国際共同研究プロジェクトにおけるコロナウィルス感染感受性増強及びウィルス産生から血栓形成へ至るAdverse Outcome Pathway (AOP)の開発

○田邊思帆里[1] (Shihori Tanabe), Youngjun Kim [2], Alicia Paini [3], Sally Mayasich [4], Maria João Amorim [5], Nikolaos Parissis [3], Penny Nymark [6], Marvin Martens [7], Dan Jacobson [8], Felicity N. E. Gavins [9], Luigi Margiotta-Casaluci [9], Sabina Halappanavar [10], Natàlia Garcia-Reyero [11], Julija Filipovska [12], Stephen Edwards [13], Rebecca Ram [14], Adrienne Layton [15], Brigitte Landesmann [3], Hasmik Yepiskoposyan [16], Jukka Sund [3], Clemens Wittwehr [3], Laure-Alix Clerbaux [3] for CIAO

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第11回レギュラトリーサイエンス学会学術大会
一般口演
2021年9月17日（金）16:00 O-1
（講演8分、討論4分）

COI開示

発表者名：◎田邊思帆里（国立医薬品食品衛生研究所安全性生物試験研究センター安全性予測評価部）、Youngjun Kim（KIST Europe Forschungsgesellschaft mbH, Germany）、Alicia Paini（European Commission, Joint Research Centre (JRC), Ispra, Italy）、Sally Mayasich（University of Wisconsin-Madison at U.S. Environmental Protection Agency, United States）、Maria João Amorim（Instituto Gulbenkian de Ciência – Fundação Calouste Gulbenkian, Portugal）、Nikolaos Parissis（European Commission, Joint Research Centre (JRC), Ispra, Italy）、Penny Nymark（Institute of Environmental Medicine, Karolinska Institute, Sweden）、Marvin Martens（Maastricht University, Netherlands）、Dan Jacobson（Oak Ridge National Laboratory, United States）、Felicity Gavins（Brunel University London, United Kingdom）、Luigi Margiotta-Casaluci（Brunel University London, United Kingdom）、Sabina Halappanavar（Environmental Health Science and Research Bureau, Health Canada, Ottawa, Canada）、Natàlia Garcia-Reyero（U.S. Army Engineer Research and Development Center (ERDC), United States）、Julija Filipovska（Independent, North Macedonia）、Stephen Edwards（GenOmics, Bioinformatics, and Translational Research Center, RTI International, United States）、Rebecca Ram（Safer Medicines Trust, United Kingdom）、Adrienne Layton（U.S. Consumer Product Safety Commission, United States）、Brigitte Landesmann（European Commission, Joint Research Centre (JRC), Ispra, Italy）、Hasmik Yepiskoposyan（Philip Morris International, Switzerland）、Jukka Sund（European Commission, Joint Research Centre (JRC), Ispra, Italy）、Clemens Wittwehr （European Commission, Joint Research Centre (JRC), Ispra, Italy）、 Laure-Alix Clerbaux（European Commission, Joint Research Centre (JRC), Ispra, Italy）

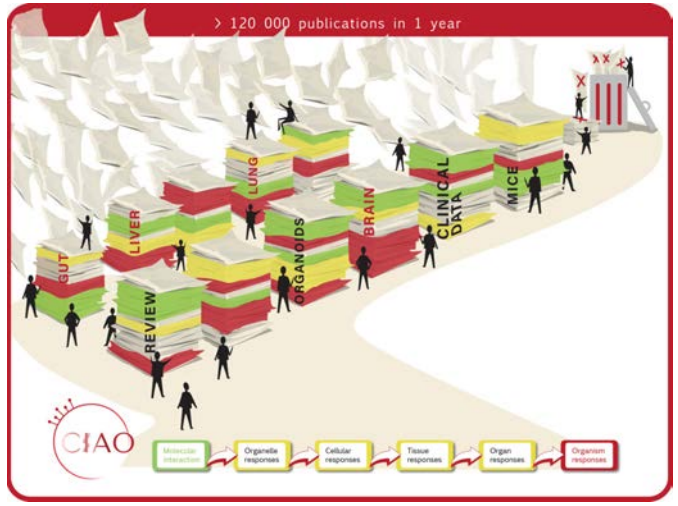
演題発表内容に関連し、発表者らに開示すべき利益相反はありません。

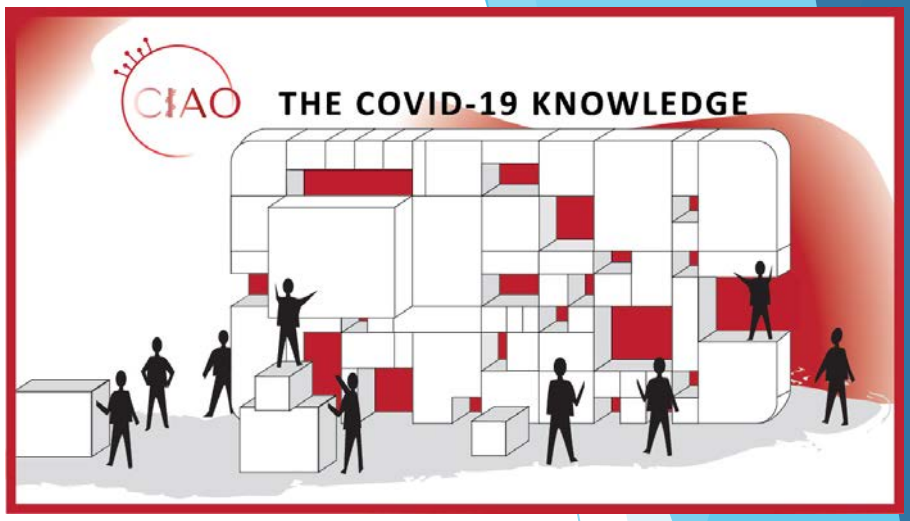
Objectives

- The emergence of new diseases has become an international threat, and it has become a common international issue in pharmaceutical administration to highly predict pathophysiological mechanisms and the adverse effects of developed drugs, and to evaluate safety of the therapeutics.
- In light of the fact that elucidation of pathophysiological mechanisms and prediction of adverse events of pharmaceuticals have become a common international issue, the development of AOP (Adverse Outcome Pathway) in terms of COVID-19 is progressing internationally.
- The purpose of this study is to elucidate pathophysiological mechanism network of the new coronavirus infectious disease using literature survey and *in silico* analysis.

Methods

- Microarray data and RNAseq data on the database were analyzed, and molecular network analysis using Ingenuity Pathway Analysis (IPA) was performed. In order to elucidate the molecular network related to COVID-19, gene expression data of SARS-CoV-2 infected cells was profiled on the pathway of coronavirus infection.
- Literatures on coronavirus has been investigated to reveal the mechanism of COVID-19.

