Repurposing and using approved FDA drugs to treat existing illnesses

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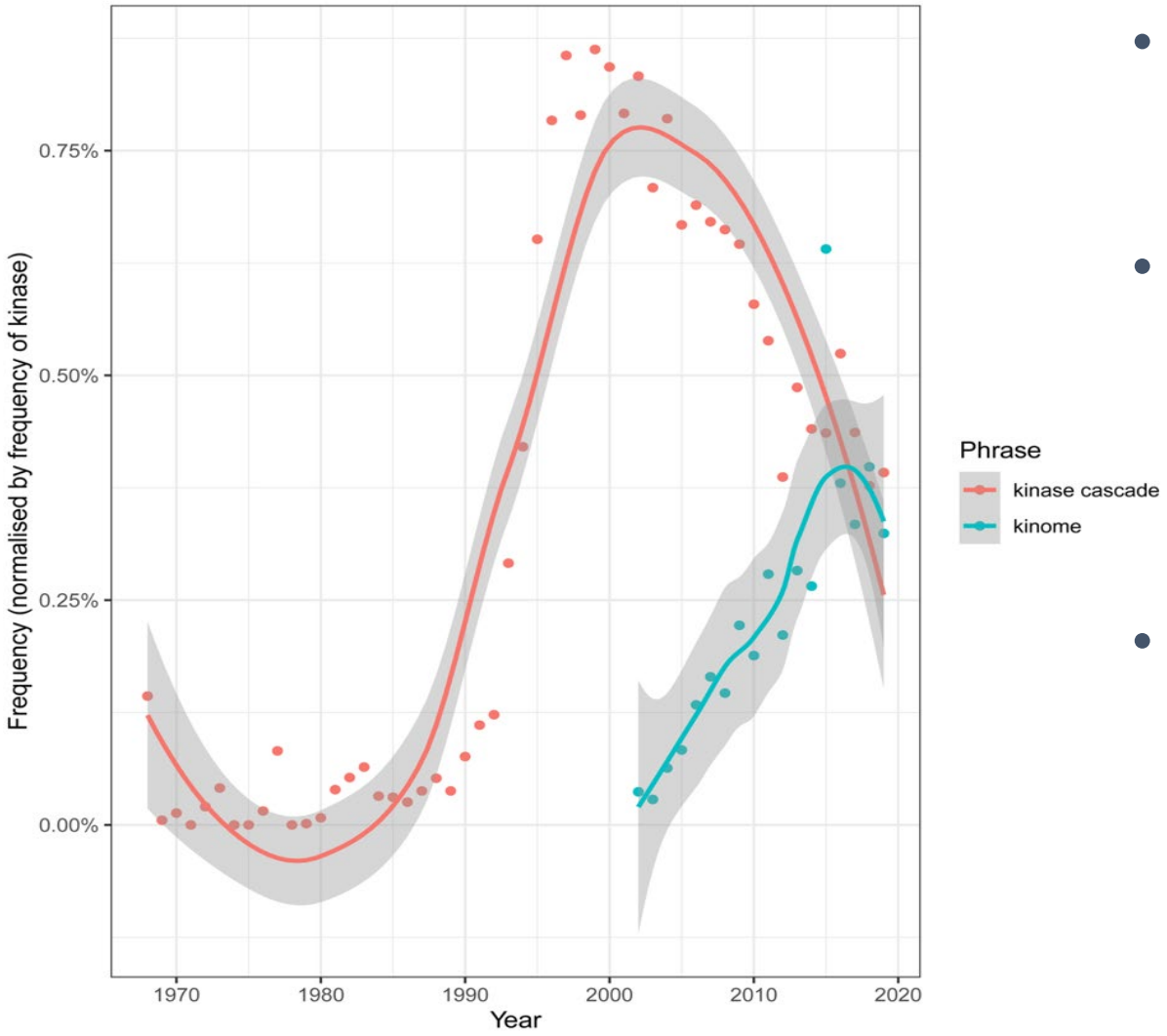
Disclosure

- No financial items to disclose

Other Disclosures

- I am not a virologist
- I am not a bioinformaticist
- I am a psychiatrist
- Educated user of bioinformatics tecniques

Trends in protein kinase research



- The Frequency patterns of “Kinase Cascade” and “Kinome” in kinase research
- Using Google Books Ngram English 2019 corpus, the frequencies of "kinase cascade" and "kinome" averaged by year and normalized by the frequency of "kinase“
- Cascade implies a linear pathway, while “kinome” encompasses the entire networks

How did we get here? A story about broken microscopes and bad reviewers

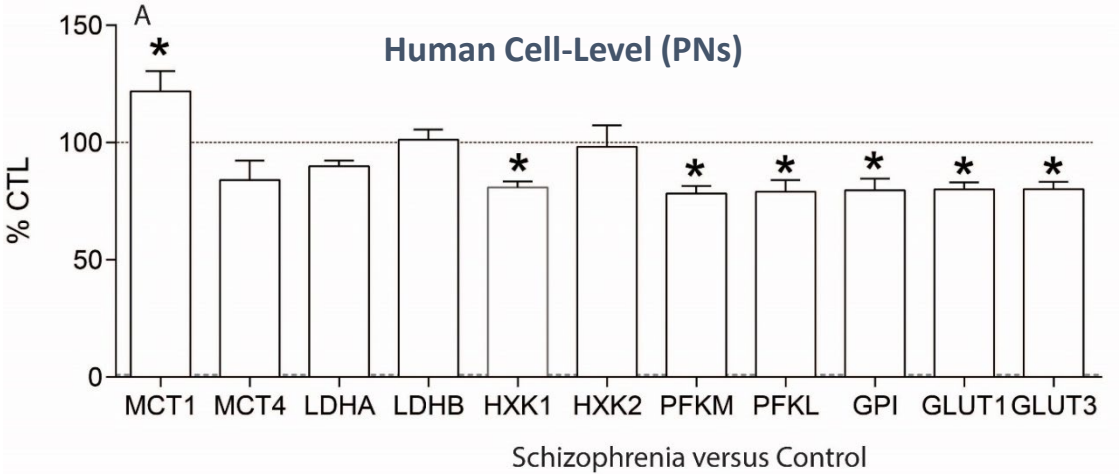
- Kaleidoscope- Novel pipeline app for in silico datamining and hypothesis testing
- https://kalganem.shinyapps.io/BrainDatabases/

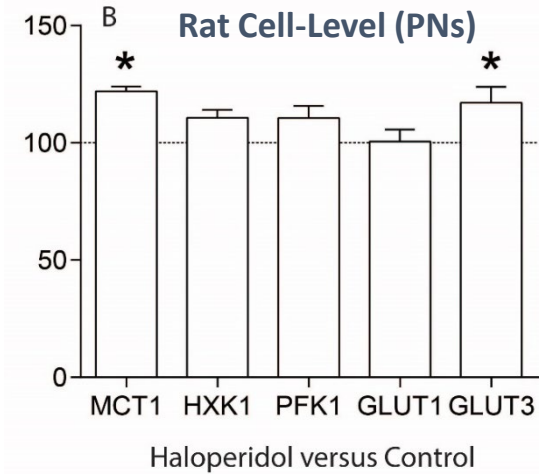
What is Schizophrenia?

- **Syndrome:** refers to the association of several clinically recognizable features, signs (observed by a physician), symptoms (reported by the patient), phenomena or characteristics that often occur together
- **Disease**: may be thought of as recognizable signs and symptoms with a known cause

The Fisher King (1991), portrayal of psychosis that is realistic

LCM-qPCR in DLPFC in Schizophrenia





Molecular Psychiatry

Neuron-specific deficits of bioenergetic processes in the dorsolateral prefrontal cortex in schizophrenia

Courtney R. Sullivan, Rachael H. Koene, Kathryn Hasselfeld, Sinead M O'Donovan, Amy Ramsey & Robert E. McCullumsmith

Summary: In PNs, but not astrocytes, abnormalities in 4 glycolytic enzymes and 2 glucose transporters.

Question: can we confirm/explore these findings in other databases?

In Silico confirmation analyses

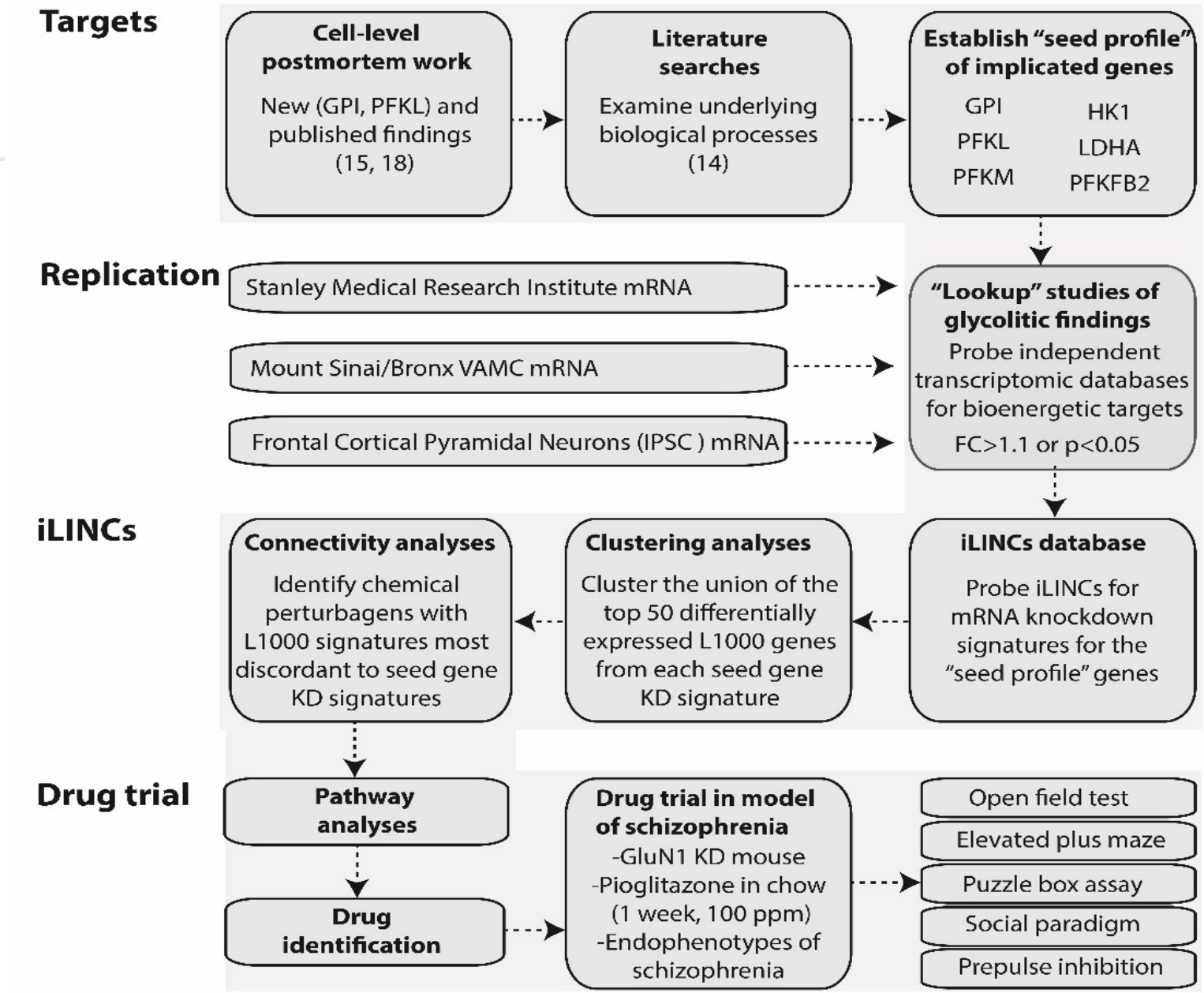
- Data mine publically available datasets

eTable 4.2 Summary of *in silico* analyses (disease versus control).

