

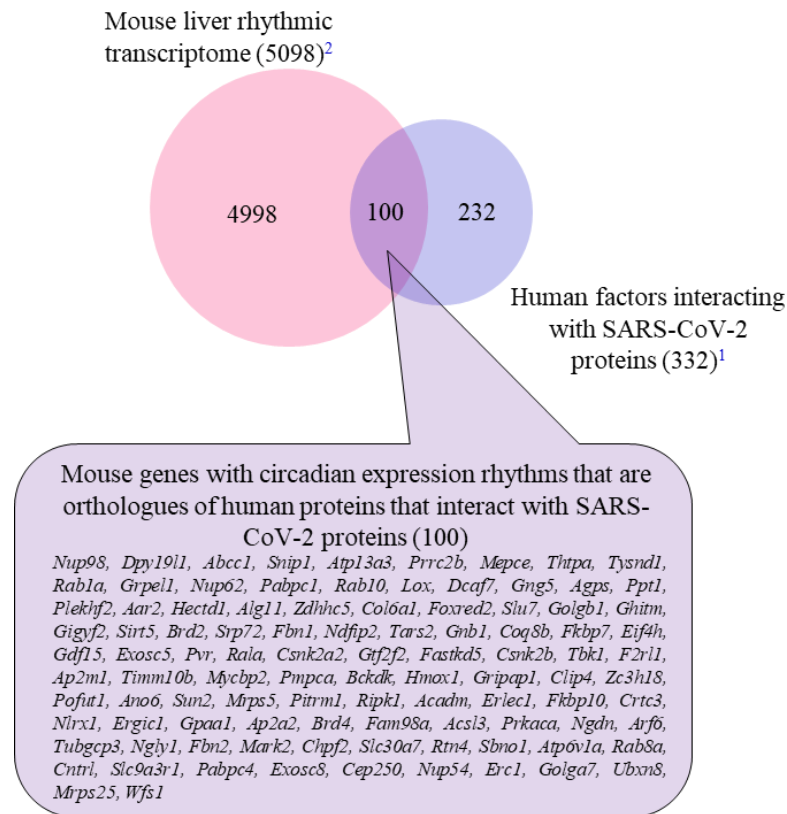
COVID-19 management in light of the circadian clock

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Supplementary Figure 1. Circadian rhythms of druggable host factors that interact with SARS-CoV-2 proteins

(a)



(a) **Circadian rhythms of host factors that interact with SARS-CoV-2.** We evaluated the circadian expression patterns of human proteins that are involved in high-confidence protein–protein interactions with SARS-CoV-2 proteins, as defined by Gordon *et al.*¹, by comparing them with our recently published circadian mouse liver transcriptome data². We have identified that 100 (out of 332) of these SARS-CoV-2 interacting factors exhibit 24-hour oscillation ($Q < 0.1$) under constant condition.

(b)

No.	Druggable human factor	SARS-CoV-2-interacting protein	Circadian expression in mammalian organs or tissues
1	Alpha-galactosidase A (GLA)	Nsp14	Heart (JTK-Q = 0.0009), Lung (JTK-Q = 0.001), Brain stem (JTK-Q = 0.0094), Suprachiasmatic nucleus (JTK-Q = 0.06), Brown adipose tissue (JTK-Q = 0.073), Kidney (JTK-Q = 0.09)

2	Protein-lysine 6-oxidase (LOX)	Orf8	Pituitary (JTK-Q = 0.0014), Aorta (JTK-Q = 0.01), Kidney (JTK-Q = 0.018), White adipose tissue (JTK-Q = 0.074), Brown adipose tissue (JTK-Q = 0.09)
3	ATP-binding cassette sub-family C member 1 (ABCC1)	Orf9c	Muscle (JTK-Q = 0.001), Brown adipose tissue (JTK-Q = 0.0018), Hypothalamus (JTK-Q = 0.024), Lung (JTK-Q = 0.036), Heart (JTK-Q = 0.039)
4	FK506 binding protein 10 (FKBP10)	Orf8	Lung (JTK-Q = 0.0001), Brain stem (JTK-Q = 0.019), Adrenal gland (JTK-Q = 0.024), Suprachiasmatic nucleus (JTK-Q = 0.033), Distal colon (JTK-Q = 0.043)
5	Sigma non-opioid intracellular receptor 1 (SIGMAR1)	Nsp6	Liver (JTK-Q = 2.58e-05), White adipose tissue (JTK-Q = 0.023), Adrenal gland (JTK-Q = 0.029), Kidney (JTK-Q = 0.051)
6	Sigma intracellular receptor 2 (TMEM97)	Orf9c	Liver (JTK-Q = 1.72e-05), Lung (JTK-Q = 0.014), Kidney (JTK-Q = 0.071), Adrenal gland (JTK-Q = 0.083)
7	Valosin containing protein (VCP)	Orf10	Liver (JTK-Q = 0.009), Lung (JTK-Q = 0.03), Kidney (JTK-Q = 0.043), Suprachiasmatic nucleus (JTK-Q = 0.075)
8	La-related protein 1 (LARP1)	N	Liver (JTK-Q = 8.70e-07), Lung (JTK-Q = 0.0048), Heart (JTK-Q = 0.039), Suprachiasmatic nucleus (JTK-Q = 0.064)
9	Catechol O-methyltransferase (COMT)	Nsp7	Liver (JTK-Q = 4.23e-06), Kidney (JTK-Q = 0.0002), Aorta (JTK-Q = 0.0016), White adipose tissue (JTK-Q = 0.028)
10	Bromodomain-containing protein 2 (BRD2)	E	Aorta (JTK-Q = 0.006), Brown adipose tissue (JTK-Q = 0.006), Lung (JTK-Q = 0.02)
11	Receptor-interacting serine/threonine-protein kinase 1 (RIPK1)	Nsp12	Kidney (JTK-Q = 0.0086), Liver (JTK-Q = 0.011), Heart (JTK-Q = 0.068)
12	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 (PLOD2)	Orf8	Kidney (JTK-Q = 0.003), Heart (JTK-Q = 0.018), Adrenal gland (JTK-Q = 0.024)
13	FK506 binding protein 7 (FKBP7)	Orf8	Kidney (JTK-Q = 0.027), Liver (JTK-Q = 0.046), Aorta (JTK-Q = 0.08)

