{16}N_1O_4S_1$ (M+NH_4-H_2O): 222.0800. Found: 222.0808.

[0053] Thioacetic acid 2-[2-(2-{[(galactopyranosyl-2'-methyl)-carbamoyl]-methoxy}-ethoxy)-ethyl] ester (10): Under an argon atmosphere, a suspension of PS-carbodiimide (Argonaut Technologies Inc., 575 mg, 0.78 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was gently stirred for 5 min, then a solution of [2-(2-thioacetyl-ethoxy)ethoxy]acetic acid (9) (150 mg, 0.67 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added. After an additional 5 min, C-(β-D-galactopyranosyl)methylamine (5) (100 mg, 0.52 mmol) in a 1:1 mixture of anhydrous DMF and pyridine (3 mL) was cannulated into the suspension. The reaction was allowed to stir for 18 h at ambient temperature under inert conditions. In the work-up, the resin was filtered off and washed with MeOH and CH_2Cl_2, the filtrate was concentrated and the resulting material was purified by column chromatography (eluent: CH_2Cl_2/MeOH v/v 10:1 to 5:1). The desired compound (10) (153 mg, 0.38 mmol) was obtained in 74% yield as a colorless foam. ^1H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3 H, $SCOCH_3$), 3.13 (t, 2 H, $J_{5,6}$ = 6.4 Hz, H-6), 3.30 (m, 1 H, H-2'), 3.52 – 3.53 (m, 2 H, H-3', H-1'), 3.55 – 3.71 (m, 8 H, H-6', H-5, H-4', H-3, H-4), 3.78 – 3.86 (m, 3 H, H-1'', H-7'', H-7'), 4.06 – 4.10 (m, 3 H, H-5', H-2), 7.62 (t, 1 H, J

= 5.8 Hz, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.50 (C-6), 30.13 ($SCOCH_3$), 40.03 (C-1'), 63.32 (C-7'), 68.20 (C-3'), 69.60 (C-5'), 69.88 (C-5), 70.12, 70.82 (C-3, C-4), 70.19 (C-2), 74.12 (C-4'), 77.99 (C-6'), 78.74 (C-2'), 172.04 (C-1), 195.78 ($SCOCH_3$). $[\alpha]_D^{29}$ = +43° (c 0.8, $CHCl_3$). High-resolution mass spectrum (FAB+) calcd. for $C_{15}H_{28}N_1O_9S_1$ (M+H): 398.1485. Found: 398.1472.

[0054] Thioacetic acid 2-[2-(2-{[(glucopyranosyl-2'-methyl)-carbamoyl]-methoxy}-ethoxy)-ethyl] ester (11): Compound (11) (186 mg, 0.47 mmol) was obtained as a colorless foam from C-(β-D-glucopyranosyl)methylamine (6) (119 mg, 0.62 mmol) in 76% yield performing the same procedure as for (10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3 H, $SCOCH_3$), 3.08 (t, 2 H, $J_{5,6}$ = 6.4 Hz , H-6), 3.17 (dt, 1 H, H-3'), 3.27 – 3.33 (m, 2 H, H-6', H-2'), 3.44 – 3.64 (m, 9 H, H-5', H-4', H-5, H-1', H-3, H-4), 3.77 – 3.84 (m, 3 H, H-7', H-7'', H-1''), 4.02 (s, 2 H, H-2), 7.54 (t, 1 H, J = 5.8 Hz, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.01 (C-6), 31.04 ($SCOCH_3$), 40.59 (C-1'), 62.20 (C-7'), 70.28 (C-5), 70.33, 71.27 (C-3, C-4), 70.41 (C-5'), 70.57 (C-2), 71.57 (C-3'), 77.94 (C-4'), 78.72 (C-2'), 80.10 (C-6'), 172.26 (C-1), 195.95 ($SCOCH_3$). $[\alpha]_D^{29}$ = +20° (c 2.0, $CHCl_3$). High-resolution mass spectrum (FAB+) calcd. for $C_{15}H_{28}N_1O_9S_1$ (M+H): 398.1485. Found: 398.1479.

[0055] 2-[2-(2-Mercapto-ethoxy)-ethoxy]-N-(galactopyranosyl-2'-methyl)-acetamide (12): Compound (10) (80 mg, 0.2 mmol) was dissolved in anhydrous MeOH (4 mL) under an argon atmosphere, and a catalytic amount of NaOMe-solution (0.5 M in MeOH) was added. The reaction mixture was allowed to stir for 30 min at ambient temperature, at which point acidic DOWEX-ion exchange resin was added. The resin was filtered off and washed with MeOH (3 x 10 mL). After evaporation, (12) was obtained as a colorless foam in 98% yield (60 mg, 0.2 mmol). ^{1}H NMR (500MHz, CD_3OD) δ 2.71 (t, 2 H, $J_{5,6}$ = 6.4 Hz, H-6), 3.26 (dq, 1 H, $J_{2',3'}$ = 9.9 Hz, $J_{1',2'}$ = 8.5 Hz, $J_{1'',2'}$ = 2.5 Hz, H-2'), 3.41 (dd, 1 H, $J_{1',1''}$ = 14.0 Hz, H-1'), 3.74 – 3.52 (m, 3 H, H-4', H-3', H-6'), 3.65 (t, 2 H, H-5), 3.69 – 3.72 (m, 5 H, H-7'', H-3, H-4), 3.77 (dd, 1 H, $J_{7',7''}$ = 11.7 Hz, H-7'), 3.79 (dd, 1 H, H-1''), 4.05 (s, 2 H, H-2). ^{13}C NMR (125 MHz, CD_3OD) δ 23.66 (C-6), 40.53 (C-1'), 61.93 (C-7'), 69.26 (C-3'), 69.79 (C-5'), 70.07, 70.96 (C-3, C-4), 70.19 (C-2), 73.12 (C-5), 74.91 (C-4'), 79.09 (C-2'), 79.31 (C-6'), 171.93 (C-1). $[\alpha]_D^{29}$ = -3.3° (c 1.0, MeOH). High-resolution mass spectrum (FAB+) calcd. for $C_{13}H_{25}N_1O_8Na_1S_1$ (M+Na): 378.1199. Found: 378.1209.

[0056] 2-[2-(2-Mercapto-ethoxy)-ethoxy]-N-(glucopyranosyl-2'-methyl)-acetamide (13): (13) was obtained as a colorless foam in 98 % yield (87 mg, 0.25 mmol) by reacting

starting material (11) (100 mg, 0.25 mmol) as described for (12). ^{1}H NMR (600MHz, CD_3OD) δ 2.68 (app t, 2 H, $J_{5,6}$ = 6.4 Hz, H-6), 3.11 (app t, 1 H, $J_{2',3'} = J_{3',4'}$ = 9.4 Hz, H-3'), 3.24 – 3.34 (m, 3 H, H-5, H-2', H-6'), 3.34 – 3.40 (m, 2 H, H-4', H-1'), 3.62 (app t, 2 H, H-5), 3.62 (m, 1 H, H-7'), 3.65 - 3.68 (m, 4 H, H-3, H-4), 3.71 (dd, 1 H, $J_{1'',2'}$ = 2.6 Hz, H-1''), 3.83 (d, 1 H, $J_{7',7''}$ = 11.8 Hz, H-7''), 4.02 (s, 2 H, H-2). ^{13}C NMR (150 MHz, CD_3OD) δ 23.72 (C-6), 40.49 (C-1'), 62.12 (C-7'), 70.34 (C-2), 70.16, 70.97 (C-3, C-4), 70.79 (C-5'), 72.09 (C-3'), 73.19 (C-5), 78.28 (C-4'), 78.65 (C-6'), 80.64 (C-2'), 171.10 (C-1). $[\alpha]_D^{29}$ = -8.3° (c 2.0, MeOH). High-resolution mass spectrum (FAB+) calcd. for $C_{13}H_{25}N_1O_8Na_1S_1$ (M+Na): 378.1199. Found: 378.1205.

[0057] N-(Galactopyranosyl-2'-methyl)-2-(2-{2-[2-(2-{[(galactopyranosyl-2'-methyl)-carbamoyl]-methoxy}-ethoxy)-ethyldisulfanyl]-ethoxy}-ethoxy)-acetamide (14): Compound (10) (80 mg, 0.2 mmol) was dissolved in anhydrous MeOH (5 mL), and NaOMe (0.5 M in MeOH, 0.6 mmol, 1.2 mL) was added. The reaction mixture was allowed to stir for 10 h at ambient temperature, at which point acidic DOWEX-ion exchange resin was added. At neutralization, the resin was filtered off and washed with MeOH (3 x 10 mL). After evaporation and purification by silica gel column chromatography (CH_2Cl_2/MeOH v/v 2:1) product (14) was obtained as a colorless foam (65 mg, 0.1 mmol) in 91% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.90 (t, 4 H, $J_{5,6}$ = 6.4 Hz, 2 x H-6), 3.05 – 3.07 (m, 4 H, 2 x H-2', 2 x H-1'), 3.25 – 3.29 (m, 6 H, 2 x H-4', 2 x H-3', 2 x H-6'), 3.44 – 3.49 (m, 4 H, 2 x H-7'', 2 x H-7'), 3.56 – 3.64 (m, 10 H, 2 x H-3, 2 x H-4, 2 x H-1''), 3.65 – 3.66 (m, 6 H, 2 x H-5, 2 x H-5'), 4.32 (d, 2 H, J = 5.0 Hz, 2 x OH-5'), 4.49 (t, 2 H, J = 5.8 Hz, 2 x OH-7'), 4.72 (d, 2 H, J = 4.3 Hz, 2 x OH-4'), 4.91 (d, 2 H, J = 4.7 Hz, 2 x OH-3'), 3.88 (s, 4 H, 2 x H-2), 7.44 (t, 2 H, J = 5.9 Hz, 2 x NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 38.54 (C-6), 41.18 (C-1'), 61.49 (C-7'), 69.32 (C-5'), 69.46 (C-5), 69.88 (C-3'), 70.20, 70.98 (C-3, C-4), 70.66 (C-2), 75.16 (C-4'), 79.36 (C-2'), 79.66 (C-6'), 170.05 (C-1). $[\alpha]_D^{29}$ = +2.8° (c 2.0, MeOH). High-resolution mass spectrum (FAB+) calcd. for $C_{26}H_{48}N_2O_{16}Na_1S_2$ (M+Na): 731.2343. Found: 731.2346.

