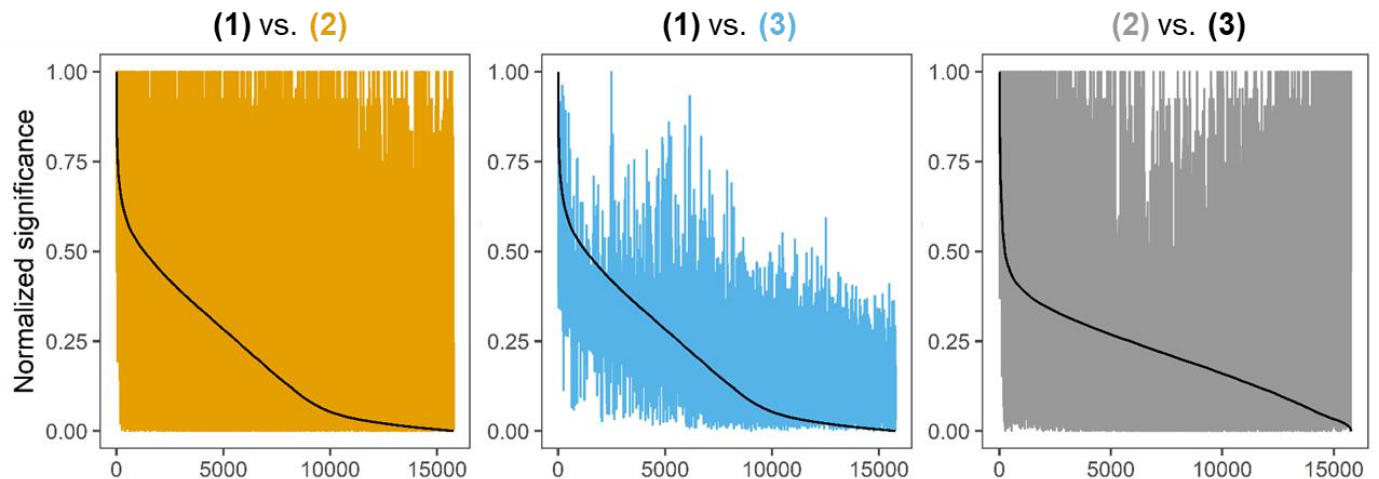


Supplementary information

Δ ORF6	(2)	(3)	SARS	(2)	(3)
(1)	0.60	0.70	(1)	0.33	0.69
(2)		0.49	(2)		0.25

Supplementary Figure 1. Correlation coefficients between genes' normalized significance values across methods (1), (2) and (3) in Δ ORF6- and SARS-infected cells.



Supplementary Figure 2. Line plots showing pairwise comparison of the normalized significance values between three methods in SARS-infected cells.

