CHAPTER 11

Nanotechnology and sialic acid biology

1 Introduction

Nanotechnology, the science of matter with dimensions ranging from 1 to 100 nm, with unique size (Fig. 1), physical and chemical properties including compatibility, catalytic, photonic, electronic, or magnetic properties has found myriads of diverse applications as biosensors by detecting minute quantities of matter like microorganisms, detection of pathogens, allergens, unwanted matters in food, detection, imaging and targeting of diseases, as vaccine adjuvants, as biomedicine, in postimplantation monitoring, in nanoarrays to detect toxic molecules and infectious agents, in monitoring of signaling pathways of stem cells, in environmental remediation, in personal care products like products related to improvement of the brightness of teeth, development of optical tags, and nanoplex biotags [1–7].

2 Nanotechnology

Nanotechnology encompasses the science of matter at dimensions and tolerances at nanoscales of less than 100 nm, with manipulation of individual atoms and molecules. Their unique size-dependent properties enable their superior applications to human use. Bionanotechnology is the science encompassing the application of biotechnology and nanotechnology and has applications in products used in our everyday lives including personal care products to drugs and medicine.

Nanoparticles (NPs) are now gaining much importance due to their application in biology and medicine. The major biological applications include as fluorescent biological labels, detection of pathogens and proteins, probing of the DNA, engineering applications in tissues, targeting tumor and targeted delivery of drugs, genes, and small molecules, identification, estimation separation, purification, and characterization of biological molecules and cells, as magnetic resonance imaging (MRI) contrast enhancement agents and in phagokinetic studies [8].

Sialic Acids and Sialoglycoconjugates in the Biology of life, Health and Disease
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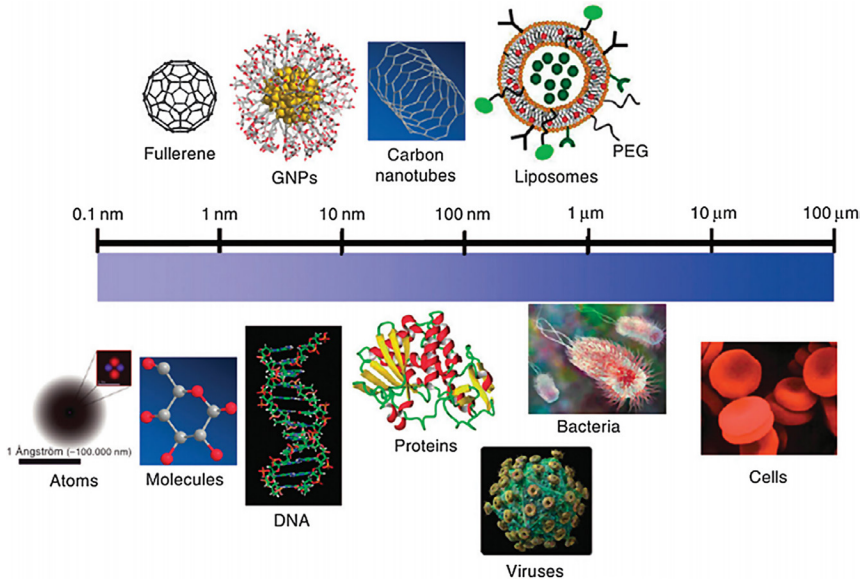

Fig. 1 Similar dimensions of nanoparticles and biological entities are represented. *(Reproduced with permission from M. Marradi, M. Martin-Lomas and S. Penade's, Adv. Carbohydr. Chem. Biochem., 2010, 64, 211–290.)*

NPs with similar size as proteins enable applications of NPs in biotagging or labeling. To interact with biological target, a biological molecule antibodies, including biopolymers like collagen, or monolayers of small molecules acting as bioinorganic interface rendering the property of biocompatibility. To enable optical detection, NPs with fluorescent properties of that alter their optical properties are applied [8]. Some of the modifications of NPs for biomedical applications are enlisted in Fig. 2.

3 Glyconanotechnology

Nanotechnology has been applied to glycobiology forming the new science of glyconanotechnology and is a synergy between nanotechnology and glycans playing role in biological and medical applications [1]. More recently, they have been applied in the sialic acid biology.

Glycans occur as surface lining macromolecules and form the first line of contact for any other cell or pathogen and protein-carbohydrate interactions and are known to play role in cell signaling, molecular recognition, immunity, and inflammation. Carbohydrate comprising of wood, insect shells, or cartilage, with mechanical properties serve as biomaterials of importance. Cellulose nanocrystals find importance in processes for degradation of biomass to biofuels and chemicals.

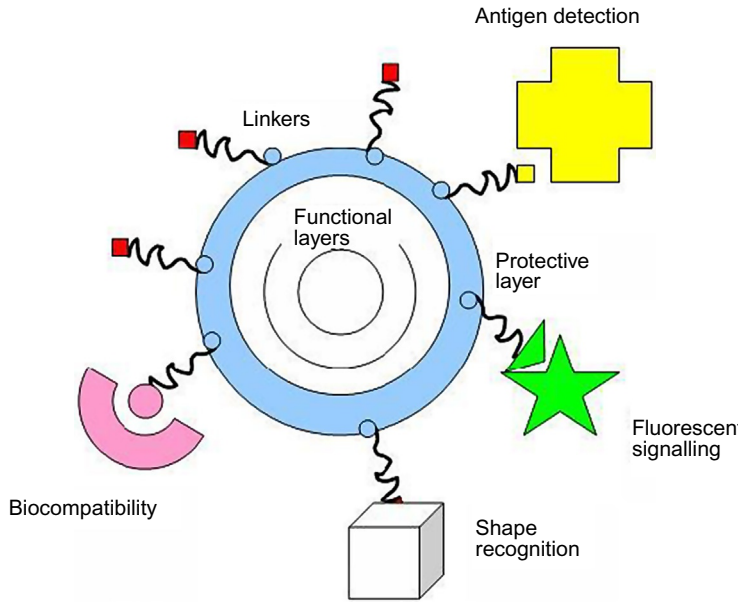

Fig. 2 Configurations utilized in nano-biomaterials applied to medical or biological problems. *(Reproduced with permission from Salata O. Applications of nanoparticles in biology and medicine. J Nanobiotechnol 2004;2:3. Published online April 30, 2004. doi: https://doi.org/10.1186/1477-3155-2-3.)*

Glyconanomaterials (Fig. 3) with properties of nanomaterials of better solubility, biocompatibility, lower cytotoxicity with the uniqueness of their size, chemical properties, surface engineering, surface charge and electronic, photonic, and magnetic like physical properties and properties of glycans of water solubility, biocompatibility, structural diversity, and specific targets [7] have major applications in biology encompassing the domains of (i) as sensitive biological probes in cells and tissues enabling building of different scaffolds, (ii) as imaging agents, (iii) as spectroscopic tools for their detection, (iv) monitoring of cellular systems, and (v) application in vaccination and drug delivery.

