COMPUTATIONAL ANDSTRUCTURAL BIOTECHNOLOGY J O U R N A L





journal homepage: www.elsevier.com/locate/csbj

L1000 connectivity map interrogation identifies candidate drugs for repurposing as SARS-CoV-2 antiviral therapies



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ARTICLE INFO

Article history: Received 22 October 2020 Received in revised form 25 November 2020 Accepted 28 November 2020 Available online 6 December 2020

Keywords: Drug repurposing Connectivity map Drug screening Coronavirus Antiviral TMPRSS2

ABSTRACT

Adaptive clinical trials are underway to determine the efficacy of potential therapies for COVID-19, with flexibility to include emerging therapies if there is sufficient preclinical evidence for their potential utility. *In silico* screening of connectivity maps, which link gene expression profiles to libraries of perturbagens, may facilitate the identification of such emerging therapies. The L1000 Connectivity Map is built from samples of transcripts taken from gene expression profiles of cells in various experimental conditions followed by computational inferences of the remainder of the transcriptome. Searching the L1000 Connectivity Map for modulators of a protease that facilitates coronavirus infection identifies plausible candidate drugs for repurposing as antiviral agents against SARS-CoV-2 following further investigation.

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The pace of propagation of the COVID-19 pandemic has necessitated a search for effective therapeutics for the disease. Adaptive clinical trials such as the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial (ISRCTN number ISRCTN50189673; ClinicalTrials.gov identifier NCT04381936; <u>https://www.recoverytrial.</u> <u>net/</u>) have facilitated the evaluation of plausible therapies while remaining flexible to incorporate study arms for emerging therapies as and when preclinical studies suggest their efficacy. The design of the RECOVERY trial in particular allows for its Trial Steering Committee to amend its protocol to include or exclude treatment arms in response to new evidence.

Computational screening of libraries of drugs and tool compounds may help to identify compounds with the potential to treat COVID-19. The translation of such compounds to the clinic may be accelerated if they are identified from libraries of drugs that have prior approval for other indications and therefore have known safety and interaction profiles. The L1000 Connectivity Map provides such a platform for *in silico* screening by cataloguing a sample of the gene expression profiles of cancer cell lines exposed to a library of perturbagens, with computational inference of the remainder of the transcriptomes with acceptable accuracy on the basis of the 978 measured transcripts [1]. Using data from the more limited predecessor to the L1000 Connectivity Map, Dudley and colleagues were able to repurpose the anticonvulsant medication topiramate to treat a rodent model of inflammatory bowel disease where topiramate had not previously been described to have efficacy for such an indication [2].

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which infects a target cell by engaging its spike (S) protein with the host cell receptor ACE2 and subsequently fusing its membrane with that of the cell. In order for the virion to enter the target cell, the S protein must be primed by the cellular serine protease TMPRSS2, the inhibition of which has been demonstrated to limit SARS-CoV-2 infection of a human lung cancer cell line *in vitro* [3]. Given this, I hypothesised that some of the perturbagens in the L1000 library would have caused a reduction in expression of *TMPRSS2* mRNA in the tested human lung cancer cell line, and furthermore, some of the identified perturbagens might be drugs with prior approvals for use in humans, meaning that they could plausibly be repurposed for use as sole or adjunctive antiviral therapies for COVID-19 after further *in vitro* and *in vivo* evaluation.

I searched the L1000 database using Genevestigator v8.0.1 (Nebion AG, Zürich). Genevestigator is a computer software platform that incorporates a suite of data analysis tools and a search engine for public high throughput functional genomics data that has been curated, quality controlled, annotated and normalised

https://doi.org/10.1016/j.csbj.2020.11.054

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Table 1

Change in TMPRSS2 expression in A549 cells exposed to perturbagens or DMSO control for 24 h. All listed drugs are approved by the United States Food and Drug Administration for various clinical indications. Asterisk (*) denotes p < 0.05. Dagger (†) denotes data only available from n = 2 experiments; n = 3 for all other experiments. DMSO = dimethyl sulfoxide; PI3K = phosphatidylinositol 3-kinase; ALK = anaplastic lymphoma kinase; JAK = Janus kinase; MEK = mitogen-activated protein kinase kinase.

