Recent Developments in the Use of Glyconanoparticles and Related Quantum Dots for the Detection of Lectins, Viruses, Bacteria and Cancer Cells

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Carbohydrate-coated nanoparticles—glyconanoparticles—are finding increased interest as tools in biomedicine. This compilation, mainly covering the past five years, comprises the use of gold, silver and ferrite (magnetic) nanoparticles, silicon-based and cadmium-based quantum dots. Applications in the detection of lectins/protein toxins, viruses and bacteria are covered, as well as advances in detection of cancer cells. The role of the carbohydrate moieties in stabilising nanoparticles and providing selectivity in bioassays is discussed, the issue of cytotoxicity encountered in some systems, especially semiconductor quantum dots, is also considered. Efforts to overcome the latter problem by using other types of nanoparticles, based on gold or silicon, are also presented.

Keywords: glyconanoparticles, gold nanoparticles, rapid diagnostics, pathogen detection, cancer imaging, glycobiology

INTRODUCTION

The use of nanoparticles (NPs) as biomedical tools has developed at pace in recent years, with NPs functionalised with carbohydrates (glyconanoparticles) emerging in diagnostics and cell imaging. Since the first report of glyconanoparticles (de la Fuente et al., 2001), interest in these materials has risen considerably. The main approaches to the preparation and early applications of glyconanoparticles have been reviewed previously (de la Fuente and Penadés, 2006; Marradi et al., 2013; Chen et al., 2014), as has the application of glyconanoparticles in biomedicine (Dosekova et al., 2017; Kveton et al., 2020), the use of magnetic glyconanoparticles in biosensing (Fratila et al., 2016), and glyconanoparticles for the detection of cancer cells and the early diagnosis of cancer (Hockl et al., 2016; Torres-Pérez et al., 2020).

The first examples of glyconanoparticles focused on gold, silver, and iron oxide systems. The impact of the size and shape of the nanoparticle, as well as the density of carbohydrates on the surface of the nanoparticle and the importance of the tether employed for the functionalisation, have been studied and reviewed (Compostella et al., 2017). Key conclusions are that, for certain applications, nanoparticles with larger size present flatter surfaces, enhancing carbohydrate-target interactions (Chien et al., 2008); the shape of the particle (rods vs. spheres) can also impact on the detection limit of Escherichia coli-glyconanoparticle interactions, for instance (Chaudhary et al., 2015).
FIGURE 1 | Glyconanoparticle-based assays for the detection of carbohydrate-binding targets. (A): the presence of the target reduces the interparticle distance as result of the aggregation of the NPs. Insets show the impact on i) plasmonic (reproduced from Poonthiyil et al., 2015 with permission from the Royal Society of Chemistry), ii) colorimetric (reproduced from Marin et al., 2015 with permission from the Royal Society of Chemistry) and iii) TEM (reproduced from Poonthiyil et al., 2015 with permission from the Royal Society of Chemistry) detection.

(B): FRET-based assay—a fluorophore is quenched upon attachment to a glycoNP and the fluorescence is recovered in the presence of the target. Inset shows the fluorescence recovery observed by fluorescence spectroscopy (adapted with permission from Ajish et al., 2020. Copyright 2020 American Chemical Society).

(C): FRET-based assay—glycoQDs are quenched in the presence of the target, due to a decrease in the distance with equally functionalised glycoNPs. Inset shows the decrease in fluorescence emission intensity of the QDs (adapted from Zhang et al., 2018 with permission from Taylor & Francis Ltd) with increasing concentrations of the target.

(D): MagMED-based assay to study bacteria death using MNPs and an alternating magnetic field. Insets show i) a TEM image of the NPs dispersion, and ii) TEM of the target in the presence of the MNPs before and after treatment with the magnetic field which causes bacterial death consequently to the temperature increase (adapted from Raval et al., 2017 with permission from John Wiley and Sons).
Nanoparticles have a high surface to volume ratio, enabling multivalent ligand presentation, which has been widely exploited to overcome the inherently weak nature of carbohydrate-protein interactions (Lundquist and Toone, 2002). However, a too high density of the carbohydrate on the surface can hamper accessibility of the glycan to protein partners—a challenge that can be addressed through longer, more flexible tethers (Marradi et al., 2013; Compostella et al., 2015). The evident cytotoxicity of semiconductor QDs has also been extensively studied to target, image and treat tumours (Hockl et al., 2016; Torres-Pérez et al., 2020). Herein, we survey recent advances in these fields: key features of the systems discussed can be found in Figure 1 and Table 1.

