

## REVIEW

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# Multivalent sialic acid materials for biomedical applications

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Sialic acid is a kind of monosaccharide expressed on the non-reducing end of glycoproteins or glycolipids. It acts as a signal molecule combining with its natural receptors such as selectins and siglecs (sialic acid-binding immunoglobulin-like lectins) in intercellular interactions like immunological surveillance and leukocyte infiltration. The last few decades have witnessed the exploration of the roles that sialic acid plays in different physiological and pathological processes and the use of sialic acid-modified materials as therapeutics for related diseases like immune dysregulation and virus infection. In this review, we will briefly introduce the biomedical function of sialic acids in organisms and the utilization of multivalent sialic acid materials for targeted drug delivery as well as therapeutic applications including anti-inflammation and anti-virus.

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## Introduction

Apart from nucleic acids, proteins, and lipids, almost half of the 'building blocks of life' are glycans – sugar chains composed of various monosaccharides.<sup>1</sup> Glycans cover the mem-

brane of every living cell and possess a staggering structural variety (the glycome), greatly exceeding the diversity of the genome and proteome. Carbohydrates or glycans are indispensable components of the cell surface. They play crucial biological and structural roles including establishing protective physical barriers against the outside environment, participating in cell-cell and cell-extracellular matrix interactions and modulating intracellular signaling.<sup>2</sup>

One family of monosaccharides that stands out from other glycan components are the sialic acids.<sup>3</sup> Since it was first defined by Landsteiner<sup>4</sup> and Walz<sup>5</sup> simultaneously, more than

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50 natural derivatives have been identified, mainly containing *N*-acetylneuraminic acid (Neu5Ac, also called sialic acid without specific demonstration), *N*-glycolylneuraminic acid (Neu5Gc) and deaminoneuraminic acid (KDN). This nine-carbon  $\alpha$ -keto aldonic acid monosaccharide family is usually found at the non-reducing end of cell-surface glycoproteins or glycosphingolipids.<sup>6</sup> The structural diversity of sialic acids and their derivatives and the ways of linking them with other monosaccharides determine the diversity of their roles in physiological and pathological processes.<sup>7</sup> Sialic acids often act as a signal molecule for self-recognition to protect the cell surface and glycoproteins from proteases,<sup>8</sup> regulate the serum half-life of glycoproteins and erythrocytes that are cleared in the liver upon desialylation,<sup>9–11</sup> and promote the formation of the blood vessel lumen.<sup>12</sup> In the immune system, sialoglycans such as sialyl Lewis x contribute to immune cell trafficking *via* binding to selectins on the endothelium,<sup>13</sup> and they also act as ligands of the immunomodulatory Siglec (Sialic acid-binding Immunoglobulin-like lectins) receptors that set the threshold for immune activation.<sup>14,15</sup> However, the Siglecs could also be utilized by pathogens as binding sites to enter into cells through sialoglycan–Siglec interactions.<sup>16,17</sup> Furthermore, aberrant sialoglycan expressed on tumor cells could help tumor cell immune evasion and metastasis.<sup>18,19</sup>

Tremendous efforts have been made to obtain insight into what is happening during these processes, and the multivalent interactions between sialoglycans and the protein receptors have been proven to be the culprit.<sup>20,21</sup> Studies in these fields have enabled scientists to develop materials containing multivalent sialic acids for modulating these physiological and pathological processes that could potentially be used as novel treatments for autoimmune disease, infectious disease and cancer. However, few reviews have been published in the past few decades that systematically introduce the roles of sialic

acid in physiological and pathological processes, and especially describe using sialic acid materials in treatments for relevant diseases. Hence, in this review, we aim to give a brief introduction of sialic acid and its physiological and pathological roles in immune regulation, tumor metastasis and infectious disease, and then focus on reporting some excellent pioneer studies on materials containing multivalent sialic acids for regulating these processes and diseases.

## The role of sialic acid and its receptors in biological processes

Sialic acids play important roles in many physiological processes including cell–cell interactions, immune surveillance and nerve development as well as pathological processes such as pathogen infection, autoimmunity and cancer.<sup>22</sup> Sialic acids exert their functions in biology through interaction with multiple sialic acid-binding receptors such as selectins, Siglecs, and proteins of pathogens like viruses. In this part, we will give a brief introduction of the complicated roles and functions of sialic acid *via* interaction with different receptors including selectins, siglecs and virus proteins.

### Siglecs and their roles in immune regulation

It was in 1998 when the name “siglecs”, short for “sialic-acid-binding immunoglobulin-like lectins”, was used to describe a subset of I-type lectins within the immunoglobulin gene superfamily that specifically bind sialylated glycans and have highly similar structural motifs within their N-terminal and C-2 set domains for the first time.<sup>23</sup> Since sialic acids are expressed by all mammalian cells, siglecs can help the immune system in distinguishing between self and non-self signals. Recognition of their sialylated ligands by the N-terminal variable (V)-Ig like domain triggers cell signalling through their regulatory motifs in their cytoplasmic domains. In this immunoglobulin-like lectin family, 15 members in humans and 9 members in mice have been found up to now. According to their structural similarity and evolutionary conservation, they are classified into two subsets. Conserved Siglecs include Siglec-1 (also known as sialoadhesin and CD169), Siglec-2 (also known as CD22), Siglec-4 (also known as myelin-associated glycoprotein, MAG) and the recently discovered Siglec-15 (which has a different structure from the other siglecs, with ~25–30% sequence identity). These four members and their orthologues exist in almost all mammalian species examined. Another group of siglecs containing Siglec-3, Siglec-5 to Siglec-12, Siglec-14 and Siglec-16 are named CD33-related Siglecs since they share ~50–99% identity.<sup>24</sup> However, this group of siglecs seem to be evolving rapidly by multiple processes, including gene duplication, exon shuffling, and exon loss, resulting in important diversity in the sequence structures and functions among mammalian species.