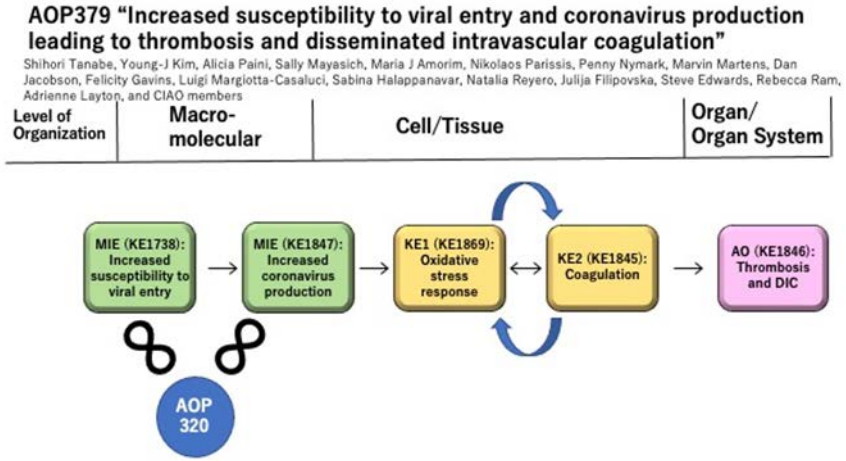


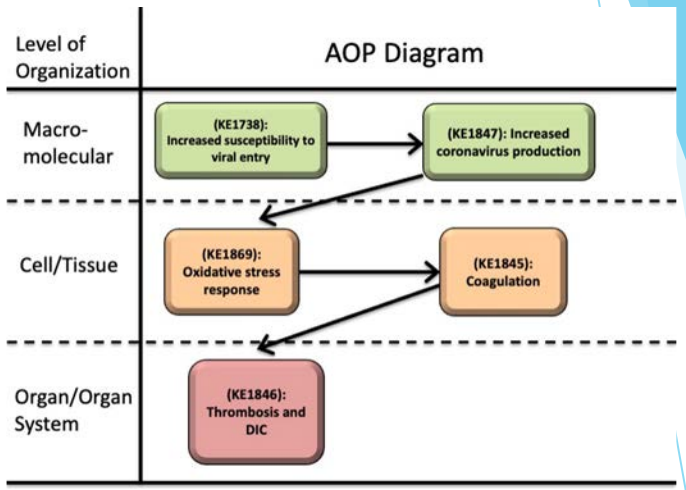


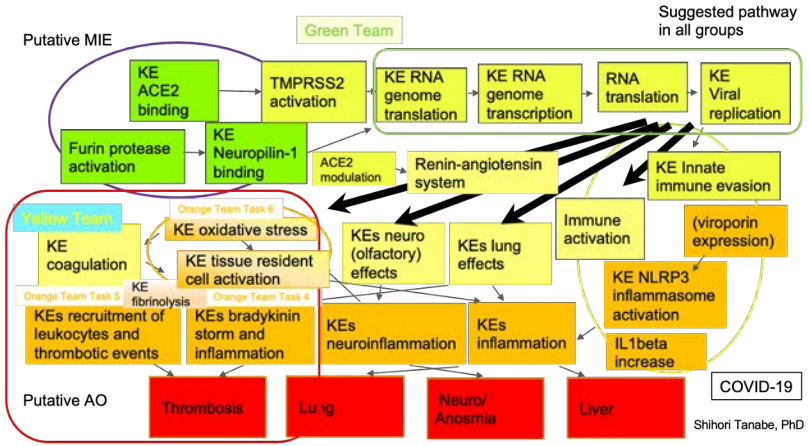
Modelling the pathogenesis of COVID-19 using the Adverse Outcome Pathway (AOP) Framework

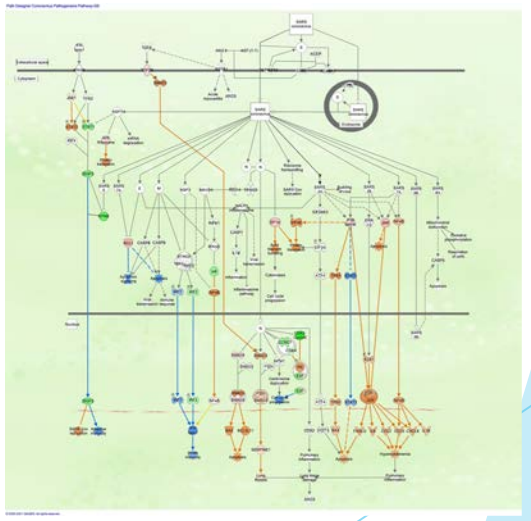
AOP379 “Increased susceptibility to viral entry and coronavirus production leading to thrombosis and disseminated intravascular coagulation”

Shihori Tanabe, National Institute of Health Sciences, Japan
Youngjun Kim, KIST Europe Forschungsgesellschaft mbH, Germany
Alicia Paini, European Commission, Joint Research Centre (JRC), Ispra, Italy
Sally Mayasich, University of Wisconsin-Madison at U.S. Environmental Protection Agency, United States
Maria João Amorim, Instituto Gulbenkian de Ciência – Fundação Calouste Gulbenkian, Portugal
Nikolaos Parissis, European Commission, Joint Research Centre (JRC), Ispra, Italy
Penny Nymark, Institute of Environmental Medicine, Karolinska Institute, Sweden
Marvin Martens, Maastricht University, Netherlands
Dan Jacobson, Oak Ridge National Laboratory, United States
Felicity Gavins, Brunel University London, United Kingdom
Luigi Margiotta-Casaluci, Brunel University London, United Kingdom
Sabina Halappanavar, Environmental Health Science and Research Bureau, Health Canada, Ottawa, Canada
Natàlia Garcia-Reyero, U.S. Army Engineer Research and Development Center (ERDC), United States
Julija Filipovska, Independent, North Macedonia
Stephen Edwards, GenOmics, Bioinformatics, and Translational Research Center, RTI International, United States
Rebecca Ram, Safer Medicines Trust, United Kingdom
Adrienne Layton, U.S. Consumer Product Safety Commission, United States
Brigitte Landesmann, European Commission, Joint Research Centre (JRC), Ispra, Italy
Hasmik Yepiskoposyan, Philip Morris International, Switzerland
and CIAO members

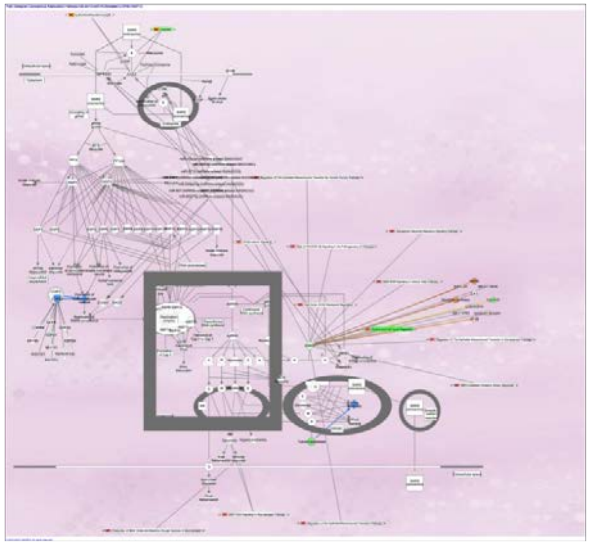

AOP379 "Increased susceptibility to viral entry and coronavirus production leading to thrombosis and disseminated intravascular coagulation"
Shihori Tanabe, Young-J Kim, Alicia Paini, Sally Mayasich, Maria J Amorim, Nikolaos Parissis, Penny Nymark, Marvin Martens, Dan Jacobson, Felicity Gavins, Luigi Margiotta-Casaluci, Sabina Halappanavar, Natalia Reyero, Julija Filipovska, Steve Edwards, Rebecca Ram, Adrienne Layton, and CIAO members
Level of Organization
Macro-molecular
Cell/Tissue
Organ/ Organ System
MIE (KE1738): Increased susceptibility to viral entry
MIE (KE1847): Increased coronavirus production
KE1 (KE1869): Oxidative stress response
KE2 (KE1845): Coagulation
AO (KE1846): Thrombosis and DIC
AOP 320


Level of Organization
AOP Diagram
Macro-molecular
Cell/Tissue
Organ/Organ System
(KE1738): Increased susceptibility to viral entry
(KE1847): Increased coronavirus production
(KE1869): Oxidative stress response
(KE1845): Coagulation
(KE1846): Thrombosis and DIC


Putative MIE
Green Team
Suggested pathway in all groups
KE ACE2 binding
TMPRSS2 activation
KE RNA genome translation
KE RNA genome transcription
RNA translation
KE Viral replication
Furin protease activation
KE Neuropilin-1 binding
ACE2 modulation
Renin-angiotensin system
KE Innate immune evasion
Yellow Team
KE oxidative stress
KE coagulation
KE tissue resident cell activation
KE fibrinolysis
KEs neuro (olfactory) effects
KEs lung effects
Immune activation
(viroporin expression)
KE NLRP3 inflammasome activation
KEs recruitment of leukocytes and thrombotic events
KEs bradykinin storm and inflammation
KEs neuroinflammation
KEs inflammation
IL1beta increase
Putative AO
Thrombosis
Lung
Neuro/ Anosmia
Liver
COVID-19
Shihori Tanabe, PhD



Coronavirus Replication Pathway

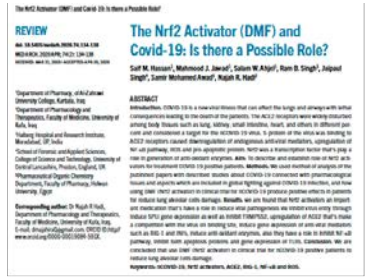


KE4 Viral replication

KE oxidative stress

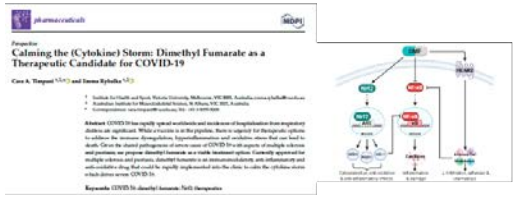
GSK3 is involved in
NRF2-mediated oxidative stress response,
MSP-RON signaling in cancer cells pathway,
Cell cycle: G1/S checkpoint regulation,
Cyclins and cell cycle regulation,
Role of Wnt/GSK-3beta signalling in the pathogenesis of influenza,
Regulation of the epithelial mesenchymal transition by growth factors pathway,
Regulation of the epithelial mesenchymal transition in development pathway.