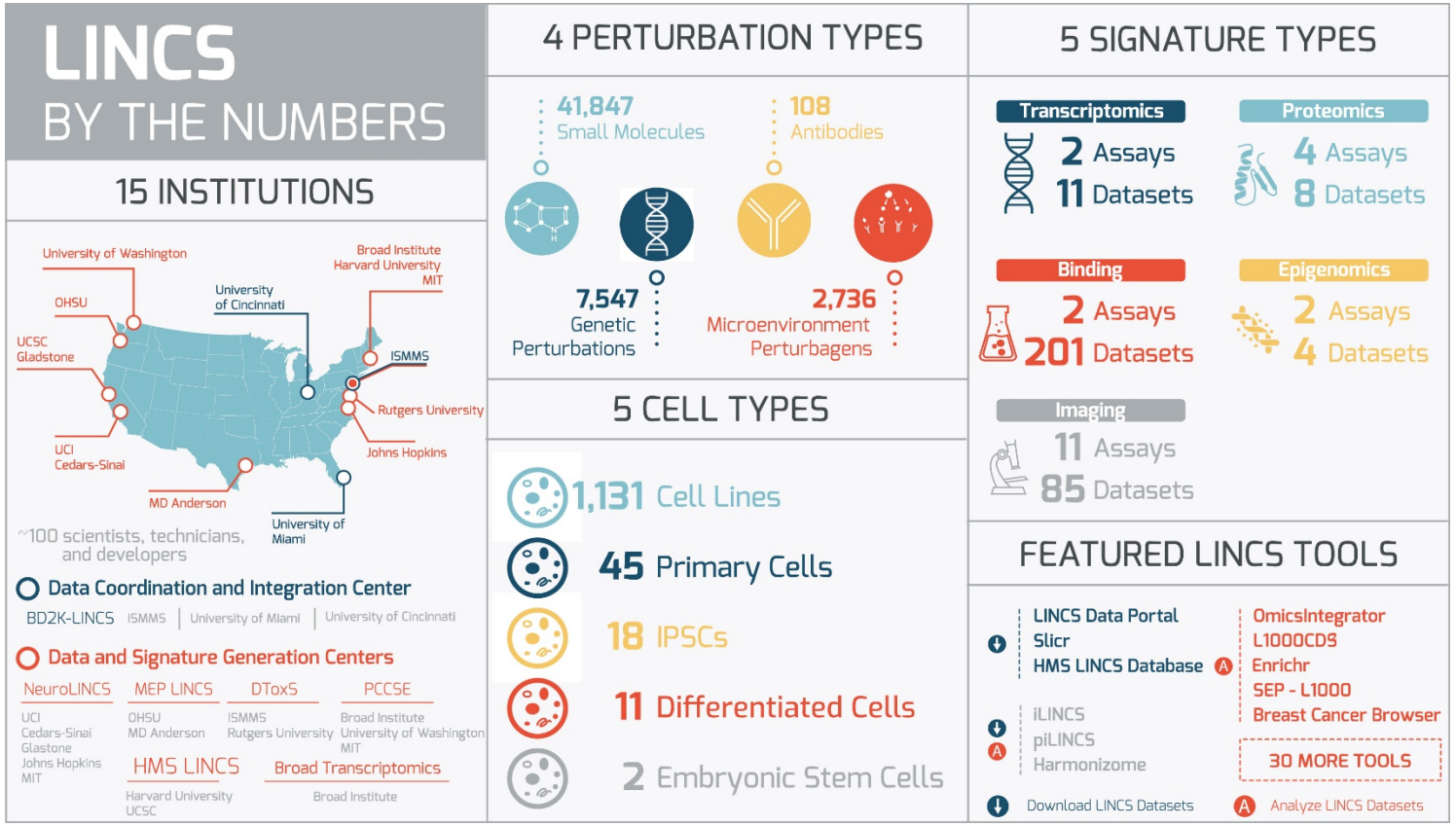
Target	Human DLPFC mRNA	Pyramidal Neurons mRNA	Cortical Neurons Protein	SMRI Genomics mRNA	Mt. Sinai
MCT1	1.24 FC, p=0.165	1.22 FC, p=0.039	ND	1.03 FC, p=0.345	-1.15 FC#
MCT2	NM	1.03 FC, p=0.846	ND	1.04 FC, p=0.055	-1.16 FC#
MCT4	1.07 FC, p=0.752	-1.19 FC, p=0.230	-1.69 FC, p=0.0008	1.01 FC, p=0.160	-1.31 FC, p=0.137
LDHA	-1.15 FC, p=0.359	-1.11 FC, p=0.285	-1.46 FC, p=0.004	-1.11 FC, p=0.022	-1.06 FC, p=0.320
LDHB	-1.02 FC, p=0.703	1.01 FC, p=0.860	ND	-1.07 FC, p=0.041	1.08 FC#
HXK1	1.10 FC, p=0.397	-1.24 FC, p=0.003	1.44 FC, p=0.034	1.12 FC, p=0.065	-1.01 FC, p=0.831
HXK2	-1.23 FC, p=0.323	-1.02 FC, p=0.589	-1.28 FC, p=0.017	-1.02 FC, p=0.267	ND
PFKM	-1.32 FC, p=0.039	-1.43 FC, p=0.0001	1.36 FC, p=0.003	1.05 FC, p=0.225	1.03 FC, p=0.694
PFKL	NM	-1.27 FC, p=0.011	ND	-1.00 FC, p=0.920	-1.03 FC#
PFKP	NM	-1.09 FC, p=0.249	ND	-1.02 FC, p=0.679	-1.23 FC, p=0.047
GLUT1	-1.04 FC, p=0.776	-1.19 FC, p=0.009	-1.58 FC, p=0.003	1.07 FC, p=0.029	-1.03 FC, p=0.790
GLUT3	1.01 FC, p=0.907	-1.19 FC, p=0.012	-1.01 FC, p=0.962	1.12 FC, p=0.001	-1.34 FC#
GPI	NM	-1.26 FC, p=0.015	ND	-1.01 FC, p=0.659	-1.01 FC, p=0.878

Kaleidoscope: https://kalganem.shinyapps.io/BrainDatabases/

Question: Can we use a bioinformatics approach to identify new leads for treatment?


Targets
Cell-level postmortem work
New (GPI, PFKL) and published findings (15, 18)
Literature searches
Examine underlying biological processes (14)
Establish "seed profile" of implicated genes
GPI
PFKL
PFKM
HK1
LDHA
PFKFB2
Replication
Stanley Medical Research Institute mRNA
Mount Sinai/Bronx VAMC mRNA
Frontal Cortical Pyramidal Neurons (IPSC) mRNA
"Lookup" studies of glycolitic findings
Probe independent transcriptomic databases for bioenergetic targets
FC>1.1 or p<0.05
iLINCs
Connectivity analyses
Identify chemical perturbagens with L1000 signatures most discordant to seed gene KD signatures
Clustering analyses
Cluster the union of the top 50 differentially expressed L1000 genes from each seed gene KD signature
iLINCs database
Probe iLINCs for mRNA knockdown signatures for the "seed profile" genes
Drug trial
Pathway analyses
Drug identification
Drug trial in model of schizophrenia
-GluN1 KD mouse
-Pioglitazone in chow (1 week, 100 ppm)
-Endophenotypes of schizophrenia
Open field test
Elevated plus maze
Puzzle box assay
Social paradigm
Prepulse inhibition

The Library of Integrated Network-based Cellular Signatures (LINCS)



The Library of Integrated Network-Based Cellular Signatures NIH Program: System-Level Cataloging of Human Cells Response to Perturbations

Alexandra B. Keenan [1], Sherry L. Jenkins [1], Kathleen M. Jagodnik [1], Simon Koplev [1], Edward He [1], Denis Torre [1], Zichen Wang [1], Anders B. Dohlman [1], Moshe C. Silverstein [1], Alexander Lachmann [1], Maxim V. Kuleshov [1], Avi Ma'ayan [1,*], Vasileios Stathias [2], Raymond Terryn [2], Daniel Cooper [2], Michele Forlin [2], Amar Koleti [2], Dusica Vidovic [2] ... Ajay Pillai [19]

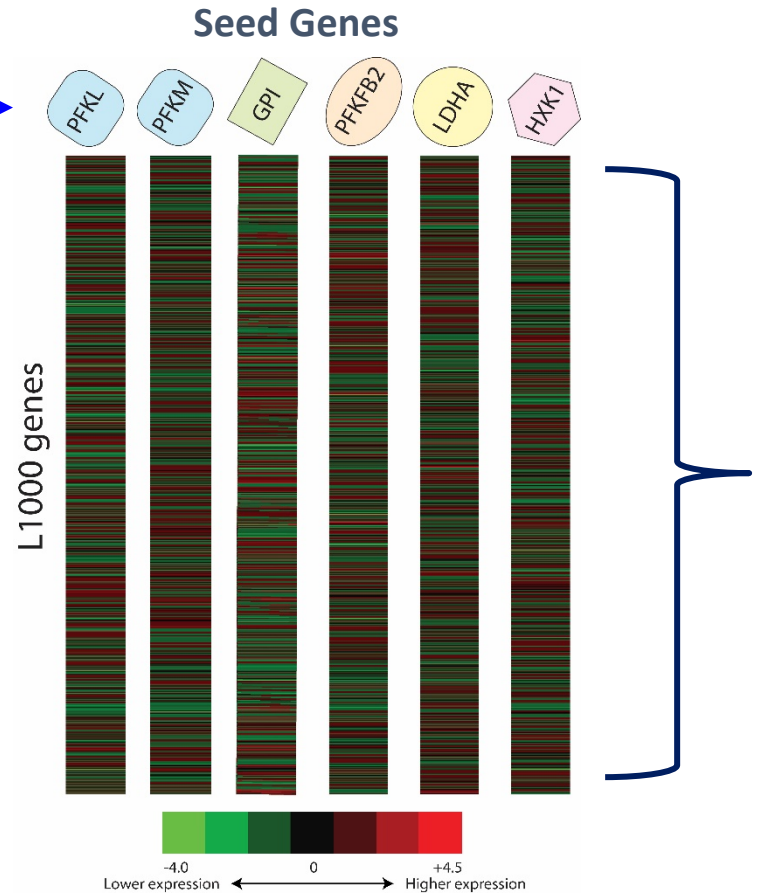
CellPress

Bioinformatic analyses of SCZ profile

2. Probe iLINCS for L1000 signatures for each of our seed genes

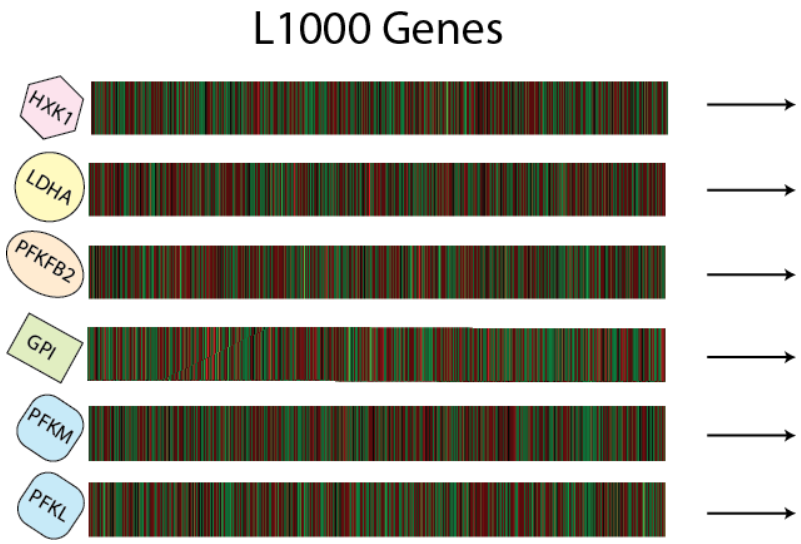
Targets knocked down

How do the L1000 genes change in response to the seed gene being knocked down?