Although Siglec-4 expresses on oligodendrocytes and Schwann cells, and Siglec-6 expresses on placental trophoblasts, most of the siglecs are expressed on the surface of



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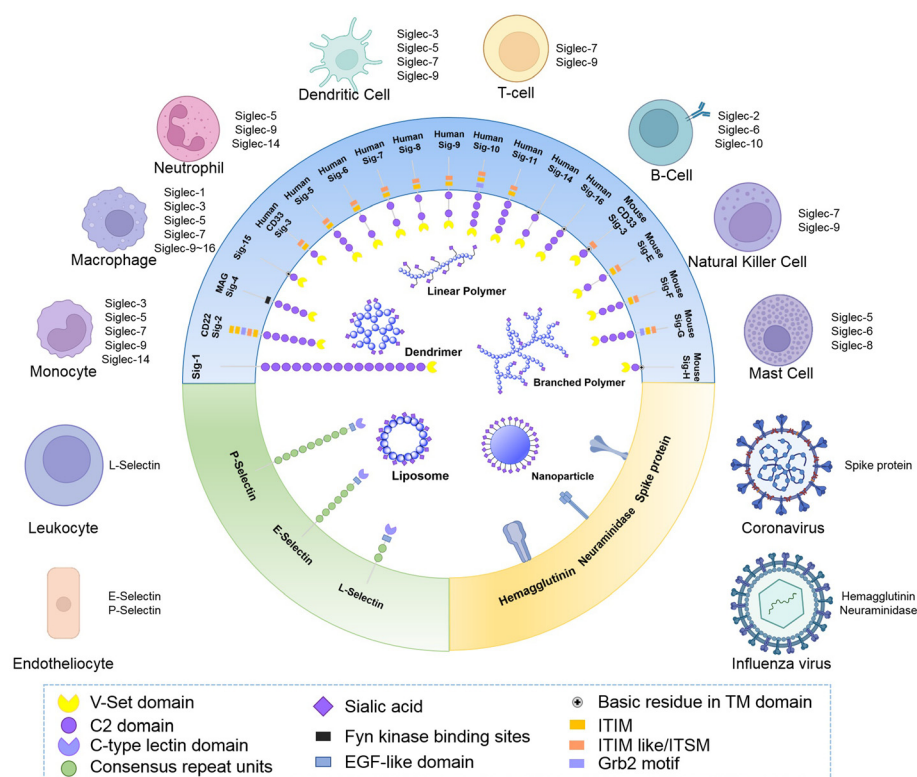
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immune cells and act as cell function regulators in the innate and adaptive immune systems through glycan recognition.<sup>25</sup> Some siglecs only express on specific species of immune cells. For instance, Siglec-1 is highly restrictedly expressed on subsets of resident tissue and inflammatory macrophages and activated monocytes.<sup>26</sup> Siglec-2 only expresses on immature B cells and its expression decays during B cell maturation and differentiation into plasma cells.<sup>27</sup> Siglec-8 expresses on eosinophils in a highly cell-type-restricted manner, and also expresses on basophils with relatively weak expression. Although there is no ortholog of Siglec-8 in mice, it was found that Siglec-F could act as a functional paralog due to its restricted expression on eosinophils.<sup>28</sup> Besides, Siglec-9 is primarily expressed on monocytes, neutrophils and dendritic cells; Siglec-15 is mainly expressed on osteoclasts and as a potential therapeutic target for osteoporosis.<sup>29</sup> Fig. 1 shows a schematic diagram of the structures and expression of different kinds of siglecs that have been detected.

Siglecs expressed on immune cells are immune regulatory molecules. Different siglecs have different preferences in terms

of the structure of sialylated glycans. With the development of molecular biology and analytical methods, more and more structures of sialic acid and its derivatives as ligands of siglecs have been identified. However, no matter how the DNA encoding of siglecs changes, there is one consensus that sialic acid is bound to a shallow pocket in the N-terminal immunoglobulin domain of the Siglec, mainly *via* a salt bridge formed by the negatively charged carboxyl group of sialic acid and a conserved essential arginine of the siglecs. Siglec-2 to 12 carry immunoreceptor tyrosine-based inhibitory motifs (ITIMs). The prototype ITIM contains a 6-amino acid sequence of (Ile/Val/Leu/Ser)-X-Tyr-X-X-(Leu/Val), where X denotes any amino acid. Ligand induced clustering of these inhibitory receptors results in tyrosine phosphorylation, often by an Src family kinase, which provides a docking site for the recruitment of cytoplasmic phosphatases having an Src homology 2(SH2) domain. Two classes of SH2-containing inhibitory signaling effector molecules have been identified: the tyrosine phosphatase SHP-1 and the inositol phosphatase SHIP (SH2-containing inositol polyphosphate 5-phosphatase).<sup>30</sup> These phosphatases



**Fig. 1** Receptors of sialic acid include siglecs, selectins and virus proteins. A variety of materials containing sialic acids have been developed to combine with these receptors to achieve the goal of immune modulation, targeted drug delivery and anti-virus treatments. The extracellular domain of siglecs often contains of a V-set domain for combining with sialic acid (except for Siglec-12 whose V-set domain mutated and lost this function) and several C2 domains. For most siglecs, these regulatory motifs are composed of immunoreceptor tyrosine-base inhibitory motifs (ITIMs), which serve to recruit phosphatases to phosphorylate downstream signaling molecules and inhibit cell activation. Some have other intracellular regulatory motifs like the immunoreceptor tyrosine switch motif (ITSM); growth factor receptor-bound 2 motif (Grb 2); Fyn kinase binding site. Some have positively charged amino acids in the transmembrane (TM) domain that associate with activating adaptors. The selectins often contain a sialic acid combining C-type lectin domain and EGF-like domain, which is an evolutionary conserved protein domain and derives its name from the epidermal growth factor. Several coronavirus adhere to host cells via the sialic acid binding sites on their spike proteins, and the hemagglutinin on the influenza virus has a similar role during the infection process. The schematic image was created with BioRender.com.

could phosphorylate the signal molecules generated by toll-like receptors (TLRs) and the B cell receptor and other receptors and block the activating cascades.<sup>31</sup> However, Siglec-12 lost its sialic acid-binding capacity and Siglec-13 and Siglec-17 have been inactivated during human evolution and so are not discussed in this review.<sup>15,32</sup> In contrast, Siglec-14, -15, and 16 have a positive charge in their transmembrane domains that mediates association with DAP12 to generate active immune responses. Siglec-1 has no tyrosine-based signalling motifs in its intracellular domain so it is thought to play a role in cell adhesion and endocytosis instead of cell signalling.