AlpeisablPUT.19P3K inhibitor0.04-040.0120.37-0.690.0080.37-0.690.0683.33-0.500.0683.33-0.500.01850.10-0.520.01850.12-0.520.01850.12-0.520.01850.12-0.520.01850.12-0.520.01850.11-0.400.0211.11-0.410.0210.12-0.570.01810.13-0.760.01810.14-0.650.01810.15-0.760.01810.16-0.650.01810.17-0.650.03370.18-0.360.03170.19-0.410.2280.11-0.650.03170.12-0.360.03110.11-0.650.01150.12-0.360.01150.11-0.410.2280.11-0.650.01150.11-0.650.01150.12-0.510.01150.11-0.650.01150.11-0.410.2160.11-0.410.2160.11-0.650.01150.11-0.650.01150.11-0.650.01150.11-0.650.01150.11-0.650.01150.11-0.650.01550.11-0.650.01550.11-0.610.0150.11 <th>Perturbagen</th> <th>Drug class</th> <th>$Concentration \ (\mu M)$</th> <th>log_2 ratio change in <i>TMPRSS2</i> expression (perturbagen/DMSO)</th> <th>p value</th>	Perturbagen	Drug class	$Concentration \ (\mu M)$	log_2 ratio change in <i>TMPRSS2</i> expression (perturbagen/DMSO)	p value
0.12-0.6900011.11-0.750.04671.11-0.750.04671.11-0.520.1620.12-0.520.1620.12-0.520.1620.12-0.520.1620.11-0.440.2330.11-0.440.2330.12-0.690.043*0.12-0.690.043*0.11-0.440.0330.12-0.690.043*0.11-0.690.043*0.12-0.690.043*0.12-0.690.043*0.12-0.690.043*0.12-0.600.042*0.13-0.600.043*0.14-0.430.043*0.15-0.440.0370.16-0.430.043*0.17-0.510.043*0.11-0.510.0510.11-0.510.0510.11-0.510.031*0.12-0.510.031*0.14-0.550.031*0.150.11*-0.510.16-0.120.54*0.16-0.120.54*0.11-0.220.54*0.11-0.430.03*0.11-0.120.54*0.11-0.120.54*0.12-0.550.03*0.14-0.120.14*0.150.14*0.14*0.14-0.140.14*0.150.14*0.14*0.160	Alpelisib/BYL719	PI3K inhibitor	0.04	-0.94	0.012*
Crizotinib0.37-0.690.0683.33-0.500.1620.12-0.520.1620.12-0.520.1621.11-0.440.237-0.570.1361.11-0.440.2337-0.570.1367-0.570.1371.11-0.440.2337-0.670.0397-0.670.0398-0.760.0271.11-0.660.0279-0.760.0271.11-0.650.0271.11-0.660.0391.11-0.660.1091.11-0.660.1091.11-0.660.1091.11-0.610.1091.11-0.610.1091.11-0.610.1091.11-0.610.1091.11-0.610.1091.11-0.610.1091.11-0.610.0111.11-0.610.0111.11-0.610.0111.11-0.610.0111.11-0.610.0111.11-0.610.0121.11-0.610.0111.11-0.610.0121.11-0.610.0121.11-0.610.0121.11-0.610.0121.11-0.610.0141.11-0.610.0141.11-0.610.0141.11-0.610.014<	x ,		0.12	-0.97	0.010*
1.11-0.750.046'CrizotinibAK inhibitor0.12 °-0.520.12 °0.27-0.520.4850.12 °0.37-0.570.230.4850.37-0.570.230.4853.33-0.760.0430.0437-0.090.8440.0120.80101-0.090.8440.0120.800.12-0.680.0230.023111-0.650.0330.370.131-0.650.0330.37111-0.650.0310.37111-0.650.0310.37111-0.640.370.66111-0.650.0310.016111-0.650.0310.016111-0.650.0310.016111-0.650.0310.016111-0.650.0310.017111-0.650.0310.017111-0.650.0310.017111-0.650.0310.011111-0.650.0330.036111-0.650.0310.031111-0.650.0310.031111-0.650.0310.031111-0.650.0310.031111-0.650.0310.031111-0.650.0310.031111-0.650.0310.031111-0.650.0310.031111-0.650.031 <td></td> <td></td> <td>0.37</td> <td>-0.69</td> <td>0.068</td>			0.37	-0.69	0.068
10-0.500.160CriotinibAlK inhibitor0.12 -0.520.650.12 -0.520.4850.4851.11-0.440.2310.231Fefratinib/TC-10134AlZ kinase inhibitor0.100.041.11-0.090.8440.600.6420.12-0.680.0690.04221.11-0.650.0330.371.11-0.650.0330.371.11-0.610.0310.3361.11-0.610.0310.3611.11-0.690.0110.3361.11-0.690.0110.3361.11-0.690.0110.3361.11-0.690.0110.3361.11-0.690.0110.0111.11-0.690.0110.0111.11-0.690.0110.0111.11-0.610.0110.0111.11-0.610.0110.0111.11-0.610.0110.0111.11-0.610.0110.0111.11-0.610.0110.0111.11-0.610.0110.0111.11-0.610.0110.0111.11-0.610.0130.0131.11-0.610.0130.0211.11-0.610.0130.0211.11-0.610.0130.0211.11-0.610.0130.0211.11-0.610.0130.021<			1.11	-0.75	0.046*
CracentialIC-0.520.1620.37-0.570.1270.37-0.570.1230.33-0.760.043'1.11-0.440.040.04-0.090.043'0.04-0.090.043'0.04-0.090.043'0.04-0.090.043'0.04-0.090.042'0.12-0.680.002'0.111-0.610.022'0.111-0.610.022'0.111-0.610.022'0.111-0.610.02'0.111-0.610.02'0.111-0.610.03'0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.610.01''0.111-0.620.03''0.111-0.620.01''0.111-0.620.01''0.111-0.620.01''0.111-0.620.01''0.111-0.620.01''0.111-0.620.01''0.111-0.620.01''0.111-0.620.01''0.11			3.33	-0.50	0.186
CritotinibALK inhibitor0.12 †-0.320.4850.37-0.570.1271.11-0.440.231.33-0.760.043'0.42-0.090.8440.42-0.680.0690.41-0.650.0370.42-0.650.030'0.41-0.650.030'0.42-0.410.2780.42-0.410.2780.41-0.410.2780.42-0.360.030'0.41-0.290.041'0.42-0.360.031'0.41-0.290.011'0.42-0.260.031'0.41-0.290.011'0.42-0.260.031'0.41-0.410.011'0.42-0.450.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41-0.410.011'0.41 <td></td> <td></td> <td>10</td> <td>-0.52</td> <td>0.162</td>			10	-0.52	0.162
Fedratinib/TG-101348JAK2 kinase inhibitor0.370.670.2433.33-0.760.043'0.04-0.600.0120.050.0690.0210.12-0.680.0690.37-0.760.042'1.11-0.650.023'0.27-0.760.022'0.27-0.760.022'0.27-0.760.022'0.27-0.760.022'0.27-0.760.022'0.27-0.760.022'0.27-0.37-0.600.12-0.360.037'0.12-0.37-0.600.12-0.360.011'3.33-0.220.5640.11-0.450.011'3.33-0.220.5640.12-0.600.011'3.33-0.220.5640.11-0.420.0310.12-0.650.032'0.14-0.12-0.660.15-0.160.16-0.120.17-0.150.0340.11-0.150.024'0.12-0.360.024'0.11-0.210.025'0.11-0.120.025'0.11-0.120.025'0.11-0.120.025'0.11-0.120.025'0.12-0.130.016'0.14-0.140.025'0.150.16'0.16'0.16-0.220.016'0.17-0.15' </td <td>Crizotinib</td> <td>ALK inhibitor</td> <td>0.12 †</td> <td>-0.32</td> <td>0.485</td>	Crizotinib	ALK inhibitor	0.12 †	-0.32	0.485
Fedratinih/TG-101348JAC2 kinase inhibitor1.11-0.440.23Pedratinih/TG-101348JAC2 kinase inhibitor0.04-0.600.0420.12-0.680.0690.0420.37-0.760.0630.037J.11-0.650.0330.037J.11-0.610.0240.0440.12-0.360.0370.040.12-0.360.0360.036J.11-0.960.0190.19J.11-0.960.0190.019J.11-0.960.0119J.11-0.960.0119J.11-0.960.0119J.11-0.960.0119J.11-0.960.0119J.11-0.120			0.37	-0.57	0.127
Fedratinb/TG-101348 JAX2 kinase inhibitor 3.3 -0.76 0.043' 101 -0.00 0.844 0.12 0.084 0.12 -0.68 0.069 0.069 0.37 -0.76 0.042' 1.11 -0.65 0.0337 1.01 -0.76 0.042' 1.11 -0.65 0.0337 1.01 -0.12 0.04 0.023 Neratinib Tyrosine kinase inhibitor 0.04 -0.29 0.041 1.11 -0.66 0.036 0.036 0.036 1.11 -0.65 0.061 0.016 0.016 1.11 -0.65 0.061 0.061 0.016 0.011' 3.33 -0.25 0.054 0.083 0.037 -0.66 0.033 0.037 0.64 0.28 0.024 0.024 0.024 0.024 0.024 0.024 0.024 0.024 0.037 0.04 0.037 0.04 0.037 0.04 0.037 0.04 0.037<			1.11	-0.44	0.243