### LECTINS/PROTEIN TOXINS

The plant lectin Concanavalin A (ConA) has been widely used as a model to develop carbohydrate-based lectin detection systems. The specific interaction between glucosamine-functionalised AuNPs and ConA has been reported (Di Silvio et al., 2018) to study the intracellular exchange of protein corona, confirming that specific interactions between lectins and NPs surface ligands contribute to retain the lectins on the surface of the NP. Thioltated mannosides have been used to functionalise AuNPs, as well as ZnS/CdSe QDs, for the detection of ConA (Zhang et al., 2018). In this, and several other studies, fluorescence quenching via Förster resonance energy transfer (FRET) was used as a switch-on-off effect during the assay.

CdSe/ZnS QDs have been functionalised with quinolyl glucose (Glc) or quinolyl galactose (Gal) for the detection of ConA and peanut agglutinin (PNA), respectively (Ma et al., 2014). Both Glc and Gal systems explored the FRET effect between the QDs and the quinone, with the fluorescence recovery achieved in the presence of the specific lectins. Other studies applied glyco-QDs for the detection of lectins with a dual-colour system based on glucose-QDs for the detection of ConA and galactose-QDs for the detection of PNA, allowing the discrimination between both lectins in the same sample.
The detection of bacterial toxins has attracted attention in diagnostic. The detection of Cholera toxin (CTB) (Schofield et al., 2007) and the detection of heat-labile enterotoxin B subunit (LTB) from *E. coli* (Poonthiyil et al., 2015a), both based on galactose-functionalised AuNPs, have been reported. In the latter, 12 nm diameter AuNPs produced the most significant shift in absorbance and the toxin was detected at a concentration of 100 nM. The detection of Shiga-like toxin 1 (Stx1), often associated with bacteria such as *E. coli* or *Shigella dysenteriae*, has been also achieved with glyconanoparticles. A systematic comparison of tether lengths and nanoparticle sizes was made using globotriose-functionalised AuNPs (Chien et al., 2008), showing that larger particles with longer tethers allowed a more efficient binding to Stx1 when they were compared to the free globotriose ligand. A different approach was adopted using a magnetic nanoparticle-based system (MNPVs) (Kuo et al., 2015). Here, the glycan functionality was conveniently obtained by functionalising 30 nm particles with pigeon ovalbumin, a glycoprotein containing an oligosaccharide ligand for Stx1, namely Gal-α(1→4)-Gal-β(1→4)-GlcNAc. The assay showed specificity for Stx1 in complex matrices, where the glyconanoparticles and associated protein toxin were isolated by magnetic extraction and analysed by MALDI-ToF to confirm the presence of Stx1.

Chromophores are often combined with either an enhancing or a supressing counterpart. A surface-enhanced Raman spectroscopy (SERS)-based assay for the detection of CTB was developed using silver nanoparticles presenting both PEGylated galactose and sialic acid (SA) (Simpson et al., 2016) (optimised 15:1 ratio). This assay allowed the low nM detection of the toxin in simulated freshwater samples.

A system comprising galactose-AuNPs and amine-QDs for the detection of CTB has been developed (Ahn et al., 2016). The assay was based on the inhibition of fluorescence via FRET, upon binding of the QDs to the AuNPs via hydrogen bonds formation between the amines on the QD and the hydroxyl groups of galactose-AuNPs. In the presence of CTB, the hydrogen bonds are disrupted liberating the amine-QDs and activating their fluorescence.

Selectins have attracted attention as biomarkers for the diagnosis of brain inflammation. Lewis X (Le^a^-) capped ferrite nanoparticles were designed for the selective in *vivo* targeting of such receptors (Van Kasteren et al., 2009). This work showed potential for the early diagnosis of neuropathologies such us dementia, encephalitis or Parkinson’s disease.

VIRUSES

Influenza virus remains a serious global health concern, causing ca. 300,000 deaths every year (Paget et al., 2019). The affinity between hemagglutinin on the surface of the virus and sialic acid, which forms the basis of host cell adhesion and invasion during infection, has been explored for the development of rapid diagnostics. Human influenza strains preferentially bind to α2,6-sialylgalactose, while the animal viruses prefer the α2,3-linked isomer (Marin et al., 2013). A collection of AuNPs functionalised with seven different sialic acid derivatives (Zheng et al., 2017) was used to successfully detect 14 different influenza strains enabling discrimination from other respiratory viruses, such as hRSV and avian influenza virus.