Normally, siglecs on an immune cell surface bind to a glycoprotein or glycolipid ending with sialic acid on the same cell in a “*cis*” fashion. This kind of interaction aims to establish immune tolerance and increase the activation threshold of immune cells. Some autoimmune diseases arise due to the disruption of “*cis*” binding. For example, when Siglec-8 on mast cells and eosinophils loses its binding to sialic acid, systemic inflammation and allergic reactions may happen.<sup>33</sup> Correspondingly, “*trans*” binding refers to siglecs binding to sialic acids on other cells and regulating immune response during the inflammation stage to prevent excessive activation of immune cells and sepsis.<sup>34</sup>

Since these siglecs on immune cells can downregulate the activity of immune cells, tumor cells have developed a strategy to escape from immune surveillance by upregulating the expression of sialic acid residues. It has been proven that these sialic acids over-expressed by tumor cells could bind specifically to Siglec-7 and Siglec-9 on natural killer (NK) cells to suppress their cytotoxicity,<sup>35</sup> and at the same time inhibit neutrophil activation.<sup>36</sup> The interaction between sialic acids expressed by tumor cells and Siglec-7 and Siglec-9 on monocytes contributes to the differentiation of monocytes into macrophages with an immune-suppressive phenotype.<sup>37</sup> Sialic acid containing CD24 on tumor cells interacts with siglec-10 on tumor-associated macrophages to help tumor cells to escape from immunological surveillance.<sup>38</sup> T cells expressing Siglec-9 and Siglec-15 could also be suppressed by interaction with sialic acids on tumor cells.<sup>39–41</sup> Focusing on the immune inhibitory function of sialic acids and siglecs offers potential for developing novel therapeutic means for cancer immunotherapy and anti-tumor drug delivery strategies. Ding and coworkers have been working on anti-tumor nanodrug delivery systems for many years<sup>42–44</sup> and have made pioneering progress targeting the overexpressed sialic acid on the surface of tumor cells for drug delivery.<sup>45</sup>

### Selectin, cell–cell interaction and cell adhesion

Selectins are another category of sialic acid binding proteins. Selectins are a family of calcium-dependent (C-type) lectins that play important roles in mediating immune cell adhesion to the endothelium and promoting entry to secondary lymphoid organs and sites of inflammation.<sup>46</sup> Early in 1978, Görög and his coworkers found that removing sialic acids on the cell surface resulted in activation of aggravated neutrophil

adhesion and inflammation.<sup>47</sup> However, at that time, when characterization methods were scarce, they knew little about the existence of the selectin protein, nor that the underlying mechanism of this phenomenon was the interaction between sialic acids and selectins leading to the adhesion of neutrophils.

There are three members in the selectin family, which are named after their expression patterns: P-selectin refers to those expressed on platelets, E-selectin represents those expressed on endothelial cells and L-selectin is used to name those expressed on leukocytes (Fig. 1). These three types of selectins also have different preferences in biological activities and ligands. P-selectin was originally found to be expressed by activated platelets. Monocytes and neutrophils also express P-selectin on their surface. The function of P-selectin is to mediate the rolling of granulocytes and monocytes on the surface of endothelial cells and the adhesion of granulocytes and monocytes to platelets.<sup>48</sup> L-selectin is fundamentally expressed on all circulating leukocytes and may shed the cell surface while circulating. E-selectin is mainly found on endothelial cells in postcapillary venules of the bone marrow and skin. It is also expressed on the endothelium in other organs, which is exposed to pro-inflammatory stimuli such as endogenous tumor necrosis factor (TNF), interleukin 1 $\beta$  (IL-1 $\beta$ ) and ectogenic lipopolysaccharide (LPS).

Among the best described ligands for the selectins are tetrasaccharides and their derivatives, which include fucose and sialic acids, such as sialyl Lewis x (sLe<sup>x</sup>, Neu5Ac $\alpha$ -2-3-Gal $\beta$ -1-4 (Fuc $\alpha$ -1-3) GlcNAc) and sialyl Lewis a (sLe<sup>a</sup>, Neu5Ac $\alpha$ -2-3-Gal $\beta$ -1-3(Fuc $\alpha$ -1-4) GlcNAc).<sup>49</sup> The conditions in which these glycans are expressed determine their affinity with different selectins. For example, the primary ligand for P-selectin is a sLe<sup>x</sup><sup>50,51</sup> decorated homodimeric mucin called P-selectin glycoprotein ligand 1 (PSGL1), however P-selectin could also bind with sulfatides, non-sialylated glycosphingolipids<sup>52</sup> and CD24<sup>53</sup> with high-affinity. L-selectin prefers to bind to glycoproteins, such as CD34, glycosylation-dependent cell adhesion molecule 1 (GlyCAM1), mucosal addressing cell adhesion molecule 1 (MAdCAM1) and PSGL1, which contain sulfated sLe<sup>x</sup> incorporated into N-linked and O-linked glycans.<sup>54,55</sup>

Under normal physiological conditions, selectins play critical roles in mediating leukocyte circulation through secondary lymphoid tissues and recruitment to inflammatory sites. In the earliest stage of leukocyte extravasation,<sup>56</sup> cells flowing through the vascular compartment are captured by selectin–ligand interactions and begin rolling on endothelial cells. At secondary lymphoid tissues, L-selectin expressed by leukocytes binds to glycoproteins displayed by endothelial cells in the high endothelial venule to promote extravasation. The recruitment of leukocytes to inflammatory sites also depends on the upregulated expression of E-selectin on endothelial cells there and P-selectin on platelets. The L-selectin expressed by the gathering immune cells themselves amplifies the recruitment and adhesion of more leukocytes. Therefore, upregulated expression of selectins or their ligands in specific sites directs leukocytes to particular locations: through the combinatorial

expression of particular selectins and their ligands, leukocyte subsets can be specifically recruited to different tissues and organs in the body.<sup>46</sup>

### Spike protein of coronavirus, hemagglutinin on the influenza virus and their roles in infection processes

As well as playing an important role in regulating immune interaction, in the field of infectious diseases, sialic acid may also play a role in helping viruses to enter into cells. In the field of virology, sialic acids were the first identified virus receptors that play an essential role in post-attachment events in the entry processes.<sup>57</sup> In the process of viruses infecting host cells, sialic acid on the cell surface plays the role of a double-edged sword. Since sialic acid is widely expressed on the cytomembrane, a variety of viruses specifically bind to host sialic acids as primary receptors for cell infection. Meanwhile, the host, normally vertebrates, has developed a trap *via* equipping mucus with abundant sialic acids to protect cells from being infected.<sup>58,59</sup> However, the viruses have evolved to be selective towards specific interactions with particular sialic acid forms and linkages on different hosts and tissues.

The preference of a ligand depends on the structure of the virus' protein receptors, whose expression depends on the species of virus. The influenza virus binds to the cell surface mainly *via* hemagglutinin (HA), and it is HA that determines the preference of differently structural ligands.<sup>60,61</sup> As for coronavirus, for example OC43, HKU1,<sup>62</sup> Middle East respiratory syndrome coronavirus (MERS-CoV)<sup>63</sup> and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),<sup>64</sup> the sialic acid binding sets are often contained in the receptor-binding domain (RBD) of the spike (S) protein domain A. Other viruses such as mumps virus, also binds  $\alpha$ -2,3-linked sialic acid as the leading factor of infection. For some viruses like Zika virus, however, recognition of sialic acid facilitates internalization instead of binding, however the mechanism is still unknown.<sup>65</sup> Due to the diversity of viruses and their viral capsid protein, details will be discussed in the following part together with anti-virus materials.