[0058] N-(Glucopyranosyl-2'-methyl)-2-(2-{2-[2-(2-{[(glucopyranosyl-2'-methyl)-carbamoyl]-ethoxy}-ethoxy)-ethyldisulfanyl]-ethoxy}-ethoxy)-acetamide (15): (15) was isolated as a colorless foam (80 mg, 0.11 mmol) in 90% yield after treating starting material (11) (100 mg, 0.25 mmol) following the procedure as for (14). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.92 (app t, 4 H, $J_{5,6}$ = 6.4 Hz, 2 x H-6), 2.93 (m, 2 H, 2 x H-3'), 3.01 – 3.18 (m, 10 H, 2

x H-5', 2 x H-1', 2 x H-2', 2 x H-6', 2 x H-4'), 3.42 (dt, 2 H, $J_{7',7'\text{-OH}}$ = 5.8 Hz, $J_{7,7''}$ = 11.8 Hz, Hz, 2 x H-7'), 3.59 (m, 8 H, 2 x H-3, 2 x H-4), 3.62 – 3.71 (m, 8 H, 2 x H-1'', 2 x H-7'', 2 x H-5,5), 3.91 (s, 4 H, 2 x H-2), 4.44 (t, 2 H, 2 x OH-7'), 4.94 (d, 2 H, J = 4.9 Hz, 2 x OH-5'), 4.98 (d, 2 H, J = 4.6 Hz, 2 x OH-4'), 5.07 (d, 2 H, J = 5.1 Hz, 2 x OH-3'), 7.52 (t, 2 H, J = 5.0 Hz, 2 x NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 38.55 (C-6), 41.13 (C-1'), 62.29 (C-7'), 69.49 (C-5), 70.23, 70.98 (C-3, C-4), 70.69 (C-2), 71.18 (C-5'), 72.90 (C-3'), 78.58 (C-4'), 78.77 (C-6'), 81.39 (C-2'), 170.23 (C-1). $[\alpha]_D^{29}$ = -7.7° (c 2.0, MeOH). High-resolution mass spectrum (FAB+) calcd. for $C_{26}H_{48}N_2O_{16}Na_1S_2$ (M+Na): 731.2343. Found: 731.2375.

[0059] (2-{2-[2-(2-Carboxymethoxy-ethoxy)-ethyldisulfanyl]-ethoxy}-ethoxy)-acetic acid (16): (16) (167 mg, 0.47 mmol) was obtained in 93% yield as light yellow syrup after treating [2-(2-thioacetyl-ethoxy)ethoxy]acetic acid (9) (220 mg, 1.0 mmol) as described for preparation of (14). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (app t, 2 H, $J_{5,6}$ = 6.4 Hz, 2 x H-6), 3.67 (m, 2 H, 2 x H-5), 3.70, 3.74 (2 m, 4 H, H-3, H-4), 4.16 (s, 2 H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.95 (C-6), 68.18 (C-5), 69.14, 69.98 (C-3, C-4), 70.42 (C-2), 170.60 (C-1). FT-IR (film): ν 3362 (O=C-O-H str), 2920, 2870 (-CH_2-C=O str, -CH_2- str), 1692 (C=O str), 1128 (C-O, C-C str) cm^{-1}. High-resolution mass spectrum (EI+) calcd. for $C_{12}H_{24}N_1O_7S_2$ (M+NH_4-H_2O): 358.0518. Found: 358.0516.

Example 2

[0060] Preparation of Gold Glyconanoparticles - Gal-Au (17), Glc-Au (18) and Sp-Au (19): A freshly prepared 12 mM solution of disulfide (14, 15 or 16) (0.12 mmol, 3 eq disulfide or 6 eq sulfide) in MeOH was added to a freshly prepared aqueous 25 mM solution of hydrogen tetrachloroaurate (III) hydrate (0.04 mmol, 1 eq). Under vigorous stirring, a freshly prepared aqueous 1 M solution of $NaBH_4$ (0.83 mmol, 22 eq) was added dropwise. Under liberation of H_2, a dark-brown suspension formed instantly. Stirring was continued for an additional 2 h at ambient temperature. Subsequently, the solvents were evaporated *in vacuo* and the residue was dissolved in water (3 mL) and purified by centrifugal filtration (Centriplus YM30, microcon, MWCO = 30,000, 3000 x g, 45 min). The supernatent was collected and lyophilized. Alternatively, the residue was repeatedly suspended in MeOH (12 mL), sonicated (5 min), centrifuged (3-5 times, 30 min) and decanted, finally the salt- and disulfide-free precipitate was dissolved in water and lyophilized. Glyconanoparticles Gal-Au (17, 13 mg, 88%), Glc-Au (18, 14 mg, 93%), and Sp-Au (19, 13 mg, 91%) were obtained as dark-brown solids. The yields were calculated based upon Au as the limiting reagent.

[0061] Gal-Au (17): ^{1}H NMR (500 MHz, D_2O) δ 3.30 – 3.43 (bm, 3 H, H-2', H-1', H-3'), 3.55 – 3.79 (bm, 13 H, H-4', H-6', H-7', H-7'', H-1'', H-3, H-4, H-5, H-6 (weak)), 3.87 (bs, 1 H, H-5'), 4.06 (bs, 2 H, H-2). ^{13}C NMR (HSQC, 125 MHz, D_2O) δ 40.73 (C-1'), 61.78 (C-7'), 69.07 (C-3'), 69.41 (C-5'), 69.98 (C-2), 70.10 and 70.75 (C-3, C-4), 72.93 (C-6, broad and weak), 74.16 (C-4'), 74.26 (C-5, broad), 78.49 (C-2'), 78.86 (C-6'). FT-IR (KBr): *ν* 3383 - 3358 (O-H, N-H str); 2908, 2868 (-CH_2 str), 1662 (C=O str, amide I); 1556 (N-H bend, amide II); 1105-1081 (C-O, C-C, C-N, C-S str) cm^{-1}. Elemental analysis calcd. for $C_{1911}H_{3528}N_{147}O_{1176}S_{147}Au_{248}$: C 23.80 %, H 3.67 %, N 2.14 %; Found: C 22.41 %, H 3.63 %, N 2.22 %.

[0062] Glc-Au (18): ^{1}H NMR (500 MHz, D_2O) δ 3.18 (bm, 1 H, H-3'), 3.29 – 3.41 (bm, 5 H, H-5', H-2', H-1', H-6', H-4'), 3.62 – 3.79 (bm, 6 H, H-7, H-1'', H-3, H-4), 3.70 – 3.81 (bm, 5 H, H-5, H-6, weak H-7''), 4.06 (bs, 2 H, H-2). ^{13}C NMR (HSQC, 125 MHz, D_2O) δ 40.45 (C-1'), 61.40 (C-7'), 69.94 (C-2), 70.09 (C-5'), 70.09, 70.78 (C-3, C-4), 71.60 (C-3'), 72.97 (C-6, broad and weak), 74.14 (C-5, broad), 77.45 (C-4'), 78.00 (C-6'), 79.76 (C-2'). FT-IR (KBr): *ν* 3384-3362 (O-H, N-H str); 2904, 2861 (-CH_2 str), 1662 (C=O str, amide I); 1559 (N-H bend, amide II); 1110 - 1085 (C-O, C-C, C-N, C-S str) cm^{-1}. Elemental analysis calcd. for $C_{2041}H_{3768}N_{157}O_{1256}S_{157}Au_{234}$: C 24.08 %, H 3.71 %, N 2.16 %; Found: C 22.63 %, H 3.91 %, N 2.10 %.

[0063] Sp-Au (19): ^{1}H NMR (500 MHz, DMSO) δ 3.59 – 3.64 (m, 3 H, H-3, H-4, H-5), 4.14 (bs, 2 H, H-2). ^{13}C NMR (HSQC, 125 MHz, DMSO) δ 68.39, 6941, 70.38, 70.66 (C-2, C-3, C-4, C-5), 170.41 (C-1). FT-IR (film): 3342 (O=C-*O-H* str), 2920, 2870 (-*CH_2*-C=O str, -CH_2- str), 1752 (C=O str), 1128 (C-O, C-C str) cm^{-1}.FT-IR (KBr): *ν* 3360 (O=C-*O-H* str), 2923, 2868 (-*CH_2*-C=O str, -CH_2- str), 1697 (C=O str), 1124 (C-O, C-C str) cm^{-1}. Elemental analysis calcd. for $C_{66}H_{121}O_{44}S_{11}Au_{43}$: C 8.05 %, H 1.23 %, S 3.58 %; Found: C 6.89 %, H 1.22 %, S 3.31 %.

Example 3

[0064] This example illustrates methods for the characterization of the Au nanoparticles.

[0065] NMR and IR Characterization of the Au Nanoparticles. Evidence for incorporation of glycoconjugates onto the Au nanoparticles was provided by ^{1}H NMR spectra of Gal-Au (**17**) and Glc-Au (**18**) (ca. 5 mg per 0.8 mL D_2O), which showed typical broadening characteristic of mono-layer protected gold clusters. *See,* for example, Terrill, R.