Pedratnih/TG-101348 AK2 kinase inhibitor 10 i - 0.09 0.04 0.060 0.012 0.12 -0.68 0.069 0.042 0.37 -0.76 0.043 3.33 -0.38 0.037 Peratinib Tyrosine kinase inhibitor 0.04 -0.29 0.041 0.04 -0.29 0.041 0.278 Nitotnib Peratinib/tor 0.04 -0.29 0.041 0.12 -0.36 0.019 0.373 -0.60 0.019 3.33 -0.22 0.564 0.037 -0.60 0.011' 3.33 -0.22 0.564 0.037 -0.60 0.011' 3.33 -0.22 0.564 0.037 -0.65 0.033 0.37 -0.65 0.031 0.374 0.374 0.374 1.11 -0.424 0.231 0.243 0.374 3.33 -0.65 0.334 0.374 0.374 1.11 -0.424 0.374 0.374			3.33	-0.76	0.043*
Fedratinib/TG-101348JAK2 kinase inhibitor0.04-0.600.120.12-0.680.0690.37-0.760.042°1.11-0.650.0833.33-0.380.30710-0.410.278Neratinib101-0.2911-0.660.036012-0.360.036013-0.960.0191.11-0.660.0360.333-0.220.56410-0.590.16111-0.4810.0310.610.04-0.810.37-0.600.01121.11-0.440.2433.33-0.560.0340.37-0.600.0121.11-0.440.2433.33-0.560.0340.37-0.420.2340.37-0.420.2541.11-0.250.0340.37-0.420.2540.37-0.420.2541.11-0.250.1410.27-0.520.1681.11-0.510.1763.33-0.610.1022.12-0.510.1673.33-0.610.1073.33-0.610.1073.33-0.610.1073.33-0.610.1061.11-0.720.0441.11-0.720.0441.11-0.720.0441.11-0.720.0441.11-0.55 <td< td=""><td></td><td></td><td>10 †</td><td>-0.09</td><td>0.844</td></td<>			10 †	-0.09	0.844
Neratinib0.12-0.680.0691.11-0.630.0833.33-0.380.0373.33-0.380.2781.0-0.410.2780.12-0.360.3360.37-0.600.3360.37-0.600.0191.11-0.960.01113.33-0.220.5641.11-0.590.1161.11-0.610.0310.12-0.650.0310.13-0.610.0310.14-0.610.0310.151.11-0.640.27-0.620.3340.37-0.620.3340.33-0.520.1381.11-0.440.2331.11-0.620.2340.33-0.520.2541.11-0.420.2631.11-0.210.5641.11-0.210.5641.11-0.230.2640.27-0.360.2541.11-0.210.5641.11-0.550.1410.27-0.840.0255elumetinib0.04-0.310.021Vemurafenib0.42-0.510.1421.11-0.520.1470.0241.11-0.520.1470.0241.11-0.520.1470.0241.11-0.510.1461.11-0.510.1461.11-0.520.1471.11-0.520.14	Fedratinib/TG-101348	JAK2 kinase inhibitor	0.04	-0.60	0.112
Neratinib Tyrosine kinase inhibitor 0.37 -0.76 0.083 Neratinib Tyrosine kinase inhibitor 0.04 -0.29 0.41 0.12 -0.36 0.336 0.336 0.12 -0.36 0.109 0.112 0.137 -0.60 0.109 0.011* 1.11 -0.96 0.011* 0.031* Nilotinib Bcr-Abl tyrosine kinase inhibitor 0.04 -0.81 0.031* 0.37 -0.60 0.116 0.112 0.116 Nilotinib Bcr-Abl tyrosine kinase inhibitor 0.04 -0.81 0.031* 0.37 -0.60 0.112 0.754 0.754 Nintedanib Tyrosine kinase inhibitor 0.04 -0.81 0.024* 0.37 -0.612 0.754 0.754 0.754 Nintedanib Tyrosine kinase inhibitor 0.04 -0.81 0.024* Nintedanib McK1/2 inhibitor 0.04 -0.81 0.024* Nintedanib Jard -0.21			0.12	-0.68	0.069
Neratinib 1.11 -0.65 0.083 Neratinib 10 -0.41 0.278 0.12 -0.36 0.330 0.337 0.12 -0.60 0.019 0.019 0.019 0.019 0.011* 1.11 -0.60 0.011* 0.051 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.011* 0.024* 0.031* 0.011* 0.024* 0.031* 0.011* 0.024* 0.031* 0.024* 0.031* 0.024* 0.031* 0.024* 0.031* 0.024* 0.033* 0.031* 0.024* 0.033* 0.031* 0.024* 0.033* 0.024* 0.033* 0.024* 0.033* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* 0.024* <td< td=""><td></td><td></td><td>0.37</td><td>-0.76</td><td>0.042*</td></td<>			0.37	-0.76	0.042*
Neratinib Tyrosine kinase inhibitor 0.04 -0.21 0.336 0.04 -0.29 0.441 0.336 0.37 -0.60 0.109 0.11° 0.33 -0.96 0.019 0.011° 3.33 -0.22 0.664 0.031° Nilotinib Bcr-Abl tyrosine kinase inhibitor 0.04 -0.81 0.031° Nilotinib ptr-Abl tyrosine kinase inhibitor 0.04 -0.81 0.031° Nintedanib Tyrosine kinase inhibitor 0.04 -0.81 0.0334 Nintedanib Tyrosine kinase inhibitor 0.04 -0.05 0.024° Nintedanib Tyrosine kinase inhibitor 0.04 -0.023 0.334 0.37 -0.42 0.263 0.024° 0.33 -0.36 0.024° 0.243 0.33 -0.36 0.024° 0.263 0.33 -0.36 0.024° 0.263 0.33 -0.37 -0.42 0.263 0.33 -0.31 0.264			1.11	-0.65	0.083
Neratinib10-0410.278Neratinib0.12-0.360.3360.12-0.360.3360.3360.13-0.600.0190.011*0.14-0.960.011*0.6641.11-0.960.011*0.6641.11-0.960.011*0.6641.11-0.590.1160.031*0.12-0.650.0830.031*0.33-0.660.031*0.6430.33-0.660.012*0.6540.12-0.650.0640.121.11-0.120.160.13*Nintedanib10-0.120.6540.24*1.11-0.12-0.650.13*0.24*Nintedanib10-0.12-0.380.31*Nintedanib10-0.12-0.380.31*1.11-0.210.5640.33*0.54*1.11-0.250.16*0.16*0.17*1.11-0.510.16*0.17*0.16*1.11-0.510.16*0.17*0.17*1.11-0.510.16*0.17*0.17*1.11-0.510.16*0.17*0.17*1.11-0.510.16*0.17*0.17*1.11-0.520.16*0.37*0.6610.37*1.11-0.510.16*0.37*0.16*0.37*1.11-0.510.16*0.37*0.16*0.37*1.11-0.520.16*0.1			3.33	-0.38	0.307
Neratinib Tyrosine kinase inhibitor 0.04 -0.29 0.441 0.37 -0.36 0.336 0.336 0.37 -0.60 0.019 1.11 -0.96 0.011 3.33 -0.22 0.564 10 -0.59 0.116 Nilotinib 0.42 -0.65 0.083 0.12 -0.60 0.112 0.374 1.11 -0.44 0.243 0.334 0.37 -0.60 0.12 0.754 Nintedanib Tyrosine kinase inhibitor 0.12 -0.36 0.344 0.33 -0.56 0.334 0.344 0.344 0.12 -0.36 0.344 0.344 0.344 0.37 -0.42 0.361 0.344 0.344 0.33 -0.36 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 <			10	-0.41	0.278
Nilotinib 0.12 -0.60 0.109 1.11 -0.96 0.011* 3.33 -0.22 0.564 1.11 -0.59 0.116 Nilotinib Bcr-Abl tyrosine kinase inhibitor 0.04 -0.81 0.031* 0.37 -0.60 0.011* 0.031* 0.011* 0.37 -0.60 0.012 0.116 0.37 -0.60 0.023* 0.024* 0.33 -0.56 0.033* 0.024* 0.11 -0.44 0.233* 0.024* 0.12 -0.36 0.024* 0.33* 0.12 -0.35 0.024* 0.34* 0.12 -0.36 0.024* 0.34* 0.12 -0.36 0.025* 0.026* 0.11 -0.21 0.36* 0.31* 0.12 -0.31 0.025* 0.36* 0.11 -0.21 0.31* 0.31* 0.33 -0.55 0.36* 0.37* 0.33	Neratinib	Tyrosine kinase inhibitor	0.04	-0.29	0.441
Nilotinib Bcr-Abl tyrosine kinase inhibitor 0.37 -0.60 0.011* 3.33 -0.22 0.564 0.116 10 -0.59 0.013* 0.12 -0.60 0.112 0.37 -0.60 0.138 1.11 -0.44 0.243 3.33 -0.56 0.138 3.33 -0.56 0.138 1.11 -0.44 0.243 Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.034 Nintedanib Tyrosine kinase inhibitor 0.04 -0.36 0.334 0.37 -0.42 0.263 0.364 0.37 -0.36 0.316 0.316 10 0.21 0.568 0.368 Ruxolitinib JAK1/2 inhibitor 0.04 -0.51 0.168 0.12 -0.52 0.661 0.028 Selumetinib MEK inhibitor 0.04 -0.51 0.107 0.37 -0.52 0.616 0.107			0.12	-0.36	0.336
1.11 -0.6 0.011* Nilotinib Ber-Abl tyrosine kinase inhibitor 0.04 -0.81 0.031* 0.12 -0.65 0.083 0.116 0.041* 0.37 -0.60 0.013* 0.112 1.11 -0.44 0.243 0.243 3.33 -0.56 0.038 0.118 1.11 -0.44 0.243 0.254 1.33 -0.56 0.024* 0.254 1.11 -0.42 0.263 0.224* 1.11 -0.22 0.263 0.244* 0.24 -0.36 0.234 0.263 1.11 -0.23 0.561 0.24* 3.33 -0.28 0.263 0.263 1.11 -0.21 0.568 0.141 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141 0.37 -0.52 0.168 0.177 5elumetinib MEK inhibitor 0.04 -0.51 0.176 0.37			0.37	-0.60	0.109
