

## **Supplementary Information**

### **Identification of new drug treatments to combat COVID19: A signature-based approach using iLINCS**

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## Supplemental Figure Legends

**Figure S1. Tanimoto coefficient correlogram.** Heat map showing the Tanimoto coefficients of the 9 drugs with antiviral indications that comprise drug groupings 1-5 (x-axis) and the 14 candidate repurposable drugs identified in this study (y-axis). The Tanimoto coefficient, which represents the degree of structural similarity between two compounds, was computed using binary chemical fingerprints for each of the drugs. Coefficients range from 0 (no structural similarity) to 1 (exact structural similarity). In this analysis, Tanimoto coefficients ranged from 0.1 - 0.59, suggesting low to moderate structural similarity between antiviral treatments currently in use for treating coronavirus family pathogens and the identified candidate drugs.

**Figure S2. Heat map of disease signatures.** Unsupervised clustering of Library of Integrated Network-Based Cellular Signature (LINCS) L1000 genes, extracted from RNAseq datasets of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome-related coronavirus (MERS) (GSE56192). L1000 genes were also extracted from an Influenza A (INFL) microarray dataset (GSE47963) as a non-coronavirus pathogen comparison group. This heat map shows clustering of coronavirus pathogens SARS and MERS in contrast to INFL.

**Figure S3. Heat map of drug groupings 1-5 (MCF7 cell line).** Unsupervised clustering of Library of Integrated Network-Based Cellular Signature (LINCS) L1000 genes, extracted from RNAseq datasets of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome-related coronavirus (MERS) (GSE56192). L1000 genes were also extracted from an Influenza A (INFL) microarray dataset (GSE47963) as a non-coronavirus pathogen comparison group. L1000 genes were also extracted from five drug groupings (drug clusters 1-5) which represent drugs currently in use to treat coronavirus pathogens. Drug clusters signatures were extracted from the MCF7 cell line. Drugs are clustered based on mechanism of action, ATC

classification and/or structural similarity. Furosemide (FUR), a drug which is not utilized in the treatment of viral pathogens, was utilized as a comparison group. Drug group signatures were calculated by taking the average logFoldChange of each of the drugs within the cluster to represent the gene expression. This heat map provides an overview of the difference in patterns of gene expression between drug target groupings and disease in the MCF7 cell line, demonstrating discordance between drugs used as antivirals and disease signatures. Drug cluster 1: chloroquine and hydroxychloroquine, Drug cluster 2: Lopinavir and Ritonavir, Drug cluster 3: Fedratinib, Ruxolinitib, and Baricitinib. Drug cluster 4: azithromycin, and Drug cluster 5: Losartan.

**Figure S4. Heat map of drug target groupings 1-5 (HA1E cell line).** Unsupervised clustering of Library of Integrated Network-Based Cellular Signature (LINCS) L1000 genes, extracted from RNAseq datasets of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome-related coronavirus (MERS) (GSE56192). L1000 genes were also extracted from an Influenza A (INFL) microarray dataset (GSE47963) as a non-coronavirus pathogen comparison group. L1000 genes were also extracted from five drug groupings (drug clusters 1-5) which represent drugs currently in use to treat coronavirus pathogens. Drug clusters signatures were extracted from the HA1E cell line. Drugs are clustered based on mechanism of action, ATC classification and/or structural similarity. Furosemide (FUR), a drug which is not utilized in the treatment of viral pathogens, was utilized as a comparison group. Drug group signatures were calculated by taking the average logFoldChange of each of the drugs within the cluster to represent the gene expression. This heat map provides an overview of the difference in patterns of gene expression between drug target groupings and disease in the HA1E cell line, demonstrating discordance between drugs used as antivirals and disease signatures. Drug cluster 1: chloroquine and hydroxychloroquine, Drug cluster 2: Lopinavir and Ritonavir, Drug

cluster 3: Fedratinib, Ruxolinitib, and Baricitinib. Drug cluster 4: azithromycin, and Drug cluster 5: Losartan.

**Figure S5. Biological Pathway analysis of disease and drug target grouping signatures from MCF7 cell line.** Gene lists for drug target groupings 1-5 consisting of L1000 genes at LFC +/- 0.85 were searched in Reactome. Pathways for drug groupings 1 - 3 were determined by p-value < 0.05, and “Entities Found” ≥ 10, and groupings 4 and 5 were determined by p-value < 0.05, and “Entities Found” ≥ 3. Gene lists for disease signatures consisting of L1000 genes at LFC ≥ 0.5 and ≤ -0.5 were searched in Reactome. Pathways were determined by p-value < 0.05, and “Entities Found” ≥ 6. Drug cluster 1: chloroquine and hydroxychloroquine, Drug cluster 2: Lopinavir and Ritonavir, Drug cluster 3: Fedratinib, Ruxolinitib, and Baricitinib. Drug cluster 4: azithromycin, and Drug cluster 5: Losartan.

**Figure S6. Biological Pathway analysis of disease and drug target grouping signatures from HA1E cell line.** Gene lists for drug target groupings 1-5 consisting of L1000 genes at LFC +/- 0.85 were searched in Reactome. Pathways for drug groupings 1 - 3 were determined by p-value < 0.05, and “Entities Found” ≥ 10, and groupings 4 and 5 were determined by p-value < 0.05, and “Entities Found” ≥ 3. Gene lists for disease signatures consisting of L1000 genes at LFC ≥ 0.5 and ≤ -0.5 were searched in Reactome. Pathways were determined by p-value < 0.05, and “Entities Found” ≥ 6. Drug cluster 1: chloroquine and hydroxychloroquine, Drug cluster 2: Lopinavir and Ritonavir, Drug cluster 3: Fedratinib, Ruxolinitib, and Baricitinib. Drug cluster 4: azithromycin, and Drug cluster 5: Losartan.

**Figure S7. Heat map of 14 candidate drugs (MCF7 cell line).** Unsupervised clustering of Library of Integrated Network-Based Cellular Signature (LINCS) L1000 genes, extracted from RNAseq datasets of severe acute respiratory syndrome (SARS) and Middle East respiratory

syndrome-related coronavirus (MERS) (GSE56192). L1000 genes were also extracted from an Influenza A (INFL) microarray dataset (GSE47963) as a non-coronavirus pathogen comparison group. L1000 gene signatures for the fourteen candidate drugs were generated from MCF7 cell line. Furosemide (FUR), a drug which is not utilized in the treatment of viral pathogens, was utilized as a comparison group. A heat map was constructed using the logFoldChange from LINCS. This heat map provides an overview of the difference in patterns of gene expression between the candidate drugs and disease in the MCF7 cell line, demonstrating discordance between these putative repurposable drugs and coronavirus disease signatures. AC1MJ3VH (AC1), AT-9283 (AT), Alvocidib (ALV), BRD-K54343811 (BRD), Broad-Sai (BRO), CHEMBL2136735 (CHE), COT-10B (COT), Genistein (GEN), GSK-1059615 (GSK), GSK3 Inhibitor-IX (GIX), Idebenone (IDB), Idelalisib (IDL), Ivermectin (IVE), Pencillin V (PEN).

