Review Article

α-glucosidase inhibitors as host-directed antiviral agents with potential for the treatment of COVID-19

© Spencer J. Williams¹ and © Ethan D. Goddard-Borger²,³

¹School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville 3010, Victoria, Australia; ²The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria 3052, Australia; ³Department of Medical Biology, University of Melbourne, Parkville, Victoria 3010, Australia

Correspondence: Ethan D. Goddard-Borger (Goddard-Borger.E@wehi.edu.au) or Spencer J. Williams (sjwill@unimelb.edu.au)

The ongoing COVID-19 pandemic, caused by SARS-CoV-2, has pushed the health systems of many countries to breaking point and precipitated social distancing measures that have crippled economic activities across the globe. A return to normality is unlikely until effective therapeutics and a vaccine are available. The immediacy of this problem suggests that drug strategies should focus on repurposing approved drugs or late-stage clinical candidates, as these have the shortest path to use in the clinic. Here, we review and discuss the role of host cell N-glycosylation pathways to virus replication and the drugs available to disrupt these pathways. In particular, we make a case for evaluation of the well-tolerated drugs miglitol, celgosivir and especially miglustat for the treatment of COVID-19.

Introduction

The coronavirus disease of 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], has resulted in profound social, health and economic challenges for the global community. New therapeutic interventions are urgently needed to reduce the severity of disease and minimize the economic impact of this crisis. Repurposed drugs [2], new vaccines and convalescent plasma therapies are the approaches most likely to alleviate the present pandemic in a timely fashion: new small molecules or biologics are unlikely to resolve this pandemic unless it persists for many years. Repurposed drugs have a well-understood safety profile, pharmacokinetics and route of administration. In an ideal case, it may be possible to move approved drugs that are validated against SARS-CoV-2 in vitro directly into clinical trials, bypassing the costly and time-consuming discovery of new chemical entities and their pre-clinical evaluation in animal models that are only just being established [3–5], as well as vital phase 1 human safety testing.

In the case of SARS-CoV-2, repurposing efforts are under intensive investigation. Clinical trials have been launched for a variety of FDA-approved drugs including various combinations of chloroquine, hydroxychloroquine, and azithromycin; nitazoxanide; lopinavir/ritonavir; duranivir; sarilumab, and others [6]. Additionally, drugs in late-stage clinical development such as remdesivir, favipiravir and others are under active investigation as they could be fast-tracked into clinical use [6]. Indeed, remdesivir was approved for emergency use by the FDA while this manuscript was under review, though its efficacy leaves ample room for improvements. Potential antiviral therapies may directly target SARS-CoV-2 proteins and processes or host cell pathways that the virus requires for replication. Since most existing drugs target human biochemical pathways, it is logical to evaluate existing drugs that target host pathways required by the virus for replication. Here, we review and discuss the potential of approved or late-stage clinical assets that target host N-linked glycosylation pathways as treatments for COVID-19.

SARS-CoVs and N-linked glycosylation

The SARS-CoV-2 genome encodes 28 proteins [7], three of which are known or predicted to be glycosylated: the envelope (E), membrane (M) and spike (S) proteins (Figure 1A). The SARS-CoV S protein, which adorns the exterior of the virus and creates the characteristic corona morphology of
these viruses, engages the Angiotensin-Converting Enzyme 2 (ACE2) protein on the surface of human cells to facilitate entry of the virus into the host cell [8]. The prominence of the S protein at the surface of SARS-CoVs, and its importance for host cell invasion, makes it the most important target for neutralizing antibodies [9–11]. This selective pressure is postulated to have driven the proliferation of epitope-shielding N-glycans on the surface of the S protein [12–15]. Indeed, a single SARS-CoV-2 S protein protomer has 22 N-glycans (Figure 1B) [16]. However, this epitope-shielding effect is imperfect and COVID-19 patients readily produce neutralizing IgG and IgM against the SARS-CoV-2 S protein within 10–15 days of disease onset [8,15,17–19].