3.33 -0.22 0.564 Nilotinib Bcr-Abl tyrosine kinase inhibitor 0.04 -0.81 0.031* 0.12 -0.65 0.083 0.083 0.083 0.37 -0.60 0.112 1.11 0.243 Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.024* Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.024* 0.12 -0.36 0.334 0.37 -0.42 0.263 Nintedanib Tyrosine kinase inhibitor 0.04 -0.35 0.024* 0.334 0.37 -0.42 0.263 0.334 0.31 0.314 0.37 -0.42 0.263 0.316 0.31 0.316 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141 0.12 0.54 0.028 0.028 0.028 0.028 0.028 0.028 0.028 0.028 0.037 0.32 0.014 0.176 0.33 0.016 0.176 0.33			1.11	-0.96	0.011*
Nilotinib Bcr-Abl tyrosine kinase inhibitor 0.04 -0.59 0.031* 0.12 -0.65 0.083 0.07 -0.60 0.112 0.37 -0.60 0.112 0.12 0.112 0.112 3.33 -0.56 0.031 0.243 0.33 0.754 0.024* Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.024* 0.334 0.12 -0.36 0.263 0.334 0.334 0.334 0.37 -0.42 0.263 0.34 0.316 1.11 -0.23 0.561 0.34 0.368 0.37 -0.42 0.263 0.316 0.316 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141* 0.228 Selumetinib MEK inhibitor 0.04 -0.31 0.028 0.029 Selumetinib MEK inhibitor 0.04 -0.31 0.0402 0.017 0.37 -0.82 0.030* 0.176 0.37 0.04			3.33	-0.22	0.564
Niotinib Bcr-Abl tyrosine kinase inhibitor 0.04 -0.81 0.031 0.031* 0.12 -0.65 0.083 0.37 -0.60 0.112 1.11 -0.44 0.243 0.33 -0.56 0.034* Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.024* 0.754 Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.334 0.374 Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.334 0.334 Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.334 0.316 Nintedanib Tyrosine kinase inhibitor 0.04 -0.55 0.314 0.326 Ruxolitinib JAK1/2 inhibitor 0.04 -0.51 0.168 0.025* 0.37 -0.61 0.105 0.37 0.333 0.61 0.105 Selumetinib MEK inhibitor 0.04 -0.51 0.176 0.37 Vemurafenib B-raf inhibitor 0.04 -0.29			10	-0.59	0.116
0.12 -0.65 0.083 0.37 -0.60 0.112 1.11 -0.44 0.243 3.33 -0.56 0.138 3.33 -0.56 0.024* 10 -0.12 0.754 Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.024* 0.12 -0.36 0.334 0.37 -0.42 0.263 0.37 -0.42 0.263 0.316 0.316 0.33 -0.38 0.316 0.316 0.316 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141 0.11 -0.52 0.168 0.177 0.33 -0.61 0.022* Selumetinib MEK inhibitor 0.04 -0.31 0.028 0.030* 1.11 -0.55 0.146 0.37* 0.92 0.014* Vemurafenib MEK inhibitor 0.04 -0.31 0.402 0.37 -0.69 0.014* 0.146 0.33* 0.61	Nilotinib	Bcr-Abl tyrosine kinase inhibitor	0.04	-0.81	0.031*
0.37 -0.60 0.112 1.11 -0.44 0.243 3.33 -0.56 0.138 10 -0.12 0.754 0.12 -0.36 0.334 0.37 -0.42 0.263 1.11 -0.23 0.561 3.33 -0.38 0.316 0.37 -0.42 0.263 1.11 -0.23 0.561 3.33 -0.38 0.316 0.34 -0.55 0.141 0.30 -0.52 0.168 1.11 -0.51 0.168 1.11 -0.51 0.105 Selumetinib MEK inhibitor 0.04 -0.31 0.402 0.37 -0.82 0.038 0.030* 0.12 -0.51 0.168 0.176 0.37 -0.61 0.104 0.402 0.37 -0.52 0.037* 0.164 0.37 -0.51 0.164 0.33 0.37			0.12	-0.65	0.083
Nintedanib Tyrosine kinase inhibitor 0.44 0.056 0.138 Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.024* 0.12 -0.36 0.334 0.37 -0.42 0.263 0.37 -0.42 0.263 0.316 0.316 3.33 -0.38 0.316 0.316 Nintedanib JAK1/2 inhibitor 0.04 -0.55 0.141 0.12 -0.84 0.025* 0.168 1.11 -0.51 0.176 0.168 1.11 -0.51 0.176 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.0176 0.37 -0.61 0.105 0.30* 0.316 0.37 -0.62 0.038 0.316 0.30* 0.37 -0.62 0.030* 0.176 0.30* 0.316			0.37	-0.60	0.112
Nintedanib Tyrosine kinase inhibitor 0.13 0.12 0.13 Nintedanib Tyrosine kinase inhibitor 0.04 -0.85 0.024* 0.12 -0.36 0.33 0.33 0.37 -0.42 0.263 0.541 0.37 -0.42 0.263 0.316 1.11 -0.23 0.541 0.316 1.12 -0.84 0.025* 0.316 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141 0.12 -0.84 0.025* 0.025* 0.37 -0.52 0.168 0.177 3.33 -0.61 0.105 0.176 0.12 -0.51 0.106 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.0402 0.12 -0.51 0.146 0.37 0.028 Vemurafenib MEK inhibitor 0.04 -0.29 0.044* 0.12 -0.51 0.146 0.37 0.90 0.014* <			1.11	-0.44	0.243
Nintedanib Tyrosine kinase inhibitor 0.00 -0.12 0.024* Nintedanib Tyrosine kinase inhibitor 0.12 -0.36 0.034 0.37 -0.42 0.263 0.541 0.37 -0.42 0.551 0.514 3.33 -0.38 0.316 0.316 1.11 -0.23 0.541 0.316 1.33 -0.38 0.316 0.316 1.11 -0.55 0.141 0.12 -0.84 0.025* 0.37 -0.52 0.168 0.105 0.177 3.33 -0.61 0.105 0.176 0.176 Selumetinib MEK inhibitor 0.04 -0.31 0.028 0.028 Vemurafenib MEK inhibitor 0.14 0.33 -0.61 0.104 10 -0.55 0.37 -0.82 0.030* 0.14* 0.33 -0.61 0.104 0.14* 0.14* 0.14* 0.37 -0.82 0.33* 0.61			3.33	-0.56	0.138
Ninedalib Fytosine kniase initiotori 0.04 -0.03 0.024 0.034 1,12 -0.36 0.263 0.263 0.263 0.263 1,11 -0.23 0.541 0.316 0.316 0.316 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141 0.568 Ruxolitinib JAK1/2 inhibitor 0.04 -0.52 0.168 0.025* 0.12 -0.84 0.025 0.168 0.105 1.11 -0.51 0.177 3.33 -0.61 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.028 Vemurafenib B-raf inhibitor 0.04 -0.21 0.014* 0.37 -0.82 0.030* 0.030* 0.33 -0.61 0.104 0.104 0.37 -0.82 0.030* 0.030* 0.33 -0.61 0.104 0.104 0.33 -0.61 0.104 0.104 0.33 -0.61 <td< td=""><td>Nintodanih</td><td>Turosino kinaso inhibitor</td><td>10</td><td>-0.12</td><td>0.734</td></td<>	Nintodanih	Turosino kinaso inhibitor	10	-0.12	0.734
0.12 -0.56 0.54 0.77 -0.42 0.263 1.11 -0.23 0.541 3.33 -0.38 0.316 3.33 -0.25 0.141 0.12 -0.84 0.025* 0.12 -0.84 0.025* 0.11 -0.51 0.168 1.11 -0.51 0.105 10 -0.82 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.028 Vemurafenib B-raf inhibitor 0.14 -0.55 0.146 0.33 -0.61 0.104 0.039* 0.12 -0.51 0.146 0.333 0.33 -0.61 0.104 0.044 0.37 -0.82 0.039* 0.146 0.33 -0.61 0.104 0.044 0.12 -0.35 0.355 0.355 0.37 -0.90 0.01	Nintedanib	Tyrosine kinase minditor	0.04	-0.65	0.024