4 Sialic acid and nanotechnology

Sialic acid has been associated with the disease pathology in several diseases including autoimmune disorders, infection, and cancer. Recently, the sialic acid-Siglec axis discussed in the earlier chapters is revealing to be an emerging target to prevent or affect several diseases. However, the study of deeper role of sialic acid-Siglec axis in immune modulation and therapy suffers from the limitation of suitable sensitive methods.

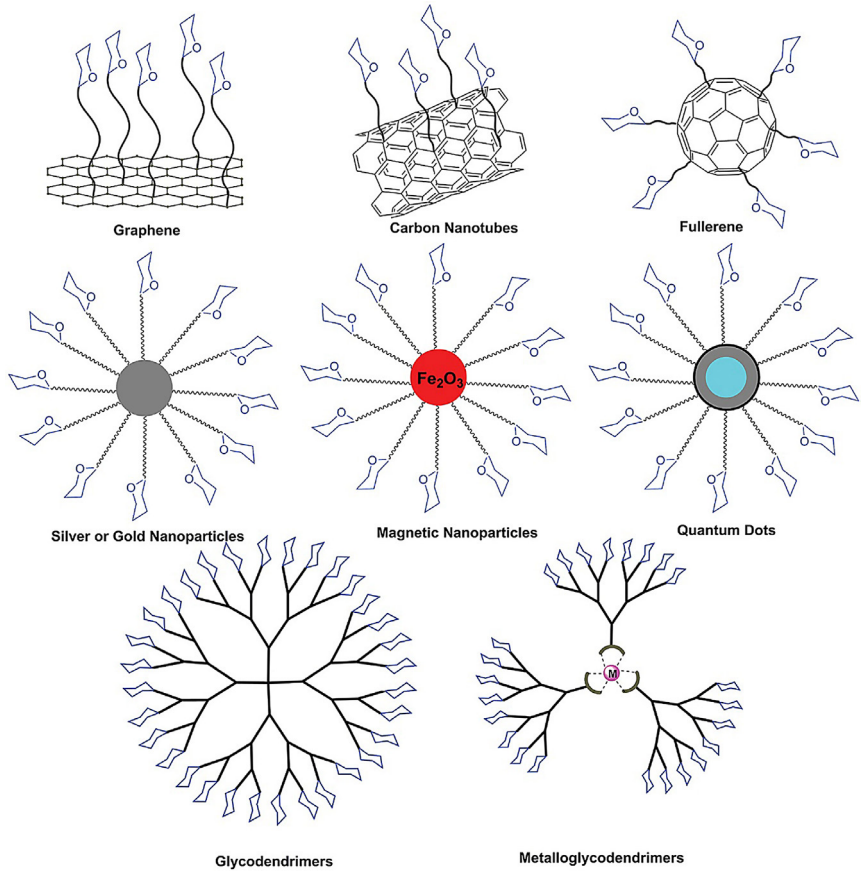

Fig. 3 Representative picture of glyconanomaterials made by coupling glycans to the surface of diverse nanomaterials. *(Reproduced with permission from Penadés S, Davis BG, Seeberger PH. Glycans in Nanotechnology. 2017. In: Varki A, Cummings RD, Esko JD et al., editors. Essentials of Glycobiology [Internet]. 3rd edition. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2015–2017. Chapter 58.)*

Natural sialic acid ligands can be modified by chemical methods leading to the development of sialic acid mimetics (SAMs) that reveal improved and selective binding affinity toward Siglecs. Glycobiotechnology involving bioorthogonal synthesis is enabling the presentation of SAMs on NPs, polymers, and living cells which finds application in the study of the sialic acid-Siglec axis and its role in immune modulation and therapeutic potential [9]. Although sialic acid and its derivatives reveal promises as stealth carriers with properties including targeting ability, cancer inhibition, viral and inflammation recognition, brain targeting and effective targets in several disorders

by in vivo and in vitro studies, design of nanocarrier in drug delivery and targeting, based on sialic acid remains as a major challenge and suffers from the limitations of multi-target side effects and calls in for more research [10].

We discuss in this chapter (i) the glycans and nanotechnology, (ii) role of nanotechnology in detection and quantitation of sialic acid, and (iii) nanotechnology and their applications in sialic acid biology and associated biology of disease, the application, and challenges.

5 Glycans and nanotechnology

Glycoproteins or glycolipids that take part in cellular communication, inflammation, and immune responses using carbohydrate-protein or carbohydrate-carbohydrate and are known for their multivalent interactions [11] with larger variation in affinity/avidity in normal individuals and reported to be disease markers in different diseases as cancer, asthma, and diabetes. Nanotechnology enabling estimation, creating, manipulation of matter at nanoscales, is finding application in study and manipulation of glycans. Various scaffolds such as glycodendrimers or glycopolymers with high surface/volume ratios, allowing better surface contact with improved multivalency effects have been constructed from diverse nanomaterials including semiconductor, carbon-based nanomaterials and have been studied for carbohydrate-protein interactions and find applications in drug delivery, imaging, diagnostics, or sensitive quantitation tools. Polysaccharides nanomaterials including chitosan, dextran, hyaluronic acid, and heparin have been designed drug delivery devices [1–13] and in pharmaceutical application with the advantages of biocompatibility, with reduced toxicity/nontoxicity, prolonged persistence, and drug release. Hybrid substructures are also constructed with metal-cored NPs coated with polysaccharides.

Inorganic nanostructures of iron oxide, noble metal, and semiconductors enable formation of synthetic scaffolds to multimerize glycans and enhance the affinity for receptors. Magnetism and fluorescence of hybrid materials finds applications in sensing, delivery, or imaging.

Gold nanoparticles (AuNPs) [13, 14] in conjugation with glycans [13–18] enable them with high aqueous solubility/dispersibility, biocompatibility and their high surface area/volume ratio of AuNPs allows enhanced sensitivity. Carbohydrate-lectin analyses have been enabled by the application of AuNPs. Mannosylated AuNPs find application in detection of complement activation and opsonization processes in macrophage-mediated endocytosis and to target *Escherichia coli*–containing type 1 pili mannose-specific receptors.

Magnetic nanoparticles (MNPs), including iron oxide and manganese oxide NPs, find application as contrast agents for MRI [19, 20]. Glyco-MNPs with high surface/volume ratio have enabled detection of early stage disease by mimicking leukocyte recruitment during inflammation [7, 21]. Tetrasaccharide sialyl-Lewis x (sLe^x)-functionalized MNPs have found application in targeting *E*-/P-selectins and find application in detection of inflammation [7, 21].