IPA



REVIEW

The Nrf2 Activator (DMF) and Covid-19: Is there a Possible Role?



Calming the (Cytokine) Storm: Dimethyl Fumarate as a Therapeutic Candidate for COVID-19

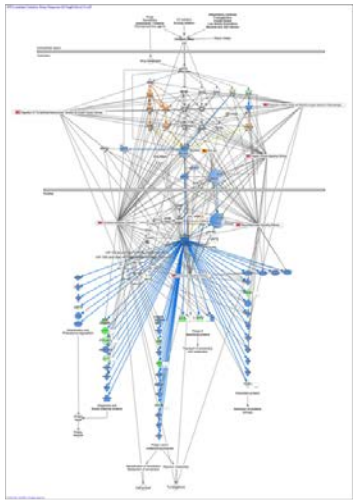
Nrf2, a master regulator of oxidative stress through enhanced expression of anti-oxidant genes of glutathione and thioredoxin-antioxidant systems, has anti-inflammatory, anti-apoptotic, and anti-oxidant effects. An activator of Nrf2 (DMF; dimethyl fumarate) may inhibit the entry of SARS-CoV-2 into the lung alveolar cells via an increase in anti-protease and decrease in the protease TRMPSS2. DMF can decrease inflammation and ROS through the inhibition of NF-kappaB by inducing anti-oxidant enzymes.

KE oxidative stress

KE tissue resident cell activation

KEs inflammation

NRF2-mediated Oxidative Stress Response network

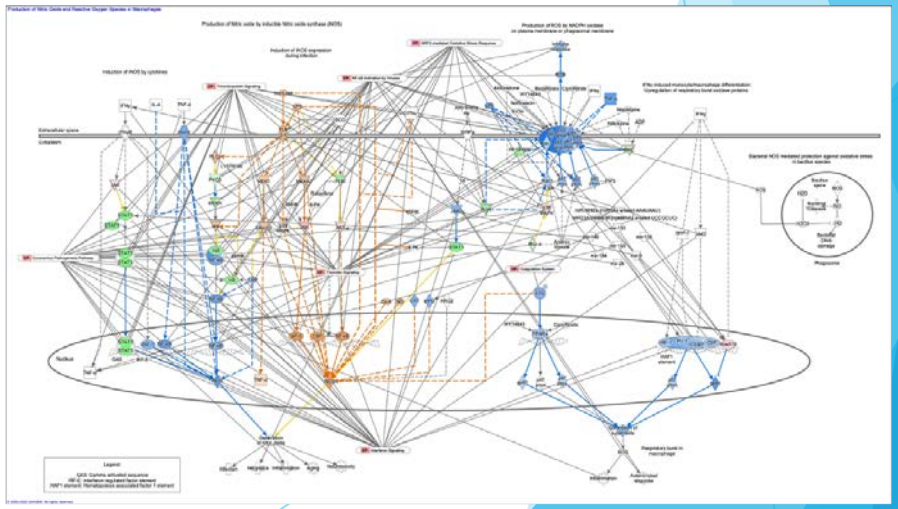


Ten microRNAs which have Direct Relationships (RNA-RNA interactions: microRNA targeting) to network molecules

mir-10
miR-1264 (and other miRNAs w/seed AAGUCUU)
miR-142-5p (and other miRNAs w/seed AUAAAGU)
mir-149
mir-155
mir-345
mir-497
miR-5087 (miRNAs w/seed GGUUUGU)
mir-637
mir-8

IPA

Production of nitric oxide and reactive oxygen species in macrophages



IPA

The relationship in ROS, coagulation and SARS-CoV-2

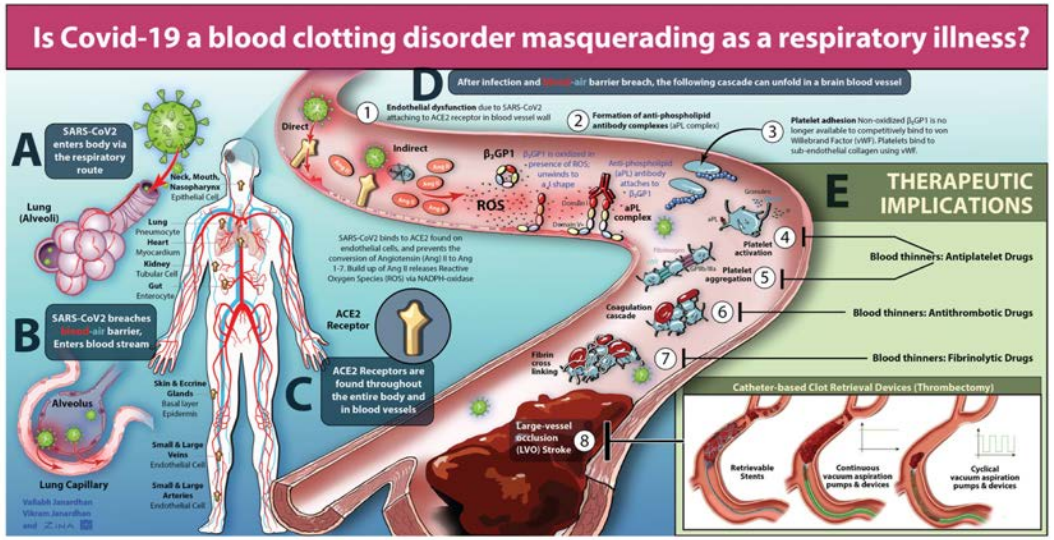
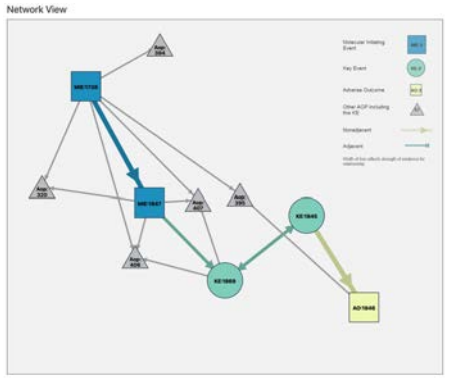