A bi-antennary sialylcyclopentide extracted from egg yolk has been used to functionalise AuNPs for the colorimetric detection of human influenza virus (Poonthiyil et al., 2015b) achieving a detection limit of 71 nM and the effective detection of two H1N1 strains, A/PuertoRico/8/34 and A/New Caledonia/29/1999.

A straightforward methodology for the preparation of AuNPs coated with α2,6-sialyllactose-containing polymer has been reported by Zhang et al. (Zhang et al., 2016) and tested for aggregation with *Sambucus* nigra agglutinin and influenza virus using dynamic light scattering or transmission electron microscopy (TEM).

Since the pandemic crisis caused by COVID-19 in early 2020, efforts have been made to detect SARS-CoV2 using glyconanoparticles. A lateral flow system for the rapid detection of coronavirus spike proteins was recently reported (Baker et al., 2020). Sialic acid-linked poly-(2-hydroxyethyl acrylate) (PHEA) was used to functionalise AuNPs, and binding to the target spike proteins was evaluated by bi-layer interferometry. The system was transferred into lateral flow format enabling the rapid, sensitive and selective detection of virus-like particles presenting the SARS-CoV2 spike protein.

Virus-glycan interactions have been shown to prevent virus internalisation in human cells through DC-SIGN/R receptors, which function as an entrance gate for viruses such as HIV or Ebola. AuNPs functionalised with the same high-mannose glycans present in the HIV glycoprotein gp120 (Chiado et al., 2013) together with PEGylated α-fucosylamides (Arosio et al., 2014), both successfully interacted with the DC-SIGN receptor with a comparable efficiency. Other works have demonstrated that such virus uptake channels can be blocked by multivalent glyconanoparticles, and their efficacy can be modulated by varying the sugar density on the nanoparticle surface (Guo et al., 2016). In addition, the glyconanoparticle approach can be used to quantify binding affinity for DC-SIGN/R receptors as well as to inhibit viral cell entry (Guo et al., 2017). Extension of this work explored the interaction of mannose (Man)-functionalised AuNPs and DC-SIGN (Budhadev et al., 2020).

BACTERIA

The detection of bacterial pathogens represents an ongoing need in the field of health care. To target the *E. coli* fimbral adhesion FimH, mannose-coated CdS QDs have been used (Mukhopadhyay et al., 2009). More recent work screened AuNPs functionalised with either mannose or glucose (Richards et al., 2014) to detect *E. coli* K-12 strain (FimH^+^) and using the TOP10 strain (FimH^-^) as negative control. The...
stability of the nanoparticles in solution was improved by using a PEG-3000 tether, rather than directly binding the respective thiosugar to the AuNPs.

Recently, a detection system for E. coli based on the fluorescent properties of glycoacrylamides (Glc-bis) has been reported (Ajish et al., 2020), where self-aggregation-induced π interactions between the acrylamide moiety installed on the glucose generate the fluorescence of the polymer (Ajish et al., 2018). The fluorescence of the glycopolymer is quenched by the AuNPs, but in the presence of a glucose-binding target the Glc-bis ligand is removed from the surface of the AuNPs, reactivating its fluorescence. This turn-on-based fluorescent system afforded a simple means to detect E. coli.

Focusing on the same FimH target, mannose-stabilised AgNPs have been synthesised for the selective detection of E. coli strain O157:H7 (Wang et al., 2017). Specificity was tested against a series of bacterial strains, demonstrating that the mannose-stabilised AgNPs were specific for the O157:H7 E. coli strain. The AgNPs construct exhibited a dual activity resulting from the targeting role of the glycan and the bactericidal properties of the stabilised AgNPs were specifically directed toward the O157:H7 strain.

Fluorescent Cu/CdS QDs functionalised with galactose, stachyose or raffinose showed discrimination between different bacteria demonstrated via linear discrimination analysis of the fluorescence signals (Qi et al., 2018). The assay could be performed in 30 min and was able to selectively differentiate between E. coli, P. aeruginosa, Micrococcus luteus, Vibrio alginolyticus, Shewanella algae and Desulfovibrio desulfuricans.

A fluorescent magnetic assay to target, block or extract Helicobacter pylori based on fucose-containing oligosaccharides Le¹, Le² or blood group H type 1 coupled to cobalt-ferrite magnetic nanoshells has been reported (Park et al., 2015). Binding of the nanoparticles to H. pylori was confirmed by confocal microscopy, while incubation of the bacteria with mammalian cells in presence of these fucose-NPs prevented the adhesion of H. pylori to the cells.