The use of sialic acid by viruses to infect host cells is not alone among pathogens. Many bacteria and protozoan also use sialic acid on the surface of host cells as the target of infection and camouflage themselves by ingesting the sialic acid to evade the immune surveillance of the host.<sup>66</sup> The ability of *V. cholerae* to take up sialic acids from the host promotes its intestinal colonization.<sup>67</sup> Other bacteria, for example, enterohemorrhagic *Escherichia coli*, *Haemophilus influenzae*, *Haemophilus ducreyi*, *Neisseria gonorrhoeae* and *Neisseria meningitidis*, coat their surfaces with sialic acid to protect their antigens from the host immune system.<sup>68</sup> Besides its roles in viral and bacterial infection, sialic acid also determines the infection of protozoan diseases. The etiological agent of malaria, Merozoites of *Plasmodium falciparum*, invades erythrocytes *via* both sialic acid independent and sialic acid dependent mechanisms<sup>69,70</sup> relying on the binding of *Plasmodium* proteins to glycophorins, the major sialylated proteins on the erythrocyte.<sup>71</sup> Other protozoan parasites, such

as *Toxoplasma gondii*, the pathogen leading to toxoplasmosis, also recognize and attach to sialic acid on the host cells during the process of invasion. In fact, the higher the abundance of sialic acid on the host cell surface, the easier it is to be infected by protozoan.<sup>72</sup> Recent proteomic analysis found sialic-acid-high-affinity binding proteins on *T. gondii* and named them SABP1 (sialic acid binding protein).<sup>72</sup> Parasites whose SABP1 have been knocked out showed lower adhesion and infection *in vitro* and lower virulence *in vivo*, indicating the reliance of parasites on SABP1-sialic acid interaction for survival and disease establishment.<sup>73</sup> An elegant review written by Jaskiewicz and coworkers enumerated these pathogens and their utilization of sialic acid as an infection target in detail,<sup>74</sup> which is worth reading if interested.

### The necessity of multivalent interaction in sialic acid-protein interactions

Normally, sialic acid residues bind to protein receptors mainly through weak interactions including electrostatic interaction *via* salt bridges and hydrogen bonds, which are so weak that they dissociate easily. Hence, a multivalent interaction is necessary whether binding siglecs or other proteins. This theory has been discussed by Whitesides and his coworkers in their review published in 1998.<sup>75</sup> They examined the theoretical framework for polyvalency, described a consistent nomenclature for polyvalent interactions, and discussed the central role of entropy in polyvalency in detail. The comprehension of the multivalent interactions guided their research on designing multivalent sialic acid decorated materials for antiviral applications.<sup>75</sup> Toone,<sup>76</sup> Stoddart,<sup>21</sup> Pieters,<sup>77</sup> Haag<sup>78</sup> *et al.* also concentrated on this field and gradually enriched this theory. Receptor clustering is activated when monovalent lectins are anchored and exposed to cell membranes in which receptors diffuse through the dynamic lipid bilayer to form a cluster that is tightened by the binding to the multivalent ligand. This mechanism is responsible for the clustering of the intracellular domains of transmembrane proteins triggering signal transduction events.<sup>79–82</sup>

As the mechanisms and effects of the interaction between sialic acid and its protein receptors are more and more clearly elucidated, organic chemists have made great efforts to use modified sialic acid and sialomimetics as artificial ligands for their respective protein receptors.<sup>83–85</sup> These monovalent derivatives can efficiently bind to siglecs as blocking or targeting ligands. However, without clustering, the function of siglecs in modulating immune activity could hardly be activated.

As discussed above, it is necessary to form multivalent clusters in order to ensure high affinity with protein receptors for biomedical application. A primary idea is to covalently bind sialic acid on polymer, dendrimer, micelle and nanoparticles to form multivalent sialic acid clusters. As Whitesides demonstrated in his review, there may be a balance between the valence and steric stabilization in interactions between multivalent sialic acid materials and protein receptors. More and more different kinds of sialic acid decorated materials for biomedical application are emerging under the unremitting

efforts of material scientists, biochemists and organic chemists. In the following part, we discuss some pioneer works and recent progress in this field.

## Multivalent sialic acid materials for biomedical application

### Multivalent sialic acids as targeting ligands for drug delivery

In the early period of identifying siglecs, scientists took them as markers of immune cells without defining the structure of siglecs and their functions in immune modulation. Therefore, multivalent sialic acid functionalized materials and monovalent chemically decorated sialylated glycans were synthesized for tracing immune cells *in vivo*, targeting cancerous leukocytes or immune cells in the tumor microenvironment for drug delivery. The research on siglecs mainly focused on Siglec-1, Siglec-2 and Siglec-4 since they are restrictedly expressed on specific immune cells.

Siglec-1, also known as sialoadhesin, is the only siglec without an intracellular function domain, meanwhile it has the longest extracellular C2 domain. The main duty of Siglec-1 is thought to be mediating cell-cell adhesion and endocytosis.<sup>86</sup> Hence, targeting Siglec-1 mainly enables tracing macrophages *in vivo* or blocking its sialic acid binding domain to inhibit cell-cell adhesion and endocytosis. High binding affinity could be achieved either by modifying sialic acid structures<sup>87</sup> or forming multivalent combinations.<sup>88</sup> As is well known, there is an inflammatory nature to the tumor microenvironment. Macrophages have been proven to be the crucial inflammatory cells within the tumor microenvironment.<sup>89</sup> These macrophages are called tumor-associated macrophages (TAMs), and are derived from monocytes in the blood and their polarized phenotype beyond M1 or M2. Although the polarized phenotype is different from normal macrophages, the expression of Siglec-1 on TAMs is abundant enough to be the target of drug delivery. Deng *et al.* made unremitting efforts to modify sialic acids with hydrophobic groups and thus cause them to assemble into liposomes carrying drugs to kill TAMs for tumor therapy.<sup>90–95</sup> Paulson and coworkers developed sialic acid decorated nanoparticles that target Siglec-1 to deliver antigens to macrophages for improving the innate immune response.<sup>96</sup>