H.; Postlethwhaite, T. A.; Chen, C.-H.; Poon, C.-D.; Terzis, A.; Chen, A.; Hutchison, J. E.; Clark, M. R.; Wignall, G. D.; Londono, J. D.; Superfine, R.; Falvo, M.; Johnson, C. S.; Samulski, E. T.; Murray, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 12537-12548; and Badia, A.; Gao, W.; Singh, S.; Demers, L.; Cuccia, L.; Reven, L.; *Langmuir* **1996**, *12*, 1262-1269. In HSQC experiments, a dramatic downfield shift and broadening of the methylene signals closest to the thiolate-gold interface from 2.9 ppm (ca. 38.6 ppm) for the disulfide precursors (**14**) and (**15**) to ca. 3.8 ppm (ca. 73.0 ppm) for Gal-Au (**17**) and Glc-Au (**18**) proved the attachment of carbohydrate ligands to the surface of the Au core via the sulfur atom. *See,* Badia, A.; Singh, S.; Demers, L.; Cuccia, L.; Brown, G. R.; Lennox, R. B. *Chem. Eur. J.* **1996**, *2*, 359-363. To a smaller extent, the same observation could be made for the next closest methylene group. Besides these features, the ^{1}H NMR and HSQC spectra of Gal-Au (**17**) and Glc-Au (**18**) are fully consistent with those of the disulfides (**14**) and (**15**). FT-IR spectroscopy (KBr pellet) indicated the presence of an amide bond (1660 cm^{-1}, C=O str, amide I; 1560 cm^{-1}, N-H bend, amide II) as well as C-O, C-C, C-N and C-S bonds (str, 1090 - 1110 cm^{-1}) and methylene groups (str, 2904 cm^{-1}, 2861 cm^{-1}), also a broad band for O-H and N-H appeared (str, 3360 – 3380 cm^{-1}).

[0066] TEM and AFM Imaging of Functionalized Au Nanoparticles. In order to establish sizes for both the core and overall particle distributions, TEM and AFM techniques were applied. Over 450 particles from different micrographs were measured and counted for the evaluation of size distribution (Figure 2). The TEM of Gal-Au (**17**) showed core diameters for the Au nanoparticles ranging from 1 nm to >4 nm, with 71% having an average core size of 2 nm (Figure 2a). The TEM of Glc-Au showed a similar distribution (Figure 2b). Complementary to TEM studies, AFM imaging provided information on the 3D structure of the nanoparticles including the ligand coating. Figure 3a represents a typical AFM topograph of the Gal-Au (**17**) nanoparticles. To avoid the convolution of the AFM tip in the lateral direction, the height measured from the cursor profiles in the AFM topographic images was utilized to quantify the particle diameter. The cursor profile in Figure 3b shows the diameters of the three particles are 2.0 nm, 1.6 nm and 2.1 nm, respectively. With 162 nanoparticles imaged, the measured height, i.e. the particle diameter ranged from 1.2 to 4.2 nm.

[0067] UV/Vis and Elemental Analyses. The UV/Vis data are also consistent with an average core size of 2 nm (Figure 4). The observed absorbances of Gal-Au (**17**) and Glc-Au (**18**) decayed approximately exponentially into the visible range with only a slightly detectable surface plasmon band (SP band). The SP band intensity correlates with core size

(Vezmar, I.; Alvarez, M. M.; Khoury, J. T.; Salisbury, B. E.; Shafigullin, M.N.; Whetten, R. L. *Z. Phys D* **1997**, *401*, 147-151; Schaaf, T. G.; Shafigullin, M. N.; Khoury, J. T.; Vezmar, I.; Whetten, R. L.; Cullen, W. G.; First, P. N.; Wing, C.; Ascensio, J.; Yacaman, M. J. *Z. Phys B* **1997**, *101*, 7885-7891; Underwood, S.; Mulvaney, P. *Langmuir* **1994**, *10* , 3427-3430; and Mulvaney, P. *Langmuir* **1996**, *12*, 788-800.), and UV/vis data of alkyl thiolated nanoparticles having a core radius of 1.0 nm and an average of 201 atoms forming the gold cluster show similar spectral features to the present Au glyconanopraticles. Considering that elemental analyses showed a carbohydrate to gold ratio of 1:1.7 for Gal-Au (**17**) and 1:1.5 for Glc-Au (**18**) with approximately 1.5% error, the average ratio of carbohydrate to Au is estimated to be 1:1.6. Assuming a gold cluster size of roughly 200 atoms, there are approximately 126 carbohydrates per 2 nm Au glyconanoparticle and considering the error involved it is reasonable to round this number to 120 carbohydrates per 2 nm gold cluster.

Example 4

[0068] Biotin NeutrAvidin™ Adhesion Assays (BNAA): Recombinant $gp120_{IIIB}$ (HIV-1)-HRP was obtained from Bartels – A Trinity Biotech Company, Reacti-Bind™ NeutrAvidin™ coated polystyrene plates from Pierce Biochemicals, phosphate buffered saline, pH 7.4 (PBS) and 3,3',5,5'-tetramethylbenzidine (TMB) from Sigma. Biotinamide and bGalCer (20) (using psychosine from bovine brain, Sigma) were prepared and assayed for their plating efficiency as previously described (*see,* McReynolds et al., *ibid.*). Assays were performed in a competetive mode as reported by McReynolds et al., *ibid.* Dried analyte 16 and freeze-dried analytes 14, 15, 17, 18, 19, and 20 were weighed out to the tenth of a microgram using a Satorius BL 120S balance. Stock solutions were prepared at 1 mg/mL in 20% DMSO/80% PBS buffer. The solutions were thoroughly mixed prior to further dilution in PBS, and they were stored at -80 °C between uses. The concentration of bGalCer as well as biotinamide (blocking agent) utilized in the assays was 20 μg/mL. The plates were prepared by first incubating with bGalCer and biotinamide. A solution of rgp120-HRP was prepared before use by 1:3 dilution of a 500 μL stock vial containing 0.333 μg rgp120-HRP with PBS buffer and introduced into the wells. In the competition step, analytes 14, 15, 16 were incubated at concentrations of 0.1, 1, 10, 100, 500, 1000 μg/mL and the Au nanoparticles 17, 18, 19 were assayed at concentrations of 1, 10, 20, 40, 80, 100, 200, 400 μg/mL on a Jitterbug™ microplate incubator (Boekel). In separate experiments, the addition of rgp120 was omitted and the contribution of Sp-Au (19) to background absorbance was

monitored at each concentration. The plate absorbances were read every min for 20 min at 630 nm (with 5 s shaking before each reading) using a Bio-Rad model 550 microplate reader. Each well reading had the TMB blank automatically subtracted through the use of the Biorad Microplate manager software. Endpoints were read at 415 nm after addition of 100 μL of 2 N H_2SO_4 to each well. The results given for these assays are representative of several separate experiments.

[0069] Calculation of EC_{50} values: The EC_{50} value represents the concentration of the compound required to induce 50% displacement of rgp120-HRP bound to bGalCer. The EC_{50} values were calculated from dose-response curves (rgp120 bound to bGalCer in % vs. analyte conc.) plotted using exponential trendlines (Microsoft® Excel 2000). The error was determined using a transformed regression model (Microsoft® Excel 2000). The calculated EC_{50} values for Au glyconanoparticles include an additional error reflected in the elemental analysis (Gal-Au (17):1.5%; Glc-Au (18): 1.4%; and Sp-Au (19): 1.2%).

[0070] Biological Evaluation. In competitive BNAA studies with irreversibly bound bGalCer on NeutrAvidin™ coated plates (Figure 5), the binding affinity of the carbohydrate clusters **17** and **18** as well as precursors **14** and **15** to rgp120-HRP was evaluated. As non-specific ligands, Au nanoparticles **19** and disulfide **16** were also tested and biotinamide served as the blocking agent. The extent of competition for gp120-HRP, reversibly bound to bGalCer, was monitored by absorbance. As a model of monovalent GalCer, biotinylated GalCer (**20**, Scheme 5) was also evaluated for its ability to displace rgp120 from plate-bound ligand. The averaged endpoint results from 4 separate experiments using Au nanoparticle concentrations between 1 and 400 μg/mL are plotted in Graph 1. In addition to non-specific binding, background absorbance of the Au nanoparticles was determined using Sp-Au (**19**) at the corresponding concentrations. The data are representative of several different trials.

[0071] EC_{50} values. Dose-response curves were plotted from the BNAA data in order to calculate EC_{50}, which represents the concentration of the compound required to displace 50% of bound rgp120 (Table 1). As expected, the disulfide derivatives of the linker Sp-S2 (**16**) showed no activity. The Gal-S2 (**14**) required approximately 1 mg/mL to displace 50% of bound rgp120 indicating that it was about twice as active as the Glc-S2 (**15**) analog. These data correlated well with earlier studies performed by the present inventors. Interestingly, Au nanoparticles functionalized with only the spacer acid (**19**) showed similar activity to the glycosylated disulfides (2.4 mg/mL). This activity is attributed to non-specific electrostatic

interactions of the highly negatively charged surface (free acid functionality) with basic amino acids present in rgp120. *See,* Rico-Lattes, I.; Gouzy, M.-F., Andre-Barres, C.; Guidetti, B.; Lattes, A. *New J. Chem.* **1998**, *22*, 451.

Table 1

EC_{50} values calculated from dose-response curves (graph: % rgp120 bound to bGalCer vs. analyte conc.) plotted using exponential trendlines (Microsoft® Exel 2000). * According to elemental analysis.