Quantum dots (QDs) including binary cadmium or zinc selenides or sulfides are luminescent semiconducting nanomaterials and can emit light with broader excitation spectrum and sharper emission bands [22, 23]. Glyco-QDs functionalized with carboxymethyldextran and polylysine have found application in study of carbohydrate-protein interactions. QDs can be stabilized with glycodendrimers [7, 21].

Buckminsterfullerene C_{60}, and carbon nanotubes (CNTs) [24–27] glycosylated as in α-D-mannosyl fullerenes and fullerenols have been known to inhibit erythrocyte aggregation [28, 29]. Single-walled CNTs (SWCNTs) and multiwalled CNTs (MWCNTs) linked to C_{18}-lipid tail with α-GalNAc residues have been applied as probes or radiotracers in developing sensitive in vivo imaging or radiation delivery systems with high radioisotope loading [21, 30].

Glycan-linked graphene has been reported to enable agglutination and inhibition of bacterial motility. Chitosan-based NPs [31] are reported to deliver proteins, oligonucleotides, and plasmid DNA. Multifunctional glycol-chitosan NPs with a near-infrared (NIR) fluorophore for fluorescence imaging [32] have found application in encapsulating anticancer drugs or complex small interfering (siRNA) as drug delivery device. Chitosan-polyethylene glycol (PEG)-coated iron oxide NPs have been reported to make better intracellular delivery of a DNA repair inhibitor (O^6-benzylguanine) to glioblastoma multiform cells and enable treatment monitoring by MRI. Dextran enables improved water solubility and stability of iron oxide MNPs while sulfated dextran can electrostatically interact with positively charged polycations. Functionalization of dextran-coated iron oxide NPs with sLe^x tetrasaccharide has enabled recording of inflammation in mouse brain. Hyaluronic acid and heparin-based NPs offer promises in cancer therapy by targeted, magnetic, photodynamic, and gene therapy [33]. Glycodendrimers enabled formation of three-dimensional (3D) supramolecular sugar scaffolds of sugars with a Ru $(bpy)_3$ core [34] that could bind to *E. coli* expressing mannose receptor of bacterial pili, displayed on virus-like particles [35] enabled picomolar inhibition of adhesion of Ebola

virus. Nanoengineered glycan sensors probes of AuNPs and CNTs may help with glycoprotein profiling. Glyconanomaterials [36–38] of gold and silver find application in cancer detection by quantifying cell-surface mannose glycans. Mannan-coated AuNP incubated with a human gastric cell line in the presence of the mannose-binding lectin ConA enabled detection of aberrant glycosylation in cancer [39]. ConA-functionalized CNTs finds application in surface glycan detection [40].

6 Role of nanotechnology in detection and quantitation of sialic acid

Sialic acid is known to be present as components of mucin component, glycoproteins, and other microbial polymers in nature food, further emphasizing the need of sensitive tools to detect them even in traces. The glycome of cells and glycoproteins and their detection and estimation finds importance in understanding glycan functions, development of diagnostics tests, and monitoring of glycoprotein pharmaceuticals. Sialic acid-containing carbohydrates, collectively grouped as sialosides, are known to play major roles in the physiology of health and disease-like infections by virus and bacteria, tumor cell metastasis, but limitation of suitable methods to study sialosides forms the major challenge in the study of their structure and function. Appropriate quantitation of sialic acid finds importance in health and disease to understand the levels correlating with the homeostasis and pathophysiology of the body in infection and disease. Although several biochemical tests find importance in detection and quantitative estimation of sialic acid in the body, the detection of minute quantities of sialic acid and the perturbation in disease states is far from complete. Nanotechnology and its diverse application and application in sensitive methods finds importance in the quantitative detection of *N*-glycans and sialic acid in the body even in very small amounts.

Synthetic sialoside chemistry, by chemoenzymatic or stereochemical approach, have produced homogeneous size- and structure-defined sialosides with array application, to mimicking cell-surface display and aids in understanding sialoside-mediated interactions. Application of nanotechnology in sialoside arrays [41] is suggested to lead to promising results in study of sialic acid biology.

N-glycans are isolated and characterized by conventional methods of enzymatic treatment, followed by their release and derivatization with a fluorochrome and separation by normal-phase high-performance liquid chromatography (HPLC). Nano Quantity Analyte Detector (NQAD) has been

designed to quantitate the nonderivatized sialic acid in glycoproteins, separated by hydrophilic interaction chromatography, detected by measuring size differences in dry aerosol and by converting the particle count rate into chromatographic output signal. This sialic acid quantitative sensitive method lacking requirement of active chromophore or fluorophore finds importance over conventional methods and HPLC/NQAD method offers advantage in reproductive results over the conventional HPLC/DMB method. While HPLC/DMB method involves derivatization of glycoproteins using 1, 2-diamino-4, 5-methylenedioxybenzene (DMB) and Dionex-based high-pH anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD), the HPLC/NQAD method is designed with elimination of the derivatization step and efficient PolyGLYCOPLEX amide column adding to the sensitivity to the detection method [42].

Simultaneous quantification and characterization of the *N*-glycans including both neutral and sialylated glycans suffers from lack of appropriate methods of identifying them. This is circumvented by applying a weak anion-exchange HPLC separation step to fractionate glycans by their sialic acid content followed by a mild acid desialylation step and then resolved by nano-LC-coupled electrospray ionization (ESI)-mass spectrometry with an intercalated nanofluorescence detector by which neutral glycans can be separated and characterized [43].

ESI-MS method finds applications in detection and characterization of the heavily polysialylated *N*-glycans in human serum with improved sensitivity [44]. Isomeric glycan profiling using nanoLC-MS with porous graphitized carbon (PGC) as the stationary phase has found importance in detection of sialylated serum proteins by high detection sensitivity and chromatographic resolution [45]. Subambient pressure ionization with nanoelectrospray (SPIN) using advanced data processing tools has increased the efficiency and sensitivity and has enabled high-resolution MS in detecting sialic acid polymer chains over conventional ESI-MS [46].

A quick, sensitive fluorimetric detection method by using a sensitive lectin-CdTe QDs nanoprobe made by conjugating *Sambucus nigra* bark lectin (SNA) as probe for sialic acid forming SNA-CdTe QDs has been designed to detect sialic acid in egg products. Sialic acid and SNA-CdTe QDs, interaction lead to generation of fluorescent signal and is able to detect as sialic acid as low as 0.67 ng/mL [47].

N-Glycolylneuraminic acid (NeuGc), is produced in animals, including cattle and mice, but not in human and is considered to be immunogenic in humans. Therefore, NeuGc contamination in human embryonic stem cells

cultured xenogeneic serum due to accumulation indicated its harmfulness and raised concerns over its safety of cell therapy products. To detect femto level the presence of Neu5GC, a nano-flow liquid chromatography/Fourier transformation ion cyclotron resonance mass spectrometry (nanoLC/FTMS) and nanoLC/MS/MS has been designed with promising results [48].