Kuxolitinib JAK1/2 inhibitor 0.57 0.54 Ruxolitinib JAK1/2 inhibitor 0.04 -0.38 0.316 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.168 1.11 -0.52 0.168 0.025* 0.37 -0.52 0.168 1.11 -0.51 0.177 3.33 -0.61 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.402 0.12 -0.51 0.176 0.176 0.37 -0.82 0.028 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.402 0.12 -0.51 0.176 0.376 0.333 -0.61 0.104 0.104 1.0 -0.92 0.014* 0.104 0.12 -0.35 0.355 0.355 0.37 -0.90 0.014* 0.054 1.11 -0.72 0.054 0.054 0.33 -0.66 0.07			0.12	-0.30	0.554
Ruxolitinib JAK1/2 inhibitor 0.04 10 0.21 0.36 0.568 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141 0.12 -0.84 0.025* 0.168 0.37 -0.52 0.168 0.105 0.37 -0.61 0.105 0.105 Selumetinib MEK inhibitor 0.04 -0.31 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.176 0.37 -0.82 0.030* 0.164 0.12 -0.51 0.176 0.176 0.333 -0.61 0.104 0.030* 1.11 -0.55 0.146 0.333 -0.61 0.014* Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 0.12 -0.35 0.355 0.355 0.37 -0.90 0.014* 0.12 -0.35 0.355 0.37 -0.90 0.014* 0.11 -0.72 0.054 0.333 0.66 0.0			1 11	-0.42	0.203
Ruxolitinib JAK1/2 inhibitor 0.01 0.021 0.568 Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141 0.12 -0.84 0.025* 0.167 0.37 -0.52 0.168 0.105 1.11 -0.51 0.176 0.105 Selumetinib MEK inhibitor 0.04 -0.31 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.030* 0.12 -0.51 0.176 0.176 0.37 -0.82 0.030* 0.141 Vemurafenib B-raf inhibitor 0.04 -0.31 0.0104 10 -0.92 0.014* 0.104 0.104 10 -0.92 0.014* 0.104 0.104* 0.12 -0.35 0.355 0.355 0.355 0.37 -0.90 0.014* 0.104* 1.11 -0.72 0.054 0.057 0.333 -0.66 0.077 0.054			2 22	0.38	0.341
Ruxolitinib JAK1/2 inhibitor 0.04 -0.55 0.141 0.12 -0.84 0.025* 0.168 0.37 -0.52 0.168 1.11 -0.51 0.177 3.33 -0.61 0.105 Selumetinib MEK inhibitor 0.04 -0.31 0.402 0.12 -0.51 0.176 0.176 0.37 -0.82 0.028 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.402 0.12 -0.51 0.176 0.30* 1.11 -0.55 0.141 0.402 Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 0.12 -0.35 0.355 0.37 -0.90 0.014* Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 0.141 0.12 -0.35 0.355 0.37 -0.90 0.014* 1.11 -0.72 0.054 0.33 -0.66 0.077 <td></td> <td></td> <td>10</td> <td>0.21</td> <td>0.568</td>			10	0.21	0.568
Kukontinib ji Kr/2 initiation 0.04 -0.03 0.013 0.025* 0.37 -0.52 0.168 1.11 -0.51 0.177 3.33 -0.61 0.105 Selumetinib MEK inhibitor 0.04 -0.31 0.402 Selumetinib MEK inhibitor 0.12 -0.51 0.176 0.12 -0.51 0.176 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.402 Vemurafenib MEK inhibitor 0.04 -0.55 0.176 Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 0.12 -0.35 0.355 0.37 0.90 0.014* 0.12 -0.35 0.355 0.37 0.90 0.014* 0.12 -0.35 0.355 0.37 0.90 0.014* 0.14 -0.72 0.054 3.33 -0.66 0.077	Ruvolitinih	IAK1/2 inhibitor	0.04	-0.55	0.300
0.12 0.05 0.168 0.37 -0.52 0.168 1.11 -0.51 0.177 3.33 -0.61 0.105 0 -0.82 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.402 0.12 -0.51 0.176 0.30* 0.12 -0.51 0.168 0.030* 1.11 -0.55 0.146 0.33 1.11 -0.55 0.146 0.014* Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 0.12 -0.35 0.355 0.355 0.37 -0.90 0.014* 0.12 -0.35 0.355 0.37 -0.90 0.014* 0.12 -0.35 0.355 0.37 -0.90 0.014* 1.11 -0.72 0.054 3.33 -0.66 0.077 0.0 -0.43 0.249	Ruxontinib	JACI/2 minoreor	0.12	-0.84	0.025*
1.11 -0.51 0.177 3.33 -0.61 0.105 10 -0.82 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.402 0.12 -0.51 0.176 0.37 0.37 -0.82 0.030* 0.146 1.11 -0.55 0.104 0.104 Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 0.12 -0.35 0.355 0.375 0.355 0.37 -0.90 0.014* 0.014* 1.11 -0.72 0.054 0.055 0.37 -0.90 0.014* 0.014* 0.12 -0.35 0.355 0.375 0.37 -0.90 0.014* 0.014* 0.11 -0.72 0.054* 0.054* 1.11 -0.72 0.054* 0.077 1.01 -0.43 0.249 0.249			0.37	-0.52	0.168
NI O.61 0.105 3.33 -0.61 0.028 Selumetinib MEK inhibitor 0.04 -0.31 0.402 0.12 -0.51 0.176 0.30* 0.37 -0.82 0.030* 0.104 1.11 -0.55 0.146 0.104 3.33 -0.61 0.104 0.104 Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 0.12 -0.35 0.355 0.37 0.90 0.014* Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 0.12 -0.35 0.355 0.37 0.90 0.014* 0.12 -0.35 0.355 0.37 0.90 0.014* 0.13 -0.66 0.077 0.057 0.057 0.14 -0.43 -0.43 0.249 0.249			1 11	-0.51	0.177
NEW NEW <td></td> <td></td> <td>3.33</td> <td>-0.61</td> <td>0.105</td>			3.33	-0.61	0.105
Selumetinib MEK inhibitor 0.0 -0.21 0.402 0.12 -0.51 0.176 0.30* 0.37 -0.82 0.030* 0.146 3.33 -0.61 0.104 0.104 Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* Vemurafenib B-raf inhibitor 0.04 -0.29 0.014* 10 -0.92 0.014* 0.402 Vemurafenib B-raf inhibitor 0.04 -0.29 0.355 0.37 -0.90 0.014* 0.355 0.355 0.37 -0.90 0.014* 0.374 0.354 0.333 -0.66 0.077 0.054 0.333 -0.66 0.077 0.249			10	-0.82	0.028
Vemurafenib B-raf inhibitor 0.12 -0.51 0.176 0.37 -0.82 0.030* 1.11 -0.55 0.146 3.33 -0.61 0.104 10 -0.92 0.014* 0.12 -0.35 0.355 0.37 -0.90 0.014* 10 -0.29 0.014* 0.12 -0.35 0.355 0.37 -0.90 0.014* 1.11 -0.72 0.054 3.33 -0.66 0.077 10 -0.43 0.249	Selumetinib	MEK inhibitor	0.04	-0.31	0.402
0.37 -0.82 0.30* 1.11 -0.55 0.146 3.33 -0.61 0.00* Vemurafenib B-raf inhibitor 0.04 -0.92 0.01** 0.12 -0.35 0.355 0.355 0.37 -0.90 0.01** 1.11 -0.72 0.054 3.33 -0.66 0.077 1.0 -0.43 0.249			0.12	-0.51	0.176
1.11 -0.55 0.146 3.33 -0.61 0.104 10 -0.92 0.014* Vemurafenib B-raf inhibitor 0.04 -0.29 0.444 0.12 -0.35 0.355 0.355 0.37 -0.90 0.014* 0.044* 1.11 -0.72 0.054 0.054 3.33 -0.66 0.077 0.0249			0.37	-0.82	0.030*
3.33 -0.61 0.104 10 -0.92 0.014* Vemurafenib B-raf inhibitor 0.04 -0.29 0.444 0.12 -0.35 0.355 0.355 0.77 -0.90 0.014* 1.11 -0.72 0.054 3.33 -0.66 0.077 10 -0.43 0.249			1.11	-0.55	0.146
Nemurafenib B-raf inhibitor 10 -0.92 0.014* 0.04 -0.29 0.444 0.12 -0.35 0.355 0.37 -0.90 0.014* 1.11 -0.72 0.054 3.33 -0.66 0.077 10 -0.43 0.249			3.33	-0.61	0.104
Vemurafenib B-raf inhibitor 0.04 -0.29 0.444 0.12 -0.35 0.355 0.355 0.37 -0.90 0.014* 1.11 -0.72 0.054 3.33 -0.66 0.077 10 -0.43 0.249			10	-0.92	0.014*
0.12-0.350.3550.37-0.900.014*1.11-0.720.0543.33-0.660.07710-0.430.249	Vemurafenib	B-raf inhibitor	0.04	-0.29	0.444
0.37-0.900.014*1.11-0.720.0543.33-0.660.07710-0.430.249			0.12	-0.35	0.355
1.11-0.720.0543.33-0.660.07710-0.430.249			0.37	-0.90	0.014*
$\begin{array}{ccc} 3.33 & -0.66 & 0.077 \\ 10 & -0.43 & 0.249 \end{array}$			1.11	-0.72	0.054
10 -0.43 0.249			3.33	-0.66	0.077
			10	-0.43	0.249