Analyte	**EC_{50} (μg/mL)**	**M (g/mol)**	**EC_{50} (mM)**	**β corrected for valency** (valency number)
Gal-S2 (**14**)	1076 ± 204	708.23	1.5 ± 0.3	0.12 (2)
Glc-S2 (**15**)	2000 ± 317	708.23	2.8 ± 0.4	0.07 (2)
Sp-S2 (**16**)	> 10000	358.43	> 10	<0.07 (2)
Gal-Au (**17**)	5.4 ± 0.4	96190*	$5.6 \pm 0.3 \times 10^{-5}$	54 (120)
Glc-Au (**18**)	13.8 ± 0.8	101676*	$13.6 \pm 0.6 \times 10^{-5}$	22 (120)
Sp-Au (**19**)	2577 ± 397	10410	0.25 ± 0.03	N.A.
bGalCer (**20**)	313 ± 19	863.11	0.36 ± 0.02	1.0 (1)

[0072] The Au glyconanoparticles **17** and **18** exhibit significantly higher activity (>300X) when compared to the corresponding disulfides **14** and **15**, respectively, even without factoring in the gold content. As shown in Table 1, according to elemental analysis, the molecular weight of Gal-Au and Glc-Au is 96,190 and 101,676 g/mol respectively, which correlates with mM EC50 values of 5.6 and 13.6 x 10-5, respectively. Whitesides and co-workers have described a term β that relates mono- and polyvalency by accounting for the difference in the number of ligands presented to the protein in each case. *See,* Mammen, M.; Choi, S.K.; Whitesides, G.M., *Angew. Chem. Int. Ed.* **1998**, *37*, 2754-2794. In the current study, it is useful to compare monovalent biotinylated GalCer (**20**), which is a water-soluble surrogate for the natural ligand GalCer, with divalent disulfides (**14** and **15**), and polyvalent (~120 carbohydrates per particle) glyconanoparticles **17** and **18**. The β values relating mMol EC_{50} are calculated by normalizing the data to bGalCer, and dividing by the valency number

(2 for the disulfides and 120 for the nanoparticles). The β values indicate that the galactosyl containing disulfide (**14**) has approximately twice the activity of the glucosyl disulfide (**15**), yet **14** is only 12% as active as biotinylated GalCer (**20**). This is not surprising, since several studies have shown that a lipid component is required for maximal affinity. The relative activity between galactosyl and glucosyl head groups is maintained in the Au glyconanoparticles with **17** being approximately twice as active as **18**. However, **17** is 450x more active than **14** (54 divided by 0.12) and **18** is > 300x more active than **15** (22 divided by 0.07). It is perhaps most interesting to compare the Au glyconanoparticles to biotinylated GalCer where polyvalent interactions increase the activity by more than 50x for the galactosyl head group. These data indicate that a lipid component is not required if multiple copies of the carbohydrate head group are presented to rgp120.

[0073] The enhanced binding activity of the Au glyconanoparticles relative to the disulfides may be due to fundamental changes in the recognition process of divalent vs. polyvalent species resulting in formation of thermodynamically more stable polyvalent ligand/rgp120 complexes. Alternatively, kinetic factors reflecting differences in on/off rates of divalent and polyvalent ligands may account for the enhanced activity. *See,* Liang, R., Loebach, J., Horan, N., Ge, M., Thompson, C., Yan, L., Kahne, D., *Proc. Natil. Acad. Sci.,* **1997**, *94*, 10554-10559 and references therein.

Example 5

[0074] This example illustrates the preparation of mixed glyconanoparticles, *i.e.,* gold glyconanoparticles containing a mixture of a glycoconjugate and a linking group, wherein the glycoconjugate to linking group ratio is about 75:25, 50:50, or 25:75. Number for the compounds prepared corresponds to the numbering in Figure 7.

[0075] **Thioacetic acid *S*-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl} ester (21):** A mixture of 2-[2-(2-chloro-ethoxy)-ethoxy]-ethanol (1.69 g, 10 mmol) and tetrabutylammonium iodide (400 mg, 1 mmol) in anhydrous DMF (20 mL) was stirred at room temperature as potassium thioacetate (3.4 g, 30 mmol) was added. The reaction was stirred for 18 h, and after completion ethyl acetate (100 mL) was added. The organic layer was washed with saturated NaCl (80 mL), dried and evaporated. Purification by column chromatography (eluent: hexanes/ethyl acetate v/v 1:1) afforded 1.48 g of product (7.1 mmol, 71%) as a slightly yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3 H, $SCOCH_3$), 2.52 (s, 1H, OH), 3.07 (t, 2 H, J = 6.4 Hz, H-6), 3.55 – 3.72 (2m, 10 H, H-1, H-2, H-3, H-4, H-5). ^{13}C NMR (100

MHz, $CDCl_3$) δ 28.76 (C-6), 30.58 ($SCOCH_3$), 61.70 (C-1), 69.68, 70.21, 70.26, 72.41 (C-2, C-3, C-4,C-5), 204.70 ($SCOCH_3$). FT-IR (film): υ 3432 (O-H str), 2927, 2886 (-CH_2- str), 1693 (C=O str), 1135, 1113, 1069 (C-O, C-C, C-S str) cm^{-1}. High-resolution mass spectrum calcd. for $C_8H_{16}O_4S_1$: 208.0769.

[0076] 2-[2-(2-Mercapto-ethoxy)-ethoxy]-ethanol (22): Compound **(21)** (417 mg, 2.0 mmol) was dissolved in anhydrous MeOH (8 mL) under an argon atmosphere, and a catalytic amount of NaOMe-solution (0.5 M in MeOH) was added. The reaction mixture was allowed to stir for 30 min at ambient temperature, at which point acidic DOWEX-ion exchange resin was added. The resin was filtered off and washed with MeOH (3 x 10 mL). After evaporation, compound **(22)** was obtained as a slightly yellowish oil in quantitative yield (332 mg, 2.0 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (t, 1 H, J= 6.4 Hz, SH), 2.63 (q, 2 H, J= 6.4, 13.2 Hz, H-6), 3.49 – 3.82 (2m, 10 H, H-1, H-2, H-3, H-4, H-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.25 (C-6), 61.71 (C-1), 70.19, 70.28, 72.44, 72.82 (C-2, C-3, C-4, C-5,). FT-IR (film): υ 2925, 2891 (-CH_2- str), 2612 (S-H str), 1113, 1069 (C-O, C-C, C-S str) cm^{-1}. High-resolution mass spectrum calcd. for $C_6H_{14}O_3S$: 166.0664.

[0077] 2-[2-(2-{2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethyldisulfanyl}-ethoxy)-ethoxy]-ethanol (23): Compound **(21)** (1.0 g, 5 mmol) was dissolved in anhydrous MeOH (30 mL), and NaOMe-solution (0.5 M in MeOH, 15 mmol, 30 mL) added. The reaction mixture was allowed to stir for 18 h at ambient temperature, while air was bubbled through the solution. After completion, acidic DOWEX-ion exchange resin was added and at neutralization, the resin was filtered off and washed with MeOH (3 x 20 mL). After evaporation and purification by silica gel column chromatography (EtOAc), product **(23)** was obtained as a slightly yellowish oil (1.5 g, 4.6 mmol) in 92 % yield. ^1H NMR (400 MHz, $CDCl_3$) δ 2.91 (t, 4 H, J= 6.4 Hz, 2 x H-6), 3.59 – 3.76 (3m, 20 H, 2 x H-1, 2 x H-2, 2 x H-3, 2 x H-4, 2 x H-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.32 (2 x C-6), 61.63 (2 x C-1), 69.51, 70.22, 70.33, 72.55 (2 x C-2, 2 x C-3, 2 x C-4, 2 x C-5). FT-IR (film): υ 3332, 3431 (O-H str), 2911, 2871 (-CH_2- str), 1069, 1111 (C-O, C-C, C-S str) cm^{-1}. High-resolution mass spectrum calcd. for $C_{12}H_{26}O_6S_2$: 330.1171.

[0078] Acetic acid 2-[2-(2-{2-[2-(2-acetoxy-ethoxy)-ethoxy]-ethyldisulfanyl}-ethoxy)-ethoxy]-ethyl ester (24): Compound **(23)** (1.3 g, 4 mmol) was dissolved in anhydrous pyridine (10 mL) and the solution cooled in an icebath, followed by addition of acetic anhydride (15 mL). The mixture was allowed to warm up to ambient temperature while

stirring it for 4 h. In the work-up, the solvents were evaporated and the residual oil purified by column chromatography (EtOAc). Compound **(24)** was isolated in 92 % yield as a slightly yellowish oil (1.5 g, 3.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 2 x 3 H, 2 x $OCOCH_3$), 2.95 (t, 4 H, J = 6.4 Hz, 2 x H-6), 3.56 – 3.85 (m, 16 H, 2 x H-2, 2 x H-3, 2 x H-4, 2 x H-5), 4.11 (m, 4 H, 2 x H-1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.00 (2 x$OCOCH_3$), 38.36 (2 x C-6), 63.50 (2 x C-1), 69.10, 69.57, 70.30, 70.42 (2 x C-2, 2 x C-3, 2 x C-4, 2 x C-5), 170.79 (2 x $OCOCH_3$). FT-IR (film): υ 2872, 2867 (-CH_2-C=O str, -CH_2- str), 1739 (C=O str), 1245, 1113, 1054 (C-O, C-C, C-S str) cm^{-1}. High-resolution mass spectrum calcd. for $C_{16}H_{30}O_8S_2$: 414.1382.