S protein N-glycosylation plays several other important functional roles beyond masking potential epitopes. In SARS-CoV-1, N-glycosylation is required for effective calnexin (CNX) chaperone-mediated folding of the S protein within the ER. For this virus, the mature S protein N-glycans also facilitate adhesion of virions to host cells through interactions with cell-surface lectins DC-SIGN (CD209) and CLEC4M (CD299), which are prevalent on human pneumocytes (Figure 1A) [21–23]. N-glycosylation of host proteins also impacts the SARS-CoV-1 replication cycle: perturbation of ACE2 N-glycosylation disrupts membrane fusion between the

Figure 1. SARS-CoV architecture and the S protein.
(A) A cartoon representation of the SARS-CoV virion illustrating how DC-SIGN and CLEC4M can mediate adhesion to the host cell, while S protein–ACE2 interactions drive host cell invasion. (B) The topology of the SARS-CoV-2 S protein (PDB ID: 6VYB) [20] with the dynamics of its extensive glycosylation (yellow) modeled based on MD simulations. The three protomers (green, blue and mauve) are comprised of an N-terminal domain (NTD) and receptor-binding domain (RBD). The N-glycosylation sites and their oligomannose occupancy are indicated at the right [16].
virus and host endosomes [24]. Taken together, these findings suggest that host N-glycosylation is a promising target for COVID-19 therapeutic interventions.

**Targeting N-linked glycosylation to disrupt the CNX cycle**

N-linked glycoproteins like the SARS-CoV S protein are biosynthesized in the secretory pathway [25,26]. Nascent polypeptides translocated into the ER lumen are modified with a pre-formed Glc₃Man₉GlcNAc₂ glycan structure transferred from a dolichol pyrophosphate precursor en bloc to Asn side-chains within the NX(S/T/C) motif by the oligosaccharyl transferase (OST) complex. The Glc₃Man₉GlcNAc₂ glycan undergoes rapid hydrolytic trimming to produce truncated glycans that play critical roles in protein folding, quality control, and maturation [27]. The first steps involve the trimming of glucose units from the newly transferred immature glycan by α-glucosidases I and II (αGI and αGII) (Figure 2): the terminal glucose unit is removed by αGI, also known asmannosyl-oligosaccharide glucosidase (MOGS), and the second two glucose units are removed by αGII, a heterodimer of the catalytic alpha subunit (GANAB) and beta subunit (PRKCSH). The truncated glycan intermediates produced by αGI and αGII are required for recognition by the chaperones CNX and calreticulin (CRT). CNX and CRT possess a lectin domain that specifically binds the immature GlcMan₉GlcNAc₂ N-glycan of misfolded...
proteins and recruits ATP, calcium and the protein disulﬁde isomerase A3 (PDIA3) to facilitate folding of the
glycoprotein [28,29]. Glycoprotein substrates that are completely de-glucosylated (Man9GlcNAc2) but have failed to
fold correctly are substrates for the UDP-Glc dependent glycosyltransferase UGGT1 that senses hydrophobic
patches on misfolded, deglycosylated glycoproteins, resulting in their re-glucosylation (GlcMan9GlcNAc2) and
re-association with the CNX and/or CRT chaperones. This is referred to as the CNX/CRT folding-cycle. Correctly
folded proteins with a Man9GlcNAc2 structure are substrates for ER mannosidase I (MAN1B1), forming
Man8GlcNAc2 glycoproteins trimmed in the B branch (M8B) that bind to lectin-like cargo–receptor complex,
ER-Golgi intermediate compartment 53 kDa protein (ERGIC-53 or LMAN1)-multiple coagulation factor defi-
ciency protein 2 (MCFD2), which is involved in the translocation of glycoproteins to the Golgi apparatus.
Proteins that fail to emerge from the CNX/CRT folding-cycle in a folded state are processed by EDEM manni-
sidoses, which trim the A and C branches of Man9GlcNAc2, and target the glycoprotein for ER-associated degrad-
ation (ERAD) [30]. The ability of αGI and αGII to regulate glycoprotein entry into, and persistence within, the
CNX/CRT folding-cycle makes them an intriguing target for disrupting the production of essential viral glycopro-
teins like the SARS-CoV S protein. However, some viral glycoproteins fold independently of CNX/CRT and it is
important to consider their fate within the context of virus replication.