by the Nebion AG team to facilitate *meta*-analysis [4]. A normalised and annotated version of the L1000 Connectivity Map dataset is available on the Genevestigator platform, derived from the publicly available data which can be downloaded from the Gene Expression Omnibus (GEO) online database (<u>http://www.ncbi.nlm.nih.gov/-</u> geo/) under accession number GSE70138. The significance of differentially expressed genes in data was tested in the software using the Linear Models for Microarray data (Limma) algorithm to perform a moderated *t*-test on the normalised data [5]. As an exploratory analysis of the dataset, no corrections were undertaken for multiple comparisons [6]. Genes were considered significantly differentially expressed with at least an absolute log₂ ratio change > 0.58 (roughly 1.5-fold change) to *p* < 0.05. This is an arbitrary threshold selected for screening of the connectivity map due to precedent for 1.5-fold change being considered differentially expressed in other published microarray experiments, and also because differential expression thresholds at that level are likely to represent a good trade-off between allowing the rejection of background noise and identifying biologically meaningful changes [7].

Of the compounds in the curated dataset that were tested in 24hour perturbation assays, 40 drugs and tool compounds were identified that significantly downregulated *TMPRSS2* expression in A549 human lung epithelial adenocarcinoma cells in at least one of the tested drug concentrations. Of these, 9 are drugs with prior approvals for use in humans for alternative indications: alpelisib/ BYL719, crizotinib, fedratinib/TG-101348, neratinib, nilotinib, nintedanib, ruxolitinib, selumetinib, and vemurafenib (Table 1). (It should be noted that the study design is suboptimal to discern dose-related *TMPRSS2* expression changes.) None of these compounds significantly affected *ACE2* expression. On the basis of literature searches, ruxolitinib and selumetinib are drugs of particular interest.