[0079] Preparation of mixed glyconanoparticles: Following a procedure described in de la Fuente *et al.*, *Angew. Chem. Int. Ed.* **2001**, 40, 2257-2261, and Penades *et al.*, PCT Publication No. WO 02/32404 A2, a freshly prepared 25 mM solution of hydrogen tetrachloroaurate (III) hydrate (0.167 mmol, 1 eq) in MeOH was added to a mixture of a freshly prepared 12 mM solution of one of the glycoconjugate disulfide derivatives **(14, 15)** and the disulfide derivative **(23)** (*i.e.*, Sp-OH) at molar ratios of 75:25, 50:50, and 25:75 (total 0.25 mmol, total 1.5 eq) in MeOH. Under vigorous stirring, a freshly prepared 1 M solution of $NaBH_4$ (3.34 mmol, 20 eq) in MeOH was added dropwise. Under liberation of H_2, dark-brown suspensions formed instantly. Stirring was continued for an additional 2 h at ambient temperature. Subsequently, MeOH was evaporated *in vacuo* and the residues were repeatedly suspended in MeOH (14 mL), sonicated (5 min), centrifuged (3-5 times, 30 min) and decanted. Finally the salt- and disulfide-free precipitates were dissolved in water and lyophilized. The mixed glyconanoparticles Gal/Sp-OH Au **(25)** and Glc/Sp-OH-Au **(26)** were obtained as dark-brown solids.

[0080] Similarly, the mixed glyconanoparticles Gal/Sp-COOH-Au **(27)** and Glc/Sp-COOH-Au **(28)** were prepared from a mixture of one of the glycoconjugate disulfide derivatives **(14, 15)** and the disulfide derivative **(16)** (*i.e.*, Sp-COOH) at molar ratios of 75:25, 50:50, and 25:75 (total 0.25 mmol, total 1.5 eq) in MeOH.

[0081] As controls, gold nanoparticles containing 100% of either the disulfide derivative Sp-OH **(23)** or Sp-COOH **(19)**, *i.e.*, Sp-OH-Au **(29)** or Sp-COOH-Au **(30)**, respectively, were synthesized following the above-described procedure. All particles showed good to very good solubility in water.

[0082] Characterization of Gal/Sp-OH Au (25) at different molar ratios: FT-IR (KBr): υ 3483 - 3258 (O-H, N-H str); 2928 - 2871 (-CH_2 str), 1662 (C=O str, amide I); 1556 (N-H bend, amide II); 1113 - 1069 (C-O, C-C, C-N, C-S str) cm^{-1}. HSQC (125 MHz, D_2O) δ 40.73 (C-1'), 61.10 (Sp-OH, C-1), 61.78 (C-7'), 69.07 (C-3'), 69.41 (C-5'), 69.98 (C-2), 70.17, 70.30, 70.42, 73.23 (Sp-OH, C-2, C-3, C-4, C-5), 70.10, 70.75 (C-3, C-4,), 72.90 (C-5), 74.16 (C-4'), 78.49 (C-2'), 78.86 (C-6').

75:25: 57.2 mg (yield 94%); contains 20 % Sp-OH by integration. ^1H NMR (500 MHz, D_2O) δ 3.26 – 3.38 (bm, 3 H, H-2', H-1', H-3'), 3.48 – 3.89 (bm, ca. 14.5 H total, from Gal-S (12 H): H-4', H-5', H-6', H-7', H-7'', H-1'', H-3, H-4, H-5; from Sp-OH-S (2.5 H): H-1, H-2, H-3, H-4, H-5), 4.01 (bs, 2 H, H-2). Elemental analysis calcd. for $C_{1241}H_{2418}N_{65}O_{718}S_{131}Au_{201}$: C 20.26 %, H 3.29 %, N 1.24 %; Found: C 16.76 %, H 2.63 %, N 1.23 %.

50:50: 50.5 mg(85% yield); contains 45 % Sp-OH by integration. ^1H NMR (500 MHz, D_2O) δ 3.21 – 3.41 (bm, 3 H, H-2', H-1', H-3'), 3.45 – 3.897 (bm, ca. 20 H total, from Gal-S (12 H): H-4', H-5', H-6', H-7', H-7'', H-1'', H-3, H-4, H-5; from Sp-OH-S (8.2 H): H-1, H-2, H-3, H-4, H-5), 3.98 (bs, 2 H, H-2). Elemental analysis calcd. for $C_{1165}H_{2245}N_{67}O_{683}S_{116}Au_{201}$: C 19.57 %, H 3.14 %, N 1.31 %; Found: C 14.11 %, H 2.59 %, N 1.31 %.

25:75: 46.3 mg (yield 96%); contains 73 % Sp-OH by integration. ^1H NMR (500 MHz, D_2O) δ 3.21 – 3.41 (bm, 3 H, H-2', H-1', H-3'), 3.45 – 3.897 (bm, ca. 37 H total, from Gal-S (12 H): H-4', H-5', H-6', H-7', H-7'', H-1'', H-3, H-4, H-5; from Sp-OH-S (15 H): H-1, H-2, H-3, H-4, H-5), 3.98 (bs, 2 H, H-2). Elemental analysis calcd. for $C_{666}H_{1368}N_{18}O_{360}S_{90}Au_{201}$: C 13.81 %, H 2.36 %, N 0.43 %; Found: C 11.82 %, H 1.74 %, N 0.44 %.

[0083] Characterization of Glc/Sp-OH-Au (26) at different molar ratios: FT-IR (KBr): υ 3475 - 3268 (O-H, N-H str); 2925 - 2865 (-CH_2 str), 1660 (C=O str, amide I); 1558 (N-H bend, amide II); 1111 - 1071 (C-O, C-C, C-N, C-S str) cm^{-1}. HSQC (125 MHz, D_2O) δ 40.45 (C-1'), 61.11 (spOH, C-1), 61.45 (C-7'), 70.17, 70.30, 70.42, 73.21 (Sp-OH, C-2, C-3, C-4, C-5), 69.94 (C-2), 70.03 (C-5'), 70.05, 70.78 (C-3, C-4), 71.62 (C-3'), 74.49 (C-5), 78.09 (C-4'), 78.09 (C-6'), 79.84 (C-2').

75:25: 63.8 mg (yield 95%); contains 24 % Sp-OH by integration. ^1H NMR (500 MHz, D_2O) δ 3.12 (bm, 1 H, H-3'), 3.23 – 3.34 (bm, 5 H, H-5', H-2', H-1', H-6', H-4'), 3.51 – 3.76

(bm, ca.12 H total, from Glc-S (9 H): H-7', H-1'', H-3, H-4, H-5, H-7''; from Sp-OH-S (2.5 H): H-1, H-2, H-3, H-4, H-5), 4.00 (bs, 2 H, H-2). Elemental analysis calcd. for $C_{1491}H_{2793}N_{105}O_{903}S_{126}Au_{201}$: C 22.30 %, H 3.48 %, N 1.83 %; Found: C 24.57 %, H 3.74 %, N 1.83 %.

50:50: 59.8 mg (yield 95%); contains 50% Sp-OH by integration. ^{1}H NMR (500 MHz, D_2O) δ 3.12 (bm, 1 H, H-3'), 3.21 – 3.36 (bm, 5 H, H-5', H-2', H-1', H-6', H-4'), 3.53 – 3.77 (bm, ca.19 H total, from Glc-S (9 H): H-7', H-1'', H-3, H-4, H-5, H-7''; from Sp-OH-S (10 H): H-1, H-2, H-3, H-4, H-5), 4.00 (bs, 2 H, H-2). Elemental analysis calcd. for $C_{1323}H_{2579}N_{69}O_{836}S_{140}Au_{201}$: C 20.65 %, H 3.36 %, N 1.26 %; Found: C 21.59 %, H 3.34 %, N 1.27 %.

25:75: 43.7 mg (74% yield); contains 66 % Sp-OH by integration. ^{1}H NMR (500 MHz, D_2O) δ 3.12 (bm, 1 H, H-3'), 3.21 – 3.34 (bm, 5 H, H-5', H-2', H-1', H-6', H-4'), 3.51 – 3.80 (bm, ca. 28 H total, from Glc-S (9 H): H-7', H-1'', H-3, H-4, H-5, H-7''; from Sp-OH-S (19 H): H-1, H-2, H-3, H-4, H-5), 4.00 (bs, 2 H, H-2). Elemental analysis calcd. for $C_{1165}H_{2370}N_{37}O_{638}S_{151}Au_{201}$: C 19.55 %, H 3.31 %, N 0.72 %; Found: C 18.28 %, H 2.93 %, N 0.73 %.

[0084] Characterization of Gal/Sp-COOH-Au (27) at different molar ratios: FT-IR (KBr): υ 3379, 3355 (O-H, N-H str); 2911, 2863 (-CH_2 str), 1660 (C=O str, amide I); 1556 (N-H bend, amide II); 1113, 1105, 1081 (C-O, C-C, C-N, C-S str) cm^{-1}. HSQC (125 MHz, D_2O) δ 40.73 (C-1'), 61.78 (C-7'), 69.07 (C-3'), 69.41 (C-5'), 69.98 (C-2), 70.10, 70.11, 70.73, 70.75 (Gal-S: C-3, C-4, Sp-COOH: C-2, C-3), 74.16 (C-4'), 73.96 (Sp-COOH, C-4), 74.26 (C-5), 78.49 (C-2'), 78.86 (C-6').