Siglec-2 is highly restrictedly expressed on B cells. This siglec mainly participates in setting a threshold for antigen-induced activation of B cells.<sup>97</sup> This function is performed *via* activation of as many as six tyrosine-based motifs in the cytoplasmic domain of Siglec-2, including three immunoreceptor tyrosine-based inhibitory motifs (ITIMs). As well as regulating the activity of B cells, targeting Siglec-2 on B cells is a potential treatment method for B-cell lymphoma. Kiessling's group developed a series of polymers using a ruthenium initiator to initiate the ring-opening metathesis polymerization (ROMP) of norbornene carboxylic acid decorated with trisaccharide, Neu5Ac- $\alpha$ -2,6-Gal- $\beta$ -1,4-Glc, and used it as an inhibitor of B cell activation *via* multivalent binding to Siglec-2 in *trans*.<sup>98,99</sup>

Paulson, Finn and coworkers performed studies on targeting Siglec-2 on B cells as a diagnosis, tracing and treatment method for B-cell lymphoma. Their works utilized a sialic acid decorated Q $\beta$  capsid packaging fluorescent protein to trace B-cell lymphoma *in vivo*,<sup>100</sup> sialic acid bearing virus-like nanoparticles for photodynamic therapy<sup>101</sup> and liposomes as drug delivery cargo.<sup>102</sup> In another work they published in 2003, they employed Siglec-2 as a target to deliver antigen to B cells for stimulation of humoral immunity.<sup>103,104</sup> Zhang and coworkers developed biocompatible sialic acid-modified chitosan-PLGA hybrid nanoparticles as a drug carrier for the targeted treatment of Siglec-2-positive non-Hodgkin's lymphoma.<sup>105</sup> As knowledge on Siglec-2 has developed, scientists have discovered its trace existence on microglia. Wyss-coray and coworkers recently found that it could suppress phagocytosis that is upregulated on aged microglia – the decreased ability of microglia endocytose protein aggregates and cellular debris may be the leading cause of neurodegenerative disease. Aminoxy glycan-conjugated polymers with a poly(methyl vinyl ketone) backbone coupled to a dipalmitoylphosphatidylethanolamine lipid anchor were used to decorate the cell surface and confirmed this significant discovery.<sup>106</sup>

Siglec-4 is also a member of the immunoglobulin (Ig) super-family whose main function is inhibiting axonal growth. The expression of Siglec-4 on neuronal and microglial cells indicated that it mainly played a role in mediating the regulation and development of the nervous system.<sup>107</sup> In the central nervous system (CNS), Siglec-4 participates in the initiation of myelination, formation of myelin sheaths, and long-term maintenance of oligodendrocyte structure and myelin integrity. In the peripheral nervous system (PNS), Siglec-4 seems to be involved only in the formation of intact myelin and long-term maintenance of myelin structure but not in the initiation of myelination.<sup>108</sup> However, due to the complexity of the nervous system and the existence of the blood-brain barrier (BBB), it is not easy to target Siglec-4 to achieve the goal of targeted drug delivery, and few works have been reported on targeting Siglec-4 with multivalent sialic acids.<sup>109</sup>

Selectins are another category of sialic acid receptors expressed on the surface of mammal cells. So, targeting selectins that are upregulated at inflammatory sites and tumor sites using drug carriers decorated with sialic acid is a promising strategy for the treatment of inflammation and tumor. Yongzhong Du's group reported a series of works on sialic acid decorated materials targeting selectins for drug delivery. Their works are mainly focused on targeting E-Selectin at inflammation sites or in the tumor environment. The backbone of the materials they used ranged from modified natural polymers such as dextran to synthesized copolymers with complex three-dimensional structures. Sialic acid and hydrophobic group, such as octadecanoic acid (OA), decorated dextran (Dex) is one of the drug delivery platforms they successfully applied. They used these materials to deliver the curcumin polymeric prodrug for targeted therapy of acute kidney injury;<sup>110</sup> methotrexate for rheumatoid arthritis;<sup>111</sup> and doxorubicin for tumor treatment.<sup>112,113</sup> They proved that this platform has a signifi-

cant binding selectivity to E-selectin and could improve the accumulation of the drugs at the inflammation sites. In more recent works, they also developed other micelles for drug delivery<sup>112,114</sup> and combined sialic acid modified polymers such as PEG with inorganic nanoparticles to form particles with more complex three-dimensional structures.<sup>115–118</sup>

### Mediating inflammation by using multivalent sialic acid materials

Innate immune cells, such as monocytes, macrophages and neutrophils, dominate early inflammation.<sup>119,120</sup> Activated inflammatory cells not only phagocytose the pathogen and clear non-apoptotic cells, but also release plenty of acute mediators of inflammation,<sup>121</sup> such as the pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$  and IL-6 to recruit and activate more leukocytes, which affects tissue regeneration, response to infection or pain, and neuronal activity significantly,<sup>122</sup> and ceaselessly amplify this cascade. When the process of production of proinflammatory neutrophil extracellular traps (NETs) and release of pro-inflammation cytokines is too acute to be under control, these pro-inflammatory cytokines can cause diseases like systemic inflammatory response syndrome, atherosclerosis, rheumatoid arthritis, multiple sclerosis and septic shock.<sup>123</sup> Human Siglec-7 and Siglec-9 and their murine orthologs Siglec-E are key immunomodulatory receptors found predominantly on hematopoietic cells and regulate immune balance in inflammatory diseases.

Siglec-7 is an inhibitory receptor mainly expressed on natural killer (NK) cells and monocytes. NK cells are important in tumor immunological surveillance and killing tumor cells. Hiroshi Tanaka and coworkers developed an allene monomer decorated by an  $\alpha(2,8)$  disialic acid and initiated polymerization by a *p*-allyl nickel complex with an azido group to produce end-functionalized glycopolymers as a competitive ligand against natural ligand GD3, aiming to modulate the activation of NK cells.<sup>124</sup> Soon after, Chihiro Sato collaborated with them and designed a new Siglec-7 ligand based on Dextran. This DiSia-Dex showed high binding avidity toward Siglec-7, with a  $K_d$  value of  $5.87 \times 10^{-10}$  M, and a high inhibitory activity for the interaction between Siglec-7 and GD3, with an IC50 value of 1.0 nM.<sup>125</sup>

The epidemic of SARS-CoV-2 caused a serious threat to global health. The main factors leading to the death of COVID-19 patients are the overreaction of the systemic immune system caused by coronavirus infection and acute respiratory distress syndrome caused by a large number of immune cells infiltrating into the lungs. Therefore, the regulation of immune cells became of great concern to scientists and clinicians. Although the glucocorticoid drugs and antibody drugs also have a certain effect, the long-term use of glucocorticoid hormone drugs can cause serious sequelae, and the antibody drugs could only neutralize the already produced inflammatory cytokines. Therefore, there is still a pressing need for developing more effective and safe drugs that can control the over activation of immune cells.