<p>Ligands: BMP10 BMP15 BMP2 BMP3 BMP4 BMP5 BMP6 BMP7 BMP8B CCL11 CCL13 CCL14 CCL15 CCL16 CCL17 CCL18 CCL19 CCL1 CCL20 CCL21 CCL22 CCL23 CCL24 CCL25 CCL26 CCL27 CCL28 CCL2 CCL3L1 CCL3L3 CCL3 CCL4 CCL5 CCL7 CCL8 CX3CL1 CXCL10 CXCL11 CXCL12 CXCL13 CXCL16 CXCL1 CXCL2 CXCL3 CXCL5 CXCL6 CXCL9 IFNA10 IFNA13 IFNA14 IFNA16 IFNA17 IFNA1 IFNA21 IFNA2 IFNA4 IFNA5 IFNA6 IFNA7 IFNA8 IFNB1 IFNG IFNL1 IFNL2 IFNL3 IFNW1 IL10 IL11 IL12A IL12B IL13 IL15 IL16 IL17A IL17B IL17F IL18 IL19 IL1A IL1B IL1F10 IL1RN IL20 IL21 IL22 IL23A IL24 IL25 IL26 IL27 IL2 IL31 IL34 IL3 IL4 IL5 IL6 IL7 CXCL8 IL9 TGFA TGFB1 TGFB2 TGFB3 TNFSF10 TNFSF11 TNFSF12 TNFSF13B TNFSF13 TNFSF14 TNFSF15 TNFSF18 TNFSF4 TNFSF8 TNFSF9 TNF CSF1 CSF2 CSF3 XCL1 XCL2</p>
<p>Receptors: ACVR1 ACVR2A ACVR2B ACVRL1 BMPR1A BMPR1B BMPR2 ENG HJV ACKR2 ACKR4 CCR2 CCR3 CCR5 CXCR3 CCR1 CCR9 CCR8 HRH4 CCR4 ACKR1 ERG28 CCR10 CCR7 CCRL2 CCR6 GPR75 SDC1 SDC4 CX3CR1 ACKR3 CD4 CXCR4 ITGB1 CXCR5 HTR2A OPRD1 CXCR6 CXCR1 CXCR2 XCR1 IFNAR1 IFNAR2 IFNGR1 IFNGR2 IFNLR1 IL10RB IL10RA SIRPG IL11RA IL6ST CD28 IL12RB1 IL12RB2 IL23R IL13RA1 IL13RA2 IL2RG IL4R IL15RA IL2RA IL2RB GRIN2C GRIN2D KCNA3 KCND1 KCND2 KCNJ10 KCNJ15 KCNJ4 IL17RA IL17RC IL17RB CD48 IL18R1 IL18RAP IL1RAPL1 IL1RL2 IL20RA IL20RB IL1R1 IL1R2 IL1RAP ADRB2 IL22RA1 IL21R IL22RA2 IL27RA CD53 GYPE NGFR IL31RA OSMR CSF1R CSF2RB IL3RA IL5RA F3 IL6R IL7R CD79A KDR SDC2 SDC3 IL9R EGFR ERBB2 ERBB3 ERBB4 CAV1 CD109 ITGAV ITGB6 ITGB8 TGFBR1 TGFBR2 TGFBR3 TNFRSF10A TNFRSF10B TNFRSF10C TNFRSF10D TNFRSF11B TNFRSF11A TNFRSF12A TNFRSF25 TNFRSF13B TNFRSF13C TNFRSF17 FAS TNFRSF14 TNFRSF1A LTBR TNFRSF6B TNFRSF18 TNFRSF4 TRAF2 TNFRSF8 TNFRSF9 SLC5A11 TNFRSF1B TNFRSF21 CSF2RA CSF3R ITGA9</p>

Supplementary Figure 3. Cytokine genes which compiled from 121 cytokines/chemokines (ligands) and 144 receptor genes that may bind with ligands.

Condition	bg.sig.no	bg.%	ligand.sig.no	ligand.%	ligand.bonf	recep.sig.no	receptor.%	recep.bonf
ΔORF6	3301	18.70	41	33.8843	0.0001057	31	21.5278	0.4393291
SARS	804	4.55	32	26.4463	7.91E-16	12	8.3333	0.0646926

bg: background genes, 17848 in total (excluding cytokinome genes).

bg.sig.no: number of significant DEGs after excluding significant cytokinome genes.

Red: Bonferroni-adjusted p -value < 0.05 .

Supplementary Figure 4. The impact of ΔORF6 to the cytokinome profile in compared to background (bg) genes.

ΔORF6-specific (ordered by significance): MAFK JUND **FOSL1** TEF CEBPB MITF MAFF HAND1 MGA GADD45A TFE3 ARID5B JUNB BACH1 FOXC1 HLF FOXJ3 GRHL1 NFIL3 TCF12 CREB1 DDIT3 ZNF207 DLX2 BHLHE41 TFAP2C PHTF1 FOXO1 GMEB2 FOXD2 IRF9 ISL2 RARA PPP1R10 ESX1 HNF1A FOXD1 GTPBP1 RIOK2 NKX3-1 RNF138 MAFG MEX3C ZNF3 SOX9 ISX ESRP2 AHR ARNT2 IRX5 DDX43 SOX4 PLAGL1 HMG20A FOXO3 MSX2 ZSCAN9

Wild-type sharing (ordered by significance): GATA3 FOSL2 ZBTB43 TWIST1 TFAP2A JUN RARB FOSB ARID3A IRF7 FOS IRF1 CLK1 KLF4 POU2F2 GLYCTK NR4A1 GBX2

Supplementary Figure 5. The enriched transcription factors (TFs) in ΔORF6-specific or wild-type/SARS-sharing DEGs upon ΔORF6 infection.