75:25: 58.1 mg (85% yield); contains 23 % Sp-COOH by integration. ^{1}H NMR (500 MHz, D_2O) δ 3.21 – 3.40 (bm, 6 H, H-2', H-1', H-3', H-4', H-6', H-7'), 3.55 – 3.79 (bm, ca. 11 H total, from Gal-S (9 H): H-7'', H-1'', H-3, H-4, H-5, H-5'; from Sp-COOH (ca. 2 H): H-2, H-3, H-4), 4.00 (bs, ca. 2.6 H total, from Gal-S (2 H): H-2, from Sp-COOH (0.6 H): H-1). Elemental analysis calcd. for $C_{1535}H_{2830}N_{95}O_{960}S_{145}Au_{201}$: C 22.42 %, H 3.44 %, N 1.62 %; Found: C 22.00 %, H 3.76 %, N 1.61 %.

50:50: 62.8 mg (89% yield); contains 53 % Sp-COOH by integration. ^{1}H NMR (500 MHz, D_2O) δ 3.21 – 3.40 (bm, 6 H, H-2', H-1', H-3', H-4', H-6', H-7'), 3.55 – 3.79 (bm, ca. 16 H total, from Gal-S (9 H): H-7'', H-1'', H-3, H-4, H-5, H-5'; from Sp-COOH (ca. 7 H): H-2, H-

3, H-4), 4.00 (bs, ca. 4.2 H total, from Gal-S (2 H): H-2, from Sp-COOH (ca. 2.2 H): H-1). Elemental analysis calcd. for $C_{1424}H_{2623}N_{74}O_{900}S_{151}Au_{201}$: C 21.47 %, H 3.29 %, N 1.30 %; Found: C 20.24 %, H 2.79 %, N 1.30 %.

25:75: 50.0 mg (82% yield); contains 76 % Sp-COOH by integration. ^{1}H NMR (500 MHz, D_2O) δ 3.21 – 3.45 (bm, 6 H, H-2', H-1', H-3', H-4', H-6', H-7'), 3.50 – 3.75 (bm, ca. 34 H total, from Gal-S (9 H): H-7'', H-1'', H-3, H-4, H-5, H-5'; from Sp-COOH (ca. 25 H): H-2, H-3, H-4), 4.01 (bs, ca. 8.2 H total, from Gal-S (2 H): H-2, from Sp-COOH (ca. 6.2 H): H-1). Elemental analysis calcd. for $C_{1198}H_{2204}N_{46}O_{768}S_{146}Au_{201}$: C 19.49 %, H 2.99 %, N 0.87 %; Found: C 17.71 %, H 2.30 %, N 0.87 %.

[0085] Characterization of Glc/Sp-COOH-Au (28) at different molar ratios: FT-IR (KBr): υ 3384 - 3362 (O-H, N-H str); 2904, 2861 (-CH_2 str), 1662 (C=O str, amide I); 1559 (N-H bend, amide II); 1085 - 1110 (C-O, C-C, C-N, C-S str) cm^{-1}. HSQC (125 MHz, D_2O) δ 40.45 (C-1'), 61.40 (C-7'), 69.94 (C-2), 70.09 (C-5'), 70.09, 70.13. 70.56, 70.78 (C-3, C-4, Sp-COOH: C-2, C-3), 71.60 (C-3'), 73.66 (Sp-COOH, C-4), 74.14 (C-5), 77.45 (C-4'), 78.00 (C-6'), 79.76 (C-2').

75:25: 53.3 mg (79%); contains 20 % Sp-COOH by integration. ^{1}H NMR (500 MHz, D_2O) δ 3.12 (bm, 1 H, H-3'), 3.21 – 3.34 (bm, 5 H, H-5', H-2', H-1', H-6', H-4'), 3.54 – 3.83 (bm, ca. 10.5 H total, Glc-S (9 H): H-7', H-1'', H-3, H-4, H-5, H-7''; from Sp-COOH (ca. 1.5 H): H-, H-3, H-4), 3.99 (bs, ca. 2.5 H total, from Glc-S (2 H): H-2; from Sp-COOH (ca. 0.5 H): H-1). Elemental analysis calcd. for $C_{1516}H_{2797}N_{106}O_{940}S_{129}Au_{201}$: C 22.39 %, H 3.44 %, N 1.83 %; Found: C 22.76 %, H 3.47 %, N 1.83 %.

50:50: 45.4 mg (68% yield); contains 50 % Sp-COOH by integration. ^{1}H NMR (500 MHz, D_2O) δ 3.12 (bm, 1 H, H-3'), 3.21 – 3.33 (bm, 5 H, H-5', H-2', H-1', H-6', H-4'), 3.53 – 3.82 (bm, ca. 15 H total, Glc-S (9 H): H-7', H-1'', H-3, H-4, H-5, H-7''; from Sp-COOH (ca. 6 H): H-, H-3, H-4), 3.99 (bs, ca. 4 H total, from Glc-S (2 H): H-2; from Sp-COOH (ca. 2 H): H-1). Elemental analysis calcd. for $C_{1456}H_{2683}N_{82}O_{916}S_{147}Au_{201}$: C 21.77 %, H 3.34 %, N 1.43 %; Found: C 20.49 %, H 2.90 %, N 1.43 %.

25:75: 43.2 mg (69% yield); contains 76 % Sp-COOH by integration. ^{1}H NMR (500 MHz, D_2O) δ 3.15 (bm, 1 H, H-3'), 3.25 – 3.39 (bm, 5 H, H-5', H-2', H-1', H-6', H-4'), 3.52 – 3.92 (bm, ca. 27.5 H total, Glc-S (9 H): H-7', H-1'', H-3, H-4, H-5, H-7''; from Sp-COOH (ca. 18.5 H): H-, H-3, H-4), 4.02 (bs, ca. 8.2 H total, from Glc-S (2 H): H-2; from Sp-COOH (ca.

6.2 H): H-1). Elemental analysis calcd. for $C_{1276}H_{2348}N_{52}O_{816}S_{152}Au_{201}$: C 20.17 %, H 3.09 %, N 0.96 %; Found: C 17.89 %, H 3.10 %, N 0.96 %.

[0086] Characterization of Sp-OH-Au (29): Yield: 32.8 mg (64% yield). ^{1}H NMR (500 MHz, DMSO) δ 3.49 – 3.72 (m, 10 H, H-, H-2, H-3, H-4, H-5), 4.58 (bs, 1H, OH). HSQC (125 MHz, DMSO) δ 61.11 (C-1), 70.56, 70.57, 70.60 (C-2, C-3, C-4), 73.21 (C-5). FT-IR (KBr): *v* 3365 (O=C-*O-H* str), 2915, 2881 (-*CH*$_2$-C=O str, -CH$_2$- str), 1699 (C=O str), 1113, 1126 (C-O, C-C str) cm^{-1}. Elemental analysis calcd. for $C_{804}H_{1742}O_{402}S_{134}Au_{201}$: C 15.64 %, H 2.82 %; Found: C 15.62 %, H 2.87 %.

[0087] Characterization of Sp-COOH-Au (30): Yield: 33.2 mg (71% yield). ^{1}H NMR (500 MHz, D_2O) δ 3.61 – 3.80 (m, 3 H, H-2, H-3, H-4), 4.24 (bs, 2 H, H-1). HSQC (125 MHz, D_2O) δ 68.39, 6941, 70.38, 70.66 (C-2, C-3, C-4, C-5), 170.41 (C-1). FT-IR (KBr): n 3360 (O=C-*O-H* str), 2923, 2868 (-*C*H$_2$ -C=O str, -CH$_2$- str), 1697 (C=O str), 1124 (C-O, C-C str) cm^{-1}. Elemental analysis calcd. for $C_{552}H_{1021}O_{368}S_{92}Au_{201}$: C 11.81 %, H 1.82 %; Found: C 12.14 %, H 1.51 %.

[0088] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WHAT IS CLAIMED IS:

1. A nanoparticle comprising a core portion and attached ligands, and optionally having attached co-ligands, wherein said core portion comprises gold, a gold alloy, or silica, and said attached ligands are the same or different, at least a portion of said attached ligands being C-glycosides.

2. A nanoparticle of claim **1**, wherein said core portion is at least 80% gold.

3. A nanoparticle of claim **1**, wherein said core portion is at least 95% gold.

4. A nanoparticle of claim **1**, wherein said core portion comprises silica coated with gold or a gold alloy.

5. A nanoparticle of claim **1**, wherein said attached ligands are the same and are C-glycosides covalently attached to said core portion with linking groups having from 6 to 50 main chain atoms selected from the group consisting of S, O, N and C.

6. A nanoparticle of claim **5**, wherein said core portion comprises a mixture of said linking groups with said attached ligands and said linking groups without said attached ligands.

7. A nanoparticle of claim **6**, wherein the ratio of said linking groups with said attached ligands to said linking groups without said attached ligands is selected from the group consisting of about 3:1 to about 1:3.

8. A nanoparticle of claim **5**, further comprising attached co-ligands.

9. A nanoparticle of claim **5**, having a mean particle diameter of from about 0.25 nm to about 160 nm.

10. A nanoparticle of claim **5**, having a mean particle diameter of from about 0.5 to about 5.0 nm.

11. A nanoparticle of claim **5**, having a mean particle diameter of from about 1.0 to about 3.0 nm.

12. A nanoparticle of claim **5**, wherein said attached ligands are selected from the group consisting of *C*-α or β, D or L, glycobiosyl alkylamines and longer oligosaccharides containing any combination of carbohydrate linkages having C, N, O and S and combinations thereof.

13. A nanoparticle of claim **12**, wherein said attached ligands are selected from the group consisting of *C*-(β-D-glycopyranosyl)methylamines and *C*-(β-D-galactopyranosyl)methylamines.