6.1 Detection of gangliosides

Gangliosides (GGs) are involved in many brain functions at the cell and molecular level and their study detection and characterization suffers limitation of suitable sensitive methods for detection and analysis. Sialic acid-coated NPs are finding applications in targeting in cancer [49]. Nanotechnology-based detection of glycans and sialic acid conjugates is finding application in detection of GG composition. In human hemangioma, GG composition and structure has been detected by highly sensitive methods of mass spectroscopy (MS) methods based on fully automated chip-nanoelectrospray (nanoESI) high-capacity ion trap (HCT) and collision-induced dissociation (CID) all integrated in the chip-nanoESI approach revealed detection of the presence of one modified *O*-Ac-GD2 and *O*-Ac-GM4 GGs and the presence of GT1a and GT1b isomers and unusual GT1c and GT1d glycoforms in brain hemangioma tumor [50]. The nanotechnology-based method offers advantage over conventional methods in its sensitivity and detection of unusual forms of GGs hitherto undetected by conventional methods in this disorder.

In all, 81 GG components were detected in human caudate nucleus (CN) by chip-nanoelectrospray MS performed on a NanoMate robot coupled to a HCT instrument in only 1.5 min revealing structures of mono-, di-, and trisialylated GGs and finds importance in detection of GG in CN-related neurodegenerative disorders [51].

Sensitive detection of Neu5Gc-containing GGs from Neu5Ac-containing analogs was separated from the lymphoma cell line derived from mouse (YAC-1) lymphoma cell monosialoganglioside fraction by nano-high-performance liquid chromatography (nanoHPLC) in online conjunction with ESI quadrupole time-of-flight (ESI-QTOF) mass spectrometry and served as a promising glycolipidomic tool [52].

7 Sialic acid in therapy

Evading the reticuloendothelial system (RES) is a major obstacle in drug delivery and targeting in cancer. Sialic acid is known for its reduced interaction with the innate immune system by Siglec, thus regulating phagocytic

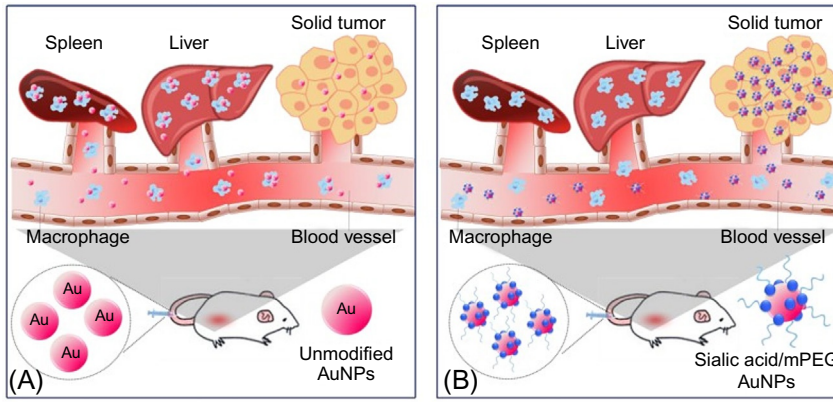

Fig. 4 AuNP distribution and tumor targeting: While (A) unmodified AuNPs undergo phagocytosis by the reticuloendothelial system (RES), (B) modified AuNPs like sialic acid-mPEG-AuNPs escape RES phagocytosis and target tumor cells. *(Reproduced with permission from Kim YH, Min KH, Wang Z et al. Development of Sialic Acid-coated Nanoparticles for Targeting Cancer and Efficient Evasion of the Immune System. Theranostics. 2017;7: 962–973.)*

evasion. Surface engineered AuNPs conjugated to sialic acid have revealed that sialic acid-mPEG-AuNPs can escape uptake by RES and therefore, efficiently target tumor cells and by targeted delivery can enhance accumulation in tumor [49] (Fig. 4).

Influenza A infection is initiated by binding of viral envelope hemagglutinin (HA) glycoproteins to cell membrane sialic acid. Free toxic sialic acid monomers cannot block HA adhesion in vivo. Polyvalent, generation 4 (G4) sialic acid-conjugated polyamidoamine (PAMAM) dendrimer (G4-sialic acid) has been found to inhibit three influenza A subtypes (H1N1, H3N2) indicative of the fact that polysialic acid (PSA) inhibitors have potential in antiviral therapeutics [53]. Amongst dendritic polymeric inhibitors, including spheroidal, linear, linear-dendron copolymers, comb-branched, and dendrigraft polymers are known for the ability to inhibit virus hemagglutination (HA) and to block infection of mammalian cells in vitro. Comb-branched and dendrigraft inhibitors revealed to be the most effective inhibitor, with up to 50,000-fold more antiviral activity [54].

Targeted delivery of sialic acid inhibitors like sialic acid-blocking glycomimetic has been reported to block cancer metastasis [7, 21, 55]. Sialic acid-blocking glycomimetic [P-3F (ax)-Neu5Ac] coated antibodies allowed targeted delivery into melanoma cells successfully preventing cancer metastasis in murine lung cancer model [55] (Fig. 5).