"Knockdown signatures"

Can we reverse the SCZ profile?



Probe iLINCS for chemical perturbagens that produce L1000 signatures **ANTI-CORRELATED** with our schizophrenia signatures

Perturbagens that “reverse” the SCZ signature

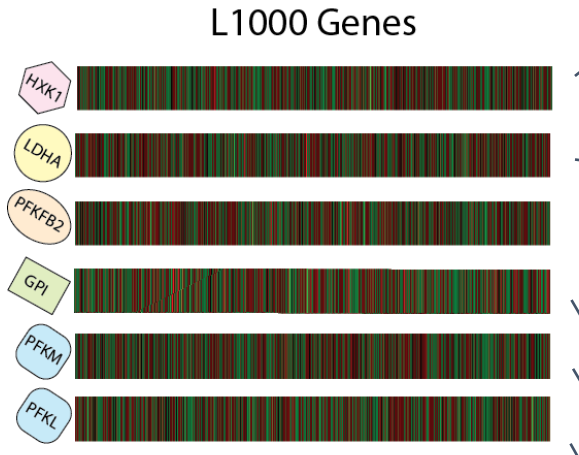


Table 4.5. Top 20 discordant chemical perturbagen signatures per seed gene.

Perturbagen	Seed Gene	Concordance	Cell Line
Trifluoperazine	HXK1	0.415168	VCAP
Tretinoin	HXK1	0.397106	VCAP
Valproic acid	HXK1	-0.394195	VCAP
ST013886	HXK1	-0.393411	VCAP
MLS002473819	HXK1	0.385226	VCAP
Dexlansoprazole	HXK1	-0.382007	VCAP
ZINC01041848	HXK1	-0.378767	VCAP
ACTNSIF7	HXK1	0.377218	VCAP
Troglitazone	HXK1	-0.377088	VCAP
CHEMBL1884008	HXK1	-0.37223	VCAP
Flumazenil	HXK1	-0.371409	VCAP
C23H24O8	HXK1	-0.370781	VCAP
AS-60b240	HXK1	-0.36989	VCAP
Iclilin	HXK1	-0.369856	VCAP
Flupirtine	HXK1	0.366641	VCAP
MLS0001062 1b	HXK1	-0.362483	SNUC5
MEGXP0_001444	HXK1	-0.3611	VCAP
Tretinoin	HXK1	0.359876	VCAP
N (3 acetamidophenyl) 3 chlorobenzamide	HXK1	-0.358602	HCC515
NS-3694	HXK1	-0.357018	VCAP
BRD-K31110964	LDHA	-0.297296	VCAP
BRD-K27503016	LDHA	-0.282251	VCAP
CGP 37157	LDHA	0.281405	VCAP
Parachlorophenol	LDHA	-0.2810016	VCAP
BRD-K65231869	LDHA	-0.27851	VCAP
PF 3845	LDHA	0.277911	HCT116
UK 356618	LDHA	-0.276899	A549
AGK 2	LDHA	-0.275713	HCT116
BRD-K75393430	LDHA	-0.272569	VCAP
BRD K04627808	LDHA	0.271066	VCAP
BRD-K19914944	LDHA	-0.270857	VCAP
MLS003130341	LDHA	-0.269348	VCAP
PP 30	LDHA	0.268455	HCT116
COT-108	LDHA	-0.265997	HEPG2
BRD-K12342216	LDHA	-0.265288	VCAP
Tangeretin	LDHA	0.264339	VCAP
HY-11007	LDHA	-0.264185	BT20
BRD-K15761174	LDHA	-0.263793	VCAP
BRD-K6865/207	LDHA	-0.263426	VCAP
CHEMBL586058	LDHA	-0.262891	HA1E
BRD-K50150285	GPI	-0.241463	VCAP
Zileuton	GPI	0.218711	HCT116
teicoplanin	GPI	-0.209458	HA1E
Fenobam	GPI	-0.208305	ASC
CHEMBL104433	GPI	0.20846	BT20
Minoxidil	GPI	-0.206587	A549
M3M3FB5	GPI	-0.203381	AGS
Rimexolone	GPI	0.20113	ASC
Valproic acid	PFKM	0.285891	VCAP
BRD-K68423345	PFKM	-0.2667/47	VCAP
Trifluoperazine	PFKM	-0.206602	VCAP
THZ 2 98 01	PFKM	0.204707	VCAP
Valproic acid	PFKL	0.507504	VCAP
Trifluoperazine	PFKL	-0.479188	VCAP
C23H24O8	PFKL	-0.442924	VCAP
Thioridazine	PFKL	-0.441215	VCAP
ST013886	PFKL	0.440599	VCAP
Tretinoin	PFKL	-0.427624	VCAP
Troglitazone	PFKL	-0.422798	VCAP
Trifluoperazine	PFKL	0.422663	VCAP
Fluphenazine	PFKL	-0.418354	VCAP
Tretinoin	PFKL	-0.41519	VCAP
MLS001214919	PFKL	0.413819	VCAP
Thioridazine	PFKL	-0.410137	VCAP
Genistein	PFKL	-0.408439	VCAP
LY-294002	PFKL	-0.403587	VCAP
Tretinoin	PFKL	-0.397361	VCAP
MLS0001062 1b	PFKL	-0.383491	SNUC5
Fluphenazine	PFKL	-0.383423	VCAP
423735 93 7	PFKL	0.380623	HCT116
ZINC01041848	PFKL	-0.379954	VCAP
Troglitazone	PFKL	-0.369054	VCAP

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Trifluoperazine	PFKL	-0.422663	VCAP
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Trifluoperazine	HXK1	-0.415168	VCAP
MLS001214919	PFKL	-0.413819	VCAP
Thioridazine	PFKL	-0.410137	VCAP
Genistein	PFKL	-0.408439	VCAP
LY-294002	PFKL	-0.403587	VCAP
Tretinoin	HXK1	-0.397106	VCAP
Valproic acid	HXK1	-0.394195	VCAP
ST013886	HXK1	-0.393411	VCAP
Tretinoin	PFKL	-0.392361	VCAP
MLS002473819	HXK1	-0.385526	VCAP

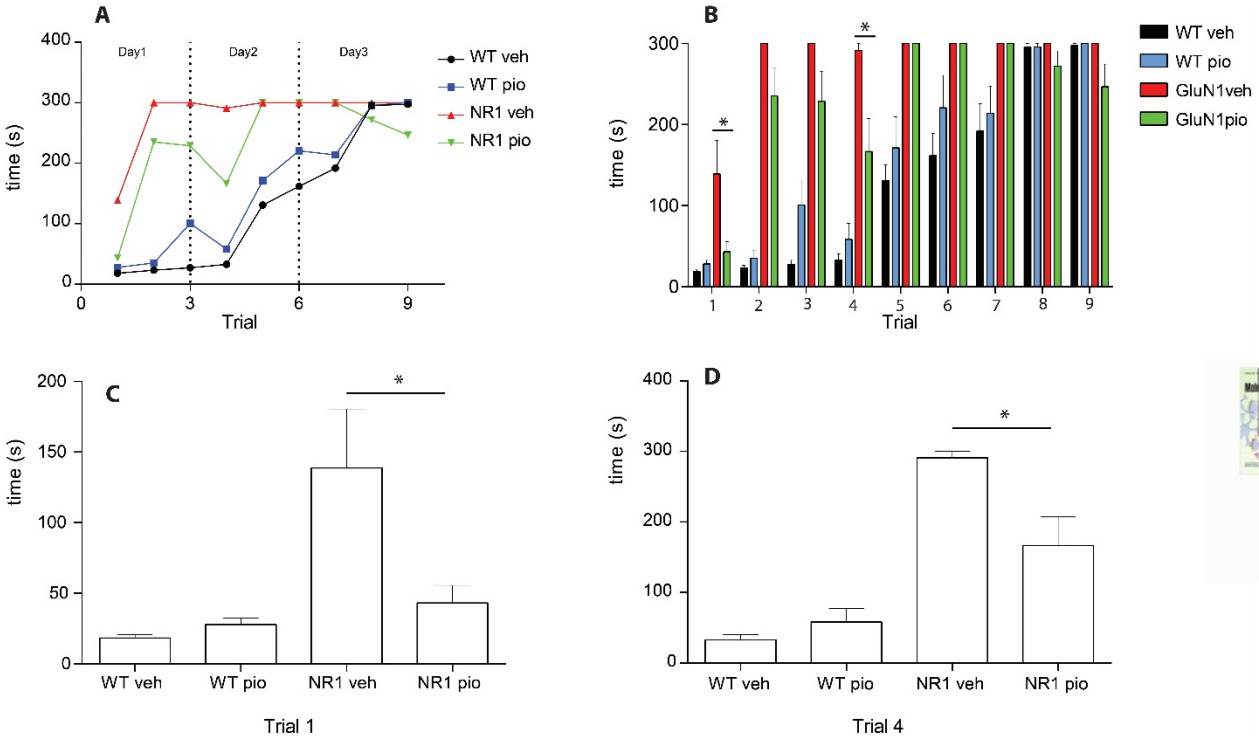
iLINCS Top hits

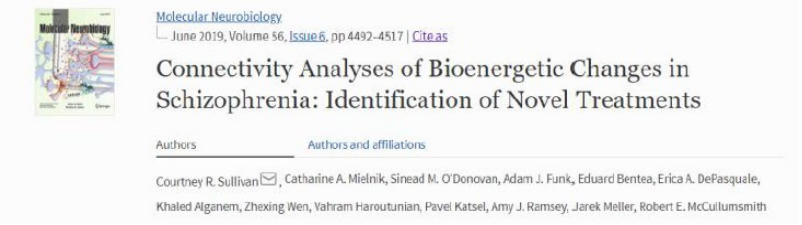
Table 4. Top 12 unique chemical perturbagens.