Tuberculosis remains an important disease globally and early diagnosis represents an unmet need. A detection assay for Mycobacterium smegmatis has been developed (Jayawardana et al., 2015) based on silica and iron NPs. The authors assembled a small library of trehalose-stabilised NPs, using previously reported methodology (Wang et al., 2013), and demonstrated the ability of the glyconanoparticles to selectively bind M. smegmatis over mammalian cells.

### CANCER

The imaging of tumours and the early detection of cancer biomarkers is topical. One of the first reported application of glyco-QDs was dedicated to the study of asialoglycoprotein receptor interaction with galactose-terminated QDs in liver cancer cell line HepG2 (Kikkeri et al., 2009). Using flow cytometry, the authors demonstrated the increased uptake of galactosamine-capped QDs in comparison to sugar-free or galactose-capped-QDs.

Sialic acid-binding immunoglobulin-type lectins (SIGLECs), together with galactose-binding galectins, are cancer markers of increasing interest (Cagnoni et al., 2016). Galectin-1, 7, and 9 have been found to be overexpressed in cancer cells and therefore represent highly relevant targets in cancer diagnostics (Sun et al., 2019). A plasmonic system based on sialic acid functionalised AuNPs has been designed for the detection of SIGLECs (Schofield et al., 2016). The assay provided a colour change upon aggregation of the AuNPs in the presence of SIGLECs (in solution), or could be localised by TEM when expressed on Chinese hamster ovary cell-surface. Recently, AuNPs stabilised with acetylated mannose were used in an image-based assay to detect A549 lung cancer cells (Adokoh et al., 2020). A comparison between different mannose-functionalised NPs, revealed that those containing acetylated mannose had better selectivity towards A549 lung cancer cells than to healthy peripheral blood mononuclear cells.

Garcia Calavia et al. reported an anti-cancer photodynamic therapy system based on bi-functionalised AuNPs (Garcia Calavia et al., 2018). The galactose-terminal lactose disaccharide was used to selectively target galectin-1, which is overexpressed in certain breast cancer cells such as MDA-MB-231 or SK-BR-3, and
a derivative of phthalocyanine was used as photosensitiser. The bi-functionalised glyco-nanoparticle conjugates could be used to achieve selective breast cancer cell death upon irradiation of the photosensitiser at 633 nm, resulting harmless to MCF-10A cells.

Human carcinoma cells have been targeted with silicon-based glyco-quantum dots (Ahire et al., 2015). Work has been done to prove that in some applications, carbohydrate-functionalised SiQDs (using galactose, mannos, glucose or lactose) are non-toxic whereas the unfunctionalised SiQDs are. Lai et al. reported prove that in some applications, carbohydrate-functionalised SiQDs could be used to image cancer cells. A similar approach showed the uptake of glucose-functionalised 4 nm SiQDs by HeLa cells (Hsu et al., 2017), while a study of the particle size-dependent uptake of mannos-functionalised SiQDs by MDA-MB-231 breast cancer cells has been reported recently (Li et al., 2020), showing that the larger 400 nm Man-SiQDs have the highest uptake rate by cells.

Magnetic glyconanoparticles have been employed in combination with magnetic resonance imaging (MRI) to detect cancer cells, avoiding the need of labelling the cells beforehand (Ei-Boubbou et al., 2010). A collection of ferrite glyconanoparticles functionalised with either mannos, fucos, galactose, sialic acid or N-acetylglucosamine were screened against a wide variety of cancer cell lines to determine the binding preferences. In other work, AuNPs bi-functionalised with thiolated glycans (glucose, galactose or mannos) and gadolinium chelates—as paramagnetic labels for MR—were used to target hepatocytes, murine glioma cells and lymphoma cell lines (Irure et al., 2013).

A reversal approach in the functionalisation of AuNPs has been used by immobilising lectin on QDs for the detection of glycan for in vitro and in vivo imaging of tumours, together with detection and theranostic applications (Ashree et al., 2020).

CONCLUSION

The range of applications of glyconanoparticles and the related carbohydrate-functionalised quantum dots is ever-expanding, with applications across detection for diagnosis of infectious diseases and cancer. For in vivo theranostic applications (i.e., combined diagnosis and therapy), efforts to produce more robust and less toxic nanomaterials is key to future in vivo applications. The field continues to progress at pace and impactful developments in the coming decade are anticipated.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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**Conflict of Interest:** Authors PH, SD, and RF were employed by the company Iceni Diagnostics Ltd. Iceni Diagnostics employs glyconanoparticles in diagnostic devices for virus detection.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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