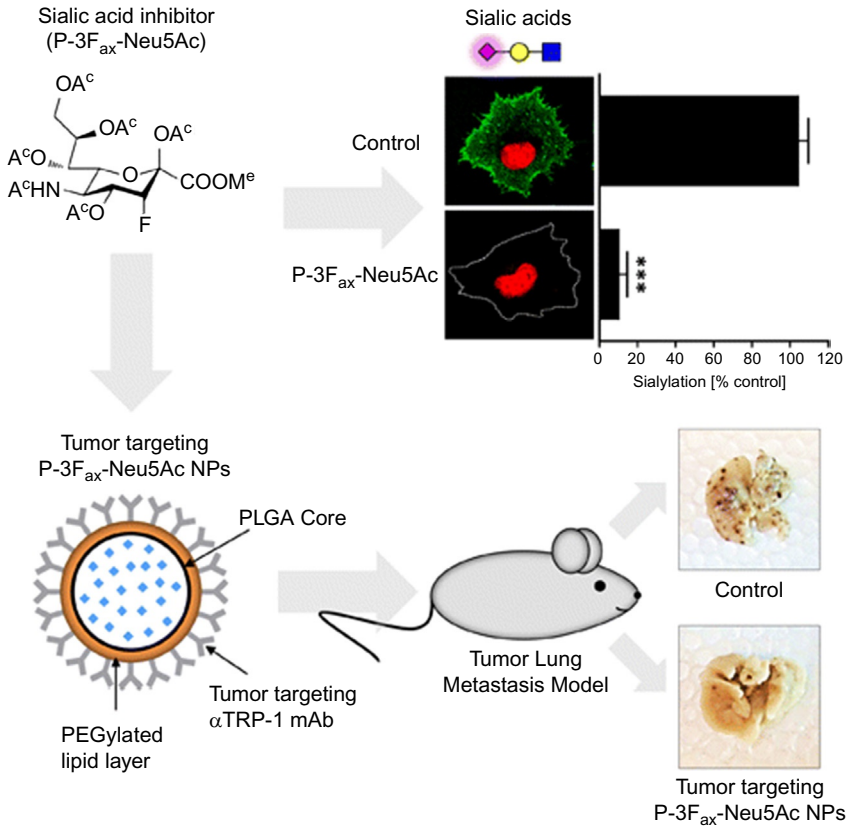

Fig. 5 Targeted delivery of a sialic acid-blocking glycomimetic to cancer cells inhibits metastasis. *(Reproduced with permission from Christian Büll, Thomas Jan Boltje, Eric A. W. van Dinther, Timo Peters, Annemarie M. A. de Graaf, Jeanette H. W. Leusen, Martin Kreutz, Carl G. Figdor, Martijn H. den Brok, and Gosse J. Adema ACS Nano, 2015, 9(1), pp. 733–745.)*

Linkage-specific sialylated glycans could be characterized from reaction with condensation reagent 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) in methanol with nanoscale liquid chromatographic separation prior to accurate mass Orbitrap MS analysis and improve separation and enrichment of trisialylated *N*-glycan fraction from haptoglobin and human plasma, as trisialylated fraction has been linked with cancer-associated changes in the serum *N*-glycome [56].

The identification of sialylated Thomsen-Friedenreich antigens in proteins finds importance in cancer research. Sialylated antigens in minute quantities (0.1 μg) and plasminogen (1.0 μg) could be detected from gels by reductive β-elimination, permethylated and analyzed by nano-LC-matrix

assisted laser desorption/ionization (MALDI)-TOF-MS and using a computational algorithm to filter spectral noise and enhance/isolate the signals of interest [57].

Integrating a fast preparation protocol of mucins with high-throughput nanoLC/MS have enabled the study the *O*-glycosylation of the colon MUC2 mucin from biopsy of sigmoid colon during routine colonoscopy of 25 normal control patients [58].

Negative ion nano-liquid chromatography/mass spectrometry (nano-LC/MS) and tandem mass spectrometry (nano-LC/MS [2], using graphitized carbon as separating medium, could analyze neutral and acidic *O*- and *N*-linked oligosaccharide alditols. Automated glycofragment mass fingerprinting using the GlycosidIQ software confirmed the oligosaccharide sequence for both neutral desialylated as well as sialylated structures in membrane proteins from ovarian tissue [59].

Attachment of α-*N*-acetylneuraminic acid (Neu5Acα) to the terminal glycine residues tetraantennary peptides [glycine (n)-NHCH [2]] [4] C is reported to give rise to water-soluble assembled glycopeptides that can to bind influenza virus multivalently and inhibit adhesion of the virus to cells more effectively is a promising antiviral strategy in the design of multivalent antivirals [60].

8 Nanotechnology bioimaging application, detection of cellular sialic acid expression and targeting

Polyacrylamide hydrogel-based lectin microarray with 27 lectins on colorectal cancer (CRC) cell lines SW480, SW620, and HCT116 revealed high glycan expression of d-galactose, D-glucose, and/or sialic acid residues with Uelx Europaeus Agglutinin-I (UEA–I) showing specificity to SW480 cells. UEA-I conjugated with silica-coated $NaGdF_4$:Yb^{3+}, Er^{3+}@ $NaGdF_4$ has been reported to be effective designs to target tumor molecule in SW480 tumor detected by upconversion luminescence imaging, T_1-weighted MRI, and X-ray computed tomography (CT) imaging [61].

CD22 finds importance as an important drug target in autoimmune diseases and B cell-derived malignancies. Nanoprobe of sialic acid/*N*-acetylneuraminic (NANA) acid conjugated to carboxyl groups modified CdSe/ZnS quantum dots (COOH-QDs) by the NHS/EDC esterification chemistry led to the formation of functionalized QD nanoconjugate which has been applied to target CD22 and the targeting could be detected by fluorescence imaging [62]. An immobilized mercaptophenyl boronic acid

(MPBA) nanochip with nanocone-array substrate on Au and Ag NPs for dynamic electro-optical by the metal-S bond could detect selective sialic acid as low as 17 μM [63].

Nano-TiO_2 has been proved to have cytotoxic and phototoxic effects on different crystalline phases for human skin keratinocytes (HaCaT cells) under ultraviolet (UV) irradiation revealing increased α2,6-sialylated glycans. Although mixture of crystalline P25 revealed highest cytotoxicity and phototoxicity, followed by pure anatase A25, and pure rutile R25 but A25 and R25 did not affect sialic acid expression on HaCaT cells [64].

Nanomaterials find application in tumor targeting and find application in cancer therapy. PEGylated, borate-coordination-polymer-coated polydopamine NP (PDA@CP-PEG) with DOX (Doxorubicin) reveal synergetic targeting of sialic acid-overexpressed tumor cells. Photothermal effect of the polydopamine core and the DOX-loading capacity of the polymer layer enable their potential for chemo-photothermal combination therapy with less toxicity, efficient tumor targeting ability, and chemo-photothermal activity for tumor inhibition with promising potential clinical applications [65].

4-MPBA, a surface-enhanced Raman scattering (SERS) nanoprobe (glucose-MPBA-AgNPs) prepared with 10 times stronger SERS enhancement ability as compared to MPBA-AgNPs could detect sialic acid expression by amplifying their expression on cancer cells, by the differential accumulation of glucose-MPBA-AgNPs on cancer vs normal cells due to the differences of sialic acid expression on cancer vs normal cells enabling detection of cancer cell with diagnostic and prognostic potential [65, 66].

Carbon dot (Cdot) NPs offer promising potential for drug delivery and bioimaging applications. J774.1 macrophages have been shown to take up phenylboronic acid (PBA)-modified NPs as PB binds to sialic acid residues overexpressed on diseased cell surfaces and finds application in drug targeting to macrophages associated with tumors [67].

Sialic acid as a ligand by dexamethasone (DM)-loaded solid lipid NPs has been used for targeting renal ischemia–reperfusion injury (IRI)-induced acute kidney injury (AKI). DM-loaded sialic acid-conjugated PEGylated NPs (sialic acid-NPs) could reduce apoptotic human umbilical vein endothelial cells (HUVECs) via downregulating oxidative stress-induced Bax, upregulating Bcl-xL, and inhibiting caspase-3 and caspase-9 activation being internalized by inflamed vein endothelial cells (VEC) mediated by specific binding between sialic acid and *E*-selectin receptor expressed on the inflamed VEC and could effectively ameliorate renal functions in AKI mice, causing improved blood biochemical indexes, histopathological changes, oxidative stress

levels, and pro-inflammatory cytokines proving to be efficient and targeted delivery of DM for ischemia–reperfusion-induced injury-induced AKI, with improved therapeutic outcomes and reduced side effects [68].