**Figure S8. Heat map of top 8 candidate drugs (MCF7 cell line).** Unsupervised clustering of Library of Integrated Network-Based Cellular Signature (LINCS) L1000 genes, extracted from RNAseq datasets of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome-related coronavirus (MERS) (GSE56192). L1000 genes were also extracted from an Influenza A (INFL) microarray dataset (GSE47963) as a non-coronavirus pathogen comparison group. L1000 gene signatures for the 8 candidate drugs that are currently approved for use in humans were generated from MCF7 cell line. Furosemide (FUR), a drug which is not utilized in the treatment of viral pathogens, was utilized as a comparison group. A heat map was constructed using the logFoldChange from LINCS. This heat map provides an overview of the difference in patterns of gene expression between the candidate drugs and disease in the MCF7 cell line, demonstrating discordance between these putative repurposable drugs and coronavirus disease signatures. AT-9283 (AT), Alvocidib (ALV), Genistein (GEN), GSK-1059615 (GSK), Idebenone (IDB), Idelalisib (IDL), Ivermectin (IVE), Pencillin V (PEN)

**Figure S9. Heat map of 14 candidate drugs (HA1E cell line).** Unsupervised clustering of Library of Integrated Network-Based Cellular Signature (LINCS) L1000 genes, extracted from RNAseq datasets of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome-related coronavirus (MERS) (GSE56192). L1000 genes were also extracted from an Influenza A (INFL) microarray dataset (GSE47963) as a non-coronavirus pathogen comparison group. L1000 gene signatures for the fourteen candidate drugs were generated from HA1E cell line. Furosemide (FUR), a drug which is not utilized in the treatment of viral pathogens, was utilized as a comparison group. A heat map was constructed using the logFoldChange from LINCS. This heat map provides an overview of the difference in patterns of gene expression between the candidate drugs and disease in the HA1E cell line, demonstrating discordance between these putative repurposable drugs and coronavirus disease signatures. AC1MJ3VH (AC1), AT-9283 (AT), Alvocidib (ALV), BRD-K54343811 (BRD), Broad-Sai (BRO), CHEMBL2136735 (CHE), COT-10B (COT), Genistein (GEN), GSK-1059615 (GSK), GSK3 Inhibitor-IX (GIX), Idebenone (IDB), Idelalisib (IDL), Ivermectin (IVE), Pencillin V (PEN).

**Figure S10. Heat map of top 8 candidate drugs (HA1E cell line).** Unsupervised clustering of Library of Integrated Network-Based Cellular Signature (LINCS) L1000 genes, extracted from RNAseq datasets of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome-related coronavirus (MERS) (GSE56192). L1000 genes were also extracted from an Influenza A (INFL) microarray dataset (GSE47963) as a non-coronavirus pathogen comparison group. L1000 gene signatures for the 8 candidate drugs that are currently approved for use in humans were generated from HA1E cell line. Furosemide (FUR), a drug which is not utilized in the treatment of viral pathogens, was utilized as a comparison group. A heat map was constructed using the logFoldChange from LINCS. This heat map provides an overview of the difference in patterns of gene expression between the candidate drugs and disease in the HA1E

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**Figure S11. Biological Pathway analysis of disease and candidate repurposable drug signatures from MCF7 cell line.** Gene lists for candidate drugs consisting of L1000 genes at LFC +/- 0.85 were searched in Reactome. Pathways were determined by p-value < 0.05, and “Entities Found” ≥ 30. Gene lists for disease signatures consisting of L1000 genes at LFC ≥ 0.5 and ≤ -0.5 were searched in Reactome. Pathways were determined by p-value < 0.05, and “Entities Found” ≥ 6. AC1MJ3VH (AC1), AT-9283 (AT), Alvocidib (ALV), BRD-K54343811 (BRD), Broad-Sai (BRO), ChEMBL2136735 (CHE), COT-10B (COT), Genistein (GEN), GSK-1059615 (GSK), GSK3 Inhibitor-IX (GIX), Idebenone (IDB), Idelalisib (IDL), Ivermectin (IVE), Pencillin V (PEN).

**Figure S12. Biological Pathway analysis of disease and candidate repurposable drug signatures from HA1E cell line.** Gene lists for candidate drugs consisting of L1000 genes at LFC +/- 0.85 were searched in Reactome. Pathways were determined by p-value < 0.05, and “Entities Found” ≥ 30. Gene lists for disease signatures consisting of L1000 genes at LFC ≥ 0.5 and ≤ -0.5 were searched in Reactome. Pathways were determined by p-value < 0.05, and “Entities Found” ≥ 6. AC1MJ3VH (AC1), AT-9283 (AT), Alvocidib (ALV), BRD-K54343811 (BRD), Broad-Sai (BRO), ChEMBL2136735 (CHE), COT-10B (COT), Genistein (GEN), GSK-1059615 (GSK), GSK3 Inhibitor-IX (GIX), Idebenone (IDB), Idelalisib (IDL), Ivermectin (IVE), Pencillin V (PEN).