Chemical	Description
Valproic acid	Histone deacetylase (HDAC) inhibitor, voltage-gated sodium channel blocker
Trifluoperazine	Typical antipsychotic drug
C23H24O8, "Wortmannin"	Irreversible phosphoinositide 3-kinase (PI3K) inhibitor, mitogen-activated protein kinase (MAPK) inhibitor at high concentrations
Thioridazine	Typical antipsychotic drug
ST013886	Estradiol
Tretinoin	Medication used for the treatment of acne and acute promyelocytic leukemia (APL), prevents APL cells from proliferating
Troglitazone	Ligand to both PPARα and more strongly PPARγ, thiazolidinedione (TZD) drug class, reduces inflammation, enhances insulin sensitivity
Fluphenazine	Typical antipsychotic drug
MLS001214919	Small molecule
Genistein	Isoflavone with antioxidant abilities, activates PPAR isoforms α, δ, and γ
LY-294002	Strong (reversible) inhibitor of phosphoinositide 3-kinases (PI3Ks)
MLS002473819	Small molecule

PPAR agonists appear...
Including class of drugs called thiazolidinediones (TZDS)

Pioglitazone in NR1 model





Molecular Neurobiology
June 2019, Volume 56, Issue 6, pp 4492–4517 | Cite as

Connectivity Analyses of Bioenergetic Changes in Schizophrenia: Identification of Novel Treatments

Authors | Authors and affiliations

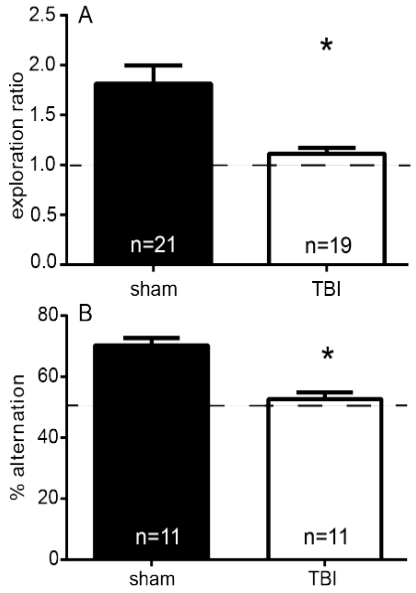
Courtney R. Sullivan, Catharine A. Mielnik, Sinead M. O'Donovan, Adam J. Funk, Eduard Bentea, Erica A. DePasquale, Khaled Alganem, Zhexing Wen, Yahram Haroutunian, Pavel Katsel, Amy J. Ramsey, Jarek Meller, Robert E. McCullumsmith

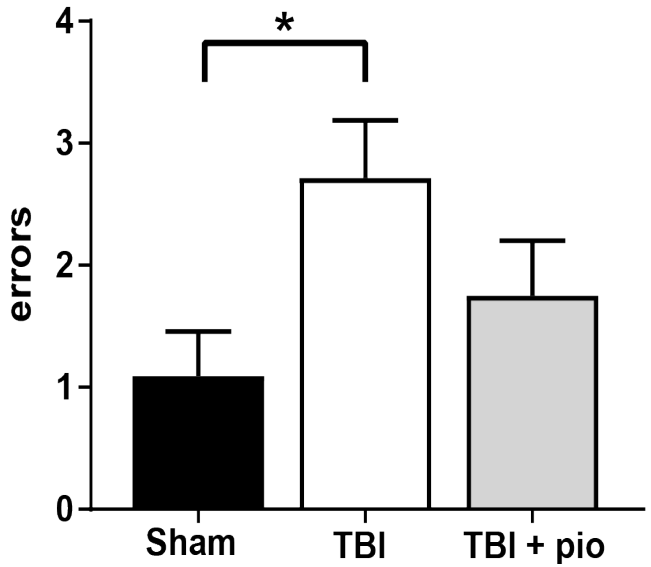
Puzzle box is progressively difficult
Day 1 testing: Open door, closed, closed
Day 2 testing: closed door, then underpass filled
Day 3: underpass filled, then plug, plug

Pio improves explicit memory in GluN1 animals

Does not improve PPI, locomotor, or anxiety measures.

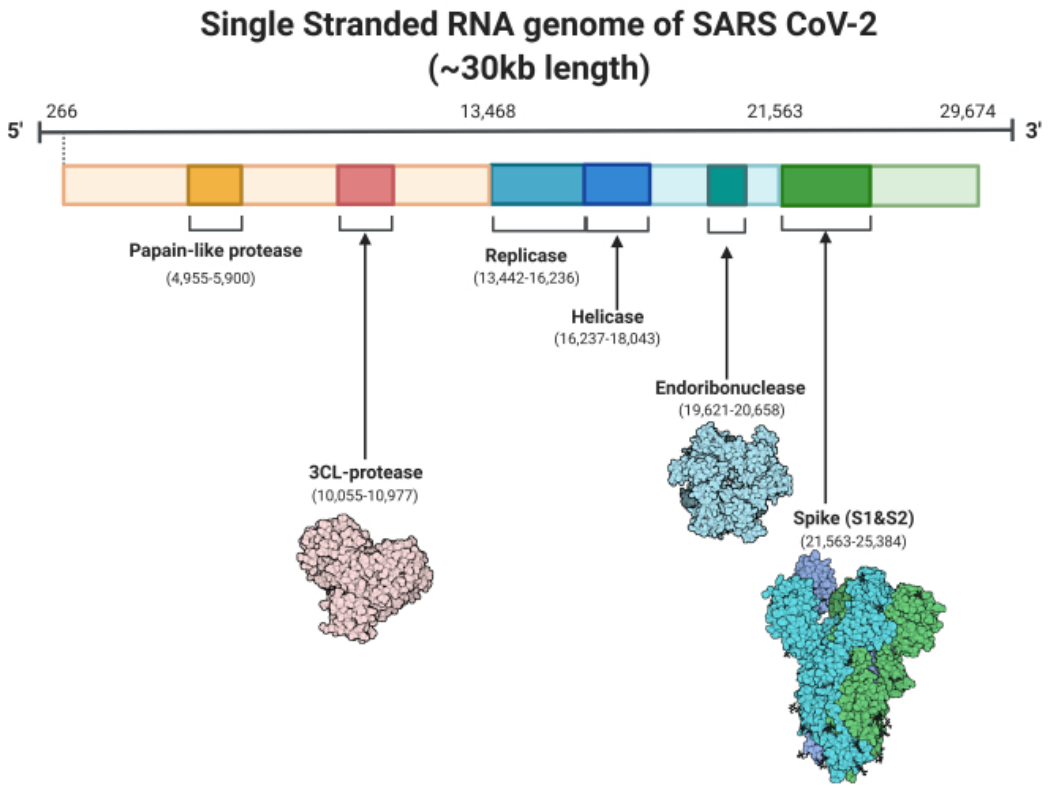
Pioglitazone in disorders of cognition: Chronic TBI

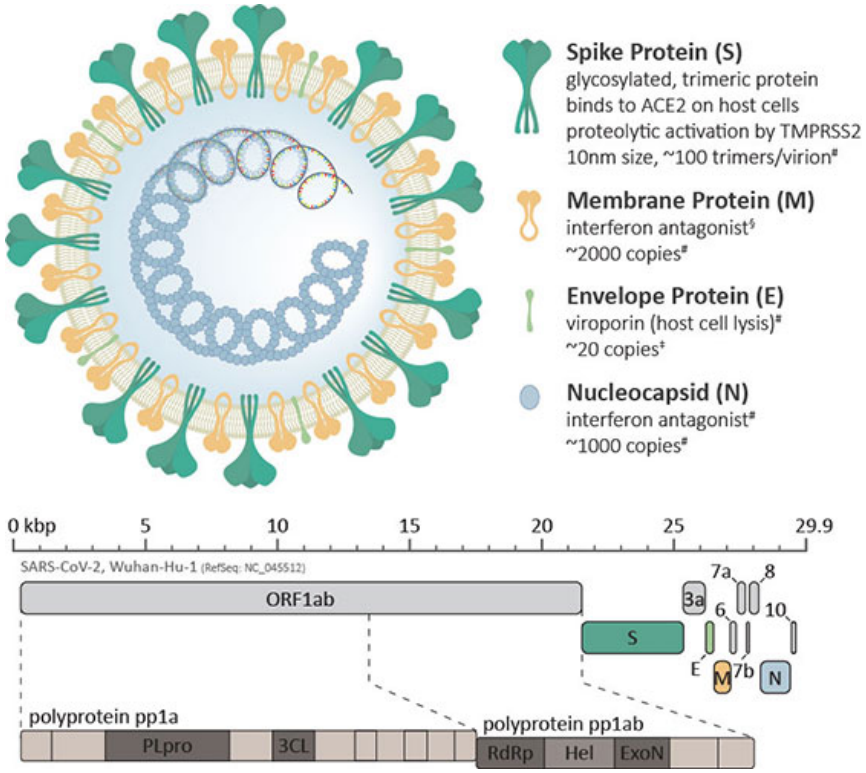




N=5

Can we apply this to COVID-19?





Multiple possible strategies

- Target the virus directly- antiviral therapy
- Target the host immune response- suppression of cytokine storm
- Target the host immune response- vaccination

Multiple possible strategies

- **Target the virus directly- antiviral therapy**
- **Target the host immune response- suppression of cytokine storm**
- Target the host immune response- vaccination

Multiple possible strategies

- **Target the virus directly- antiviral therapy**
- Target the host immune response- suppression of cytokine storm
- Target the host immune response- vaccination

OPEN

Identification of candidate repurposable drugs to combat COVID-19 using a signature-based approach

Sinead M. O'Donovan[1,10], Ali Imami[1,10], Hunter Eby[1], Nicholas D. Henkel[1], Justin Fortune Creeden[1], Sophie Asah[1], Xiaolu Zhang[1], Xiaojun Wu[1], Rawan Alnafisah[1], R. Travis Taylor[2], James Reigle[3,4], Alexander Thorman[6], Behrouz Shamsaei[4], Jarek Meller[4,5,6,7,8] & Robert E. McCullumsmith[1,9]✉

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Target the COVID-19 virus directly

- Identification of putative COVID-19 antivirals
- Assessment of the structure of putative antivirals from transcriptional signatures
- Transcriptional profiles of infected cells
- Identification of drugs in large databases that “reverse” the disease signature
- Combination of putative drugs (concordant) and transcriptional disease signatures (discordant) into hit list of drugs

Identification of putative COVID-19 antivirals

Table 1. Drug target groupings.

Drug Cluster	Drug	Canonical Mechanism of Action	Anatomical Therapeutic Chemical *First Level*
1	Chloroquine Hydroxychloroquine	Toll-like receptor antagonists	Antiparasitic Products, Insecticides and Repellants
2	Lopinavir Ritonavir	Protease inhibitors	Anti-Infective for Systemic Use
3	Fedratinib Ruxolinitib Bariticinib	JAK inhibitors	Antineoplastic and Immunomodulating Agents
4	Azithromycin	Macrolide antibiotic	Anti-Infective for Systemic Use
5	Losartan	Angiotensin receptor blocker antagonist	Cardiovascular System