14. A nanoparticle of claim **8**, wherein a portion of said co-ligands are positively charged at physiological pH.

15. A method for treating diseases dependent on glycoprotein recognition, said method involving administering to a subject in need thereof, a therapeutically effective amount of a composition comprising nanoparticles having a core portion and attached ligands, and optionally having attached co-ligands, wherein said core portion comprises gold, a gold alloy, or silica, and said attached ligands are the same or different, at least a portion of said attached ligands being C-glycosides that are capable of disrupting glycoprotein recognition.

16. A method in accordance with claim **15**, wherein said core portion is at least 80% gold.

17. A method in accordance with claim **15**, wherein said core portion is at least 95% gold.

18. A method in accordance with claim **15**, wherein said core portion comprises silica coated with gold or a gold alloy.

19. A method in accordance with claim **15**, wherein said attached ligands are the same and are C-α or β glycosides covalently attached to said core portion with linking groups having from 6 to 50 main chain atoms selected from the group consisting of S, O, N and C.

20. A method in accordance with claim **19**, further comprising attached co-ligands, said co-ligands being positively charged at physiological pH.

21. A method in accordance with claim **19**, wherein said disease is HIV and said attached ligands interfere with gp120 interactions with cellular receptors.

22. A method in accordance with claim **19**, wherein said attached ligands are selected from the group consisting of *C*-(β-D-glycopyranosyl)methylamines and *C*-(β-D-galactopyranosyl)methylamines and are attached to said core portion by a spacer comprising a thiolated ethylene glycol moiety.

23. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and nanoparticles having a core portion and attached ligands, and optionally having attached co-ligands, wherein said core portion comprises gold, a gold alloy, or silica, and said attached ligands are the same or different, at least a portion of said attached ligands being C-glycosides that are capable of disrupting glycoprotein recognition.

24. A pharmaceutical composition of claim **23**, wherein said pharmaceutically acceptable excipient is a topical gel useful for topical delivery of said nanoparticles.

FIGURE 1

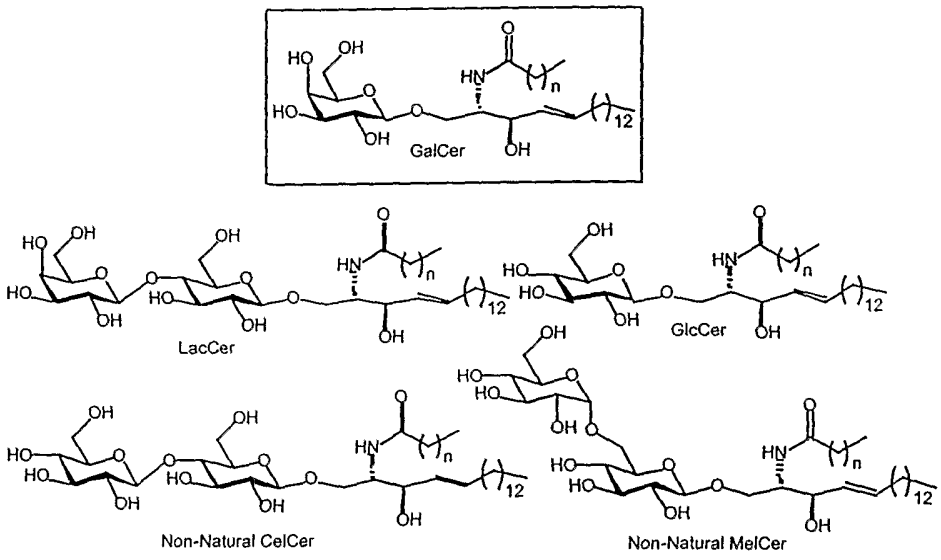
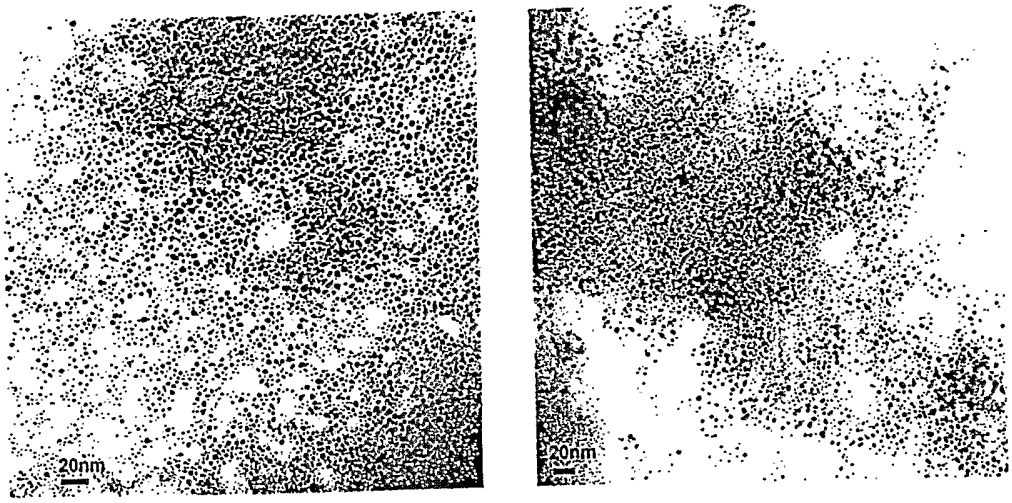
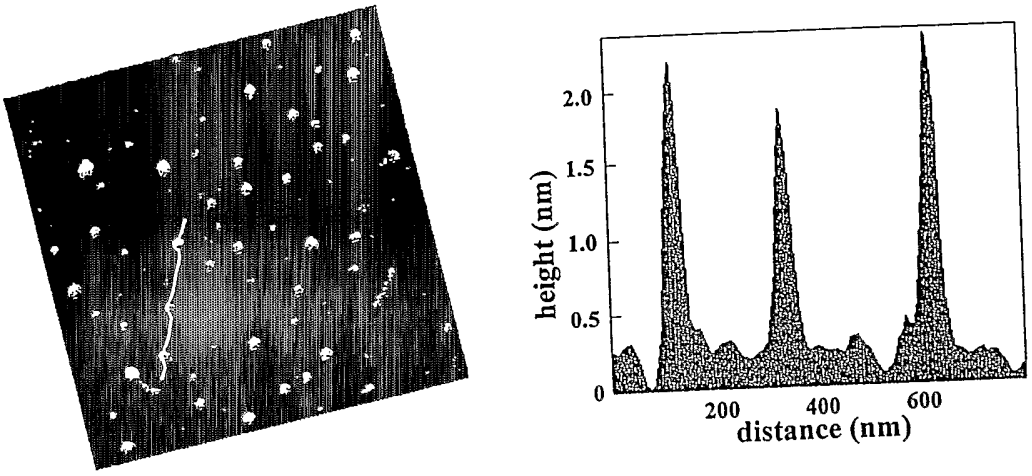

GalCer
LacCer
GlcCer
Non-Natural CelCer
Non-Natural MelCer

FIGURE 2



(a) (b)

FIGURE 3



a) b)

Figure 3. a) AFM topograph of the Gal-Au (**17**) nanoparticles. b) cursor profile along a selected line showing three particles with diameters of 2.0 nm, 1.6 nm and 2.1 nm.

FIGURE 4

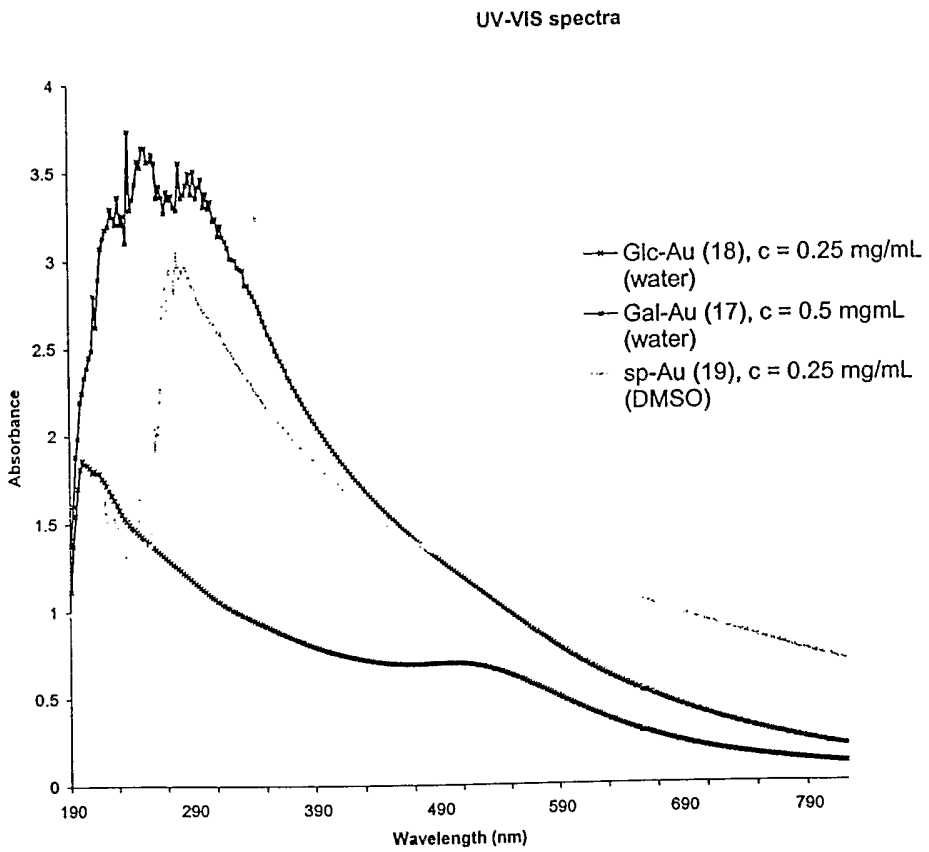


Figure 4. UV/Vis spectra of the Au nanoparticles.

