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The case for re-examining glycosylation inhibitors, mimetics, primers and glycosylation decoys as antivirals and anti-inflammatories in COVID19

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Introduction

The SARS COV2 and other SARS viruses employ a heavily glycosylated spike S protein (Watanabe et al. 2020; Shajahan et al. 2020a) to bind to the ACE2 cellular receptor, also heavily glycosylated (Shajahan et al. 2020b), on host cells. Historically, there is abundant information of glycosylation inhibitors for antiviral activity to stimulate their investigation for COVID19 treatment. While there are certain to be side effects by interfering systematically with glycosylation, a short-term dose of primers, decoys or glycosylation inhibitors might be sufficient to stop or slow the COVID19 infection cycle with minimal or temporary side effects. For example, castanospermine derivative celgosivir (6-O-butanoylcastanospermine) (Sels et al. 1999) and Miglitol, Miglustat (N-butyl −1-deoxynojirimycin) (Campo et al. 2013; Zamoner et al. 2019) are already FDA approved for type 2 diabetes and Gaucher's disease (Rosenbloom and Weinreb 2013), passing safety and effectivity phases. This article is to stimulate repurpose testing of these already-approved compounds and others for COVID19 therapeutics.

Previously reported efficacy of antiviral activities

Copious literature suggests that glycosylation inhibitors are potent antivirals for enveloped viruses with a coat or spike protein. In the 1970s and 1980s, a number of investigators examined interference with glycan synthesis on viral coat proteins as a mode for viral inhibition. Compans showed in 1971, *D*-glucosamine and 2-deoxy-*D*-glucose inhibited glycoprotein maturation in Sindbis virus (Compans 1971). Several other studies used these two compounds for inhibition of Semliki Forest virus (Kaluza et al. 1972), enveloped RNA viruses (Kaluza et al. 1973), Influenza (Klenk et al. 1972), VSV, Newcastle disease (Scholtissek et al. 1974) and enveloped viruses in general (Scholtissek et al. 1975). In 1973, Okayama et al. showed

that ß-xylosides could stimulate free GAG chains and inhibit GAG formation on proteoglycan core proteins (Okayama et al. 1973). Later, a number of researchers showed that GAGs were important as cellular receptors in HSV and HCV and that ß-xylosides could inhibit viral infectivity by sidetracking GAG synthesis to soluble saccharides (see below).

Schwartz reported, in 1974, tunicamycin inhibition of glycosylation of influenza virus hemagglutinin (Schwartz et al. 1974) and in 1976 showed that tunicamycin, which inhibits the formation of N-acetylglucosamine-lipid intermediates in N-linked glycan synthesis (Lennarz 1975), suppressed glycoprotein synthesis in Semliki Forest, influenza and avian sarcoma virus (Schwarz et al. 1976). Kornfeld *et al.* (1977) examined the effect of tunicamycin (Leavitt et al. 1977a) on growth of Sindbis and VSV in BHK cells and found at 500 ng/ml, 99.9% inhibition of replication without detection of non-infectious particles (Leavitt et al. 1977b). Viral proteins were synthesized, but glycoproteins were under-glycosylated (Leavitt et al. 1977b) and temperature sensitive (Gibson et al. 1979). Their conclusion was that in enveloped viruses, glycosylation was essential for normal viral particle assembly. Morrison et al. (1978) found that tunicamycin had no effect on glycoprotein attachment to intracellular membranes or protein transport to the endoplasmic reticulum lumen, but instead prevented glycoprotein migration from the rough to smooth. Kornfeld et al. (1979) found that VSV non-glycosylated glycoprotein underwent intracellular aggregation upon tunicamycin treatment (Gibson et al. 1979), an indication of improper folding or exposure of hydrophobic peptide due to pauciglycosylation. Diggelman (1979) showed biosynthesis of an unglycosylated envelope glycoprotein of Rous sarcoma virus in the presence of tunicamycin. Pizer et al. (1980) showed that tunicamycin inhibited production of infectious herpes simplex virus-1 (HSV1). Blocking addition of carbohydrate to glycoprotein precursors with tunicamycin resulted in disappearance

of proteins, postulated due to degradation of unglycosylated polypeptides. They concluded that the glycans either stabilize the envelope proteins or provide proper structure for processing of the proteins necessary for infectivity. Stallcup and Fields (1981) inhibited measles virus with tunicamycin (24).

Holmes et al. (1981) showed that a **corona virus**, mouse hepatitis virus, MHV, had a glycoprotein E1 glycosylated normally in the presence of tunicamycin. This indicated that E1 bore O-linked instead of N-linked glycans. The "peplomeric glycoprotein E2 was not detectable upon tunicamycin treatment," indicating its synthesis was interdicted or its degradation was facilitated by lack of N-linked glycosylation and was improperly processed (Holmes et al. 1981). E2 may be analogous to the S-spike glycoprotein. Viral particles were produced with tunicamycin treatment but were noninfective, lacking E2, which was required for attachment to viral receptors on cells, probably analogous ACE2 by today's knowledge. At that time, no drug was known to inhibit O-glycosylation, such as α-benzyl-GalNAc, in use today. Because of these observations, either N-linked or O-linked glycosylation interference may potentially interdict SARS-Cov2 infectivity.