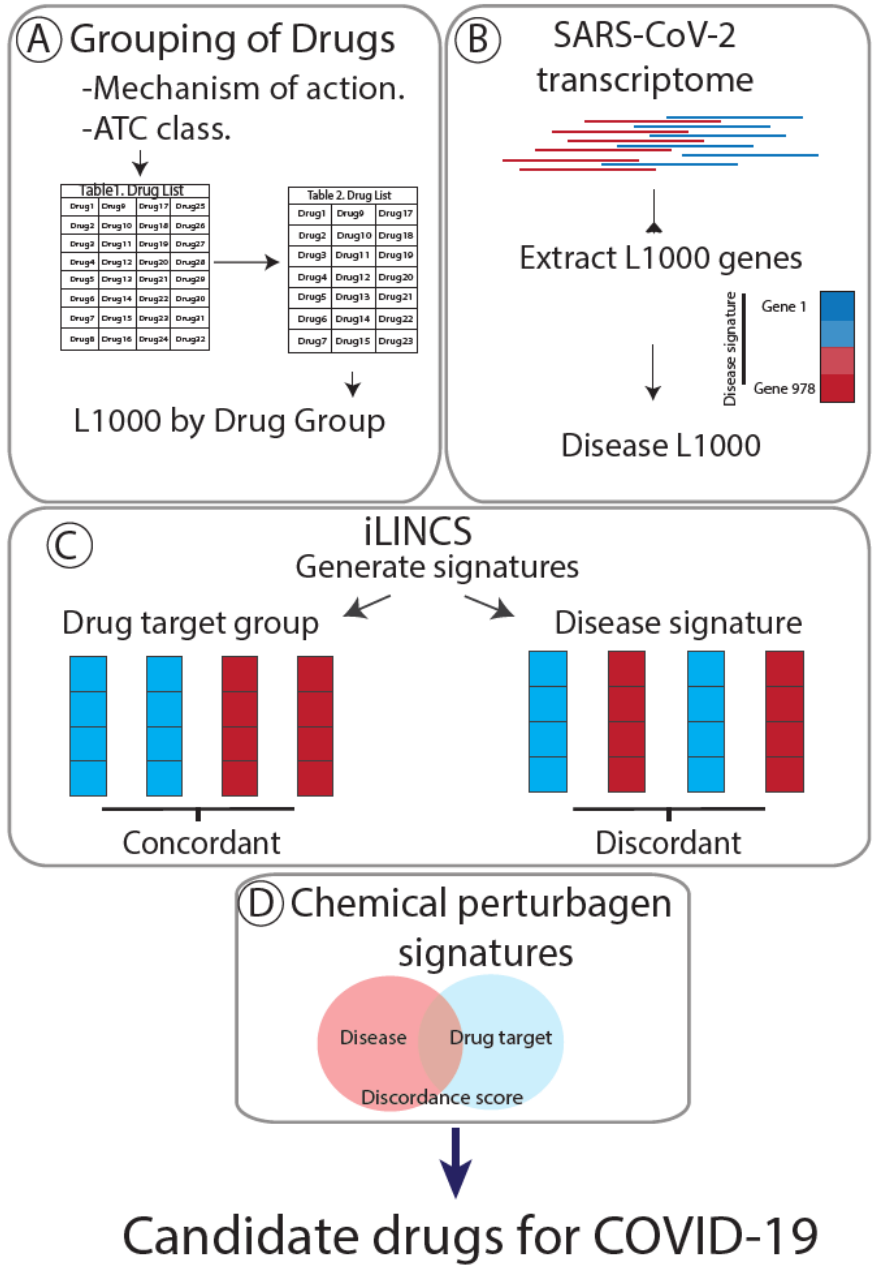

A Grouping of Drugs
-Mechanism of action.
-ATC class.
Table1. Drug List
Table 2. Drug List
L1000 by Drug Group
B
SARS-CoV-2
transcriptome
Extract L1000 genes
Disease signature
Gene 1
Gene 978
Disease L1000
C
iLINCS
Generate signatures
Drug target group
Disease signature
Concordant
Discordant
D Chemical perturbagen
signatures
Disease
Drug target
Discordance score
Candidate drugs for COVID-19

Figure 2

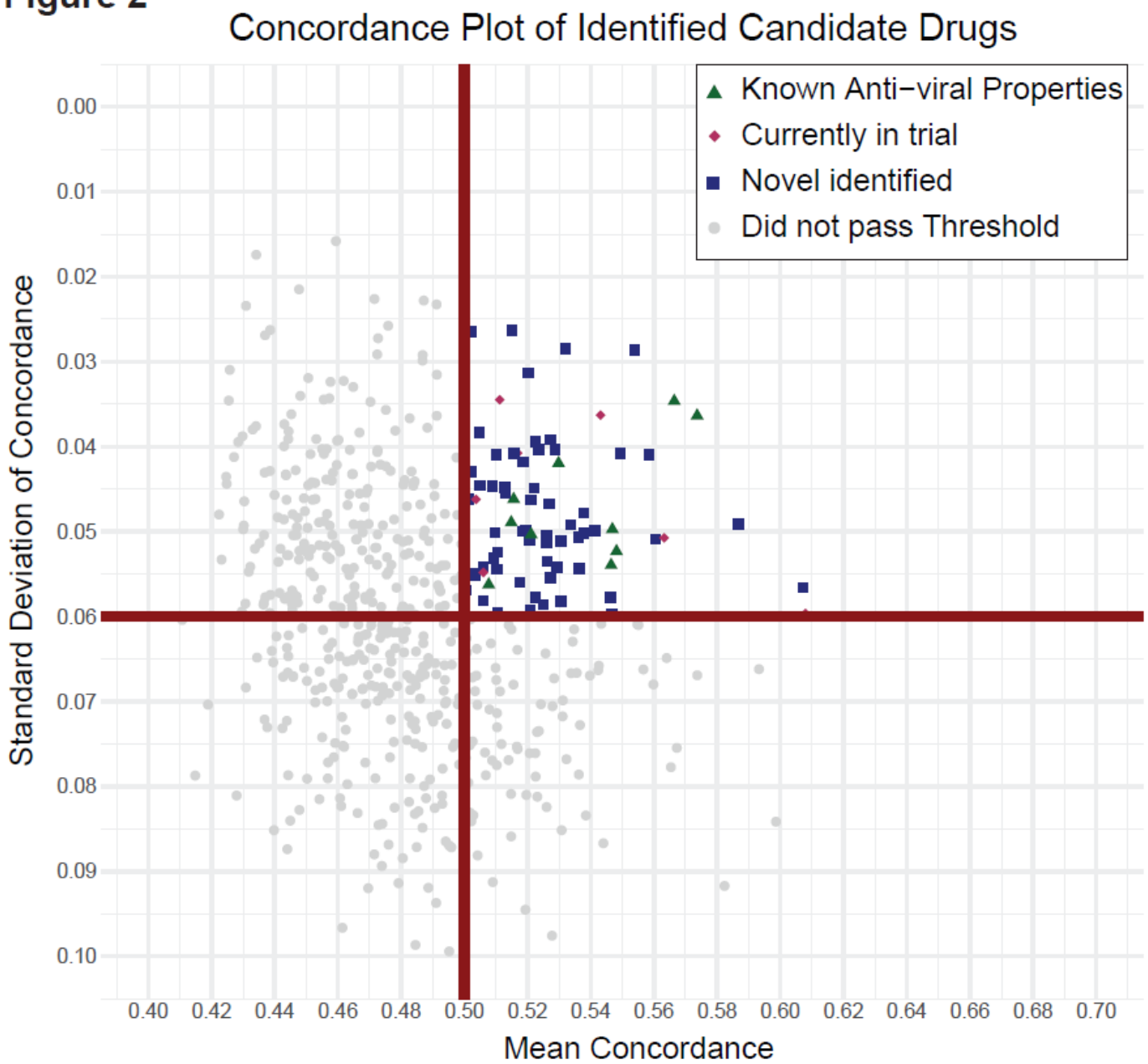
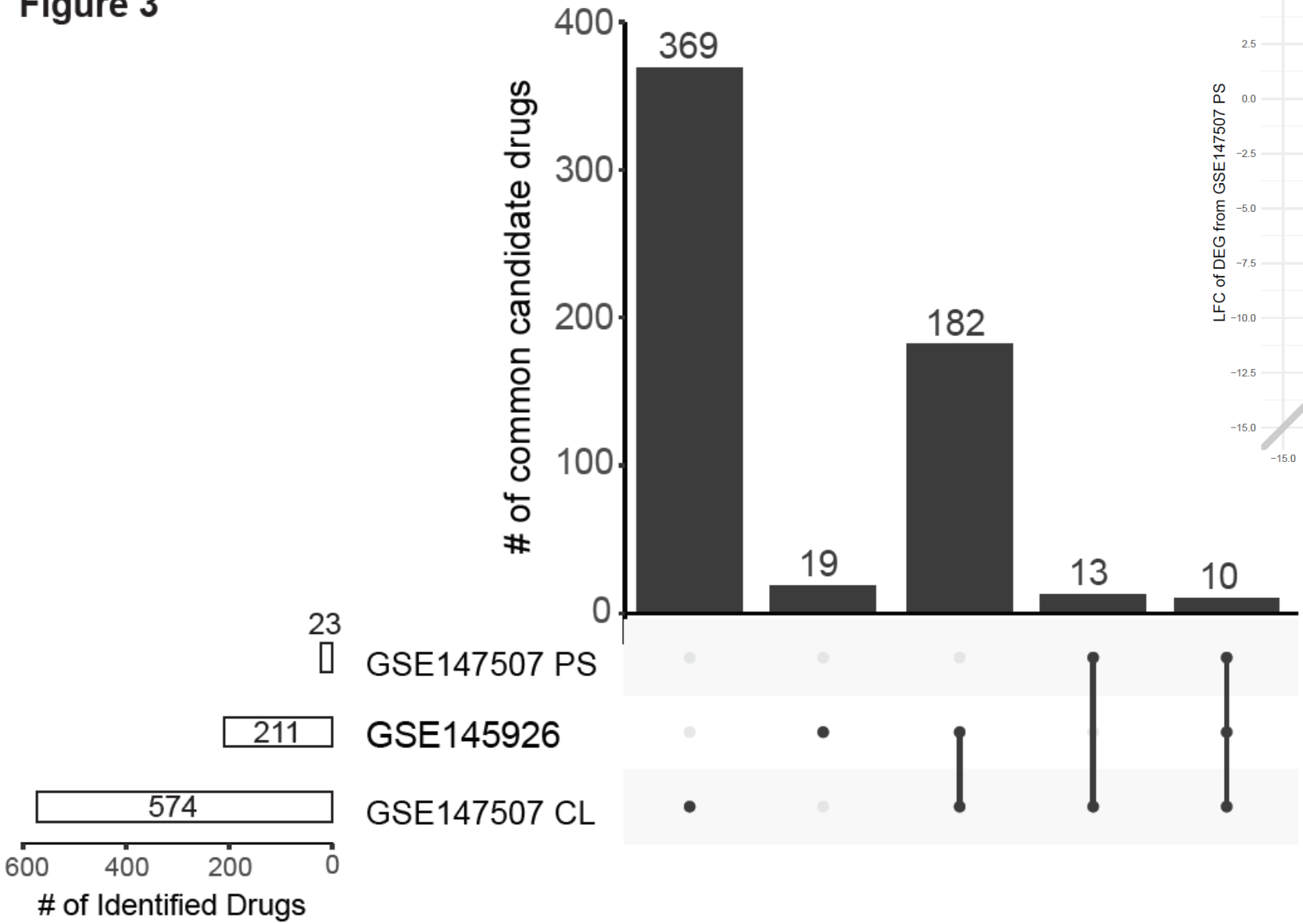
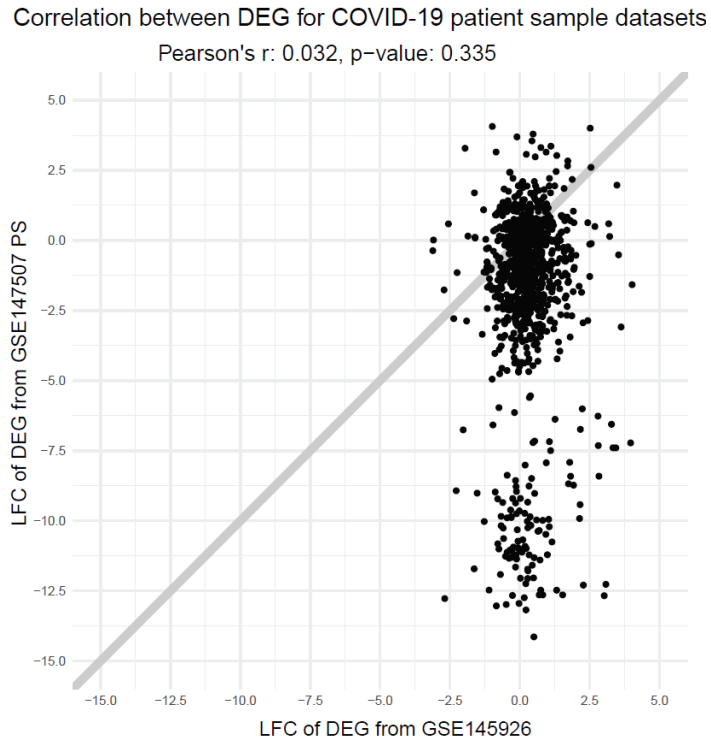

Concordance Plot of Identified Candidate Drugs
Known Anti−viral Properties
Currently in trial
Novel identified
Did not pass Threshold
Standard Deviation of Concordance
0.00
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.10
0.40
0.42
0.44
0.46
0.48
0.50
0.52
0.54
0.56
0.58
0.60
0.62
0.64
0.66
0.68
0.70
Mean Concordance

Figure 3


400
300
200
100
0
# of common candidate drugs
369
19
182
13
10
23
GSE147507 PS
211
GSE145926
574
GSE147507 CL
600
400
200
0
# of Identified Drugs