Ruxolitinib is an inhibitor of Janus kinase (JAK) enzymes that has been approved by the United States Food and Drug Administration (FDA) for the treatment of myelofibrosis, a condition characterised by abnormal clonal proliferation of haematopoietic stem cells. JAKs operate as transducers downstream of several receptors for pro-inflammatory cytokines, which makes them attractive candidates for treatment of conditions in which inflammation is dysregulated, as can be the case in COVID-19 [8]. With that rationale, Cao and colleagues undertook a single-blind, randomised controlled phase 2 trial of ruxolitinib versus placebo in addition to standard of care treatment in severe COVID-19. The results are instructive but perhaps disappointing for the potential of ruxolitinib as an antiviral medication aside from its anti-inflammatory effect: there was no significant difference in the secondary outcome of time to SARS-CoV-2 clearance between ruxolitinib and placebo recipients, although the authors concede their sample size was limited [9].

Selumetinib is a mitogen-activated protein kinase (MAPK/ERK) kinase (MAPKK/MEK) inhibitor that has FDA approval for the treatment of neurofibromatosis type 1, a multisystem disorder that is most often characterised by a propensity for neurofibroma formation. Although selumetinib has not been trialled in COVID-19 patients like ruxolitinib has, in vitro data suggest it may have some antiviral activity. Selumetinib (as well as some other MAPK pathway modulators) was found to inhibit the infection of a human hepatoma cell line with Middle East respiratory syndrome coronavirus (MERS-CoV) [10]. MERS-CoV is a coronavirus related to SARS-CoV-2 that also requires TMPRSS2 for S protein priming before cell entry, and similarly to SARS-CoV-2, inhibition of TMPRSS2 with a serine protease inhibitor limits MERS-CoV infection of simian kidney epithelial cells in vitro [11]. This, in conjunction with the observation from the *in silico* screen that suggests reduced mRNA expression of TMPRSS2 in cells exposed to selumetinib, identifies the MEK inhibitor as a plausible candidate for further evaluation in experimental models relevant to COVID-19.