Enrichment in FOSL1 targets.

regulator	up_regs_no	mean_perm_no	p_value
FOSL1	444	328.4805	1E-05

Supplementary Figure 6. The enrichment of targets of *FOSL1* gene using ChIP-seq data from ENCODE database.

Method	Significance threshold
(1)	6.031026e-46
(2)	0.0008234463
(3)	6.078022e-61

Supplementary Figure 7. *IL6* gene was identified as significant genes in three DEG identification methods.

		Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Non-cluster genes
Color		Brown	Black	Pink	Red	Turquoise	Blue	Grey
Gene size		3083	391	232	521	4517	1999	6390
(1) Intersection with DEGs	Specific	1891 (61.34%)	0 (0.00%)	26 (11.21%)	0 (0.00%)	1 (0.02%)	3 (0.15%)	614 (9.61%)
	Shared	567 (18.39%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.05%)	167 (2.61%)
(2) Druggable genes	Specific	149	0	1	0	1	0	48
	Shared	87	0	0	0	0	0	18
(3) Drug-gene pairs	Specific	971	0	10	0	10	0	457
	Shared	927	0	0	0	0	0	132
(4) Candidate ligands	Specific	732	0	10	0	10	0	376
	Shared	842	0	0	0	0	0	128

Supplementary Figure 8. Comparing across Clusters 1~6.