The role of endomannosidase in rescuing immature
N-glycans in the Golgi
Glycoproteins that fold independently of CNX/CRT, either under normal conditions or under αGI and αGII
blockade, transit to the Golgi with immature N-glycans (Glc1-3Man9GlcNAc2) that cannot be elaborated to their
mature glycan structures, which can perturb the function and localization of these glycoproteins. In many
but not all mammalian cells, glycoproteins with immature N-glycans within the Golgi are rescued by
endo-α-1,2-mannosidase (MANEA), which removes the terminal Glc1-3Man oligosaccharides from the imma-
ture N-glycans to facilitate glycoprotein maturation by the Golgi machinery (Figure 2) [31]. The ability of
MANEA to rescue immature glycoproteins produced by αGI and αGII blockade has been demonstrated for the
inhibitors castanospermine and the iminosugar deoxynojirimycin [31]. MANEA also plays an important role
under normal conditions where it can rescue as much as 50% of glycoprotein flux through the Golgi [31],
though this depends on MANEA expression levels in the cell of interest [32]. Indeed, MANEA activity is suffi-
cient to partially rescue the complete abrogation of αGI activity in MOGS-CDG patients, at least in the short
term, and explains the excretion of Glc3Man tetrasaccharide in their urine [33].

The relevance of MANEA to virus replication has been thoroughly examined for the hepatitis B virus (HBV).
HBV produces three glycoproteins (L, M and S) and in the presence of the α-glucosidase inhibitor miglustat,
virions lack the M protein and their DNA is not efficiently secreted [34]. Under αGI and αGII blockade, the M
protein produced in infected cells bears triglucosylated glycans and is not retained within the ER but instead traf-
fi cks to the lysosome [34]. In contrast, the L and S glycoproteins still possess mature glycan structures, which arise
due to processing by MANEA in the host cell Golgi compartment [35]. In the context of SARS-CoV under αGI
and αGII blockade, MANEA may enable escaped S protein to achieve its normal glycosylation status and retain
its optimal affinity for engaging DC-SIGN/CLEC4M. However, MANEA is not expressed in human pneumocytes,
so this pathway is likely to be less relevant to SARS-CoV than for other viruses that have been targeted with
α-glucosidase inhibitors (e.g. HIV, HCV, HSV, HBV, EBOV and DENV) [36].

Clinic-ready α-glucosidase inhibitors
The resistance of MOGS-CDG patients to viral infection has provided in-human validation of the ER
α-glucosidases as a target [37] for broad-spectrum antiviral therapeutics, and this concept has been explored
for many viruses [36]. While none of these efforts have led to approved antiviral drugs with this mode of
action, there are FDA-approved α-glucosidase inhibitors for other indications, such as miglustat and miglitol.
Celgosivir is another asset: it has been investigated in phase I/II clinical studies but is not presently
FDA-approved. The merits and limitations associated with repurposing these drugs for the treatment of
COVID-19 are discussed below.

Miglustat (Zavesca® by Actelion, NB-DNJ) is FDA-approved for the treatment of Gaucher and Niemann Pick
disease. It was originally identifi ed and developed as an anti-HIV agent with activity against αGI [38–41] and,
while early trials in combination with AZT were promising [39], dose escalation trials using miglustat as a mono-
therapy were halted due to fears of toxicity, which were ultimately unfounded [38]. Subsequently, miglustat was
discovered to inhibit ceramide glucosyltransferase (UGCG) [42], leading to its successful re-development and deployment as a drug for the treatment of Gaucher disease and Niemann-Pick disease type C [43]. These diseases are rare autosomal-recessive lysosomal storage disorders that involve the accumulation of glycosphingolipids (GSLs): miglustat blockade of UGCG limits the production of GSLs and alleviates the symptoms of these diseases. Miglustat also inhibits intestinal glucosidases, impairing the digestion of starch in the small intestine and resulting in colonic fermentation of starch that can cause diarrhea and flatulence: the main side effect of this drug [44]. While this can be distressing, anti-diarrheal agents and dietary changes to minimize the consumption of starch and sucrose can effectively mitigate this issue. Importantly, there are already two reports of miglustat activity in vitro against SARS-CoV-1 at concentrations ∼100 μg/ml [45,46], which is analogous to the effective doses reported for miglustat against HIV-1 in vitro [40]. Miglustat has excellent oral bioavailability, is inexpensive to produce and is extremely well tolerated (up to 64 mg/kg/day [38]). Typical doses for Gaucher disease patients are 100–300 mg t.i.d. for long-term chronic treatment [47], although higher acute doses are feasible. It is also now available from several generic manufacturers, which could be enabling for investigator-led trials. Collectively, this data suggests that miglustat is a prime candidate for repurposing as a drug to combat COVID-19.