Considering that macrophages and neutrophils act as the leading cause of inflammation cascade, Siglec-9 on their plasmalemma has become an ideal regulator of over-activated immune cells. Bertozzi and her group have been working in this field for years. By ring-opening polymerization of glycosylated NCA monomers, they synthesized a series of materials based on polyaminoacids to target Siglec-9 on the surface of macrophages and neutrophils to inhibit the expression of macrophage pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  and the release of NETs. They employed a hydrophobic tail at the end of the polymer and realized *cis* binding between Siglec-9 and the materials using a novel method. The result showed that compared with soluble polymers, the hydrophobic tail could anchor in the cell membrane and promote the interaction between Siglec-9 and sialic acid on the materials in a *cis* pattern, and the glycosylated peptides anchored on the cell surface form mimic glycoproteins and exhibit excellent inhibiting effects on the expression of pro-inflammation cytokines and the release of NETs.<sup>126,127</sup> Bertozzi also did lots of outstanding research on biological orthogonal reaction to modify saccharide on the cell surface on-site with the aim of regulating immune activation and just won the Nobel Prize in 2022.<sup>128</sup>

Many studies have also been reported by other groups to modulate systemic inflammation overresponses through siglecs. Scott and coworkers decorated  $\alpha(2,8)$ -linked sialic acid on PLGA nanoparticles, and proved their therapeutic effect in a variety of systemic inflammation on mouse models *via* interaction with Siglec-E on macrophages.<sup>129</sup> Paulson and his coworkers developed an antibody connected siglec ligand that targeted immune cells *via* anti-IgD/E antibody and inhibited unwanted immune cell activation.<sup>130</sup> This work defined a new idea of antibody–drug conjugates. Ohmae coated poly(sarcosine)-block-poly(L-lactic acid) (lactosome) with sialic acid monosaccharides and oligosaccharides to prevent accelerated blood clearance (ABC) *via* interaction with Siglec-E. They proved in this study that sialic acid interacting with Siglec-E could not only inhibit the expression of pro-inflammation cytokines but also suppress phagocytosis of the opsonized nanocarriers.<sup>131</sup>

### Multivalent sialic acid materials against viruses

The Spanish flu pandemic of 1918 killed 50 million people, even more than those killed in World War I, and flu still kills hundreds of thousands of people around the world every year. So, humans have been struggling with pandemics caused by the viruses since then. After realizing that multivalent interactions in adhesion are the very first step in the infection process of pathogens like virus,<sup>132,133</sup> bacteria,<sup>80,134</sup> or fungi<sup>135,136</sup> to host cells, multivalent sialic acid inhibitors have been seen as a promising tool and focus of research. Since the SARS-CoV-2 pandemic began, investigation of multivalent sialic acid inhibitors as antiviral drugs has been brought back in trend. In this part, we will review a few works of interest mainly on the application of multivalent sialic acid materials as anti-viral agents.

Current anti-virus therapies usually require high doses of small molecule drugs that have potential side effects and can lead to drug resistance in patients. Multivalent sialic acid materials as inhibitors do not kill pathogens but can block them from binding to cells, which can reduce the chances of developing drug-resistant strains.<sup>116</sup> The efficiency of the virus binding materials highly depends on the valence, steric structure and size of materials. An elegant review written by Haag and his coworkers systemically demonstrated the relationship between inhibition efficacy of materials and these factors.<sup>137</sup>

Metallic nanoparticles absorb and scatter with great efficiency when interacting with light. The chemical properties of gold and silver indicated that different ligands can be linked to metal particles easily *via* reaction between these noble metals and sulfhydryl. Thus, a few works have reported that multivalent sialic acid decorated metal nanoparticles could be used to detect virus. Niikura and coworkers linked monovalent sialic acid trisaccharides *via* a sulfate sulfhydryl functional amphiphilic linker. They proved that due to the regular steric structure of the virus capsids, their nanoparticles could arrange on mock virions neatly and cause a large red shift ( $\sim 200$  nm) of the plasmon band, which could be used to detect virus.<sup>138</sup> Russell and coworkers developed a novel system that specifically binds and detects human virus with a rapid reaction period of 30 min by decorating trivalent  $\alpha$ -2,6-linked sialic acid on gold nanoparticles.<sup>139</sup> Although these kinds of materials have been widely used in virus detection using other precise instruments,<sup>140–142</sup> facing a virus like SARS-CoV-2 causing a pandemic, the simpler the test, the more efficient it is. Several scientists have reported a simple, visual and rapid detection of SARS-CoV-2.<sup>143–145</sup>

As a killer that has threatened human beings several times, the influenza virus has been investigated widely during the past century. Since the structure of the sialic acid binding protein HA and the mechanism of binding have been clearly characterized,<sup>146</sup> plenty of multivalent sialic acid materials have been developed as inhibitors of influenza virus infection.<sup>147</sup> Early in the 1990s, Whitesides and Roy led the trend of application of multivalent sialic acid materials as antiviral agents. While Roy focused on diverse dendritic structures,<sup>148–150</sup> Whitesides was more interested in studying the mechanism and kinetics of multivalent interactions between this kind of material and the natural receptors.<sup>75,151–154</sup> Based on these early findings, numerous research studies have been conducted in this field in the past few decades. Nishimura *et al.* ameliorated methods by employing trivalent  $\alpha$ -2,3-sialyl trisaccharide and  $\alpha$ -2,6-sialyl trisaccharide with poly(acrylic acid) (PAA) instead of monovalent sialic acid, and their materials exhibited much higher biological activities than the effects achieved by glycopolymers derived from the simple monovalent-type glycomonomers.<sup>155</sup> They also employed cyclic glycopeptides as the backbone and linked three oligosaccharides containing sialic acid to the trimeric structure of HA.<sup>156</sup> In another work, they replaced the oxygen of the glycoside bond of sialoside with sulfur to prevent hydrolytic digestion of the *N*-acetylneuraminic acid

residue by viral neuraminidase and linked several sialic acids to gold and silver nanoparticles.<sup>157</sup> Different from Whitesides's study preferring polyacrylamides as the backbone, Haag employed flexible and biocompatible polyglycerols as their novel backbone of multivalent sialic acid materials. Both linear and dendritic polyglycerols were employed to estimate the influence of several factors such as size, flexibility, steric structure and valence on the efficacy of inhibition. They precisely controlled the diameter of dendritic polyglycerol sialoside particles and found that the inhibitory activity of the tested polymeric nanoparticles drastically increased with size and particles with similar dimensions to the virus (50–100 nm) are exceedingly effective. They also observed a saturation point in degree of surface functionalization (*i.e.* ligand density), above which inhibition was not significantly improved.<sup>158</sup> They proved that compared with rigid nanoparticles like gold nanoparticles, adaptive flexible sialylated nanogels based on polyglycerol achieved improved IAV inhibition by 400 times.<sup>159,160</sup> The more flexible linear polyglycerol sialosides (PGSAs) exhibited higher inhibition potential than the dendritic polyglycerol sialosides to prevent virus attachment to the host cells.<sup>161</sup> More recently, Haag cooperated with Kai Ludwig and Mohsen Adeli to decorate multivalent sialic acids on a flexible 2D graphene platform to achieve the trapping, blocking, and deactivation of respiratory viruses.<sup>162</sup> Electron microscopy techniques such as cryo-TEM and single-molecule force spectroscopy were used to characterize their materials in a more direct way and promoted their investigation further and in a more quantitative manner.<sup>162,163</sup>