Correlation between DEG for COVID-19 patient sample datasets
Pearson's r: 0.032, p−value: 0.335
LFC of DEG from GSE147507 PS
LFC of DEG from GSE145926
5.0
2.5
0.0
−2.5
−5.0
−7.5
−10.0
−12.5
−15.0

Candidate repurposable drugs for the treatment of COVID-19

Drug	Drug class	Antiviral properties
Gemcitabine	Antineoplastic, nucleoside analog	SARS-CoV-2, SARS-CoV, MERS [30]
Trametinib	Kinase inhibitor	MERS-CoV [31]
Withaferin A	steroidal lactone	SARS-CoV-2 [32-35]
Saracatinib	Antitumor, SRC/ABL tyrosine kinase inhibitor	MERS-CoV [36]
Erlotinib	Antineoplastic, tyrosine kinase inhibitor	HCV, RNA viruses, dengue, Ebola [37-39]
Alvocidib	CDK Inhibitor	HSV, HIV, Flu [40-45]
Itrazole	Antifungal	Influenza [46]
Elesclomol	Investigational antineoplastic, elevates ROS	Tuberculosis [47]
Dasatinib	SRC tyrosine kinase inhibitor	HIV [48,49]
Panobinostat	HDAC inhibitor	HIV [50]
Candidate repurposable drugs currently in trial for COVID-19		
Gallocatechin Gallate		Antioxidant
Genistein		Antineoplastic, Antihelminitic
Imatinib		Antineoplastic
Dexamethasone Acetate		Corticosteroid
Simvastatin		Antilipemic
Sirolimus		Macrolide lactams
Tamoxifen		Methoxyaniline

Candidate drugs are FDA-approved or currently undergoing trial; have reported antiviral properties and/or anticoronavirus properties (bold). Several of the candidate drugs identified for repurposing are already undergoing clinical trial for COVID-19.

Multiple possible strategies

- Target the virus directly- antiviral therapy
- **Target the host immune response- suppression of cytokine storm**
- Target the host immune response- vaccination

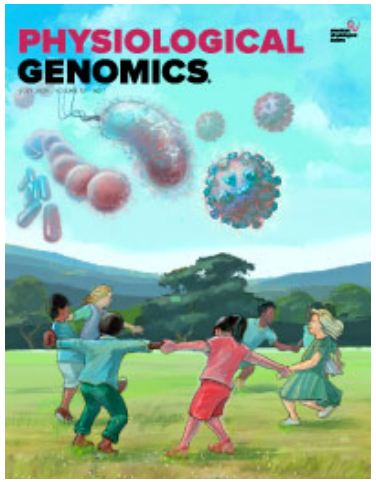
RESEARCH ARTICLE | *Comparative, Statistical, and Computational Genomics and Model Organism Databases*

Oxytocin's anti-inflammatory and proimmune functions in COVID-19: a transcriptomic signature-based approach

Ali S. Imami,[1] Sinead M. O'Donovan,[1] Justin F. Creeden,[1] Xiaojun Wu,[1] Hunter Eby,[1] Cheryl B. McCullumsmith,[2] Kerstin Uvnäs-Moberg,[3] Robert E. McCullumsmith,[1,4] and Elissar Andari[2]

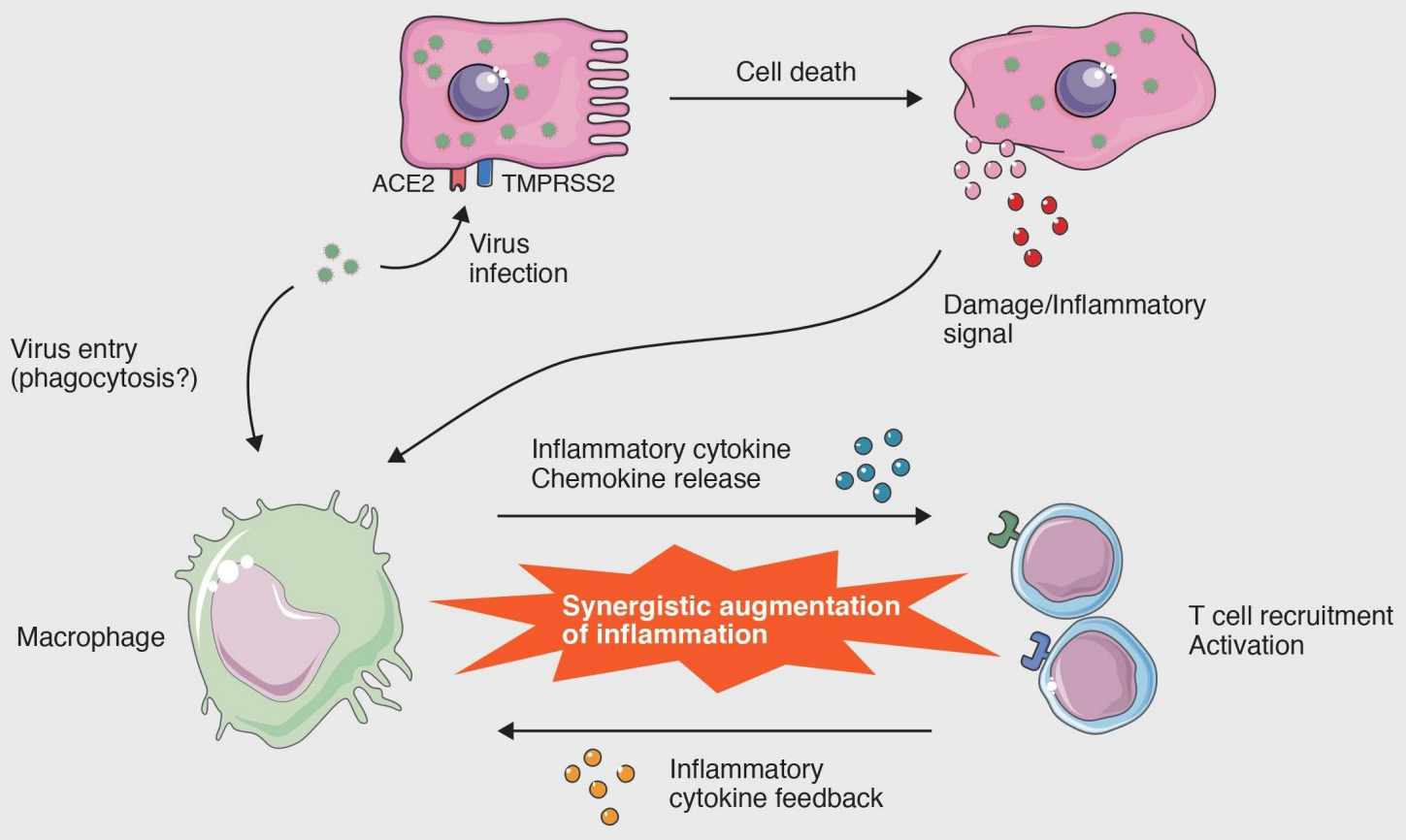
[1]University of Toledo, Department of Neurosciences, College of Medicine and Life Sciences, Toledo, Ohio; [2]University of Toledo, Department of Psychiatry, College of Medicine and Life Sciences, Toledo, Ohio; [3]Department of Animal Environment and Health, Swedish University of Agricultural Sciences, Skara, Sweden; and [4]Neurosciences Institute, ProMedica, Toledo, Ohio

Submitted 4 August 2020; accepted in final form 17 August 2020



Editor: Dr. Bina Joe (UTCOMLS)

COVID and the cytokine storm

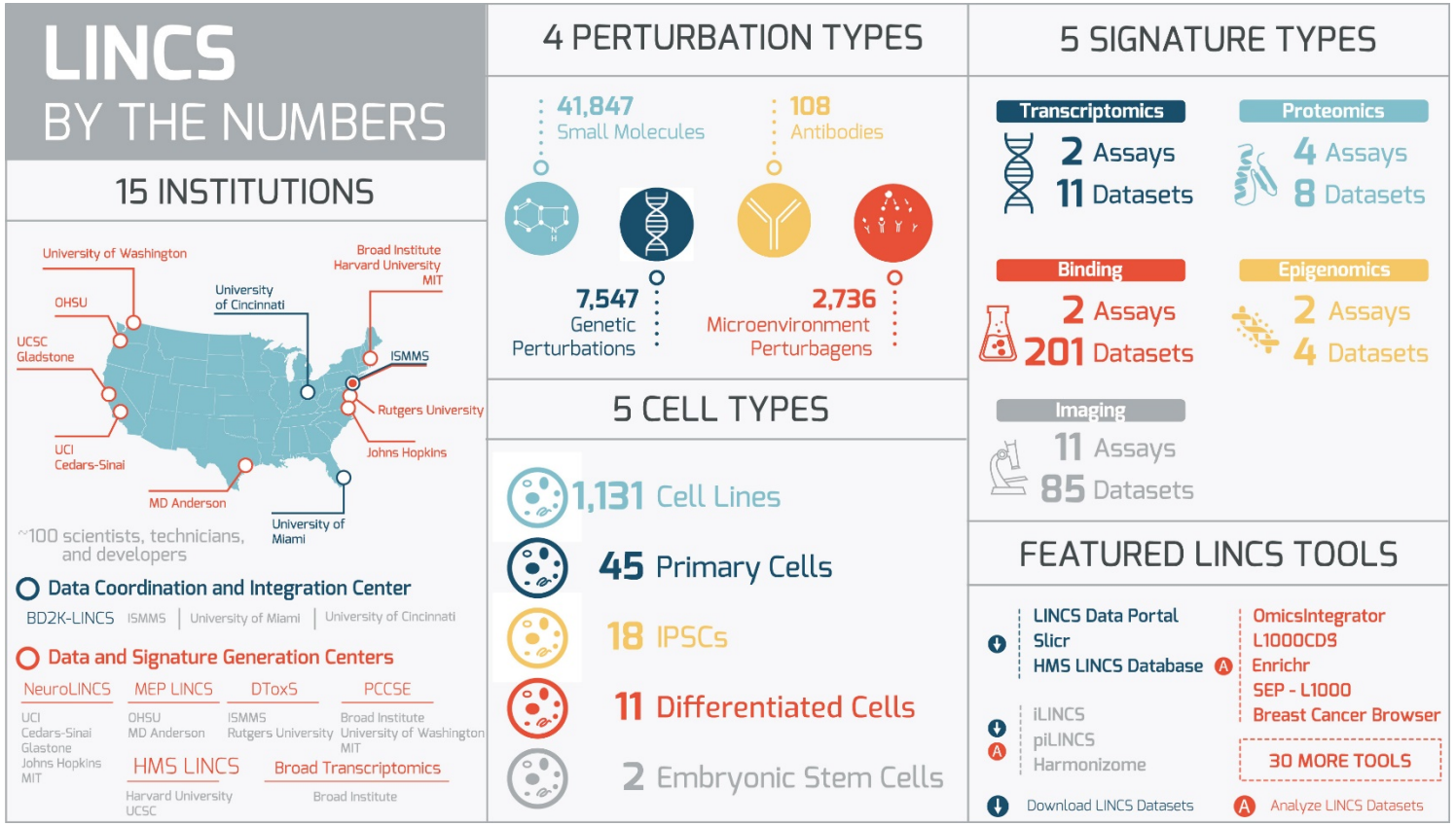


https://www.asiaresearchnews.com/sites/default/files/articles_images/Fig1_3.jpg

Cytokine storm has no definition. Broadly speaking, it denotes a hyperactive immune response characterized by the release of interferons, interleukins, tumor-necrosis factors, chemokines, and several other mediators.