Figure S1

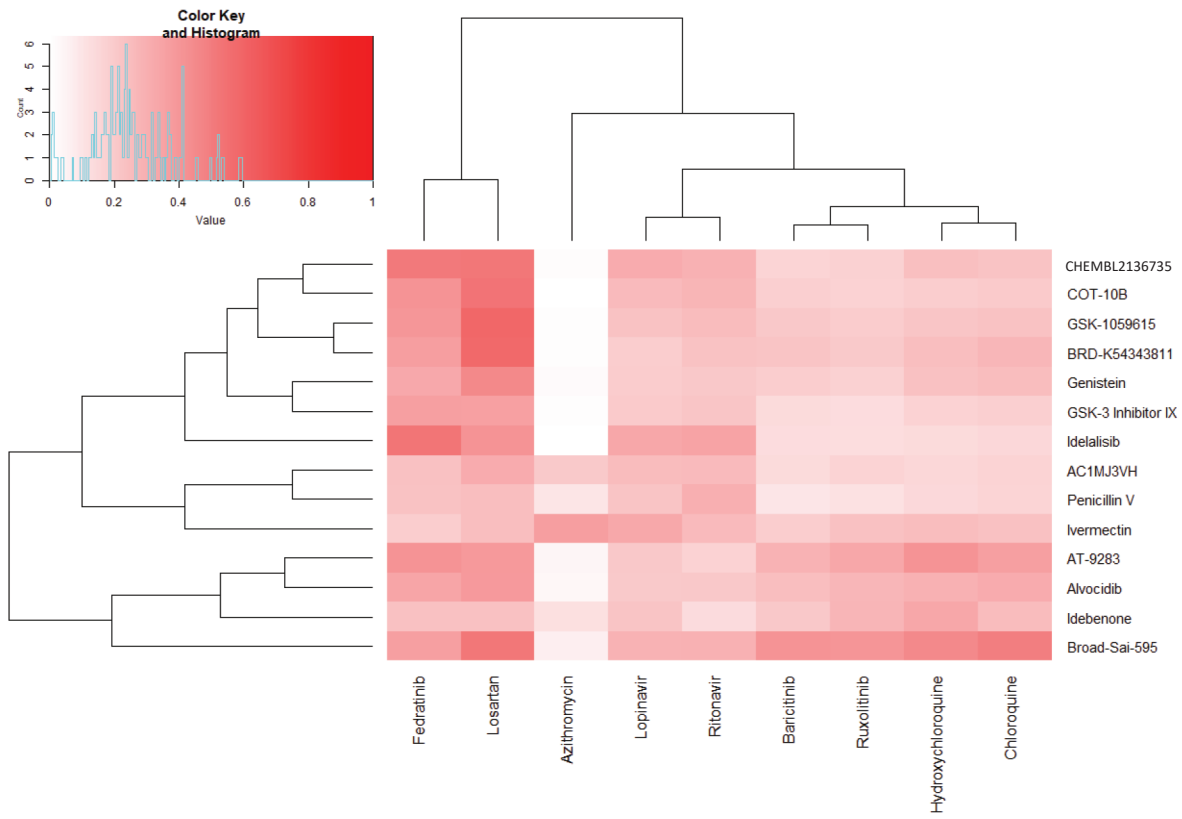




Figure S2

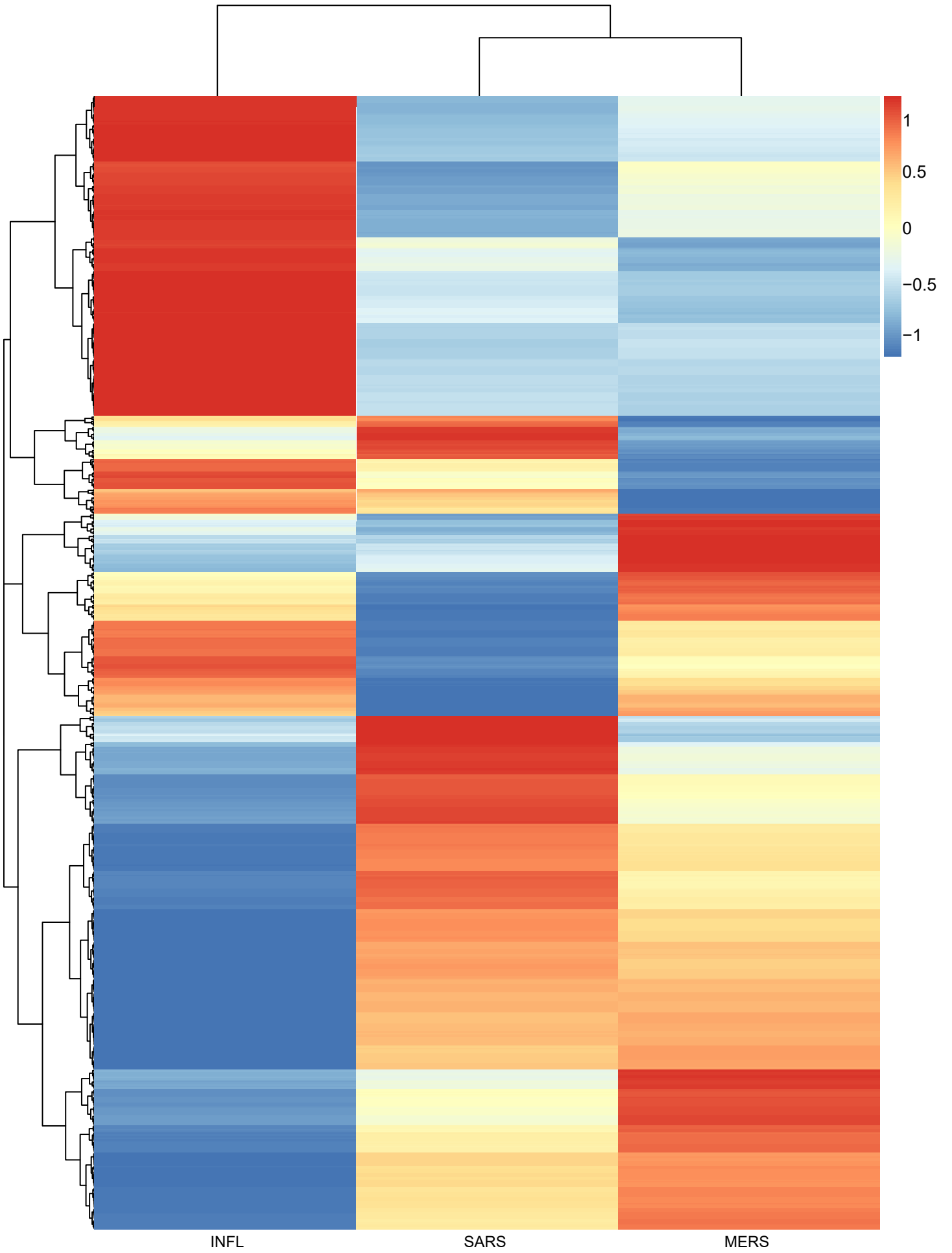


Figure S3

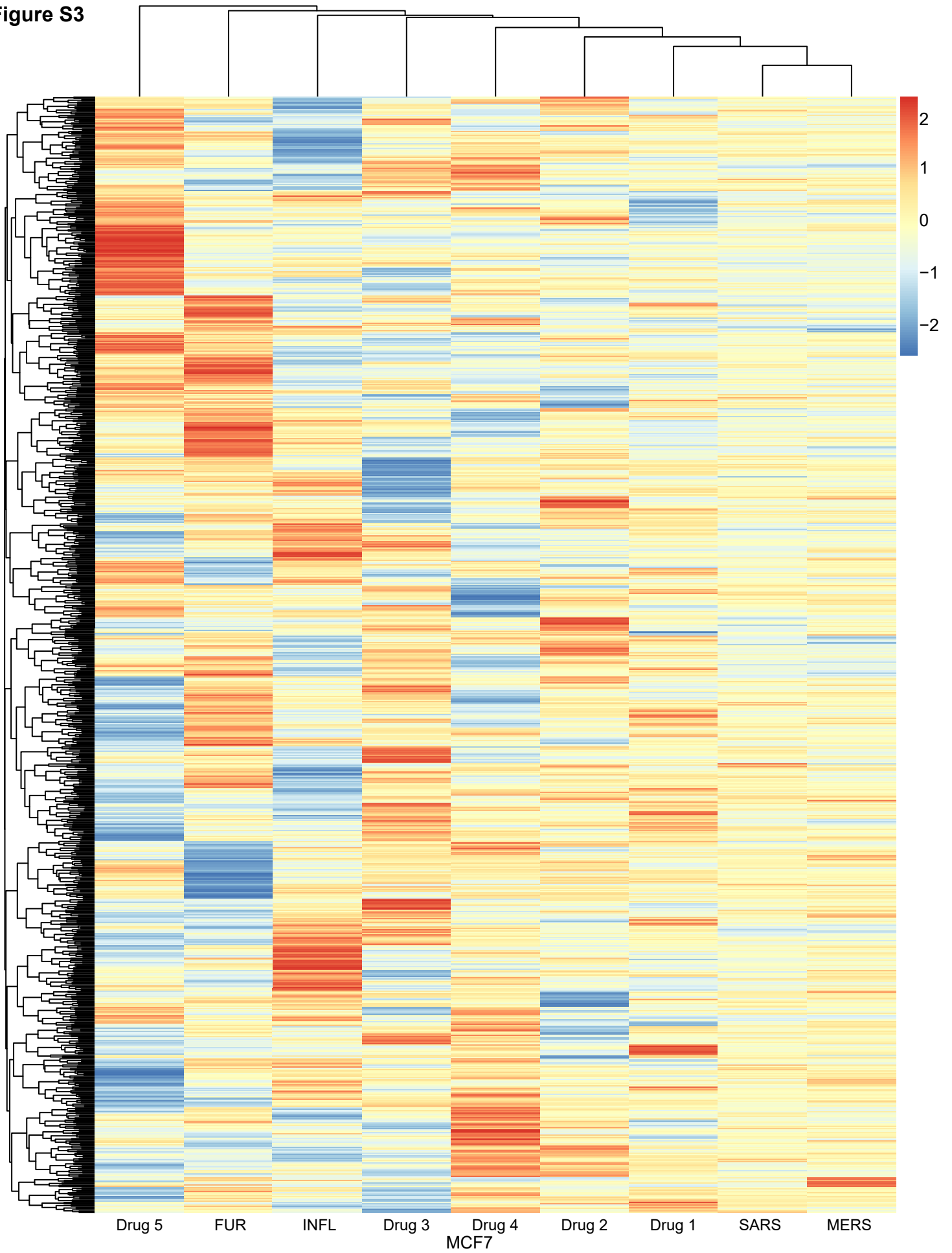
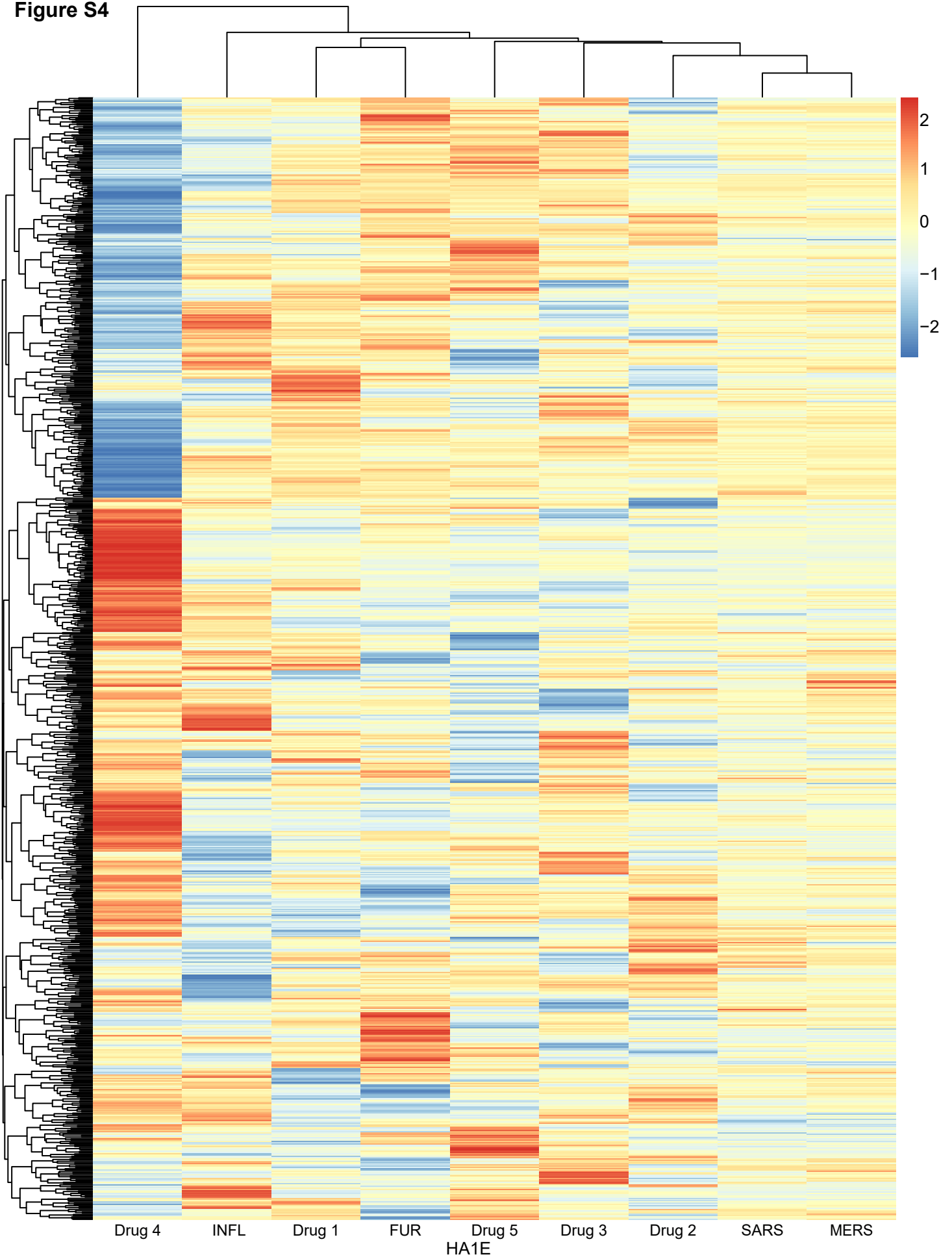


Figure S4



**Figure S5**

Biological Pathways		Drug Cluster					Disease		
		1	2	3	4	5	SARS	MERS	INFL
Cellular responses to external stimuli	Cellular responses to stress								
	Cellular response to heat stress								
	Cellular Senescence								
Cell-Cell Communication	Cell junction organization								
Cell Cycle	Cell Cycle Checkpoints								
	G2/M Checkpoints								
	Cell Cycle, Mitotic								
	Mitotic G1 phase and G1/S transition								
	S Phase								
	Mitotic G2-G2/M phases								
M Phase									
Developmental Biology	Nervous system development								
Disease	Diseases of signal transduction by growth factor receptors and second messengers								
	PI3K/AKT Signaling in Cancer								
DNA Repair									
Gene expression (Transcription)	RNA Polymerase II Transcription								
	Generic Transcription Pathway								
	Transcriptional Regulation by TP53								
Immune System	Cytokine Signaling in Immune system								
	Signaling by Interleukins								
	Interleukin-4 and Interleukin-13 signaling								
	Interleukin-10 signaling								
	FLT3 Signaling								
	TNFR2 non-canonical NF-kB pathway								
Innate Immune System									
TCR signaling									
Metabolism	Regulation of lipid metabolism by PPARalpha								
	Metabolism of steroids								
Metabolism of proteins	Post-translational protein modification								
	Ubiquitination								
	SUMOylation								
	SUMO E3 ligases SUMOylate target proteins								
Signal Transduction	Signaling by Nuclear Receptors								
	ESR-mediated signaling								
	Signaling by Receptor Tyrosine Kinases								
	Signaling by NTRKs								
	Signaling by PDGF								
	Signaling by WNT								
	TCF dependent signaling in response to WNT								
	Signaling by Rho GTPases								
	RHO GTPase Effectors								
	MAPK family signaling cascades								
	MAPK1/MAPK3 signaling								
	Intracellular signaling by second messengers								
	PIP3 activates AKT signaling								