Miglitol (Glyset® by Pfizer) is closely related to miglustat. Miglitol is an FDA-approved drug used for minimizing postprandial glucose uptake in diabetes mellitus patients. It achieves this by inhibiting intestinal α-glucosidases of the brush border to reduce peak glucose blood levels [48]. Miglitol is efficiently absorbed in the small intestine and oral ingestion of 2 mg/kg gives a plasma half-life of 2.4 h with a peak plasma concentration of 1.1 mg l−1 and a peak T\text{max} of 2.3 h. Miglitol has a low volume of distribution indicating low tissue penetration, and binding to plasma proteins is minimal (4%) [49]. Permeation across the blood brain barrier is low, and miglitol is excreted exclusively and unchanged from the kidneys. The major short-term side effect is osmotic diarrhea, caused by colonic fermentation of starch, as for miglustat. It has not been reported if miglitol can inhibit ER α-glucosidases but its similarity to miglustat, excellent safety profile and clinical availability suggest that it may be worth considering as a SARS-CoV-2 treatment or prophylactic. This optimism is mitigated by the low volume of distribution, which suggests that sufficient concentrations of this drug may be difficult to attain at the primary sites of infection in the airways. While prophylactic drugs are inherently inferior to vaccines, there are good public health reasons for their use, safety permitting, even in the event of limited efficacy. This strategy is particularly important for the protection of frontline health care workers and the treatment of index cases in an outbreak to limit their spread. Identification of the prophylactic potential of very safe approved drugs like miglitol may form part of a broader, long-term strategy for SARS-CoV-2 suppression.

Celsosivir is a prodrug of the potent αGI inhibitor castanospermine and was originally developed as an anti-HIV agent [50–52]. Once in the cell, celsosivir is hydrolytically converted to castanospermine [53,54]. This compound has demonstrated excellent activity against a broad range of viruses in vitro and in vivo [55]. Phase I clinical trials by Hoechst established good tolerability of celsosivir and a phase II trial as an anti-HIV agent was conducted as early as 1985. While no details of the trial results are available, it can be assumed that the anti-HIV effects of celsosivir were modest and less favorable than other contemporary antivirals [55]. A series of phase II studies of celsosivir (alone, or in combination with PEGylated IFN\text{2b}, or PEGylated IFN\text{2b} plus ribavirin) have been conducted to assess safety and efficacy in patients with HCV-1 infection. In these studies modest reductions in viral load were observed, and side effects were similar to those observed in HIV infected patients: diarrhea and flatulence, which could be controlled with anti-diarrhea agents and a low sucrose/starch diet [55]. Celsosivir treatment causes the dengue virus (DENV) NS1 glycoprotein to accumulate in the ER and induces the unfolded protein response in infected cells [56]. The phase Ib CELADEN trial in patients with dengue fever using an initial 400 mg loading dose, followed by 200 mg every 12 h for a total of nine doses (2.0 g total) demonstrated that it is generally safe and well tolerated [57]. However, this trial failed to reduce DENV load or fever [57]. One possible contribution for this limited efficacy is the need for early intervention. Celsosivir is more effective when administered at day 0 after infection rather than day 3 in DENV infected AG129 mice [58]. An extended evaluation of the CELADEN trial highlighted new dosing regimens that are predicted to achieve higher C\text{min} between doses, and suggested a likelihood of better responses in patients with secondary DENV infection [59].