(agents acting on the renin-angiotensin system) verapamil; (all other therapeutic products) pralidoxime; (anabolic agents for systemic use) ethylestrenol; (analgesics) dihydroergotamine/ methysergide/ sumatriptan; (anti-acne preparations) adapalene/ tretinoin/ trifarotene/ methylprednisolone/ adapalene/ tretinoin/ trifarotene; (anti-parkinson drugs) biperiden/ cabergoline/ pergolide/ rotigotine/ bromocriptine/ ropinirole/ rotigotine/ pramipexole/ bromocriptine/ cabergoline/ pergolide/ piribedil; (antianemic preparations) peginesatide; (antibacterials for systemic use) troleandomycin/ enoxacin; (antibiotics and chemotherapeutics for dermatological use) ingenol mebutate; (antidiarrheals) prednisone; (antihistamines for systemic use) cyproheptadine; (antihypertensives) ketanserin/ ketanserin; (antiinflammatory and antirheumatic products) celecoxib/ fenoprofen/ ketoprofen/ ketorolac/ meclofenamic acid/ mefenamic acid/ meloxicam/ naproxcinod/ oxaprozin/ phenylbutazone/ piroxicam/ sulindac/ suprofen/ celecoxib/ etodolac/ etoricoxib/ ketoprofen/ ketorolac/ lumiracoxib/ meclofenamic acid/ mefenamic acid/ meloxicam/ naproxcinod/ oxaprozin/ phenylbutazone/ piroxicam/ rofecoxib/ sulindac/ suprofen/ valdecoxib; (antineoplastic agents) ponatinib/ sorafenib/ nintedanib/ pazopanib/ sorafenib/ sunitinib/ bosutinib/ ruxolitinib/ bosutinib/ sorafenib/ vemurafenib/ ponatinib/ bosutinib/ dasatinib/ alectinib/ brigatinib/ ceritinib/ crizotinib/ lorlatinib/ daratumumab/ cediranib/ pazopanib/ belinostat/ panobinostat/ romidepsin/ vorinostat/ epacadostat/ ponatinib/ ibrutinib/ bermekimab/ atezolizumab/ avelumab/ durvalumab; (antiobesity preparations) orlistat; (antiprotozoals) eflornithine; (antipsoriatics) tazarotene/ tazarotene; (antithrombotic agents) beraprost/ treprostinil/ iloprost/ iloprost/ iloprost/ treprostinil; (antivirals for systemic use) ritonavir; (beta blocking agents) pindolol/ alprenolol/ atenolol/ bupranolol/ carvedilol/ labetalol/ metoprolol/ nadolol/ propranolol/ sotalol/ timolol; (calcium channel blockers) nimodipine/ mibefradil; (cardiac therapy) adenosine/ isoprenaline/ propafenone/ fenoldopam; (corticosteroids) budesonide/ prednisolone/ budesonide/ desoximetasone/ difluprednate/ fluorometholone/ mometasone/ triamcinolone/ prednisolone; (diuretics) eplerenone/ spironolactone; (drugs for acid related disorders) enprostil/ enprostil/ pirenzepine; (drugs for constipation) linaclotide/ plecanatide; (drugs for functional gastrointestinal disorders) clidinium/ dicyclomine/ hexocyclium/ propantheline/ domperidone; (drugs for obstructive airway diseases) aclidinium/ ipratropium/ tiotropium/ umeclidinium/ fenoterol/ formoterol/ indacaterol/ olodaterol/ orciprenaline/ procaterol/ vilanterol/ salmeterol/ salbutamol/ terbutaline/ ciclesonide/ fluticasone; (endocrine therapy) apalutamide/ bicalutamide/ enzalutamide/ flutamide/ nilutamide; (gynecological antiinfectives and antiseptics) ketoconazole; (immunostimulants) plerixafor; (immunosuppressants) baricitinib/ tofacitinib/ tildrakizumab/ siltuximab/ sirukumab/ etanercept/ adalimumab/ certolizumab pegol/ golimumab/ infliximab; (lipid modifying agents) dextrothyroxine; (muscle relaxants) alcuronium; (nasal preparations) dexamethasone/ dexamethasone/ flunisolide/ betamethasone; (ophthalmologicals) echothiophate/ physostigmine/ bromfenac/ diclofenac/ indomethacin/ tafluprost/ bimatoprost/ atropine/ tropicamide/ nandrolone/ ephedrine/ betaxolol/ levobunolol/ diclofenac/ indomethacin/ fluocinolone acetone; (other alimentary tract and metabolism products) miglustat; (other dermatological preparations) dupilumab/ crisaborole/ alitretinoin/ alitretinoin; (other gynecologicals) ibuprofen/ naproxen/ sulprostone/ metergoline/ ibuprofen/ naproxen/ lisuride/ lisuride/ terguride; (other hematological agents) icatibant; (other nervous system drugs) neostigmine/ pyridostigmine/ cevimeline/ bethanechol/ pilocarpine; (otologicals) fludrocortisone; (pituitary and hypothalamic hormones and analogues) lanreotide/ octreotide/ pasireotide/ vapreotide; (psychoanaleptics) donepezil/ galantamine/ rivastigmine/ tacrine/ nefazodone/ amitriptyline/ dosulepin/ vinpocetine/ mianserin/ vortioxetine/ vilazodone; (psycholeptics) scopolamine/ cyamemazine/ haloperidol/ iloperidone/ lurasidone/ olanzapine/ chlorpromazine/ clozapine/ fluphenazine/ perphenazine/ risperidone/ thioridazine/ ziprasidone/ zotepine/ chlorpromazine/ clozapine/ flupentixol/ fluphenazine/ haloperidol/ mesoridazine/ periciazine/ prochlorperazine/ thioridazine/ cariprazine/ chlorpromazine/ clozapine/ flupentixol/ haloperidol/ loxapine/ mesoridazine/ pimozide/ prochlorperazine/ promazine/ risperidone/ sertindole/ sulpiride/ zotepine; (sex hormones and modulators of the genital system) drospirenone/ fluoxymesterone/ methyltestosterone/ cyproterone acetate/ mifepristone/ mifepristone; (stomatological preparations) amlexanox; (thyroid therapy) tiratricol/ methimazole/ propylthiouracil; (topical products for joint and muscular pain) flurbiprofen/ nimesulide/ flurbiprofen/ nimesulide; (urologicals) darifenacin/ oxybutynin/ solifenacin/ tolterodine/ yohimbine/ mirabegron/ apomorphine/ apomorphine; (vasoprotectives) flucinonide

Supplementary Figure 9. Candidate ligands and targetable genes after prioritization. 238 candidate ligands that may be repositioned for the treatment of COVID-19 infection.