Fig 1. Coronavirus disease 2019 (COVID-19), blood clots, and stroke—mechanisms and therapeutic implications: In **Panel A**, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the body predominantly via the respiratory route. In **Panel B**, SARS-CoV-2 breaches the blood-air barrier, and enters the blood stream via the lung capillary that is adjacent to the alveolus. In **Panel C**, once SARS-CoV-2 enters the blood stream, the spike protein (key) can attach to angiotensin-converting enzyme 2 (ACE2) receptors (lock) across the body including endothelial cells in neck or brain blood vessels. Mechanisms of blood clots and stroke in COVID-19: In **Panel D**, a cascade of events unfolds resulting in blood clots and strokes. In Step 1, endothelial dysfunction can occur either directly by viral entry into the endothelial cell or indirectly with the accumulation of Angiotensin (Ang) II as SARS-CoV-2 attaches to ACE2 and is not able to convert Ang II to Ang 1,7. Ang II can result in reactive oxygen species (ROS), oxidative stress, and endothelial dysfunction. In Step 2, oxidation of beta 2 glycoprotein 1 (β_2GP1) occurs due to endothelial dysfunction and ROS, and results in the formation of antiphospholipid (aPL) antibody complexes. In Step 3, platelet adhesion occurs and platelets attach to the subendothelial collagen using von Willebrand Factor (vWF). This happens because the non-oxidized β_2GP1 is no longer available to competitively bind vWF. In Step 4, platelet activation occurs due to platelets binding to vWF resulting in granule release (α and dense) and the presence of aPL complexes further promotes platelet activation. In Steps 5-7, platelet aggregation using vWF or fibrinogen (released by α granules), formation of thrombus via the coagulation cascade, and subsequent cross-linking of fibrin strands to stabilize the clot occur. In Step 8, a pulmonary embolism (PE) and/or a large vessel occlusion stroke occurs. Therapeutic implications: In **Panel E**, several blood thinners like antiplatelet drugs can impact Steps 4 and 5 (eg, oral aspirin, oral clopidogrel, etc), antithrombotic drugs can impact Step 6 (antithrombin III binding agent, eg, parenteral heparin, vitamin K antagonist, eg, oral warfarin, newer direct Xa or thrombin inhibitors, etc), and fibrinolytic drugs can impact Step 7 (eg, intravenous tissue plasminogen activator or tenecteplase, etc). Several catheter-based devices (approved in Europe, and cleared to market in the United States) can impact Step 8 (eg, clot retrieval devices that try to use clot integration, continuous vacuum aspiration pumps, and devices that try to use uniform negative suction pressure to ingest clots) or newer devices (approved in Europe) can impact Step 8 (eg, cyclical vacuum aspiration pumps and devices that use pulsating negative suction pressure to improve complete clot ingestion and reduce clot fragmentation), help remove blood clots, and treat PE and large vessel strokes.

Ref. Janardhan V, Janardhan V, Kalousek V. COVID-19 as a Blood Clotting Disorder Masquerading as a Respiratory Illness: A Cerebrovascular Perspective and Therapeutic Implications for Stroke Thrombectomy. J Neuroimaging. 2020 Sep;30(5):555-561. doi: 10.1111/jon.12770. Epub 2020 Aug 18. PMID: 32776617; PMCID: PMC7436381.



CIAO AOP379 Network

Maria, Sally, Shihori et al.

MIE (KE1738): Increased susceptibility to viral entry

Brigitte

MIE (KE1847): Increased coronavirus production

Shihori

KE1 (KE1869): Oxidative stress response

Shihori, Penny, et al.

KE2 (KE1845): Coagulation

Dan J

Adrienne

AO (KE1846): Thrombosis and DIC

Luigi, Felicity

KE1857 Platelet-neutrophil interactions, Increased

AOP 395 — Magda

AOP 394 — Sandra

AOP 320 — Young-J Kim

AOP 385 — Julija

AOP 406

AOP 407

NLRP3 — Hasmik

AOP 392 — Penny

AOP 377 — Gillina

AOP 395 — Magda

KE1115: Increase, ROS

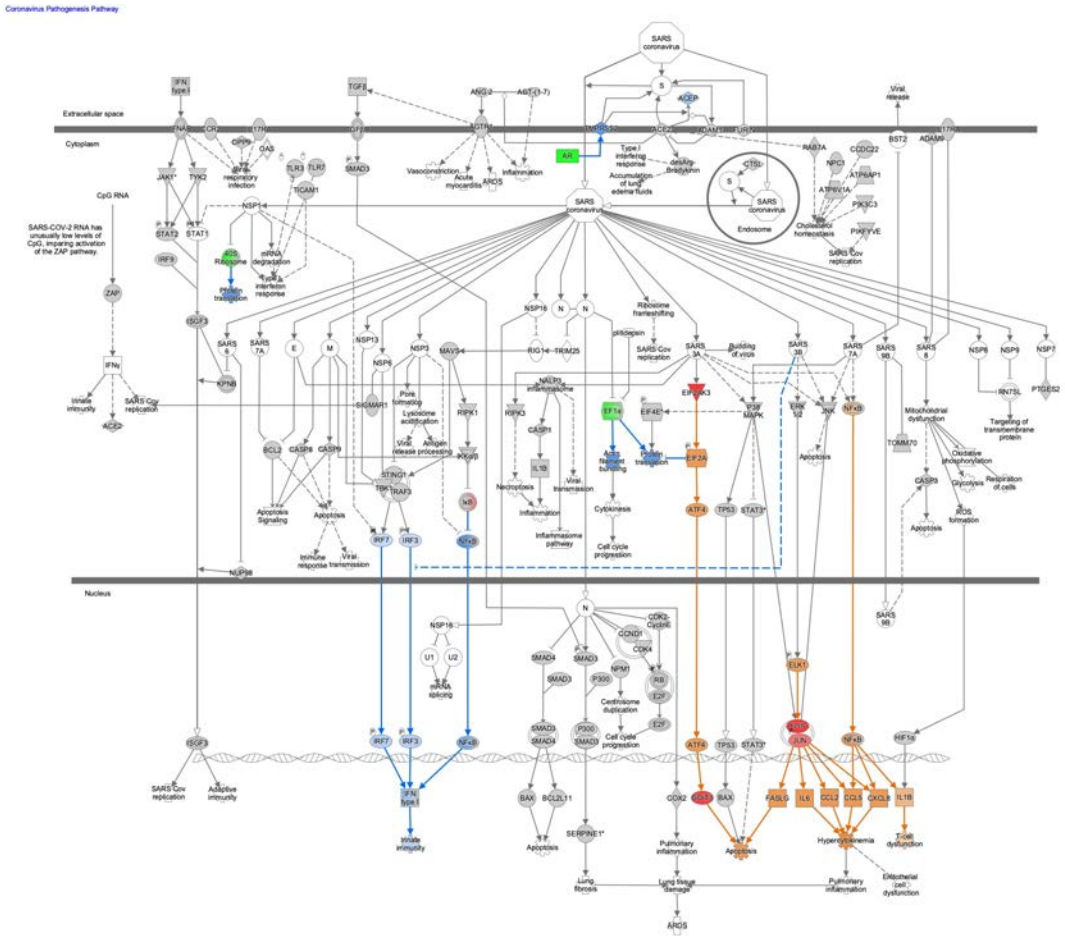
Lung fibrosis, etc.