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2767939

The Library of Integrated Network-based Cellular Signatures (LINCS)



The Library of Integrated Network-Based Cellular Signatures NIH Program: System-Level Cataloging of Human Cells Response to Perturbations

Alexandra B. Keenan [1], Sherry L. Jenkins [1], Kathleen M. Jagodnik [1], Simon Koplev [1], Edward He [1], Denis Torre [1], Zichen Wang [1], Anders B. Dohlman [1], Moshe C. Silverstein [1], Alexander Lachmann [1], Maxim V. Kuleshov [1], Avi Ma'ayan [1,*], Vasileios Stathias [2], Raymond Terryn [2], Daniel Cooper [2], Michele Forlin [2], Amar Koleti [2], Dusica Vidovic [2] ... Ajay Pillai [19]

CellPress

Fig. 1

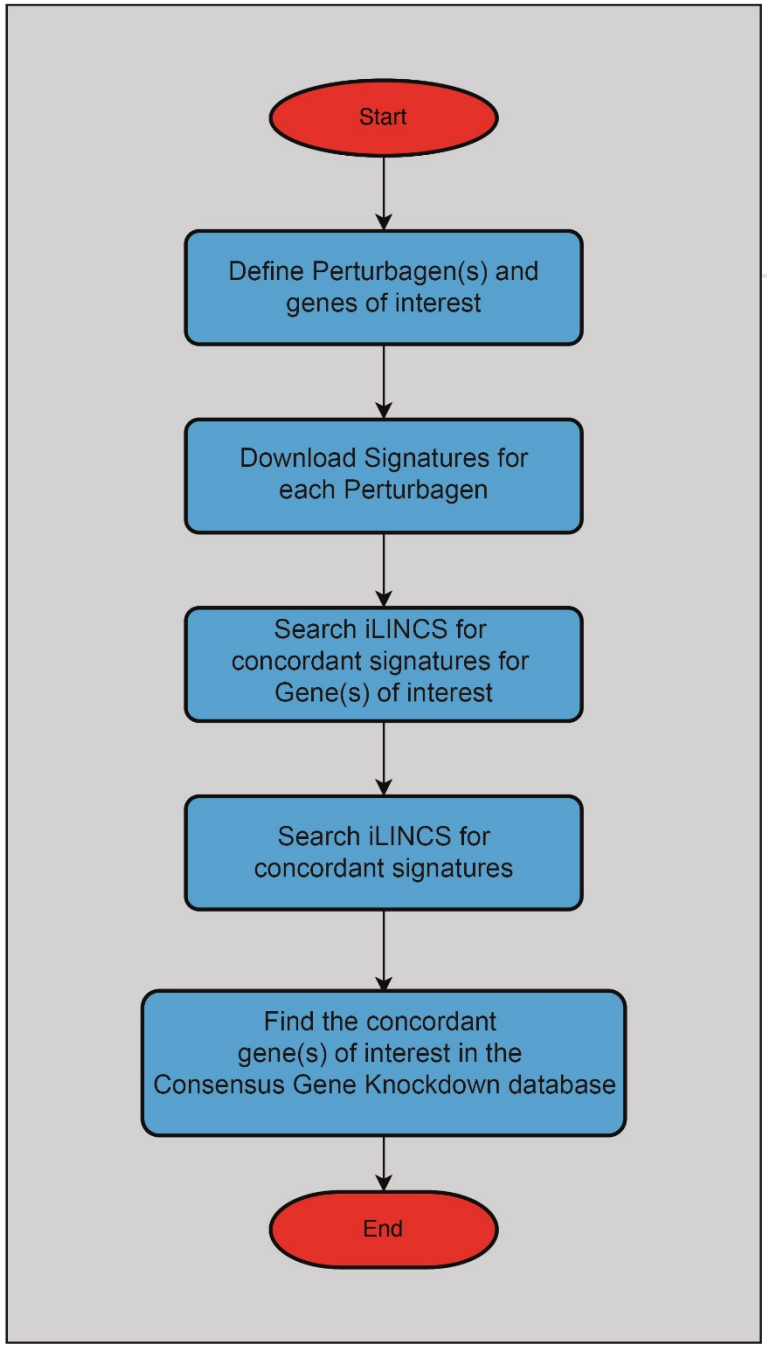
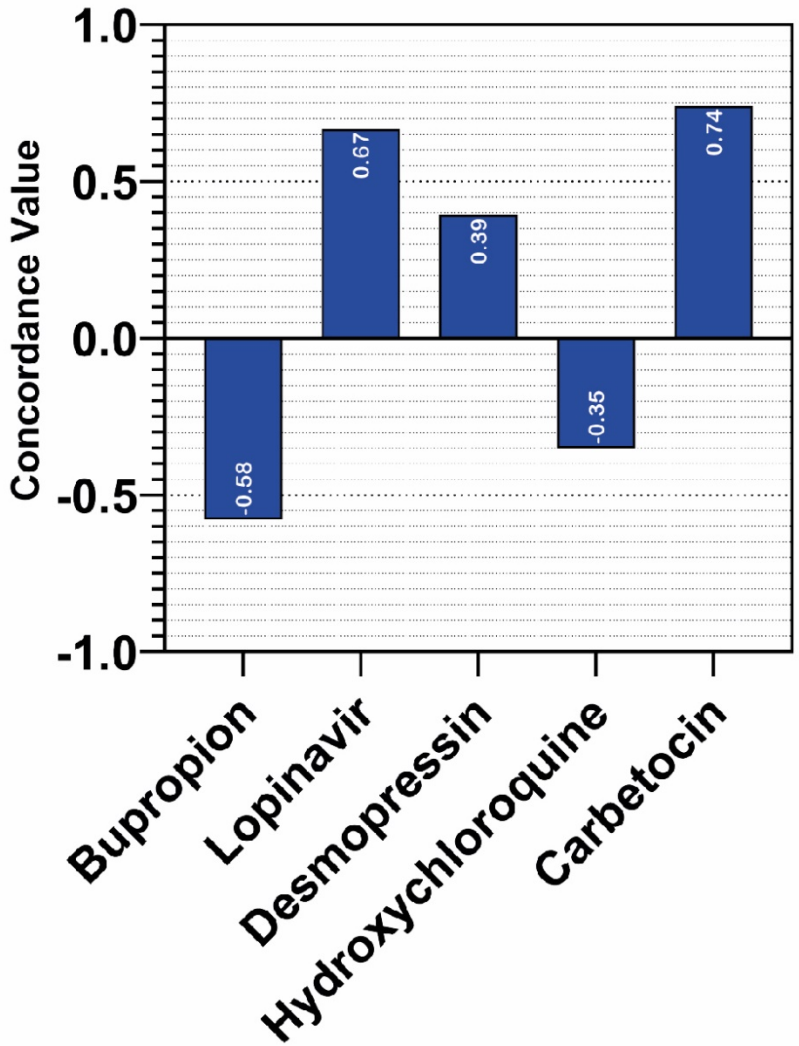
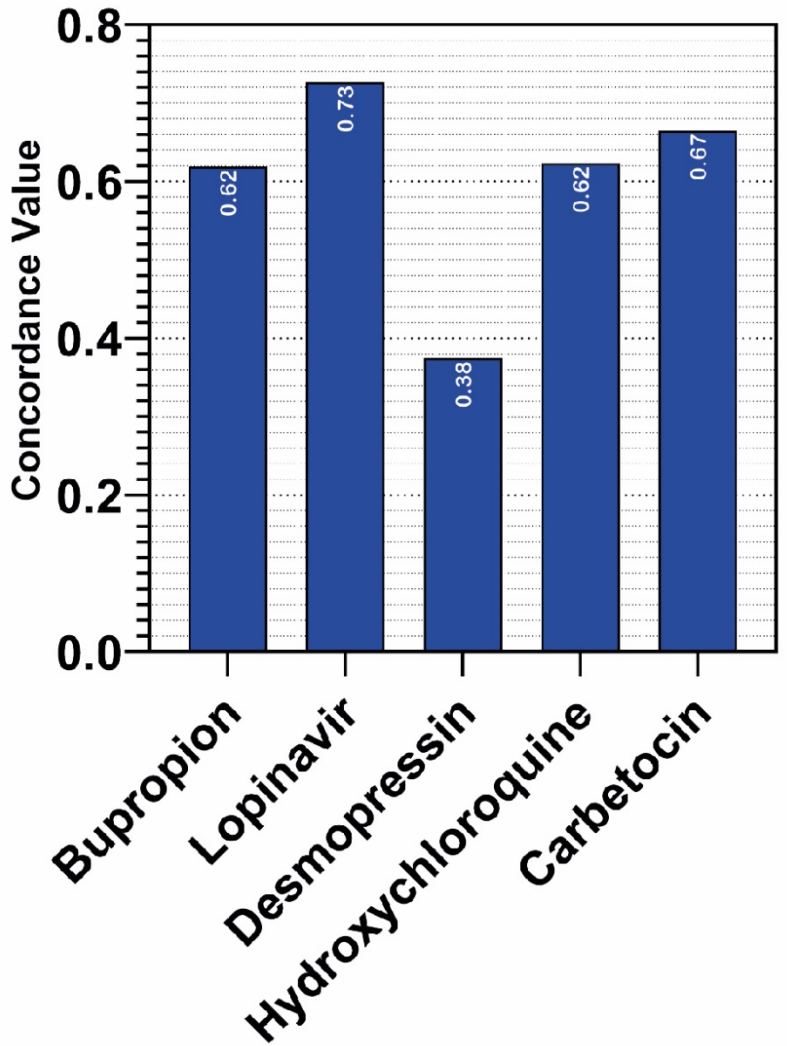

Start
Define Perturbagen(s) and genes of interest
Download Signatures for each Perturbagen
Search iLINCS for concordant signatures for Gene(s) of interest
Search iLINCS for concordant signatures
Find the concordant gene(s) of interest in the Consensus Gene Knockdown database
End

Fig. 2

A) Gene Expression Signature Comparison: Drug Treatment vs IL6 KO



B) Gene Expression Signature Comparison: Drug Treatment vs TNF KO



c)