**Will α-glucosidase inhibitors be useful as COVID-19 therapies?**

While there are many lines of evidence suggesting that α-glucosidase inhibitors could be useful for treating COVID-19, one is confronted by the failure of miglustat and celsosivir in the clinic against HIV and DENV. In the
case of HIV, it appears as though this modality was abandoned early-on as the more efficacious anti-retrovirals came to the fore. For DENV and celgosivir, the major post-hoc rationalization for its failure was that drug intervention came too late post-infection. Experience with inhibitors of the influenza replication cycle, such as zanamivir and oseltamivir, has highlighted that dosing in the early stages of infection is critical to reduce viral load, which in turn reduces the severity of symptoms and recovery time [60]. It is likely that a similar situation will apply to SARS-CoV-2 infection. Fortunately, reverse-transcriptase polymerase chain reaction tests allow detection of early-stage infections, even in asymptomatic individuals, and broad-scale testing may be required to support intervention with α-glucosidase inhibitors and perhaps most other antivirals. Another factor that may have limited the efficacy of α-glucosidase inhibitors against viruses is the confounding effect of host cell MANEA, which has been shown to rescue the antiviral effect of αGI and αGII blockade on VSV [61]. In fact, it is possible that the excellent safety profile of miglustat may, at least in part, arise from MANEA rescuing the effect of α-glucosidase inhibition in most human cell types. This suggests that α-glucosidase inhibitors may be more effective in tissues with low MANEA expression levels, or at very high doses that give more complete suppression of α-glucosidase activity. It is encouraging that human pneumocytes do not produce detectable levels of MANEA [62–64], supporting the hypothesis that miglustat and other α-glucosidase inhibitors could be effective for managing respiratory viruses like SARS-CoV-2.

A major flaw in many clinical trials that evaluated α-glucosidase inhibitors was the absence of biomarker-detection to demonstrate a PK/PD target-engagement relationship. Glycomic and glycoproteomic experiments are required in infected animal models and in human studies in order to better understand how α-glucosidase inhibitor dosing tracks with the anticipated changes in host and virus N-glycosylation. For example, it has been shown that animals treated with N-nonyl-DNJ, a candidate antiviral α-glucosidase inhibitor related to miglustat, results in accumulation of the triglucosylated Glc₃Man₇GlcNAc₂ glycans in serum [65]. However, more detailed analysis revealed that N-nonyl-DNJ retained antiviral activity against HBV at concentrations where it had no significant impact on ER glucosidase function [66]. Any future investigation of miglustat, miglitol or celgosivir in COVID-19 models or patients must be accompanied with rigorous experiments that test for target engagement and how this correlates with viral load and disease progression.

Among the three compounds discussed here, we consider miglustat to be the highest priority target for drug repurposing. It possesses a well-understood safety profile, evidence for good tolerance, favorable distribution, oral availability, and has demonstrated activity against SARS-CoV-1 in vitro [45,46]. It stands apart as a particularly enticing prospect for drug repurposing to combat the COVID-19 crisis. The greatest uncertainty associated with repurposing miglustat is whether a therapeutic dose for SARS-CoV-2 can be delivered within the currently approved safety margin. A bridging human phase 1 safety study could widen the therapeutic window further; it should be noted that prior safety studies did not identify any dose-limiting toxicity, even up to 64 mg/kg/day [38]. Miglitol is similar in many respects to miglustat but is less bioavailable and with a lower volume of distribution. Thus, it is a lower priority target for drug repurposing. Nonetheless, its truly exceptional safety profile suggests it might be used as a prophylactic, provided dietary changes or other interventions can relieve gastrointestinal side effects that may impact patient compliance. The available data for celgosivir suggests that it could be superior to miglustat against SARS-CoV-2: it is a more potent and specific inhibitor and out-performs miglustat in many in vitro virus assays. However, it is less worthy of development because it is not yet an FDA-approved drug and, to our knowledge, is not under active development by any pharmaceutical company.