Since sialic acid is naturally expressed as the terminal unit of glycoproteins and glycolipids, sialoglycopolymer and sialic acid decorated lipid micelles were employed as natural ligand mimics to inhibit virus infection.<sup>164–173</sup> Natural polysaccharides like chitosan could also be employed as a backbone due to their low immunogenicity, biocompatibility and degradability.<sup>174,175</sup> As another biomacromolecule, nucleic acids could also be used as flexible backbones of sialic acid decorated materials.<sup>176</sup> Since Haag and coworkers observed that nanoparticles with a size similar to influenza virus possess a higher inhibition efficacy, Hackenberger and coworkers decorated sialic acids on phage capsid to obtain a defined ligand arrangement block inhibitor for influenza virus entry.<sup>177</sup> The high efficacy of inhibition also benefits from the host cell HA ligands on bacteriophage capsids. These host cell HA ligands are in an arrangement matching the geometry of binding sites of the spike protein, and can bind to viruses in a defined multivalent mode. Sialyllactose-conjugated filamentous bacteriophages were also used as antiviral agents *via* blocking HA with sialic acids decorated on them.<sup>178</sup>

Besides these works utilizing natural multivalent sialic acids to inhibit virus infection,<sup>179</sup> more and more synthetic materials with novel structures have been used as backbones with the development of organic chemistry, materials chemistry and polymer science. A variety of molecules,<sup>180</sup> dendrimers,<sup>181–183</sup> polymers<sup>184–186</sup> and nanoparticles<sup>123,187–189</sup> have been developed as sialic acid carriers. Calixarene and

**Table 1** Materials and their reported applications

Target	Materials	Targeted protein subset	Function	Ref.
Siglecs	Benzene	Siglec-1	Not mentioned	88
	Sialic acid-octadecylamine conjugate liposome	Siglec-1	Antitumor drug delivery	90–95
	Sialic acid-modified polynorbornene	Siglec-2	Inhibiting activation of B cells	98 and 99
	Q $\beta$ capsid	Siglec-2	Tracing B-cell lymphoma	100
	Q $\beta$ virus-like particles	Siglec-2	Photodynamic therapy	101
	Sialic conjugate liposome	Siglec-2	Antitumor drug delivery	102
	Sialic conjugate liposome	Siglec-2	Inhibiting activation of B cells	103 and 104
	Sialic acid-modified chitosan-PLGA hybrid nanoparticles	Siglec-2	Antitumor drug delivery	106
	Polymers with a poly(methyl vinyl ketone) backbone coupled to a dipalmitoylphosphatidylethanolamine lipid anchor	Siglec-2	Inhibiting microglia phagocytosis	108
	Sialic acid modified chitosan-poly(lactic-co-glycolic acid) (PLGA) nanoparticles	Siglec-4	Drug delivery to the central nervous system	119
	Poly(allene monomer containing an a(2,8) disialic acid)	Siglec-7	Modulating the activation of NK cells	125
	Sialic conjugate liposome	Siglec-7	Antigen delivery to DCs	126
	Sialic acid decorated polyamino acids	Siglec-9	Suppressing the activation of immune cells	127
	$\alpha$ -2,8-Linked sialic acid decorated PLGA nanoparticles	Siglec-E	Suppressing the activation of immune cells	129
Siglecs	Poly(sarcosine)- <i>block</i> -poly(L-lactic acid) (Lactosome) with sialic acid monosaccharides	Siglec-E	Suppressing phagocytosis of the opsonized nanocarriers	130
	Sialic acid decorated dextran	E-Selectin	Drug delivery	109–111
	Sialic acid-dextran-octadecanoic acid (SDO) micelles	E-Selectin	Drug delivery	112
	Sialic acid-functionalized PEG-PLGA microspheres	E-Selectin	Drug delivery	113
	Sialic acid (SA)-modified chitosan oligosaccharide-based biphasic calcium phosphate	E-Selectin	Drug delivery	114
	Sialic acid poly(ethylene glycol)-poly(acrylamide-co-acrylonitrile)	E-Selectin	Drug delivery	115
	Sialic acid modified and Fe <sup>3+</sup> chelated	E-Selectin	Drug delivery	116
	Superparamagnetic iron oxide-loaded MPDA NPs	E-Selectin	Drug delivery	117
	Sialic acid-PEG-modified mesoporous polydopamine nanoparticles	E-Selectin	Drug delivery	117
	Sialic acid decorated gold nanoparticles	Virus proteins	Detecting virus	137–140
	Sialic acid decorated gold nanoparticles	Influenza Hemagglutinins	Investigate binding affinity	141
	Sialic acid decorated gold nanoparticles	SARS-CoV-2 spike protein	Detecting virus	142–145
	Dendritic sialoside	Influenza virus haemagglutinin	Antivirus therapy	147, 149 and 181
	Sialic acid decorated poly(acrylic acid)	Influenza virus haemagglutinin	Antivirus therapy	151
	Sialic acid decorated polyacrylamide	Influenza virus haemagglutinin	Antivirus therapy	152–154 and 184
Virus proteins	Sialic acid decorated cyclic glycopeptides	Influenza virus haemagglutinin	Antivirus therapy	155
	Thiosialosides conjugated metal nanoparticles	Influenza virus haemagglutinin	Antivirus therapy	156
	Sialic acid-conjugated polyglycerol-based nanoparticles	Influenza virus haemagglutinin	Antivirus therapy	157
	Sialic acid-functionalized gold nanoparticles	Influenza virus haemagglutinin	Antivirus therapy	158
	Sialic acid-conjugated polyglycerol-based nanogels	Influenza virus haemagglutinin	Antivirus therapy	159
	Linear and dendritic polyglycerol sialosides	Influenza virus haemagglutinin	Antivirus therapy	160
	Sialic acid-functionalized graphene	Influenza virus haemagglutinin	Antivirus therapy	161
	Sialoglycopolypeptide	Influenza virus haemagglutinin	Antivirus therapy	163 and 164
	Ganglioside ligand	Influenza virus haemagglutinin	Antivirus therapy	165
	Sialic acid bearing liposomes	Influenza virus haemagglutinin	Antivirus therapy	166–168
	Multivalent sialoside protein conjugates	Influenza hemagglutinin and neuraminidase	Antivirus therapy	167 and 169–172
	Sialyloligosaccharide decorated chitosan	Influenza virus haemagglutinin	Antivirus therapy	173 and 174
	Sialic acid decorated nucleic acids	Influenza virus haemagglutinin	Antivirus therapy	175
	Sialic acids decorated phage capsid	Influenza virus haemagglutinin	Antivirus therapy	176
	Sialyllactose-conjugated filamentous bacteriophages	Influenza virus haemagglutinin	Antivirus therapy	177
Virus proteins	Trivalent glycopeptide mimetic and analogues	Influenza virus haemagglutinin	Antivirus therapy	179
	Multivalent sialic acid molecules	Influenza virus haemagglutinin	Antivirus therapy	180