AOP 302 — Jorid

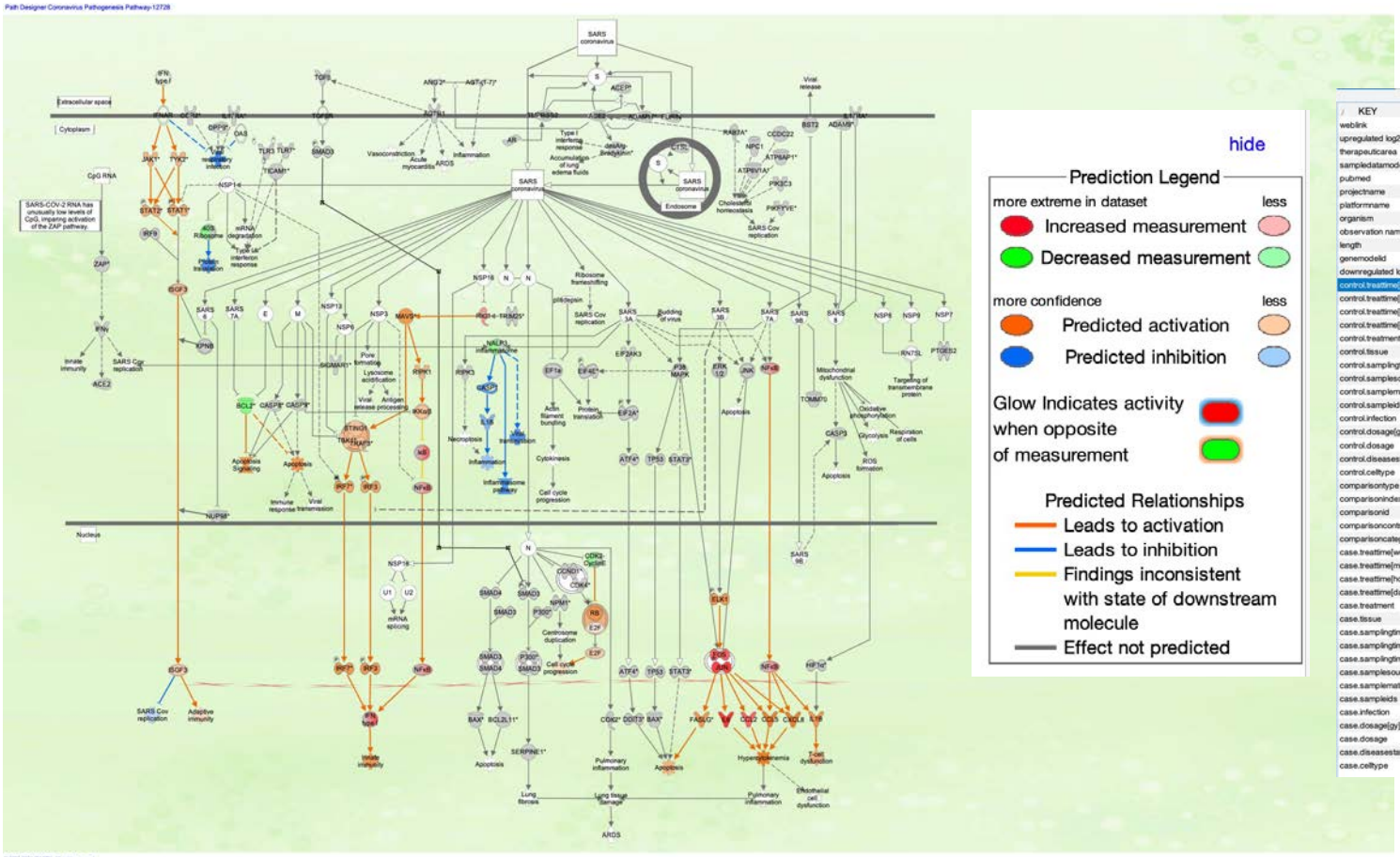
AOP 173 — Sabina

AOP 382 — Young-J Kim

Coronavirus pathogenesis pathway (overlay: 7-normal control [skin] Infection_SARS coronavirus 2 (SARS-CoV-2) 3632, Expr Log Ratio : iPSC-derived cardiomyocyte SARS-CoV-2, 0.1 MOI vs mock



Coronavirus pathogenesis pathway (overlay: 12-lung adenocarcinoma (LUAD) [bronchial epithelium] Infection_SARS coronavirus 12728, Expr Log Ratio



hide

Prediction Legend

more extreme in dataset — less

Increased measurement

Decreased measurement

more confidence — less

Predicted activation

Predicted inhibition

Glow Indicates activity when opposite of measurement

Predicted Relationships

Leads to activation

Leads to inhibition

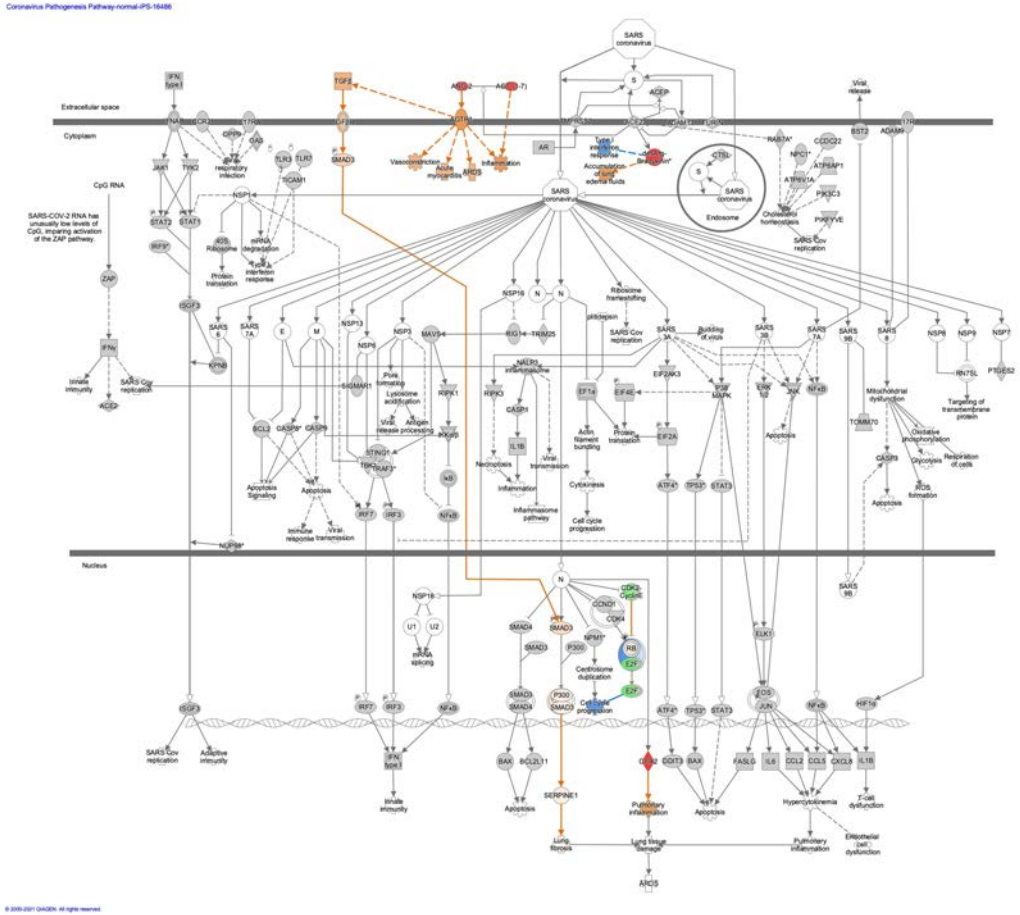
Findings inconsistent with state of downstream molecule