Tunicamycin was employed in antiviral tests and was very effective, but it was considered too toxic by most investigators to be developed as a drug at the concentrations used. However, Banerjee et al. (2011), in cancer treatment, found a safe concentration of a purified tunicamycin and dosage in mice (250 µg/kg oral twice a week for 4 weeks) that inhibited MDA-MB0231 triple negative breast-cancer tumor formation in live mice, without overt toxicity and involved the unfolded protein response. Nanoformulations were effective (Banerjee et al. 2013). Recent articles define the detailed basis for tunicamycin's activity (Hakulinen et al. 2017; Yoo et al. 2018). Tunicamycins should be tested now for infectivity assays with SARS COV2 alone or in combinations with other inhibitors.

Elbein et al. (1982) showed swainsonine, an α-mannosidase inhibitor, to inhibit processing of oligosaccharides on influenza viral hemagglutinin, and in 1983 showed its effect on vesicular stomatitis virus (Kang and Elbein 1983). In 1983, he showed castanospermine, an α-glucosidase inhibitor, inhibited influenza hemagglutinin expression (Pan et al. 1983). Both inhibited N-glycan processing. Tyms et al. (1987) showed castanospermine and other plant alkaloid glucosidase inhibitors to block HIV growth. Sunkara et al. (1987) tested castanospermine and 1-deoxynojirimycin (Duvoglustat) showing anti-retroviral activity. Dwek *et al.* (1998) later suggested α-glucosidase inhibitors as general antiviral agents (Mehta et al. 1998). Chapel et al. (2006) showed antiviral effects of α-glucosidase inhibitors on hepatitis C virus. Chang et al. (2013a) reported that iminosugar α-glucosidase inhibitors related to 1-deoxynojirimycin (that interfered with N-linked glycan maturation in the calnexin-mediated folding pathway) were also effective as antivirals for *Arenaviridae, Bunyaviridae, Filoviridae and Flaviviridae* including hemorrhagic fever Marburg and Ebola in mice. 1-Deoxynojirimycin (Duvoglustat) suppresses postprandial blood glucose and is used for treatment of diabetics in doses of 20-110 mg/kg (Gao et al. 2016, Tong et al. 2018). Qu et al. (2011), inhibitors of endoplasmic reticulum α-glucosidases potently suppress hepatitis C virus virion assembly and release. Howe et al. (2013) applied similar compounds to HCV and BVDV. Castanospermine and its O- and N-butyl derivatives were tested in many viral systems with positive results and FDA approval for type 2 diabetes and Gaucher's treatments as described below. Off-label, repurposing treatments for COVID19 should be considered.

Celgosivir (6-O-butanoyl castanospermine), an approved α-glucosidase inhibitor drug for type 2 diabetes and Gaucher's disease, inhibits all four Dengue, DENV serotypes (Sayce et al. 2010; Rathore et al. 2011). "Fluorescence microscopy showed that the antiviral mechanism of Celgosivir, is in part, due to misfolding and accumulation of DENV non-structural protein 1 (NS1) in the endoplasmic reticulum" (Lachmann 2003). Moreover, Celgosivir modulates the host's unfolded protein response (UPR) for its antiviral action. Significantly, Celgosivir is effective in lethal challenge mouse models that recapitulate primary or secondary antibody-dependent enhanced DENV infection. Celgosivir-treated mice showed enhanced survival, reduced viremia and robust immune response, as reflected by serum cytokine analysis. Importantly, survival increased even after treatment was delayed till 2 days post-infection." (Rathore et al. 2011). Together, this suggests that Celgosivir, which has been clinically determined to be safe in humans, may be a valuable candidate for clinical testing in COVID19 patients. (Ibid).

Safety

Celgosivir has passed safety studies in humans (Sels et al. 1999; Rathore et al. 2011). N-butyl-deoxynojirimycin (Miglustat) has been approved for clinical use since 2002 for Gaucher's disease (Cox et al. 2000; Lachmann 2003), after tests in 2000 to show its activity was to decrease substrate biosynthesis. This safety data suggests that both should be investigated repurposed off-label for COVID19 infectivity, since safety, PK and dosage has already been established. Also, long-term, 24-month studies of Miglustat have established safety and efficacy (Pastores et al. 2005), where COVID19 treatment may require very brief application. Chang et al. (2013b) and Pérez-García et al. (2017) reviewed and recommended the use of ER glycosylation inhibitors as potential targets for viral therapeutics. Main side effects were GI, manageable by diet and anti-propulsives. Duvoglustat, (1-deoxymannojirimycin) (Fuhrmann et al. 1984) amphomycin and related compounds should also be tested. Considering the seriousness of this pandemic, researchers with access to these and other glycosylation inhibitors should collaborate with virology labs that can test the infectivity cycle of SARS COV2.