MCF7 Cell Line

Figure S6

	Biological Pathways	Drug Cluster					Disease		
		1	2	3	4	5	SARS	MERS	INFL
Cellular responses to external stimuli	Cellular responses to stress Cellular response to heat stress Cellular Senescence								
Cell-Cell communication									
Cell Cycle	Cell Cycle Checkpoints G1/S DNA Damage Checkpoints G2/M Checkpoints Cell Cycle, Mitotic Mitotic G1 phase and G1/S transition S Phase Mitotic G2-G2/M phases M Phase Regulation of mitotic cell cycle								
Chromatin organization	Chromatin modifying enzymes								
Developmental Biology	Nervous system development Axon guidance								
Disease	Infectious disease HIV Infection Diseases of signal transduction by growth factor receptors and second messengers PI3K/AKT Signaling in Cancer								
DNA Repair	Base Excision Repair Resolution of Abasic Sites (AP sites) DNA Double-Strand Break Repair Homology Directed Repair Nucleotide Excision Repair Transcription-Coupled Nucleotide Excision Repair (TC-NER) Global Genome Nucleotide Excision Repair (GG-NER)								
DNA Replication	Synthesis of DNA DNA strand elongation Switching of origins to a post-replicative state DNA Replication Pre-Initiation								
Extracellular matrix organization	Degradation of the extracellular matrix								
Gene expression (Transcription)	RNA Polymerase II Transcription Generic Transcription Pathway Transcriptional Regulation by TP53 Regulation of TP53 Activity Epigenetic regulation of gene expression								
Hemostasis	Platelet activation, signaling and aggregation								
Immune System	Cytokine Signaling in Immune system Signaling by Interleukins Interleukin-4 and Interleukin-13 signaling Interleukin-10 signaling FLT3 Signaling Interferon Signaling Innate Immune System Neutrophil degranulation Toll-like Receptor Cascades C-type lectin receptors (CLRs) Fc epsilon receptor (FCER1) signaling Adaptive Immune System Signaling by the B Cell Receptor (BCR)								
Metabolism	Metabolism of lipids Regulation of lipid metabolism by PPARalpha Metabolism of carbohydrates Glucose metabolism								
Metabolism of proteins	Post-translational protein modification Deubiquitination SUMOylation SUMO E3 ligases SUMOylate target proteins Neddylation Unfolded Protein Response (UPR) IRE1alpha activates chaperones								
Metabolism of RNA	Regulation of mRNA stability by proteins that bind AU-rich elements								
Programmed Cell Death	Apoptosis Intrinsic Pathway for Apoptosis								
Signal Transduction	Signaling by Nuclear Receptors ESR-mediated signaling Signaling by Receptor Tyrosine Kinases Signaling by NTRKs Signaling by VEGF MAPK family signaling cascades MAPK1/MAPK3 signaling MAPK6/MAPK4 signaling Intracellular signaling by second messengers PIP3 activates AKT signaling Signaling by NOTCH Signaling by WNT TCF dependent signaling in response to WNT Signaling by Non-Receptor Tyrosine Kinases Signaling by PTK6 Signaling by Hedgehog Hedgehog 'off' state								