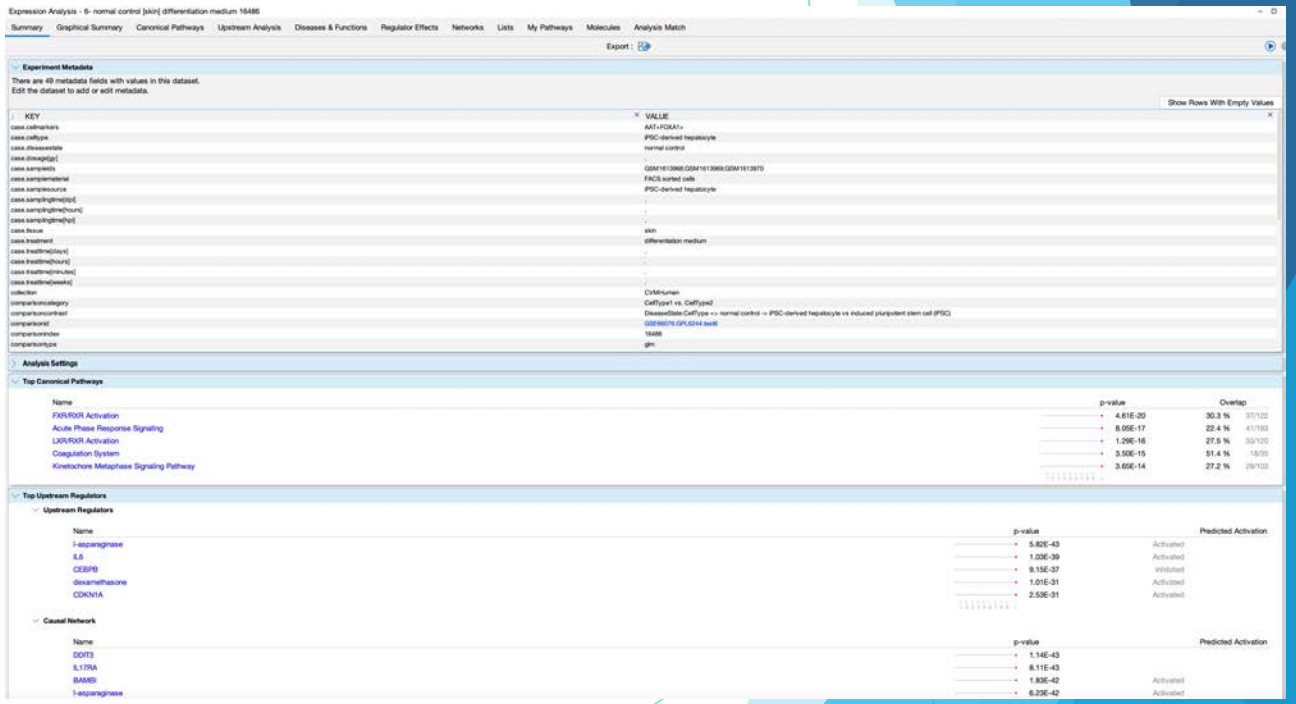
Effect not predicted

12- lung adenocarcinoma (LUAD) [bronchial epithelium] Infection_coronaviru 12728

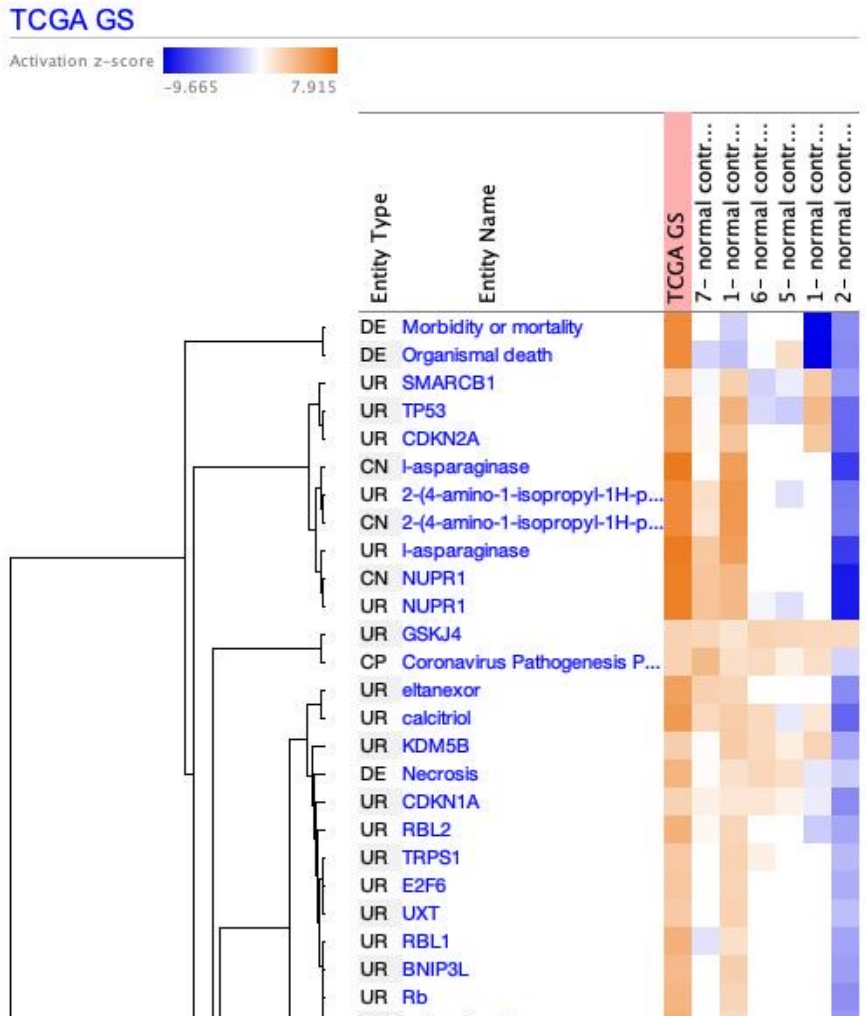
KEY	VALUE
weblink	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE33267
upregulated log2 cutoff	2.5249
therapeuticarea	Infectious Disease (viral)
sampledatamode	Expression_Intensity_Probes
pubmed	https://pubmed.ncbi.nlm.nih.gov/?term=23365422
projectname	GSE33267
platformname	Agilent.Expression.Human4x44k
organism	human
observation name	12- lung adenocarcinoma (LUAD) [bronchial epithelium] Infection_coronaviru 12728
length	30373
genemodelid	OmicsoftGene20130723
downregulated log2 cutoff	-1.323
control.treattime[weeks]	.
control.treattime[minutes]	.
control.treattime[hours]	.
control.treattime[days]	.
control.treatment	Infection_mock
control.tissue	bronchial epithelium
control.samplingtime[hpi]	36
control.samplesource	bronchial epithelial cell
control.samplematerial	cryopreserved cells;cultured tumor cells
control.sampleids	GSM823195,GSM823196,GSM823197
control.infection	mock
control.dosage[gy]	.
control.dosage	NA
control.diseasestate	lung adenocarcinoma (LUAD)
control.celltype	bronchial epithelial cell
comparisontype	glm
comparisonindex	12728
comparisonid	GSE33267.GPL4133.test12
comparisoncontrast	SamplingTime[hpi]:InfectionGroup => 36 -> icSARS coronavirus deltaORF6 (icSARS-CoV-deltaORF6) vs mock
comparisoncategory	Treatment vs. Control
case.treattime[weeks]	.
case.treattime[minutes]	.
case.treattime[hours]	.
case.treattime[days]	.
case.treatment	Infection_coronavirus
case.tissue	bronchial epithelium
case.samplingtime[hpi]	36
case.samplingtime[hours]	.
case.samplingtime[dpi]	.
case.samplesource	bronchial epithelial cell
case.samplematerial	cryopreserved cells;cultured tumor cells
case.sampleids	GSM823261;GSM823262;GSM823263
case.infection	coronavirus
case.dosage[gy]	.
case.dosage	MOI 5
case.diseasestate	lung adenocarcinoma (LUAD)
case.celltype	bronchial epithelial cell

Coronavirus pathogenesis pathway (overlay: 6-normal-control [skin] differentiation medium 16486, Expr Log Ratio : iPSC-hepatocyte)