**Perspectives**

N-glycosylation and the calnexin pathway is required for S protein folding, and so αGI and II blockade might be expected to disrupt SARS-CoV-2 replication, as it does for SARS-CoV-1 [45,46]. Miglustat is an approved α-glucosidase inhibitor that could serve this purpose, as is the advanced clinical candidate celgosivir. While clinical trials of miglustat and celgosivir against other viruses provided only modest improvements in disease state, it appears as though sub-optimal dosing regimens and timing, as well as the expression of MANEA in the relevant tissues may rationalize these results. The absence of MANEA in human pneumocytes, combined with the favorable pharmacological properties of these drugs, make them promising candidates for consideration as COVID-19 treatments.
Note added in proof

A pre-print manuscript by Marcello and coworkers reports that miglustat decreases levels of SARS-CoV-2 proteins and release of infectious virus [67].

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Open Access

Open access for this article was enabled by the participation of Walter and Eliza Hall Institute in an all-inclusive Read & Publish pilot with Portland Press and the Biochemical Society under a transformative agreement with CAUL.

Acknowledgements

We thank Dr. Elisa Fadda for her assistance in preparing Figure 1B. We also thank Profs Paul Gleeson, Marc Pellegrini and Dr Nichollas Scott for helpful discussions. The authors’ research is supported by the Australian Research Council and the National Health and Medical Research Council. The University of Melbourne and the Walter and Eliza Hall Institute of Medical Research are thanked for ongoing support.

Abbreviations

ACE2, Angiotensin-Converting Enzyme 2; CNX, calnexin; COVID-19, coronavirus disease of 2019; CRT, calreticulin; DENV, dengue virus; GSLs, glycosphingolipids; HBV, hepatitis B virus; MOGS, mannosyl-oligosaccharide glucosidase.

References

1. Gorbalenya, A.E., Baker, S.C., Baric, R.S. and de Groot, R.J. (2020) The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat. Microbiol. 5, 536–544. doi:10.1038/s41564-020-0695-z

2. Pushpakom, S., Iorio, F., Eyers, P.A., Escott, K.J., Hopper, S., Wells, A. et al. (2019) Drug repurposing: progress, challenges and recommendations. Nat. Rev. Drug Discov. 18, 41–58. doi:10.1038/s41573-018-0018-8

3. Bao, L., Deng, W., Huang, B., Gao, H., Liu, J., Ren, L. et al. (2020) The pathogenicity of 2019 novel coronavirus in hACE2 transgenic mice. bioRxiv 2020.2002.2007.939380. doi:10.1101/2020.02.07.939380

4. Shan, C., Yao, Y.-F., Yang, X.-L., Zhou, Y.-W., Wu, J., Gao, G. et al. (2020) Infection with novel coronavirus (SARS-CoV-2) causes pneumonia in the patient recovery: a case report of non-severe COVID-19. Emerg. Microbes. Infect. 9, 382–385. doi:10.1080/22221751.2020.1729069

5. Kim, Y.-I., Kim, S.-G., Kim, S.-M., Kim, E.-H., Park, S.-J., Yu, K.-M. et al. (2020) Infection and rapid transmission of SARS-CoV-2 in ferrets. bioRxiv 2020.2003.2026.010322. doi:10.1101/2020.03.26.010322

6. Wang, C., Li, W., Drabek, D., Okba, N.M.A., van Haperen, R., Osterhaus, A.D.M.E. et al. (2020) A human monoclonal antibody blocking SARS-CoV-2 and SARS-CoV. Virus Res. 270, 109924. doi:10.1016/j.virusres.2020.109924

7. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S. et al. (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280.e8. doi:10.1016/j.cell.2020.02.052

8. Sui, J., Li, W., Murakami, A., Tamim, A., Matthews, L.J., Wong, S.K. et al. (2004) Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. Proc. Natl Acad. Sci. U.S.A. 101, 2536. doi:10.1073/pnas.0307140101

9. Zhu, Z., Chakrabarti, S., Ho, Y., Roberts, A., Sheahan, T., Xiao, X. et al. (2007) Potent cross-reactive neutralization of SARS coronavirus isolates by human monoclonal antibodies. Proc. Natl Acad. Sci. U.S.A. 104, 12123. doi:10.1073/pnas.070100104