β-amyloid (Aβ) plaques in the brain are pathological features of Alzheimer's disease (AD). NP contrast agents capable of binding with Aβ highly selectively enable early detection of AD. But the major obstacle is provided by the blood brain barrier (BBB) that preclude the entrance of NPs into the brain for Aβ binding. Bovine serum albumin (BSA)-coated NPs are designed with sialic acid (NP-BSA_x-Sia) has been reported to overcome the challenges in Aβ imaging in vivo due to biocompatible and high magnetic relaxivity, indicating their suitability as contrast agents for MRI [69].

ConA-conjugated DOX-loaded mesoporous silica nanoparticles (MSNs) find applications as delivery devices in bone cancer treatment as ConA and can recognize and bind sialic acid overexpressed in human osteosarcoma (HOS) cell line [70].

Neutrophils by forming neutrophil extracellular traps (NETs) with DNA fibers and histones can combat pathogens and antimicrobial components to kill pathogens, but NETs could lead to pathological conditions like sepsis or acute lung failure due to histone-mediated toxicity. Poly sialic acid NPs with property as an antagonist of the cytotoxic properties of extracellular histones neutralize histone-mediated cytotoxicity and initiate binding of these polysialylated particles to NET filaments [71].

Middle East respiratory syndrome coronavirus (MERS-CoV) targets the epithelial cells of the respiratory tract in human and camel host, binding to the cell-surface receptor dipeptidyl peptidase 4 (DPP4) by S1B and sialic acid by S1A domain. Binding is hampered by modification of sialic acid including 5-*N*-glycolylation and (7)9-*O*-acetylation or depletion of cell surface sialic acid by neuraminidase treatment indicating that virus-sialic acid interactions are vital to viral entry and infection [72]. Inhibition of influenza A virus infection by multivalent sialic acid inhibitors is a promising strategy [73].

A red blood cell (RBC) cytosensor has been designed employing sialic acid on a quartz crystal microbalance (QCM) by immobilizing RBCs on a ConA-modified gold chip employing recognition between ConA and mannose. 4-Aminobenzeneboronic acid (APBA)-functionalized gold nanoparticles (AuNPs/APBA) were used to label sialic acid and acted as a signal amplification nanoprobe and find importance in detection of sialic acid in diabetic individuals as compared to the normal individuals [74]. MNPs find importance in molecular targeting therapy in cancer but have limitations in targeting. Sialic acid-binding lectins, wheat germ lectin (WGA) conjugate,

or nanomagnetolectin, can target sialic acids overexpressed in prostate cancer and promoted apoptosis under magnetic field (magnetofection) [75].

Early diagnosis of metastatic cancers can prevent mortality in cancer. As aberrant overexpression of sialic acid has been reported in tumors correlating with progressive metastasis, PBA-installed PEGylated AuNPs coupled with Toluidine blue O (T/BA-GNPs) as SERS probes has been reported to target surface overexpressed sialic acid revealing strong SERS signals from metastatic cancer cell lines (breast cancer; MDA-MB231 and colon cancer; Colon-26 cell lines) [76].

CD22 is a member of the Siglec family and CD22-ligand-targeted NPs with therapeutic functions have proved successful in preclinical settings for blood cancers, autoimmune diseases, and tolerance induction [77].

Biosensors for detection of virus were developed by utilizing plasmonic peak shift phenomenon of the AuNP and viral infection mechanism of HA on virus and sialic acid on animal cells [78].

Molecularly imprinted polymers (MIPs) as artificial receptors; can be designed to bind targets like hyaluronan and sialylatic acid and their conjugates and find application in labeling and imaging of cellular targets. Fluorescent-labeled MIP NPs with glucuronic acid (MIPGlcA) and sialic acid could target extracellular hyaluronan and MIP-coated InP/ZnS QDs could target hyaluronan and sialylation sites in both their intra and extracellular expression. Green and red-emitting QDs functionalized with MIPGlcA and MIPsialic acid, respectively, have been reported to enable multiplexed cell imaging [79].

(3-Aminomethylphenyl)boronic acid (AMPB)-installed hyaluronic acid (HA)-ceramide (HACE)-based NPs, including manassantin B (MB), forming HACE-AMPB/MB NPs (239 nm), when targeted on cancer cells revealed increased cellular accumulation and efficient antitumor activity and were hypothesized to react with sialic acid overexpressed in CD44 receptor-positive human adenocarcinoma cells [80].

Hydrophobically modified polysialic acid (HPSA) NPs, prepared by 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC)/N-hydroxysuccinimide (NHS) coupling between *N*-deacetylated PSA and 5β-cholanic acid loaded with DOX forming (DOX-HPSA) are reported for its anticancer drug nanocarrier activity, therapeutic efficacy, and specific targeting of cancer cells in A549 cells [81].

Fluorescent-conjugated polymer NPs with their optical properties and low cytotoxicity find applications in imaging and the fluorescent intensity was reported to further improve when these polymers were modified with a

PBA group, covalently linked with sialic acid, forming a sialic acid-imprinted NPs (30 nm) size with selective staining for DU 145 cancer cells [82] (Fig. 6).

Protamine nanocapsules (NCs) linked with PSA acted as drug delivery devices and revealed properties of enhanced stability and facilitated transport of macromolecules across the intestinal epithelial cells in cell line including Caco-2 [83].

Magnetic relaxation nanosensors (MRnS) made by conjugating entry blocker peptides to iron oxide NPs through targeted binding with HA. 2,6- and 2,3-sialic acid ligands on cell surface could detect HA variants (H1 and H5) in fats and detect the different influenza subtypes [84].