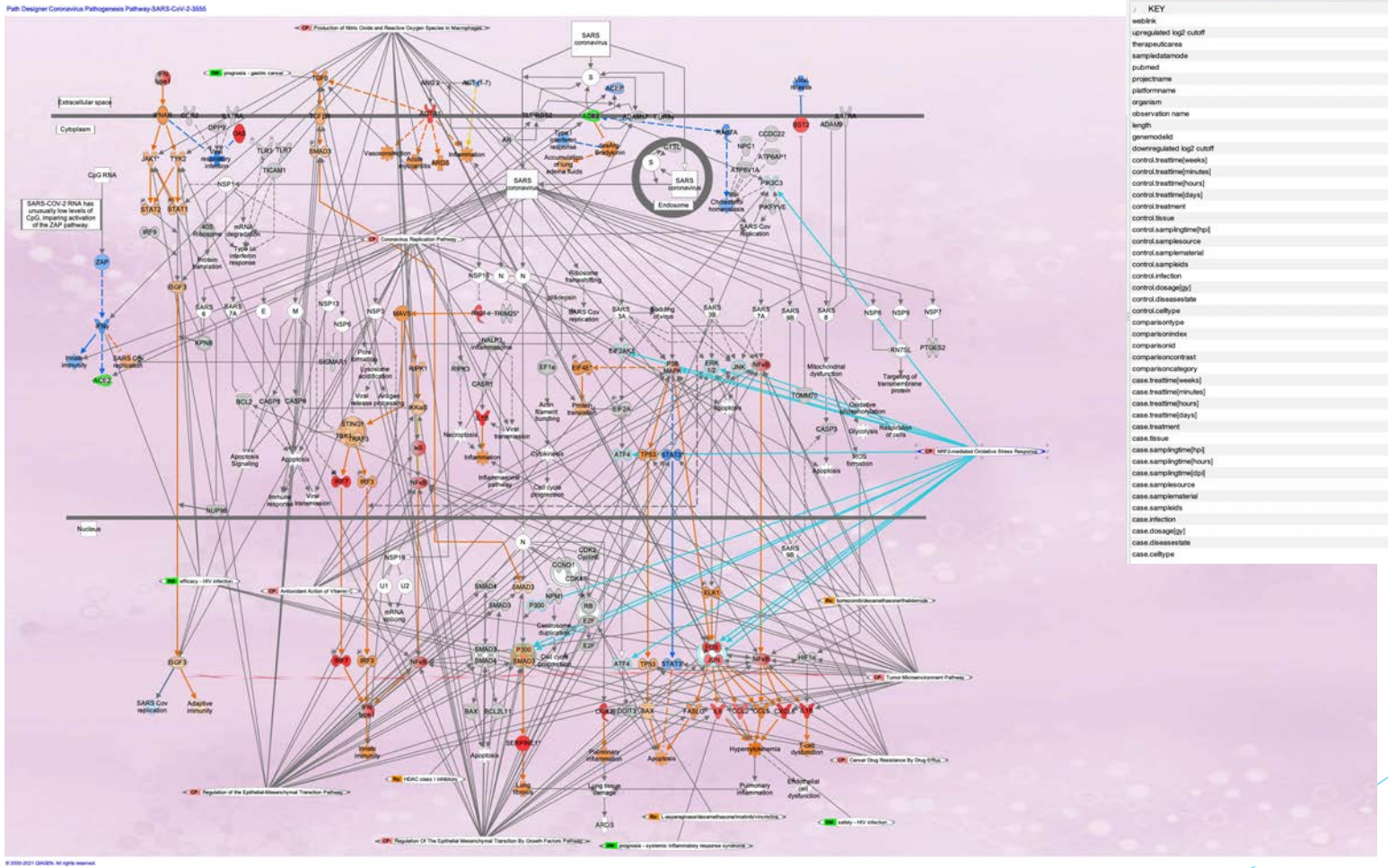




SARS-CoV-2 analysis matched to diffuse-type GC



Coronavirus pathogenesis pathway (overlay: 1-normal-control [peripheral blood] Infection_SARS coronavirus 2 (SARS-CoV-2) 3555, Expr Log Ratio: iPSC-derived cardiomyocyte)



Pathway | Molecules | Metadata

1- normal control [peripheral blood] Infection_SARS coronavirus 2 (SARS-CoV 3555

KEY	VALUE
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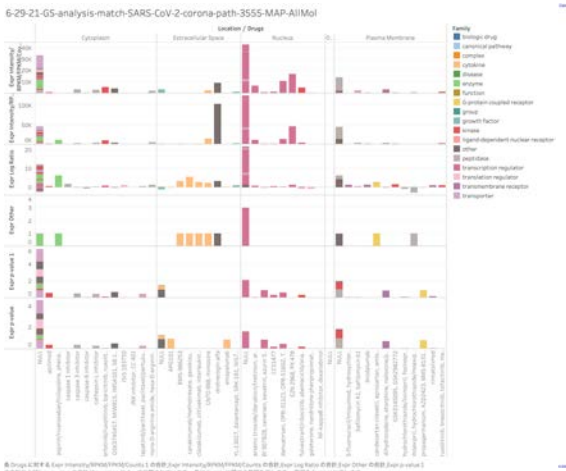
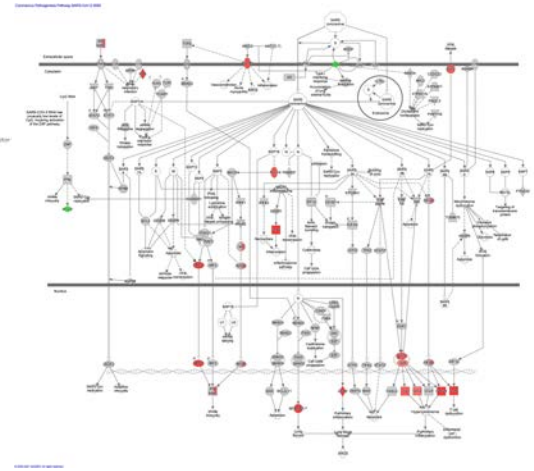
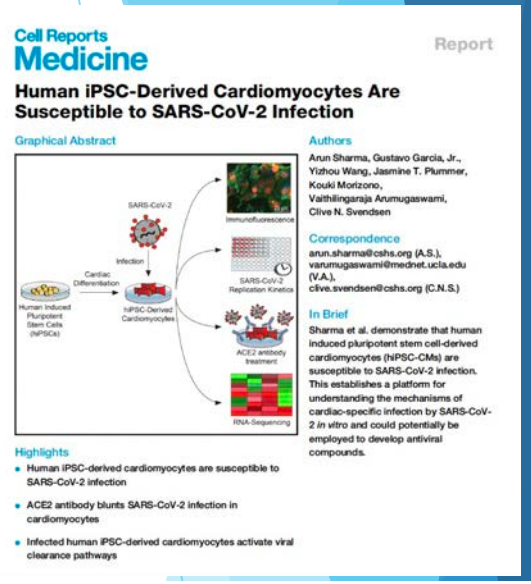
upregulated log2 cutoff	2.0511
therapeuticarea	Infectious Disease (viral)
sampledatamode	RnaSeq_Transcript
pubmed	https://pubmed.ncbi.nlm.nih.gov/?term=32835305
projectname	GSE150392
platformname	NGS.Illumina.NextSeq500
organism	human
observation name	1- normal control [peripheral blood] Infection_SARS coronavirus 2 (SARS-CoV 3555
length	30373
genemodelid	OmicsoftGene20130723
downregulated log2 cutoff	-1.9215
control.treattime[weeks]	.
control.treattime[minutes]	.
control.treattime[hours]	.
control.treattime[days]	.
control.treatment	Infection_mock
control.tissue	peripheral blood
control.samplingtime[hpi]	.
control.samplesource	iPSC-derived cardiomyocyte
control.samplematerial	cultured cells
control.sampleids	GSM4548306;GSM4548307;GSM4548308
control.infection	mock
control.dosage[gy]	.
control.diseasestate	normal control
control.celltype	iPSC-derived cardiomyocyte
comparisontype	DESeq2:v1.10.1.os.v101316
comparisonindex	3555
comparisonid	GSE150392.GPL18573.DESeq2.test1
comparisoncontrast	Infection => SARS coronavirus 2 (SARS-CoV-2) vs mock
comparisoncategory	Treatment vs. Control
case.treattime[weeks]	.
case.treattime[minutes]	.
case.treattime[hours]	.
case.treattime[days]	.
case.treatment	Infection_SARS coronavirus 2 (SARS-CoV-2)
case.tissue	peripheral blood
case.samplingtime[hpi]	.
case.samplingtime[hours]	.
case.samplingtime[dpi]	.
case.samplesource	iPSC-derived cardiomyocyte
case.samplematerial	cultured cells
case.sampleids	GSM4548303;GSM4548304;GSM4548305
case.infection	SARS coronavirus 2 (SARS-CoV-2)
case.dosage[gy]	.
case.diseasestate	normal control
case.celltype	iPSC-derived cardiomyocyte

Gene expression profile on SARS-CoV-2-infected iPSC-derived cardiomyocyte (GSE150392)
1-normal-control [peripheral blood] Infection_SARS coronavirus 2 (SARS-CoV-2) 3555, Expr Log Ratio: iPSC-derived cardiomyocyte (IPA)





Reference for RNA-Seq data GSE150392: Sharma, Arun et al. Human iPSC-derived Cardiomyocytes are susceptible to SARS-CoV-3 infection, Cell Reports Medicine, Volume 1, Issue 4, 100052


Cell Reports Medicine

Report

Human iPSC-Derived Cardiomyocytes Are Susceptible to SARS-CoV-2 Infection

Graphical Abstract

Authors

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In Brief

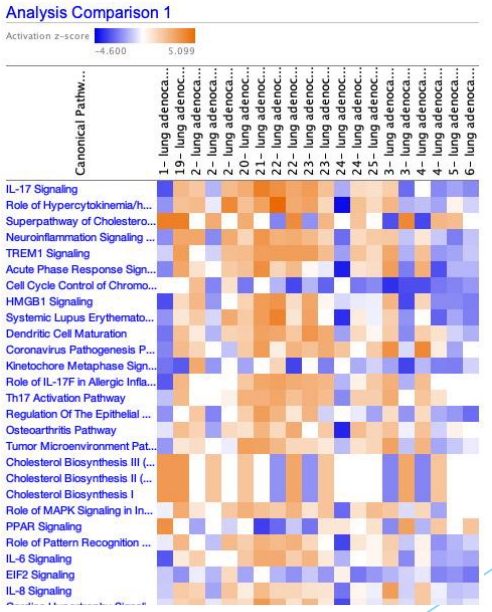
Sharma et al. demonstrate that human induced pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) are susceptible to SARS-CoV-2 infection. This establishes a platform for understanding the mechanisms of cardiac-specific infection by SARS-CoV-2 *in vitro* and could potentially be employed to develop antiviral compounds.