HA1E Cell Line

Figure S7

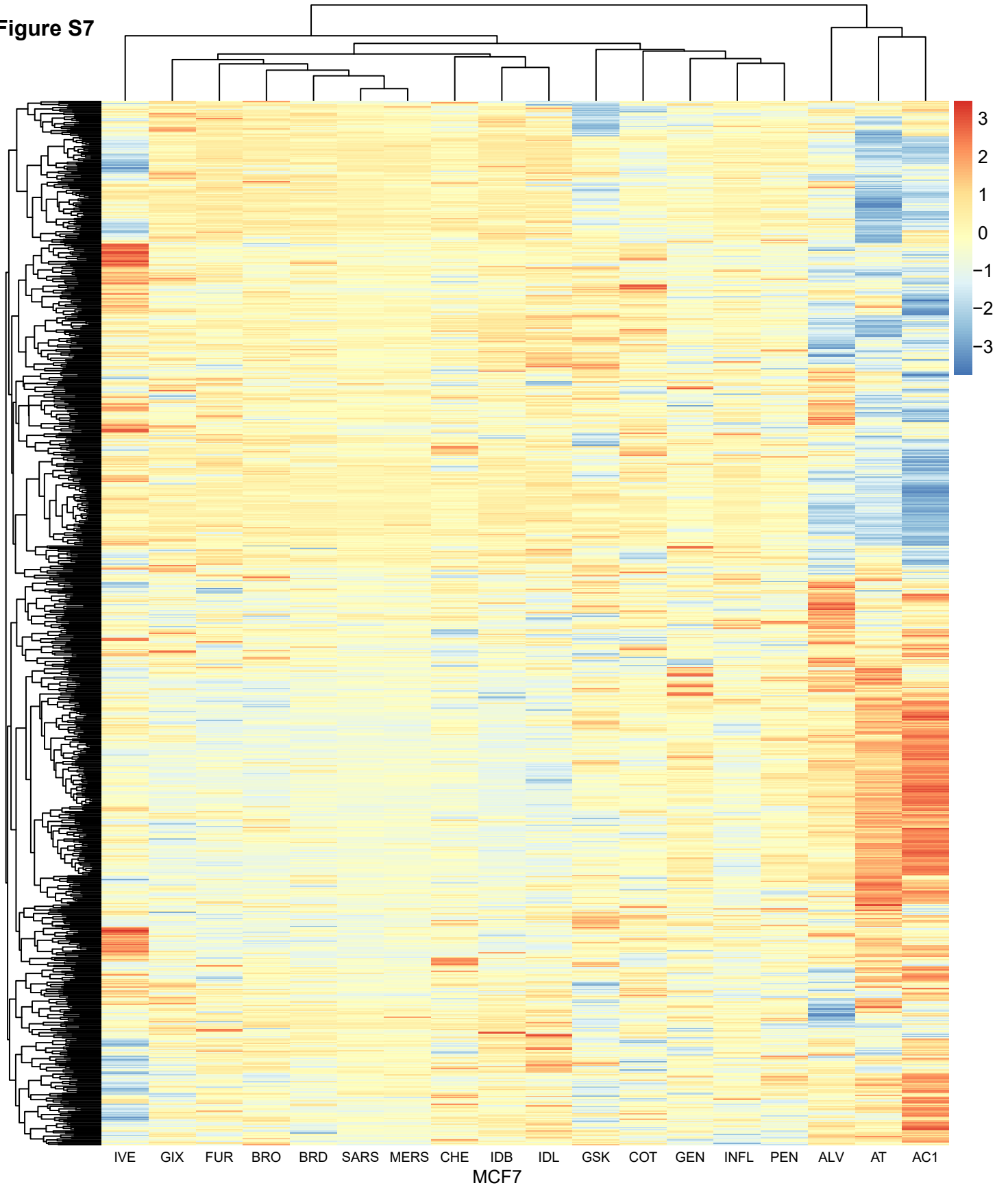


Figure S8

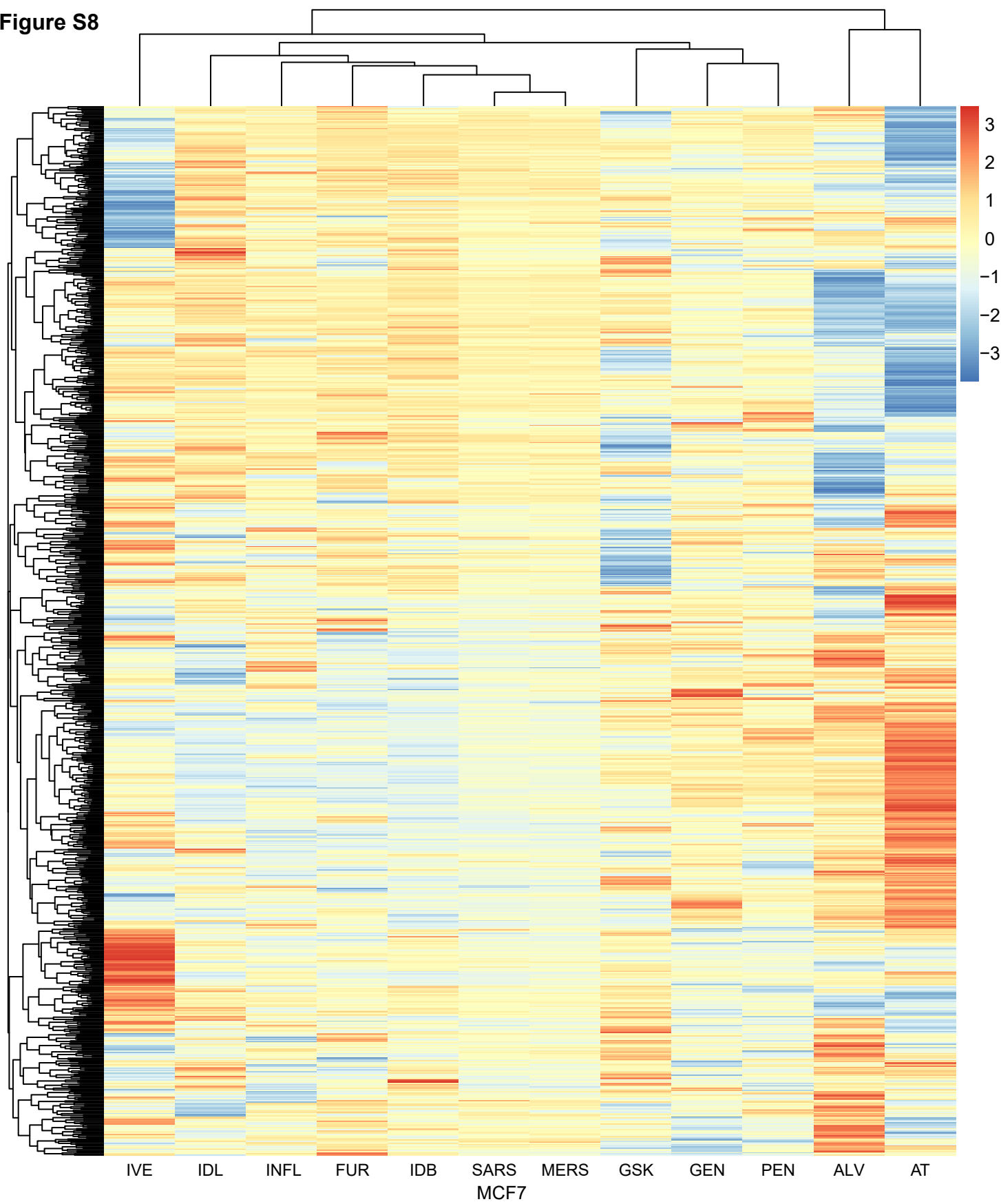


Figure S9

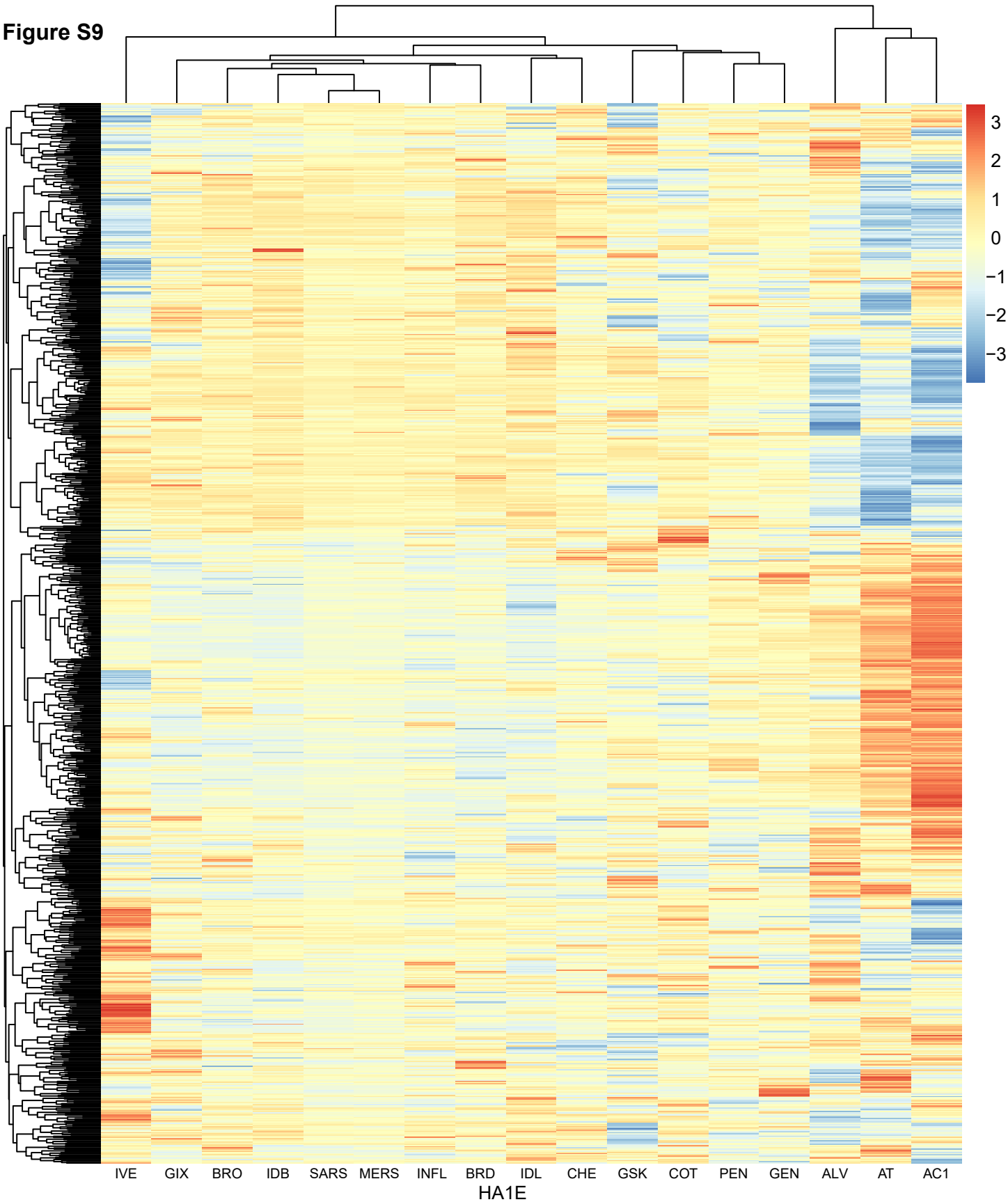




Figure S10

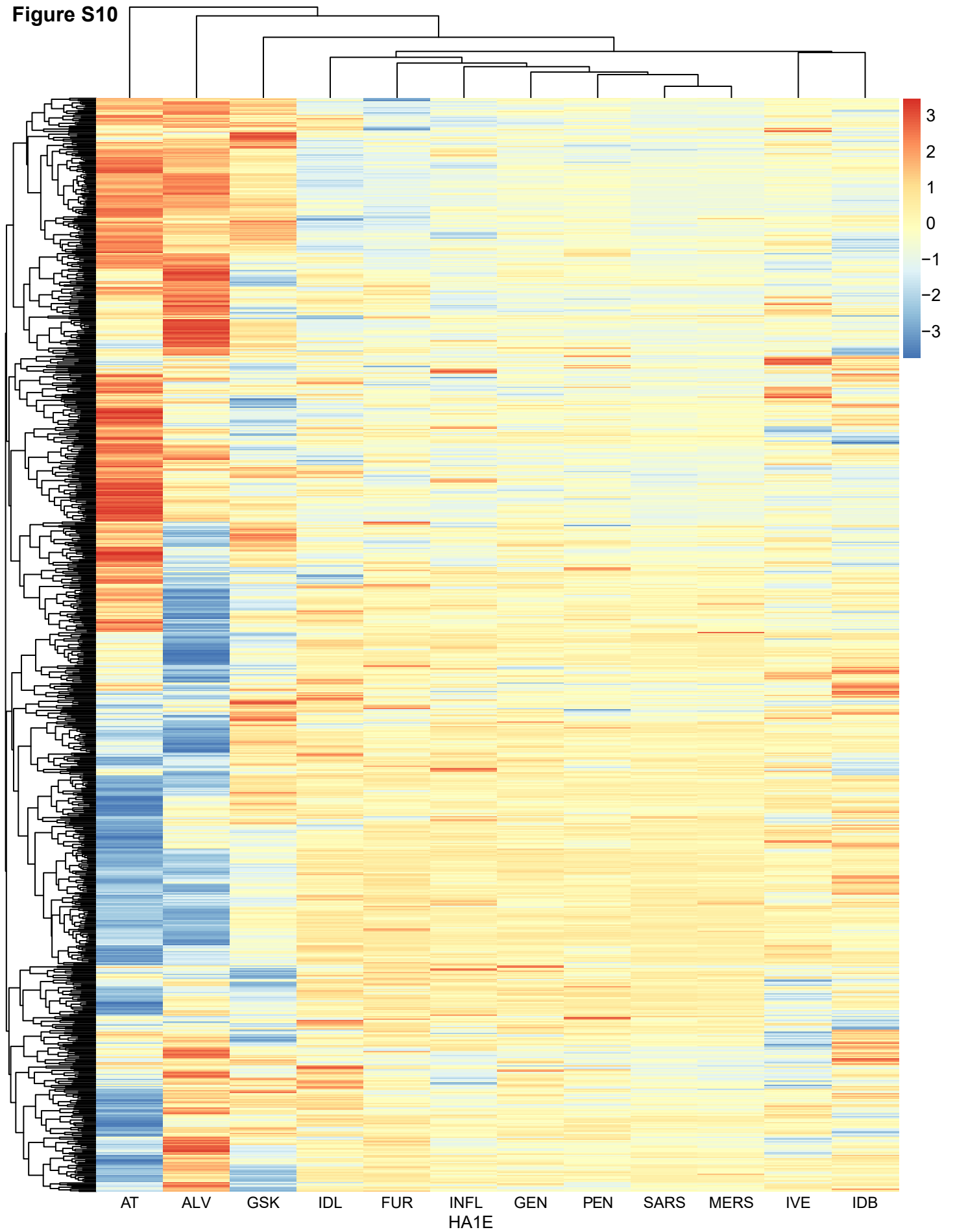


Figure S11

Biological Pathways		Candidate Drugs													Disease			
		AC1	ALV	AT	BRO	CHE	COT	GEN	GIX	GSK	IDB	IDL	IVE	PEN	SARS	MERS	INFL	
Cellular responses to external stimuli	Cellular responses to stress																	
	Cellular Senescence																	
Cell Cycle	Cell Cycle Checkpoints																	
	G2/M Checkpoints																	
	Cell Cycle, Mitotic																	
	Mitotic G1 phase and G1/S transition																	
	S Phase																	
Developmental Biology	Mitotic G2-G2/M phases																	
	M Phase																	
Disease	Nervous system development																	
	Axon guidance																	
Disease	Infectious disease																	
	HIV Infection																	
Disease	Diseases of signal transduction by growth factor receptors and second messengers																	
DNA Repair																		
Extracellular matrix organization																		
Gene expression (Transcription)	RNA Polymerase II Transcription																	
	Generic Transcription Pathway																	
	Transcriptional Regulation by TP53																	
Hemostasis	Platelet activation, signaling and aggregation																	
Immune System	Cytokine Signaling in Immune system																	
	Signaling by Interleukins																	
	Interleukin-4 and Interleukin-13 signaling																	
	Interleukin-10 signaling																	
	FLT3 Signaling																	
Metabolism of proteins	Innate Immune System																	
	Neutrophil degranulation																	
Metabolism of proteins	Post-translational protein modification																	
	Deubiquitination																	
	SUMOylation																	
Metabolism of proteins	SUMO E3 ligases SUMOylate target proteins																	
Metabolism of RNA																		
Programmed Cell Death	Apoptosis																	
Signal Transduction	Signaling by Nuclear Receptors																	
	ESR-mediated signaling																	
	Signaling by Receptor Tyrosine Kinases																	
	Signaling by NTRKs																	
	MAPK family signaling cascades																	
	MAPK1/MAPK3 signaling																	
	Intracellular signaling by second messengers																	
	PIP3 activates AKT signaling																	
	Signaling by NOTCH																	
	Signaling by WNT																	
	TCF dependent signaling in response to WNT																	
	Signaling by Rho GTPases																	
RHO GTPase Effectors																		