Following Okayama's earlier work (1973), Schwartz et al. (1974) showed stimulation of synthesis of free chondroitin sulfate chains by ß-D-xylosides in cultured cells. Esko and Montgomery (1995), following Okayama's and Schwartz's earlier work, described xyloside "primers" of glycans that could be employed in tissue culture to prevent sugars from attaching to proteins, proteoglycans and glycolipids. They found ß-_D_-xylosides initiate glycosaminoglycan (GAG) synthesis by substituting for endogenous xylosylated core proteins. Xylosides will also prime oligosaccharides that resemble glycolipids. N-acetyl-α-_D_-galactosaminides initiate O-linked oligosaccharide synthesis found on mucins and other glycoproteins and can be used to disrupt O-glycosylation. Disaccharides, (e.g. peracetylated N-acetyllactosaminide), can act as primers. Competing with endogenous substrates, they interdict proteoglycan and glycoprotein glycosylation. Esko used acetylated xylose derivatives where PNP-Xyl treatment decreased heparan sulfate expression on the cell surface of Syndecan 4 cells and abrogated the HCV transmission in a concentration-dependent manner (Shieh et al. 1992; Fritz et al. 1994; Fritz and Esko 2001). Xylosides and thioxylosides should be tested in SARS COV2 infectivity studies.

E-selectin/ligand interdiction for inflammation in the ARDS symptoms in COVID19

E-selectin is a key to the first step in inflammation where E-selectin ligand Sialyl LeX binds E-selectin on capillary endothelium for neutrophil extravasation. Mulligan et al. (1993) early showed in a mouse lung inflammation model of ARDS that oligosaccharides containing Sialyl LeX inhibited neutrophils from causing the pneumonic symptoms. Glycomimetics, Inc., under John Magnani's scientific direction, has developed pan-selectin inhibitors and follow-on compounds that may also be effective in interdiction of the ARDS pathology (Chang et al. 2010). Magnani et al. developed a potent anti-inflammatory Sialyl LeX analog that interdicted inflammation in sickle cell anemia (Chang et al. 2010), and this and follow-on compounds from glycomimetics could be employed to test COVID19 lung and cardiac inflammation. Neelamegham, Matta et al. (Wang et al. 2018) reported using thioglycoside N-glycosylation decoys to hijack E-selectin ligand glycosylation, such that neutrophils treated with acetylated GlcNAc-S-NAP are 90% inhibited in rolling and tethering, and 90% inhibited in extravasation in a mouse ex-vivo model. Experiments with lung inflammation mouse models such as used by Mulligan et al. (1993) should be pursued toward finding drugs for the deadly pneumonic phase of COVID19 that is responsible for most fatalities.

It seems a reasonable approach that interfering with host glycosylation systems hijacked by SARS COV2, plus interfering with the ACE2 receptor glycosylation may combine to 1) interdict infectivity and 2) glycosylation interference with Sialyl LeX can inhibit E-selectin-based inflammatory responses, mitigating the Covid19 ARDS pathology. Important here is that decoys of glycosylation address the host enzyme systems; therefore, the virus cannot perform a simple mutation to overcome the interdiction, as in vaccines, like influenza. In addition, several of the compounds are FDA approved for other indications, which could be repurposed and tested off-label.

Heparinoid efficacy

Coagulopathies and heparin treatment are the subject of several articles regarding the pathology of COVID19 (Becker 2020; Porfidia and Pola 2020), and heparan sulfate derivatives and sulfated oligosaccharides appear from several laboratories to play a role in the binding of spike protein to the ACE2 receptor (Clausen et al. 2020; Kim et al. 2020; Kwon et al. 2020; Mycroft-West et al. 2020; Tandon et al. 2020; Zhang et al. 2020). Thus, heparan sulfate derived or sulfated nonanticoagulant and anticoagulant oligosaccharides and derivatives may be effective interdictors of both viral infectivity and coagulopathies, and FDA-approved heparinoid products should be considered for repurposing for COVID19.

Summary

Glycobiologists with access to any of the compounds mentioned herein or related to glycosylation interdictors are encouraged to send their samples for testing to virology labs conducting SARS COV2/ACE2-binding studies, spike glycoprotein fusion tests, or infectivity assays. Repurposing of already approved drugs, and testing others with low toxicity may uncover other avenues from a solid glycobiology antiviral background for a much-needed development of COVID19 therapeutics. There are also outstanding opportunities for selectin anti-inflammatory and heparinoid anticoagulation approaches for COVID19 ARDS.

Conflict of interest statement

R.A. Laine is a managing partner of TumorEnd, LLC, a company working on thioglycoside anti-inflammatory (ref. 56) and anti-viral compounds (www.tumorend.com).

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