FIGURE 5

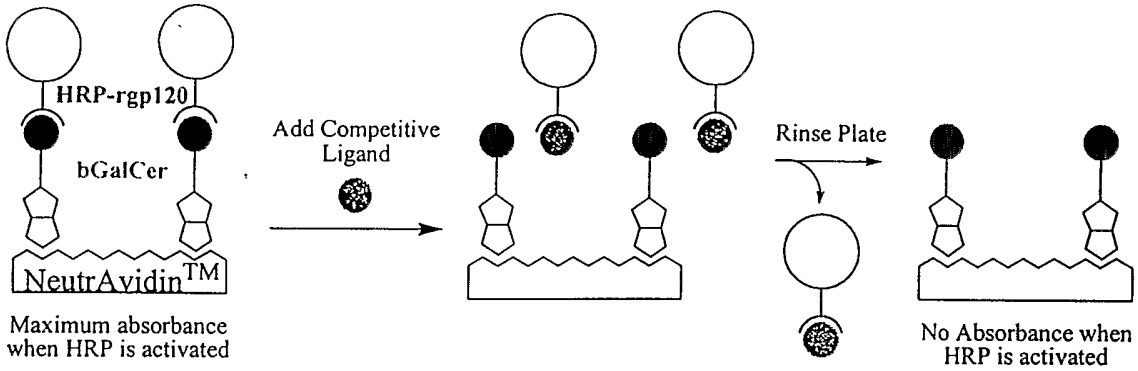
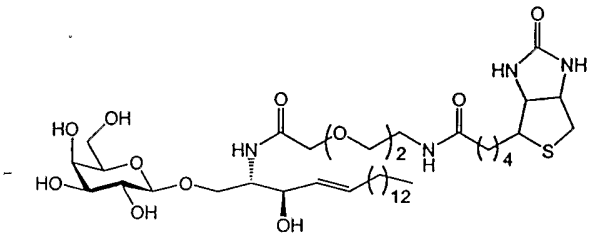
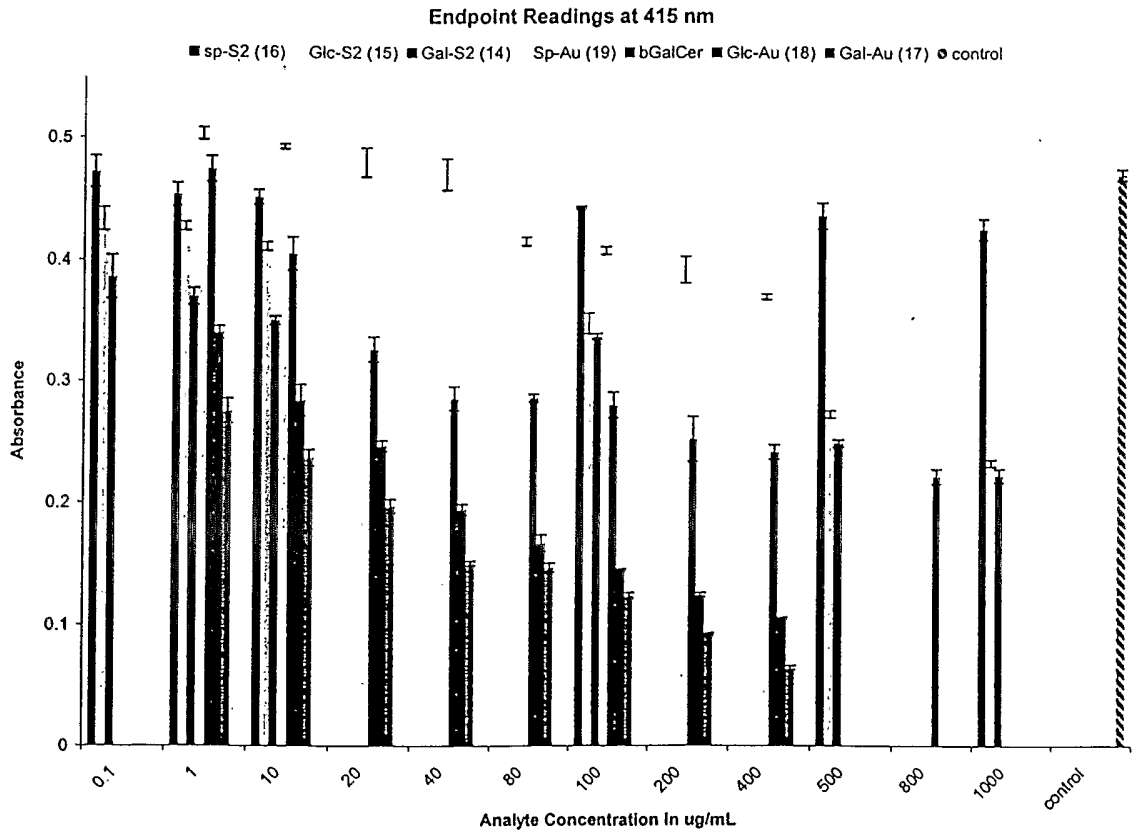


Figure 5. Competitive BNAA. Biotinylated GalCer is immobilized through interactions with NeutrAvidin™ and HRP-rgp120 is introduced. In the next step, HRP-rgp120 is competed off by the introduction of an alternate ligand. The extent to which the ligand is able to compete can be measured by comparing absorbance data from competition wells relative to bGalCer wells where no external ligand was introduced.



Biotinylated GalCer (bGalCer **20**)

FIGURE 6



BNAA competition assay data for disulfides **14**, **15**, and **16**; Au nanoparticles **17**, **18**, and **19**; and bGalCer **20** shown as endpoint readings at 415 nm after 20 min. As control, data for **20** correspond to maximal absorbance (no exposure to ligands in competition step).

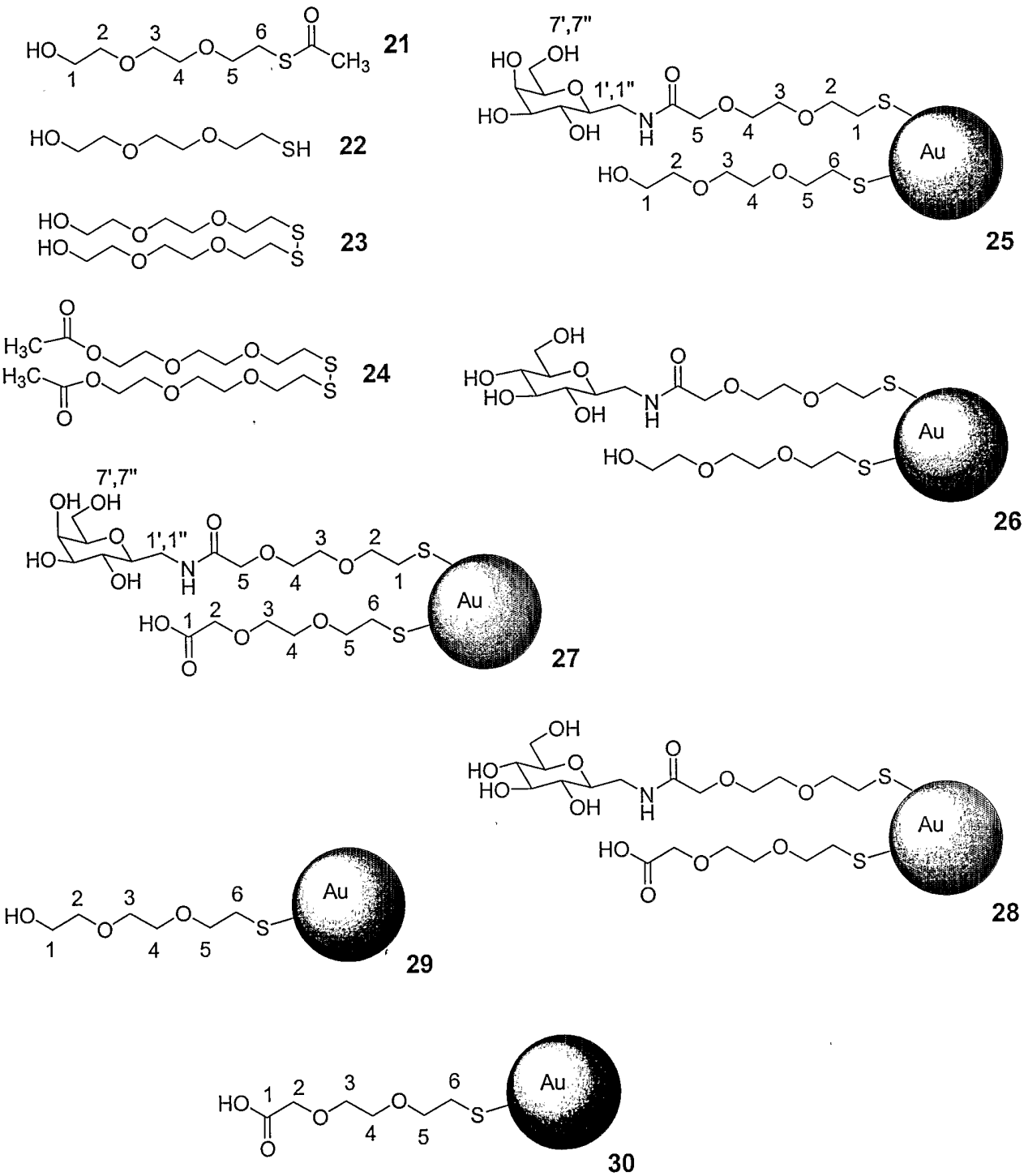


FIG. 7