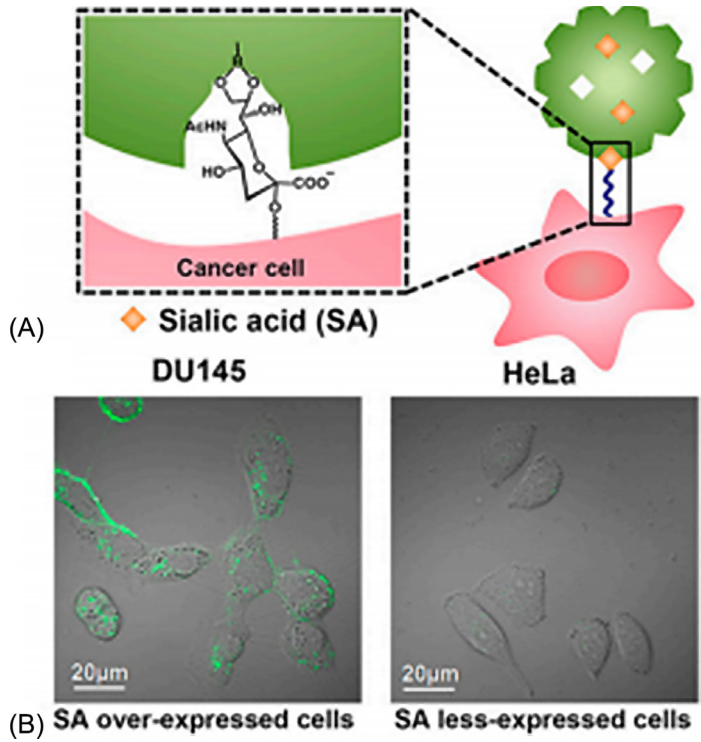

Fig. 6 (A) Selective binding of sialic acid-imprinted fluorescent conjugated polymeric nanoparticles to cancer cells. (B) Confocal laser scanning microscopic images of DU145 (left) and HeLa (right) cells incubated with sialic acid-imprinted fluorescent conjugated polymeric nanoparticles for 24 h at 37°C. *(Reproduced with permission from Liu RH, Cui QL, Wang C, Wang XY, Yang Y, Li LD. Preparation of sialic acid-imprinted fluorescent conjugated nanoparticles and their application for targeted cancer cell imaging. ACS Appl Mater Interfaces 2017;9:3006–15.)*

Sialic acid coatings on polymeric micelle consisting of poly(sarcosine)-block-poly(l-lactic acid) (lactosome) targeting the immunosuppressive receptors of Siglec-G and CD22 could prevent accelerated blood clearance (ABC) phenomenon due to the reduction of the anti-poly(sarcosine) IgM production [85].

Sialoglyco-conjugated NPs synthesized from highly branched α-glucuronic acid-linked cyclic dextrins (GlcA-HBCD) forming sialoglyco-NP (Neu5Acα2,6LacNAc-GlcA-HBCDs, sialoglycoNP [SAGNP]) could recognize and interact with human influenza virus strain A/Beijing/262/95 (H1N1) detected by HA inhibition assay and SAG-NP with sialic acid substitution of 30, have been reported to inhibit virus-binding activity [86].

Au-NPs functionalized with sialic acid diluted with a PEG forming the sialic acid functionalized gold nanoparticles could detect soluble form of murine Siglec-E (mSiglec-*E*-Fc fusion protein) on Chinese hamster ovary cells (CHO cells) and find application in detection of Siglec on mammalian cells [87].

A benzoic group functionalized gold nanoflower was designed as nanoprobes for recognition of target sialic acid and assembly of poly sialic acid by sensitive SERS signal [88].

Fluorescent biocompatible polymeric NPs designed with a hydrophobic monomeric core, fluorescent monomer, and a protein-binding monomer that conjugates lectin to target sialic acid is reported to detect and monitor progression of influenza viral infection by detecting the sialic acid expression level changes in human lung epithelial cells [89].

Fluorescent dye rhodamine and two InP/ZnS QDs emitting in the red and green-MIP particles with D-glucuronic acid (GlcA), a substructure of hyaluronan, and sialic acid capable to localize hyaluronan and sialic acid has been designed for bioimaging of human keratinocytes extracellularly viewed by epifluorescence and confocal microscopy and proves to be a promising tool toward monitoring of disease progression [90].

SNA forms strong bonds with AuNPs as compared to *Saraca indica* (saracin II), in the ground state as detected by UV–vis absorption, steady state, time-resolved fluorescence coupled with circular dichroism (CD) spectral studies, finding application in drug delivery systems [91]. AuNPs with sialic acid-terminated complex bi-antennary N-glycans, synthesized with glycans isolated from egg yolk, found application as sensor in detection of both recombinant HA and whole influenza A virus particles of the H1N1 subtype [92]. Aggregation of 4-mercaptophenylboronic acid functionalized AuNPs (4-MPBA-AuNPs) could bind to sialic acid and detected by colorimetric assays and finds importance in detection of sialic acid in blood serum samples [93].

PBA conjugated with polyethylenimine (PEI1.8k) to generate amphiphilic PBA-grafted PEI1.8k (PEI-PBA) nanovector, encapsulated siRNA to form PEI-PBA/siRNA nanocomplexes with properties of biocompatibility, serum stability, and RNase resistance enabled specific delivery to sialic acid overexpressed target cancer cells and significantly decreased polo-like kinase-1 (PLK)-1 expression in tumors, leading to apoptosis and cell cycle arrest [94].

Monosaccharide-imprinted fluorescent NPs comprising of doped silica NPs with a shell imprinted with sialic acid, fucose, or mannose as the template with probe fluorescein isothiocyanate (FITC) enabled imaging of human hepatoma carcinoma cells (HepG-2) and human primary tumor cell line michigan cancer foundation (MCF-7) derived from mammary gland [95]. Sialic acid incorporation into the GG molecule could increase fourfold anticancer compound paclitaxel loading capacity forming self-assembled nanostructures of di- and tri-sialogangliosides [96]. An inductively coupled plasma mass spectrometry (ICP-MS) is used to detect sialic acid on the cancer cell surface, recognized by biotinylated phenylboronic acid (biotin-APBA) AuNPs in HepG2 and MCF-7 cells [97]. Molecularly imprinted NPs were prepared as SERS for imaging cancer cells based on targeting of sialic acid overexpressed on cancer cells [98]. Sialic acid core-shell NPs with nitrobenzoxadiazole (NBD) fluorescent groups allowing environmentally sensitive fluorescence finds application as a biosensor [99].

Sepsis is known to lead to acute respiratory distress syndrome (ARDS). Murine Siglec-E and its human orthologs Siglec-7 and Siglec-9 play role in negatively regulating acute inflammatory responses and may act as targets in sepsis and ARDS treatment. Thus, poly(lactic-*co*-glycolic acid) NPs linked with Siglec ligand, di(α2 → 8) *N*-acetylneuraminic acid (α2,8 NANA-NP), induced enhanced oligomerization of the murine Siglec-E receptor on macrophages [100].