MCF7 Cell Line

**Figure S12**

Biological Pathways		Candidate Drugs													Disease		
		ACL	ALV	AT	BRO	CHE	COT	GEN	GIX	GSK	IDB	IDL	IVE	PEN	SARS	MERS	INFL
Cellular responses to external stimuli	Cellular responses to stress Cellular Senescence																
Cell Cycle	Cell Cycle Checkpoints G2/M Checkpoints Cell Cycle, Mitotic Mitotic G1 phase and G1/S transition S Phase Mitotic G2-G2/M phases M Phase																
Chromatin organization	Chromatin modifying enzymes																
Developmental Biology	Nervous system development Axon guidance																
Disease	HIV Infection Diseases of signal transduction by growth factor receptors and second messengers																
DNA Repair																	
Gene expression (Transcription)	RNA Polymerase II Transcription Generic Transcription Pathway Transcriptional Regulation by TP53																
Hemostasis	Platelet activation, signaling and aggregation																
Immune System	Cytokine Signaling in Immune system Signaling by Interleukins Interleukin-4 and Interleukin-13 signaling Interleukin-10 signaling FLT3 Signaling Innate Immune System Neutrophil degranulation																
Metabolism of proteins	Post-translational protein modification Ubiquitination SUMOylation SUMO E3 ligases SUMOylate target proteins																
Programmed Cell Death	Apoptosis																
Signal Transduction	Signaling by Nuclear Receptors ESR-mediated signaling Signaling by Receptor Tyrosine Kinases Signaling by NTRKs MAPK family signaling cascades MAPK1/MAPK3 signaling Intracellular signaling by second messengers PIP3 activates AKT signaling Signaling by NOTCH Signaling by WNT Signaling by Rho GTPases RHO GTPase Effectors																

HA1E Cell Line

**Table S1.** Selected drugs with transcriptional profiles in the Library for Integrated Network-Based Cellular Signatures database which were used for input.

Drug	Trade Names	Clinical Indication	Target	Canonical Mechanism of Action and Clusters	Anatomical Chemical Therapeutic Classification	Literature Citing Relevance to SARS-CoV-2 and/or Coronaviridae	Putative Effect on SARS-CoV-2
<b>Drugs with iLINCS signature present.</b>							
Hydroxychloroquine [1]	Plaquenil	Malaria; Immunosuppressant	Toll-like receptor 9; Toll-like receptor 7	Toll-like receptor antagonist	Antiparasitic products, insecticides and repellents	[2-4]	Alkalization of phagolysosome; modification of post-translation protein modifications [5, 6]
Chloroquine [7]	Aralen	Malaria; Amebiasis	Toll-like receptor 9 Glutathione S-transferase (A2); High mobility group protein B1; tumor necrosis factor				
Lopinavir [8]	Kaletra / Aluvia (with Ritonavir)	HIV/AIDS Antiviral Therapy	Human immunodeficiency virus type 1 protease	Protease inhibitor	Antiinfectives for systemic use	[9-12]	Inhibition of CoV-polyprotein processing [9, 13]
Ritonavir [14]	Norvir; Kaletra /Aluvia (with Lopinavir)						
Fedratinib [15]	Inrebic	Antineoplastic	Tyrosine-protein kinase JAK2; Receptor-type tyrosine-protein kinase FLT3	JAK Inhibitor	Antineoplastic and immunomodulating agents	[16]	Inhibition of clathrin-mediated viral endocytosis; mediation of inflammatory response, attenuation of cytokine storms from prolonged infection [16, 17]
Ruxolitinib [18]	Jakafi, Jakavi	Antineoplastic	Tyrosine-protein kinase JAK1 and JAK2				
Baricitinib [19]	Olumiant, Baricinix	Immunosuppressant	Tyrosine-protein kinase JAK1, JAK2, and JAK3; Protein-tyrosine kinase 2-beta				
Azithromycin [20]	Act Azithromycin, AzaSITE,	Bacterial infections	23S Ribosomal RNA; Protein-arginine deaminase type-4	Inhibition of bacterial protein synthesis	Antiinfectives for systemic use	[4]	Adjunct therapy with hydroxychloroquine.

	Zithromax, Zmax						
Losartan [21]	Act Losartan, Cozaar	Hypertension	Type-1 angiotensin II (AGII) receptor	AGII receptor antagonist	Cardiovascular system	[22]	Angiotensin receptor blocker.
<b>Drugs with iLINCS signature not present.</b>							
Remdesivir [23]	Remdesivir	Ebola	Replicase polyprotein 1ab; RNA-directed RNA polymerase L	Nucleoside analog, inhibition of viral RNA polymerase	No record	[24-27]	Inhibition of RNA dependent RNA polymerase [27]
Rocaglate	Not found in DrugBank.				No record	[28]	Inhibition of viral translation [28].
Silvesterol	Not found in DrugBank.				No record	[28, 29]	Inhibition of viral translation [28].
Umifenovir [30]	Arbidol	Viral prophylaxis; Broad spectrum antiviral	Cytochrome P450 3A4, 2E1, 1A2, 2D6, 2C9, 3A5; UDP-glucuronosyltransferase 2B7, 1-9; Dimethylaniline monooxygenase 1, 3	Aromatic rings interfere with viral endocytosis, exocytosis, intracellular trafficking, and destabilize membranes	Antiinfectives for systemic use	[31-33]	No specific purported mechanism yet published.
N10169	Not found in DrugBank.				No record	[34]	Inhibition of pyrimidine biosynthesis [34].
Interferon Alphacon-1 [35]	Infergen	Antineoplastic	Interferon alpha/beta receptor 1, 2	Interferon receptor agonist, JAK activator	Antineoplastic and immunomodulating agents	[36, 37]	Upregulation of MHC 1 to present viral antigens.
<i>Polygonaceae spp.; Rheum palmatum L.</i>	Not found in DrugBank.				No record	[38, 39]	Inhibition of viral cell-entry by preventing interaction of CoV Spike Protein from interacting with ACE2 receptor [39]
Camostat mesylate [40]	N/A	Pancreatitis, Japan [41, 42]	N/A	Serine protease inhibitor TMPRSS2	Blood and blood forming organs	[43-45]	Inhibition of viral cell-entry [43]

Information relating to these drugs (trade name, clinical indication, targets, and canonical mechanism of action) were referenced from DrugBank (<https://www.drugbank.ca/>). Anatomical Therapeutic Chemical (ATC) classification was referenced from ([https://www.whooc.no/atc\\_ddd\\_index/](https://www.whooc.no/atc_ddd_index/)). For simplicity, the first-level of ATC classification is indicated.

**Table S2.** Gene threshold cutoff of generating disease signatures.

Disease	Cell Line	Perturbagens Identified at LFC threshold		
		All L1000	0.26	0.5
INFL	HA1E	1	0	0
	MCF7	0	0	0
MERS	HA1E	2	28	320
	MCF7	14	142	1305
SARS	HA1E	20	172	1352
	MCF7	21	706	2181

L1000 genes with expression change at log fold change (LFC) threshold 0.5 were selected to generate severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza (INFL) gene signatures. At this threshold, following connectivity analysis, a large number of chemical perturbagen signatures were identified as discordant to the SARS signature (discordance  $\leq -0.321$ ) in both MCF7 and HA1E cell lines. At the same threshold, no chemical perturbagens were identified as discordant to the INFL signature, and fewer than 50% of the number of perturbagens were identified in MERS compared to SARS.