Highlights

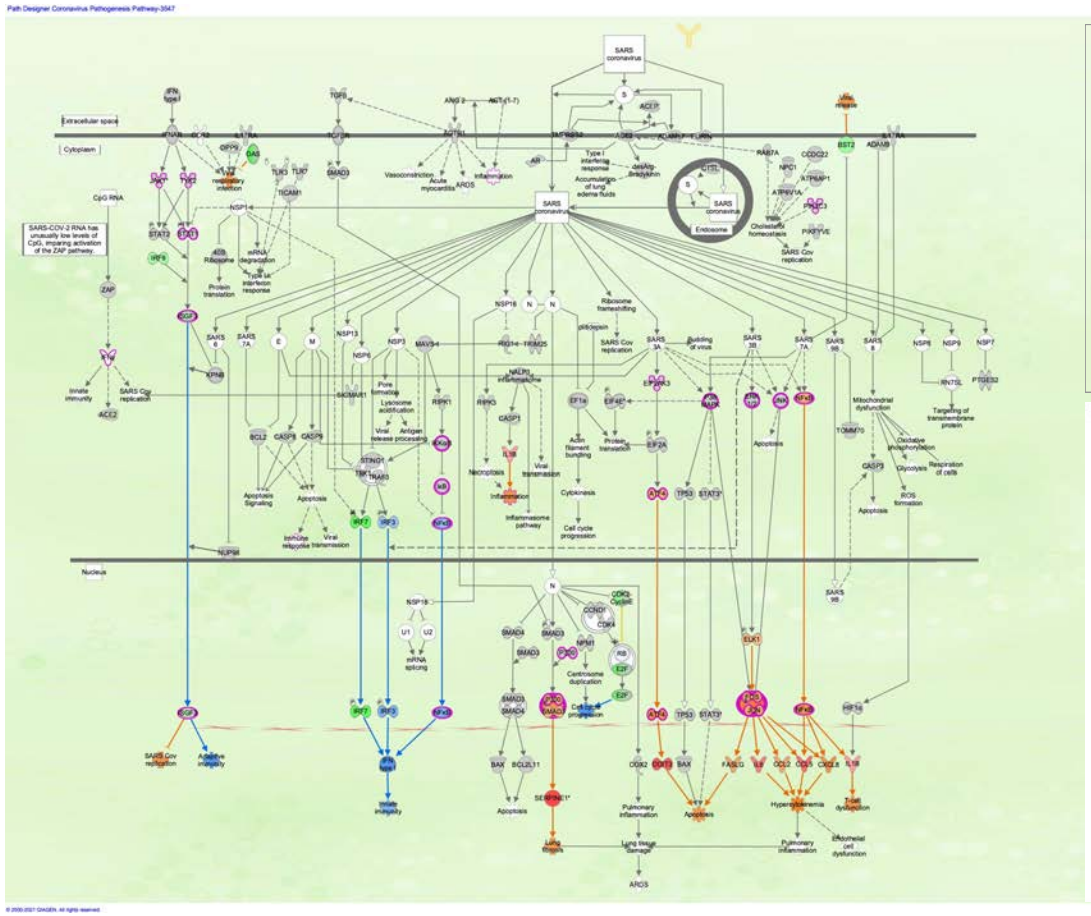
- Human iPSC-derived cardiomyocytes are susceptible to SARS-CoV-2 infection
- ACE2 antibody blunts SARS-CoV-2 infection in cardiomyocytes
- Infected human iPSC-derived cardiomyocytes activate viral clearance pathways

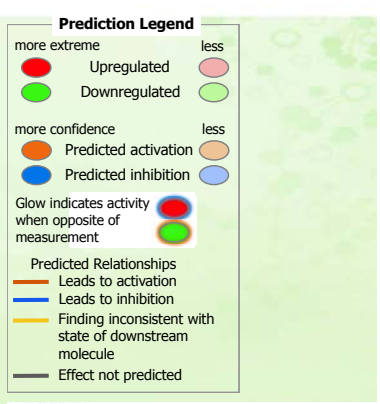
IPA analysis match for SARS-CoV-2

- 90,000 analyses and datasets
- SARS coronavirus 2: 106 analyses and 106 datasets
- SARS coronavirus 2, analysis, human: 49 analyses
- ->Normal control: 27 analyses (including 9 analyses of tissue “skin” GSE156754)
- ->Lung adenocarcinoma: 22 analyses



Coronavirus pathogenesis pathway (overlay: 4-lung adenocarcinoma (LUAD) [alveoli] SARS-CoV-2 infected A549 cell line MOI 2 (NA) 3547, Expr Log Ratio





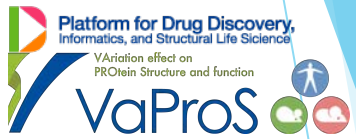
KEY	VALUE
4- lung adenocarcinoma (LUAD) [alveoli] NA 3547	
case.celldescription	SARS-CoV-2 infected A549 cell line MOI 2
case.celltype	alveolar epithelial cell
case.diseasestate	lung adenocarcinoma (LUAD)
case.dosage	MOI 2
case.dosage[gy]	-
case.infection	SARS coronavirus 2 (SARS-CoV-2)
case.sampleids	GSM4462339;GSM4462340;GSM4462341
case.samplematerial	cultured tumor cells
case.samplesource	alveolar epithelial cell
case.samplingtime[dpi]	-
case.samplingtime[hours]	-
case.samplingtime[hpi]	-
case.tissue	alveoli
case.transfection	NA
case.treatment	NA
case.treattime[days]	-
case.treattime[hours]	-
case.treattime[minutes]	-
case.treattime[weeks]	-
comparisoncategory	Treatment1 vs. Treatment2
comparisoncontrast	CellDescription => SARS-CoV-2 infected A549 cell line MOI 2 vs SARS-CoV-2 infected A549 cell line MOI 0.2
comparisonid	GSE147507.GPL18573.DESeq2.test4
comparisonindex	3547
comparisontype	DESeq2.v1.10.1.os.v101316
control.celldescription	SARS-CoV-2 infected A549 cell line MOI 0.2
control.celltype	alveolar epithelial cell
control.diseasestate	lung adenocarcinoma (LUAD)
control.dosage	MOI 0.2
control.dosage[gy]	-
control.infection	SARS coronavirus 2 (SARS-CoV-2)
control.sampleids	GSM4432387;GSM4432388;GSM4432389
control.samplematerial	cultured tumor cells
control.samplesource	alveolar epithelial cell
control.samplingtime[hpi]	-
control.tissue	alveoli
control.transfection	NA
control.treatment	NA
control.treattime[days]	-
control.treattime[hours]	-
control.treattime[minutes]	-
control.treattime[weeks]	-
downregulated log2 cutoff	-1.1937
genemodelid	OmicsoftGene20130723
length	30373
observation name	4- lung adenocarcinoma (LUAD) [alveoli] NA 3547
organism	human
platformname	NGS.Illumina.NextSeq500
projectname	GSE147507
pubmed	https://pubmed.ncbi.nlm.nih.gov/?term=32416070
sampledatamode	RnaSeq_Transcript
therapeuticarea	Infectious Disease (viral)
upregulated log2 cutoff	1.1724
weblink	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE147507

Highlighted: Production of Nitric Oxide and Reactive Oxygen Species in Macrophages, NRF2-mediated Oxidative Stress Response

Summary

- Gene expression data analysis on Gene Expression Omnibus (GEO) database revealed the increase in the expression of EIF2AK3 and FOS genes on the pathway of coronavirus infection, and predicted the activation of molecules such as IL6, FASLG, and CCL2.
- Molecules related to reactive oxygen species production, oxidative stress response, and blood clotting were mapped on the pathway of the coronavirus infection disease. Literature investigations also suggested the involvement of oxidative stress responses in novel coronavirus infections and pathways from blood clotting to thrombus formation.
- AOP379 “Increased susceptibility to viral entry and coronavirus production leading to thrombosis and disseminated intravascular coagulation” is currently developed in OECD AOP project.

Acknowledgements



http://pford.info/vapros/

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