10. Wang, C., Li, W., Drabek, D., Okba, N.M.A., van Haperen, R., Osterhaus, A.D.M.E. et al. (2020) A human monoclonal antibody blocking SARS-CoV-2 infection. bioRxiv 2020.2003.2011.987958. doi:10.1101/2020.03.11.987958

11. Wang, C., Li, W., Drabek, D., Okba, N.M.A., van Haperen, R., Osterhaus, A.D.M.E. et al. (2020) A human monoclonal antibody blocking SARS-CoV-2 infection. bioRxiv 2020.2003.2011.987958. doi:10.1101/2020.03.11.987958

12. Xiong, X., Tortorici, M.A., Yoshioka, C., Walls, A.C., Li, W. et al. (2017) Glycan shield and fusion activation of a deltacoronavirus spike glycoprotein fine-Tuned for enteric infections. J. Virol. 92, 18126–18136. doi:10.1128/JVI.01629-17

13. Walls, A.C., Tortorici, M.A., Frenz, B., Snijder, J., Li, W., Rey, F. et al. (2016) Glycan shield and epitope masking of a coronavirus spike glycoprotein. Cell 164, 1008–1019. doi:10.1016/j.cell.2016.02.022

14. Watanabe, Y., Bowden, T.A., Wilson, I.A. and Crispin, M. (2019) Exploitation of glycosylation in enveloped virus pathobiology. Nat. Struct. Mol. Biol. 26, 315–331. doi:10.1038/s41594-019-0148-0

15. Tian, X., Li, C., Huang, A., Xia, S., Lu, S., Shi, Z. et al. (2020) Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg. Microbes. Infect. 9, 382–385. doi:10.1080/22221751.2020.1729069

16. Watanabe, Y., Allen, J.D., Wrapp, D., McLellan, J.S. and Crispin, M. (2020) Site-specific analysis of the SARS-CoV-2 glycan shield. bioRxiv 2020.2003.2026.010322. doi:10.1101/2020.03.26.010322

17. Thovarajan, I., Nguyen, T.H.O., Koutsakos, M., Druce, J., Caly, L., van de Sandt, C. et al. (2020) Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat. Med. 26, 453–455. doi:10.1038/s41591-020-0819-2
Elstein, D., Holli, C., Aerts, J.M.F.G., van Weely, S., Maaë, M., Cox, T.M. et al. (2004) Sustained therapeutic effects of oral miglustat (Zavesca, N-butyldeoxynojirimycin, OGT 918) in type I Gaucher disease. J. Inherit. Metab. Dis. 27, 757–766 https://doi.org/10.1023/B:BOIL.0000045756.54006.17

Sels, J.-P.E., Huijberts, M.S.P. and Wolfenbuttel, B.H.R. (1999) Miglitol, a new α-glucosidase inhibitor. Expert Opin. Pharmacother. 1, 149–156 https://doi.org/10.1517/14656666.1.1.149

Ahr, H.J., Boberg, M., Brendel, E., Krause, H.P. and Steinke, W. (1997) Pharmacokinetics of miglitol. Absorption, distribution, metabolism, and excretion following administration to rats, dogs, and man. Arzneimittelforschung 47, 734–745 PMID:9229452

Liu, P.S., Hoekstra, W.J. and Wolffenbuttel, B.H.R. (1999) Miglitol, a new α-glucosidase inhibitor. J. Pharm. Investig. 20, 535–541 https://doi.org/10.3233/PAI1999-15607

Sung, C., Wei, Y., Watanabe, S., Lee, H.S., Khoo, Y.M., Fan, L. et al. (2016) Extended evaluation of virological, immunological and pharmacokinetic endpoints of CELADEN: a randomized, placebo-controlled trial of celgosivir in dengue fever patients. PLOS Negl. Trop. Dis. 10, e0004851 https://doi.org/10.1371/journal.pntd.0004851