Table 1 (Contd.)

Target	Materials	Targeted protein subset	Function	Ref.
Virus proteins	Multivalent sialyl oligosaccharides decorated brush polymers	Influenza virus haemagglutinin	Antivirus therapy	184
	Sialic acid decorated poly(3,4-ethylenedioxythiophene (EDOT))	Influenza virus haemagglutinin	Antivirus therapy	185
	Sialic acid modified poly(L-lactic acid)- <i>b</i> -poly(ethylene glycol) (PLLA- <i>b</i> -PEG)	Influenza virus haemagglutinin	Antivirus therapy	187
	Sialic acid decorated poly(ethylene oxide)-polycaprolactone polymersomes	Influenza virus haemagglutinin	Antivirus therapy	188
	Sialic acid conjugated highly-branched $\alpha$ -glucuronic acid-linked cyclic dextrans	Influenza virus haemagglutinin	Antivirus therapy	189
	Sulfated colominic acid	HIV	Antivirus therapy	197
	Sialic acid conjugated glycopeptide	HIV	Antivirus therapy	198
	Sialic acid-PAMAM glycodendrimers	HIV	Antivirus therapy	199
	Hexavalent sialic acid sulfoglycodendrimers	HIV	Antivirus therapy	200
	Divalent sialylated glycooligomers conjugated to resins	Polyomaviruses protein 1	Antivirus therapy	202
	Triazole linker-based trivalent sialic acid	Adenovirus type 37	Antivirus therapy	203
	Multimeric sialic acid glycoclusters	SARS-CoV-2 spike protein	Antivirus therapy	204
	Mucins	Human coronavirus OC43 spike protein	Antivirus therapy	205

dendrimers have the advantage of a defined molecular structure and thus have a strong future in clinical medical application.

There are many other viruses as well as influenza virus that use sialic acids on the surface of host cells as a binding site during the infection process.<sup>62–65,190–193</sup> Acquired immunodeficiency syndrome (AIDS) caused by infection of human immunodeficiency virus (HIV) is still an incurable disease at present. It has been reported that CD4 is a major receptor for HIV-1<sup>194,195</sup> and CD26 acts as a co-factor for entry of HIV-1 into CD4-positive cells.<sup>196</sup> An  $\alpha$ -2,8 ketosidic linked polysialic acid called colominic acid and its derivate obtained by modifying a sulfonic group at C9 showed significant inhibiting effects on HIV.<sup>197</sup> Many other works have also been published,<sup>198</sup> among which McReynolds and coworkers continually reported different anti-HIV materials based on dendrimers.<sup>199,200</sup> Polyomaviruses are small, non-enveloped DNA viruses that cause persistent asymptomatic infections in various species, and can, upon activation to productive infection, lead to serious diseases in immunocompromised individuals.<sup>201</sup> Divalent sialylated precision glycooligomers synthesized by Hartmann and coworkers *via* solid phase synthesis exhibit inhibiting effects on polyomaviruses.<sup>202</sup> Some types of adenovirus and coronavirus could also be inhibited by synthesized sialic acid materials such as different multivalent dendrimers and sialic acid linked polypeptides (Table 1).<sup>203–205</sup>

## Conclusions and perspective

Sialic acids and polysialic acids play complex roles in different processes and stages of living activities, which also determines the variety of applications of multivalent sialic acid materials in biomedicine. In this review, we summarized the role of sialic acid and the use of multivalent sialic acid materials for biomedical applications. Since the function of sialic acid in

life activities has been defined more and more clearly, the development of multivalent sialic acid materials for biomedical applications has bloomed. Based on the utilization of sialic acid combined with its receptors such as siglecs, selectins and virus proteins, various materials have been synthesized for the treatment of inflammation, tumor, virus and infectious disease. Multiple parameters such as the valence of sialic acid, the size and hardness of the material, and steric hindrance between multiple ligands collaboratively determine the affinity of the materials to the protein receptors, which, in other words, determines the efficiency of the materials.

The design of multivalent sialic acid materials based on polymers and other materials is expected to adapt to the natural characteristics of multivalent recognition in natural processes and generate unique new macromolecular therapeutic drug forms.<sup>206</sup> At present, many pioneering biomedical studies on multivalent sialic acid modified materials have verified their efficacy and safety in cells or animal models, but this field is still yet to be fully developed. In the future, there will be some key issues that need to be solved for this kind of therapeutic material: First, it is known that the biological effects of the majority of sialic acids are immune-suppressive, however, in light of the wide expression of sialic acid receptors across the body, how to realize specific binding is a difficult task. There has been many studies focusing on the structural modification of sialic acid to achieve specific binding, but the macromolecular architectural design of multivalent sialic acid materials may constitute another dimension for optimizing the specificity. Second, a charming point of the sialic acid-siglec interaction lies in the fact that siglecs are mostly expressed on the immune cells, and this provides a clear target for utilizing multivalent sialic acid materials for immune modulation. Since immune-related diseases constitute a large part of human diseases and generally lack effective therapeutic means, study on multivalent sialic acid materials may provide new treatment opportunities for these immune-related dis-

eases. Third, the concept of multivalent/polyvalent materials as therapeutic agents has not been recognized by the pharmaceutical industry, and the corresponding standardized research and evaluation methods still need to be studied and established. These factors may constitute a key hurdle to finally putting a therapeutic material into the clinic. However, considering the unique characteristics of multivalent interactions in biological processes, especially the sugar system, we believe that multivalent sialic acid materials can become a very meaningful class of therapeutic materials and play a more and more important role in biomedical and biointerface regulation within body systems.

## Conflicts of interest

There are no conflicts to declare.

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