14	cAMP-dependent protein kinase catalytic subunit alpha (PRKACA)	Nsp13	Liver (JTK-Q = 0.00039), Suprachiasmatic nucleus (JTK-Q = 0.064), Kidney (JTK-Q = 0.089)
15	Solute carrier family 6 - member 15 (SLC6A15)	Nsp6	Suprachiasmatic nucleus (JTK-Q = 0.02), Adrenal gland (JTK-Q = 0.059), Lung (JTK-Q = 0.073)
16	Solute carrier family 1 (SLC1A3)	M	Lung (JTK-Q = 0.0028), Brown adipose tissue (JTK-Q = 0.037), Aorta (JTK-Q = 0.056)
17	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1 (PLOD1)	Orf8	Liver (JTK-Q = 0.0008), Lung (JTK-Q = 0.001), Brown adipose tissue (JTK-Q = 0.086)
18	V-type proton ATPase subunit S1 (ATP6AP1)	Nsp6	Liver (JTK-Q = 0.0006), Suprachiasmatic nucleus (JTK-Q = 0.0048)
19	Casein kinase II subunit alpha (CSNK2A2)	N	Liver (JTK-Q = 0.0047), Brown adipose tissue (JTK-Q = 0.03)
20	Inosine-5'-monophosphate dehydrogenase 2 (IMPDH2)	Nsp14	Liver (JTK-Q = 0.055), Lung (JTK-Q = 0.061)
21	MAP/microtubule affinity-regulating kinase 3 (MARK3)	Orf9b	Suprachiasmatic nucleus (JTK-Q = 0.0048), Liver (JTK-Q = 0.0082)
22	V-ATPase subunit A (ATP6V1A)	M	Suprachiasmatic nucleus (JTK-Q = 0.022)
23	Bromodomain-containing protein 4 (BRD4)	E	Liver (JTK-Q = 0.05)
24	Deoxycytidine-triphosphatase 1 (DCTPP1)	Orf9b	Liver (JTK-Q = 4.8e-06)
25	DNA (cytosine-5)-methyltransferase 1 (DNMT1)	Orf8	Adrenal gland (JTK-Q = 0.024)
26	Proteinase-activated receptor 2 (F2RL1)	Orf9c	Aorta (JTK-Q = 0.093)
27	Histone deacetylase 2 (HDAC2)	Nsp5	Kidney (JTK-Q = 0.085)
28	MAP/microtubule affinity-regulating kinase 2 (MARK2)	Orf9b	Liver (JTK-Q = 0.095)

29	Serine/threonine-protein kinase TBK1 (TBK1)	Nsp13	Liver (JTK-Q = 1.03e-05)
30	FK506-binding protein 15 (FKBP15)	Nsp2	Liver (JTK-Q = 0.006)

(b) Circadian expression of potential drug targets of the SARS-CoV-2-interacting proteins. We analysed the daily rhythmicity of the druggable human factors that interact with SARS-CoV-2-proteins¹. We investigated their rhythmic expression patterns using the Circadian Expression Profiles Database (CircaDB; <http://circadb.hogeneschlab.org/>), which is a comprehensive portal allowing access to the expression profiles of almost all mammalian genes on a circadian time scale³. We observed that the majority of these druggable human factors that are targets for FDA-approved drugs or compounds in clinical and preclinical trials (see Supplementary Table 4 and Supplementary Table 6 in REF.¹), exhibit robust 24-hour oscillation (Period 24±3 h, JTK Q < 0.1) in one or multiple organs (or tissues) in mice. Importantly, the mouse model of SARS-CoV-2 infection is emerging as a very convenient tool for studying transmission and pathogenesis of this novel respiratory pathogen, and could also be useful in evaluating COVID-19 therapeutics⁴⁻⁶.

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