Matsumoto, K., Ogawa, N., Neronie, K., Numazaki, Y., Kawakami, Y., Shirato, K. et al. (1999) Castanospermine inhibits the processing of the oligosaccharide moiety of the influenza viral hemagglutinin. Biochemistry 28, 3975–3984 https://doi.org/10.1021/bi982829a

Rathore, A.P., Paradkar, P.N., Watanabe, S., Tan, K.H., Sung, C., Connolly, J.E. et al. (2011) Celgosivir treatment misfolds dengue virus NS1 protein, induces cellular pro-survival genes and protects against lethal challenge mouse model. Antivir. Res. 92, 453–460 https://doi.org/10.1016/j.antiviral.2011.10.002

Low, J.G., Sung, C., Wijaya, L., Wei, Y., Rathore, A.P.S., Watanabe, S. et al. (2014) Efficacy and safety of celgosivir in patients with dengue fever (CELADEN): a phase 1b, randomised, double-blind, placebo-controlled, proof-of-concept trial. Lancet Infect. Dis. 14, 706–715 https://doi.org/10.1016/S1473-3099(14)70370-3

Watanabe, S., Chan, K.W.-K., Dow, G., Ooi, E.E., Low, J.G. and Vasudevan, S.G. (2016) Optimising celgosivir therapy in mouse models of dengue virus infection of serotypes 1 and 2: The search for a window for potential therapeutic efficacy. Antivir. Res. 127, 10–19 https://doi.org/10.1016/j.antiviral.2015.12.006

Sung, C., Wei, Y., Watanabe, S., Lee, H.S., Kho, Y.M., Fan, L. et al. (2016) Extended evaluation of virological, immunological and pharmacokinetic endpoints of CELADEN: a randomized, placebo-controlled trial of celgosivir in dengue fever patients. PLOS Negl. Trop. Dis. 10, e0004851 https://doi.org/10.1371/journal.pntd.0004851

Matsumoto, K., Ogawa, N., Neronie, K., Numazaki, Y., Kawakami, Y., Shirato, K. et al. (1999) Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: results from Japan. GG167 group. Antivir. Ther. 4, 61–68 PMID:10682150

Karanavanova, V.K., Luan, P. and Spro, R.G. (1998) Processing of viral envelope glycoprotein by the endomannosidase pathway: evaluation of host cell specificity. Glycobiology 8, 725–730 https://doi.org/10.1093/glycob/8.7.725

Uhlen, M., Fagerberg, L., Hallström, B.M., Lindskog, C., Oksvold, P., Mardinoglu, A. et al. (2015) Tissue-based map of the human proteome. Science 347, 1260419 https://doi.org/10.1126/science.1260419

Thul, P.J., Åkesson, L., Wiking, M., Mahdessian, D., Geladaki, A., Alt Bial, H. et al. (2017) A subcellular map of the human proteome. Science 356, eaal3321 https://doi.org/10.1126/science.aal3321

Uhlen, M., Zhang, C., Lee, S., Sjöstedt, E., Fagerberg, L., Bidkhori, G. et al. (2017) A pathology atlas of the human cancer transcriptome. Science 357, eaan2507 https://doi.org/10.1126/science.aan2507

Mehta, A., Zitzmann, N., Rudd, P.M., Black, T.M. and Dwek, R.A. (1998) α-Glucosidase inhibitors as potential broad based anti-viral agents. FEBS Lett. 430, 17–22 https://doi.org/10.1016/S0014-5793(98)00325-0

Mehta, A., Carrouée, S., Conyers, B., Jordan, R., Butters, T., Dwek, R.A. et al. (2001) Inhibition of hepatitis B virus DNA replication by imino sugars without the inhibition of the DNA polymerase: therapeutic implications. Hapatology 33, 1488–1495 https://doi.org/10.1053/jhep.2001.25103

Rajasekharan, S., Bonotto, R.M., Kazungu, Y., Alves, L.N., Poggianella, M., Orellana, P.M. et al. (2020) Repurposing of Miglustat to inhibit the coronavirus Severe Acquired Respiratory Syndrome SARS-CoV-2, BioRxiv https://doi.org/10.1101/2020.05.18.101691