TMPRSS2 is under the transcriptional control of the androgen receptor (AR) [12], which translocates to the nucleus to facilitate transcription of its target genes upon binding by androgens [13]. The expression of AR itself is regulated by the transcription factor CREB1, which is activated by phosphorylated MAPK. MEK inhibitors such as selumetinib (because they are inhibitors of MAPK kinase) are therefore able to reduce the expression of AR in vivo [14], which may consequently reduce the transcription of AR target genes (including TMPRSS2). It is plausible that reduced TMPRSS2 availability as a result of MEK inhibition would limit SARS-CoV-2 cell entry, but this hypothesised mechanism would need to be validated experimentally. Androgen regulation of TMPRSS2 expression may also provide a mechanistic explanation for the observation that male sex is associated with a higher COVID-19 case fatality rate than female sex [15], but again, experimental validation would be required.

Adaptive clinical trials like the RECOVERY trial will be pivotal in gaining control of the COVID-19 pandemic and candidate compounds for inclusion in such trials will need to be identified with sound scientific rationale. Connectivity maps such as L1000 are likely to prove essential in that regard, enabling researchers to screen for drugs that may be repurposed for new indications. Screening of the L1000 Connectivity Map in this case identifies selumetinib as a plausible antiviral candidate to treat COVID-19, but it is important to note that such *in silico* screening is an aid and a precursor to further *in vitro* and *in vivo* evaluation, not a replacement for it.

CRediT authorship contribution statement

Wezi Sendama: Conceptualisation, investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

WS is supported by the Medical Research Council SHIELD antimicrobial resistance research consortium (MR/N02995X/1), the Medical Research Foundation National PhD Training Programme in Antimicrobial Resistance Research (MRF-145-0004-TPG-AVISO), and the NIHR Newcastle Biomedical Research Centre (BRC) (IS-BRC-1215-20001). The NIHR Newcastle Biomedical Research Centre (BRC) is a partnership between Newcastle upon tyne Hospitals NHS Foundation Trust and Newcastle University, funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

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