Reduced graphene oxide-tetraethylene pentamine-1-butyl-3-methylimidazolium hexafluorophosphate (BMIMPF6) hybrids with bimetallic gold platinum alloy nanoparticles (AuPtNPs) with SNA could detect α2,6-sialylated glycans in serum [101]. Sialic acid-modified selenium (Se) NPs conjugated with an alternative peptide-B6 peptide forming B6-sialic acid-SeNPs, can cross BBB and enter into cerebral endothelial cells and can act as nanomedicine in AD detected by laser-scanning confocal microscopy, flow cytometry analysis, and ICP-atomic emission spectroscopy (ICP-AES) [102]. 3-Aminophenylboronic acid functionalized CdSeTe@ZnS-SiO2 QDs (APBA-QDs) probes could detect sialic acid on K562 cells [103].

PSA can be immobilized on nanoporous silica materials silica nanoparticles (NPSNPs) of MCM-41 type [104] with different applications.

Raman spectroscopy (SERS)-based sensing platform was developed for detecting sialic acid on single cell surface by 4-(dihydroxyborophenyl) acetylene (DBA)-linked AuNPs HeLa cell [105].

Super-paramagnetic iron oxide nanoparticles (SPIO NPs), αCD22 Abs and MXD3 siRNA molecules entered leukemia cells and knocked down MXD3, leading to apoptosis in Reh cell line and in primary preB ALL samples with synergistic effects by anticancer agents vincristine or DOX [106].

Avian influenza viruses preferentially bind to sialic acid α-2,3-galactose receptors on epithelial cells and magnetic NPs coated with chitosan and functionalized with *Maackia amurensis* (MAA) lectin (NP-lectin) could isolate sialic acid α-2,3-galactose receptors from porcine trachea [107].

AuNPs immobilized with graphite oxide (GO), Prussian blue (PB), and PTC-NH_2 (an ammonolysis product of 3,4,9,10-perylenetetracarboxylic dianhydride) nanocomposite GO-PB-PTC-NH_2 modified glassy carbon electrode (GCE) linked to SNAs could detect α2,6-sialylated glycans in serum [108]. Lectin-tagged fluorescent polymeric NPs (35 nm) could detect cellular sialic acid expression [109]. QDs labeled avian influenza H9N2 virus could enable study of establishment of infection in human bronchial epithelial (HBE) cells using a 3D SPT technique [110]. DM and methotrexate (MTX) entrapped within PSA-trimethyl chitosan (TMC) NPs enabled site-specific targeting in rheumatoid arthritis [111]. QDs modified with PBA (QDs-PBA) could target sialic acid expressed on vesicular stomatitis virus (VSV) enabling the virus labeling [112].

Covalent immobilization of SNA on a mixed self-assembled monolayer (SAM) on planar gold surfaces forming a two-dimensional (2D) sensor and immobilized SNA on mixed SAM layer on AuNPs forming 3D sensor could detect sialic acid [113].

AuNPs functionalized with a thiolated trivalent α2,6-thio-linked sialic acid and a thiolated PEG has been designed to detect the human influenza virus X31 (H3N2) as the trivalent α2,6-thio-linked sialic acid bind to virus hemaglutinin [114].

Multifunctional fluorescent silica nanoparticles (FSNPs) with PBA were designed to label sialic acid on cancer cell surface with high selectivity and sensitivity [115].

Sialic acid conjugated to poly(ethylene oxide)-polycaprolactone polymersomes could interact with influenza viruses by inhibiting viral HA binding to host cell sialic acids, thus preventing viral entry. Targeting by design

of neuraminidase inhibitor zanamivir into the polymersome core, inhibited viral replication [116]. AuNPs attached to polycrystalline gold modified by an aminoalkanethiol linker layer with covalently immobilized SNA on a mixed SAM formed on AuNPs could detect sialic acid and finds application in arthritis or cancer [117].

Siglec-7 ligand, displayed on liposomal NPs, allowed targeting of Siglec-7 positive cells in peripheral human blood [118]. Signals between QDs and AuNPs-sialic acid-binding proteins (SBPs) and sialic acid moieties, respectively, enable biosensing based on the nanometal surface energy transfer (NSET) and could enable detection of glycosylation linkages (α2–6 vs α2–3), and 9-*O*-acetyl and *N*-glycolyl group modifications [119]. Gold nanocluster probe was developed to detect cell surface sialic acid [120].

Sialic acid reduced and stabilized AuNPs synthesized by a simple one-pot, green method for colorimetric detection of influenza virus by HA-sialic acid binding [121].

The liposomes targeting sialioadhesion or Sn or CD 169 could selectively bind to Sn-expressing cells and macrophages accumulating intracellularly overtime enabling antigen delivery to macrophages for their presentation to T cells [122].

A novel electrochemical strategy for in situ detection of cell surface sialic acids by chemoselective labeling technique and a dual-functionalized nanohorn probe [123] was developed.

3-Aminophenylboronic acid functionalized QDs (APBA-QDs) synthesized by covalently binding APBA to mercaptopropionic acid-capped CdS QDs, and polysialic acid stabilized gold nanoparticles (PSA-AuNPs), were prepared by a one-pot procedure. The APBA-QDs recognized the sialic acid on BGC-823 human gastric carcinoma (BGC) cells and then the PSA on AuNPs, therefore, amplifying signal [124] enabling detection of sialic acid.

Semiconductor QDs with small molecular PBA tags enabled labeling of sialic acid and imaging of cells [125]. Sialic acid surface-decorated selenium nanoparticles (sialic acid-Se-NPs) have been reported to penetrate cervical carcinoma cells and induce apoptosis by proapoptotic enzymes caspase-3 and poly(ADP-ribose) polymerase (PARP) cleavage in cancer cells [126].

Sialic acid-terminated glycerol dendron functionalized AuNPs have been reported to inhibit influenza virus infection [127].

Lectin-Au-thionine bioconjugates linked to AuNPs revealed mannose expression and expression of biomarker sialic acid in cancer detection, diagnosis, and treatment [128]. PLGA NP modified with BBB penetrating peptide (similopioid peptide) and a sialic acid residue could cross the BBB

and interact with brain receptors. [129]. Polymeric (poly(D,L-lactide-*co*-glycolide), PLGA) NPs surface modified with sialic could be devised [130].

9 Discussion

The application of nanotechnology in the study and biomedical applications of glycosylated molecules and sialic acids and their conjugates on the cells and serum, in human health and disease is a recent development and considerable work has been progressed in the last decade. Different designs of nanoparticles have enabled (i) sensitive detection of sialic acid in free forms and in conjugated form inferring on their structures and discovery of novel molecules, hitherto unknown in health and disease due to their sensitive and improved specialized nature of detection systems and (ii) targeting of sialic acids as drug delivery targets with tremendous application in targeting of infectious, pathogenic diseases and cancer. The ongoing research is their application in biomedicine, imaging, and sensor applications is thought to have a major impact on the human lives. With the advancement of the applications of nanotechnology in sialic acid biology, a new term perhaps needs to be coined now as *Sialonanotechnology* encompassing the applications of nanotechnology is study of sialic acid biology in health and disease.

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