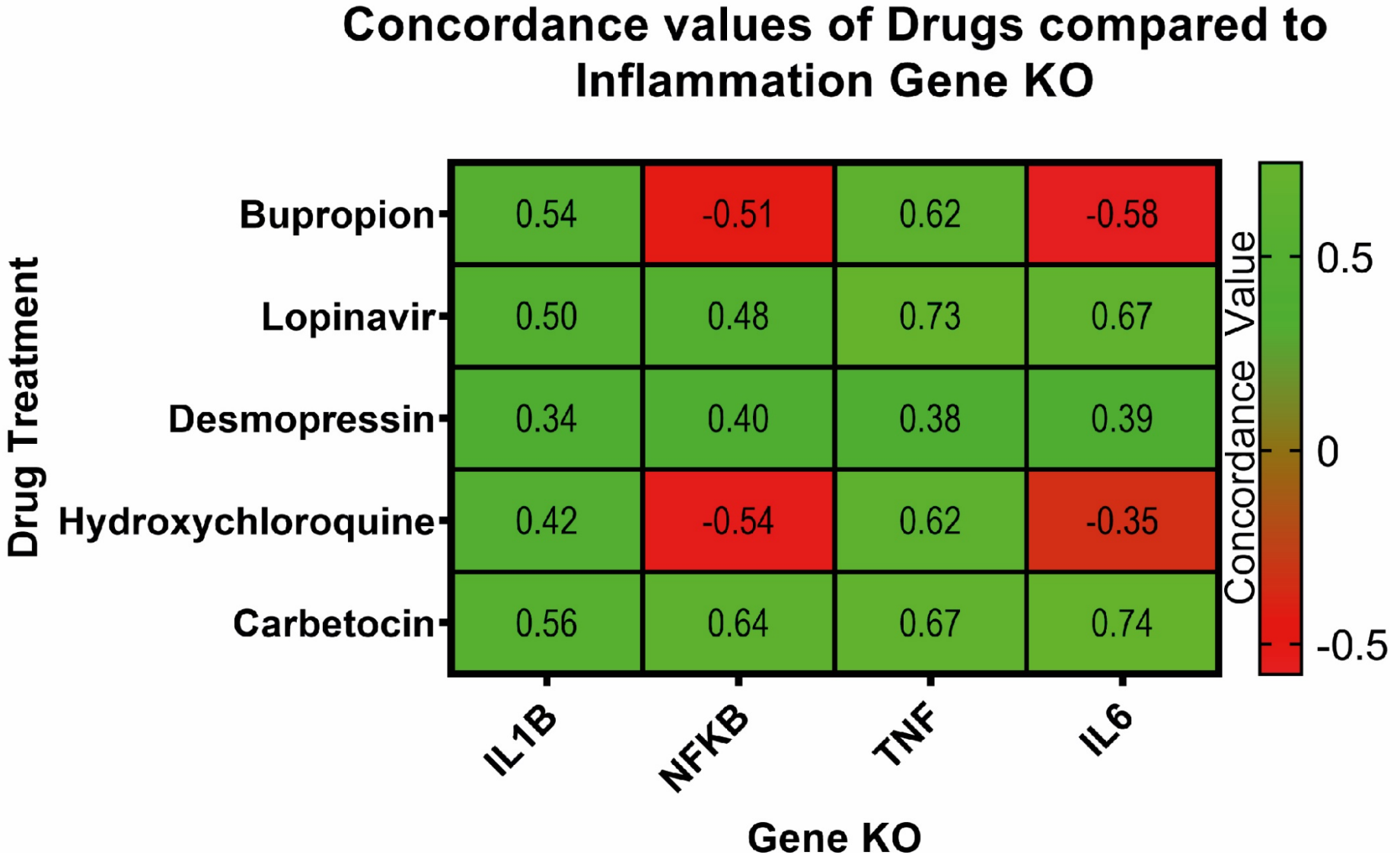
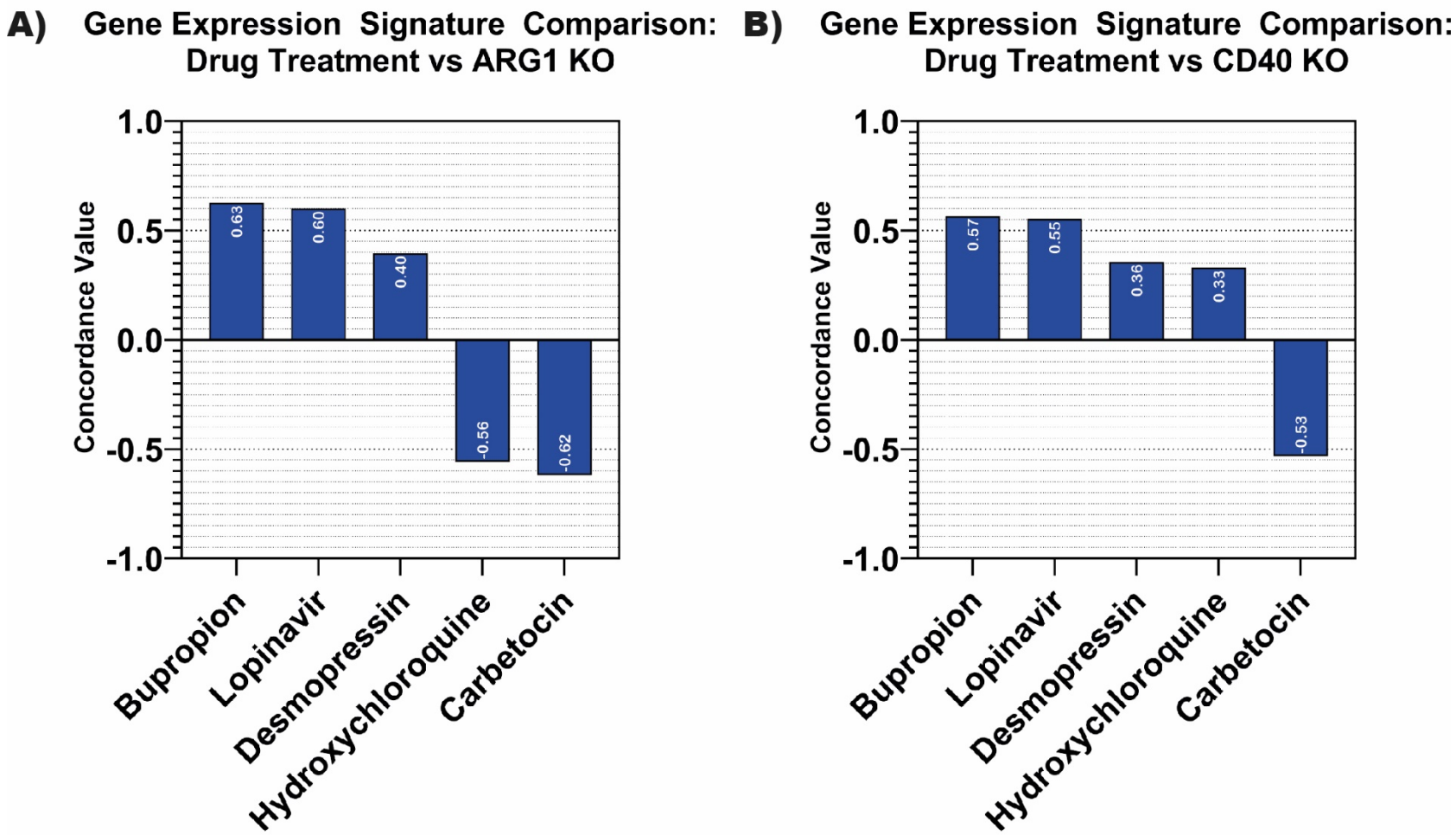
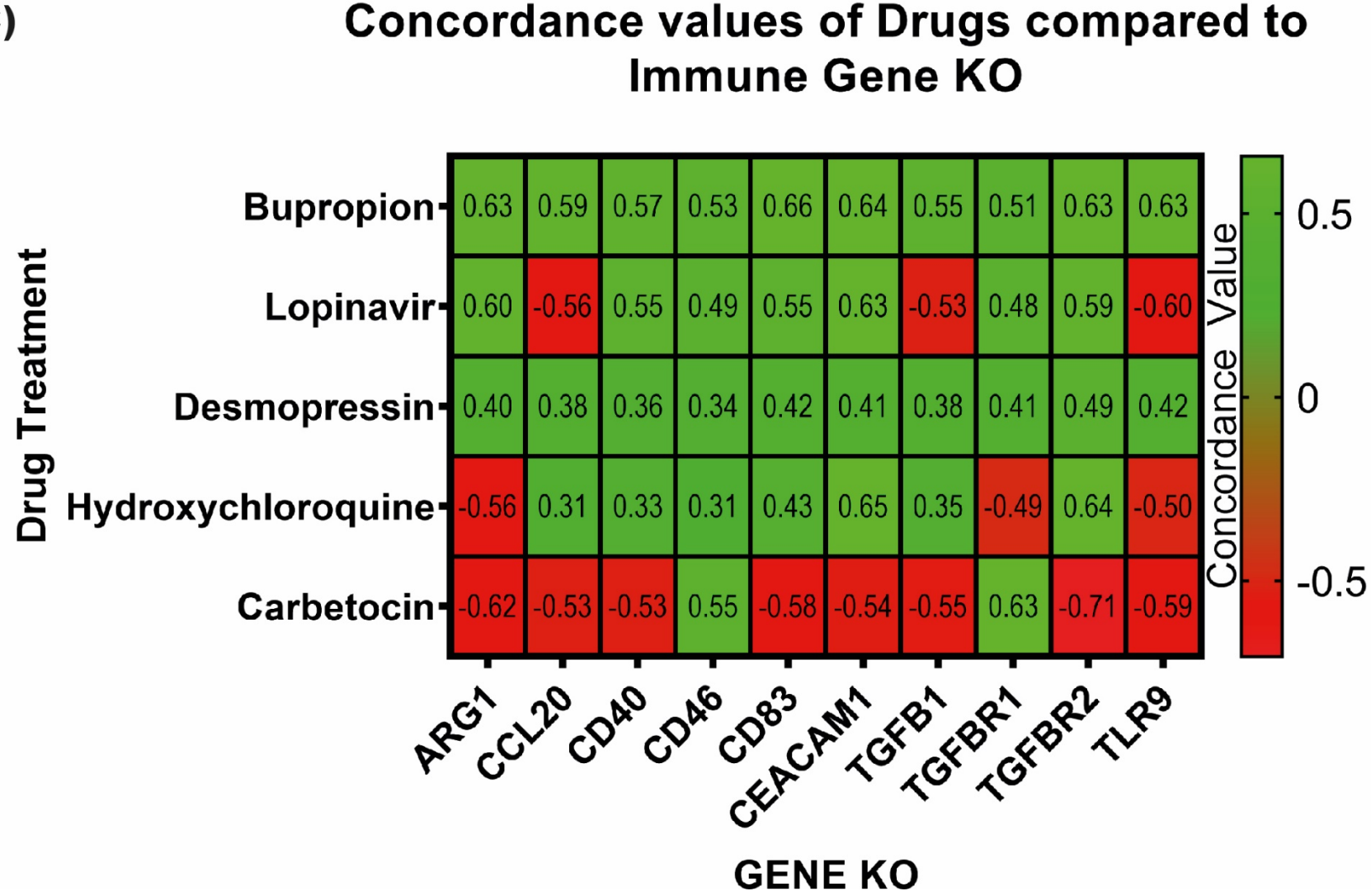

Concordance values of Drugs compared to Inflammation Gene KO
Drug Treatment
Bupropion
Lopinavir
Desmopressin
Hydroxychloroquine
Carbetocin
0.54
-0.51
0.62
-0.58
0.50
0.48
0.73
0.67
0.34
0.40
0.38
0.39
0.42
-0.54
0.62
-0.35
0.56
0.64
0.67
0.74
IL1B
NFKB
TNF
IL6
Gene KO
Concordance Value
0.5
0
-0.5

Fig. 3


A) Gene Expression Signature Comparison: Drug Treatment vs ARG1 KO
B) Gene Expression Signature Comparison: Drug Treatment vs CD40 KO
Concordance Value
1.0
0.5
0.0
-0.5
-1.0
0.63
0.60
0.40
-0.56
-0.62
0.57
0.55
0.36
0.33
-0.53
Bupropion
Lopinavir
Desmopressin
Hydroxychloroquine
Carbetocin

c)


Concordance values of Drugs compared to Immune Gene KO
Drug Treatment
Bupropion
Lopinavir
Desmopressin
Hydroxychloroquine
Carbetocin
0.63 0.59 0.57 0.53 0.66 0.64 0.55 0.51 0.63 0.63
0.60 -0.56 0.55 0.49 0.55 0.63 -0.53 0.48 0.59 -0.60
0.40 0.38 0.36 0.34 0.42 0.41 0.38 0.41 0.49 0.42
-0.56 0.31 0.33 0.31 0.43 0.65 0.35 -0.49 0.64 -0.50
-0.62 -0.53 -0.53 0.55 -0.58 -0.54 -0.55 0.63 -0.71 -0.59
ARG1
CCL20
CD40
CD46
CD83
CEACAM1
TGFB1
TGFBR1
TGFBR2
TLR9
GENE KO
Concordance Value
0.5
0
-0.5

Multiple possible strategies

- Target the virus directly- antiviral therapy
- **Target the host immune response- suppression of cytokine storm**
- Target the host immune response- vaccination

Contents lists available at ScienceDirect

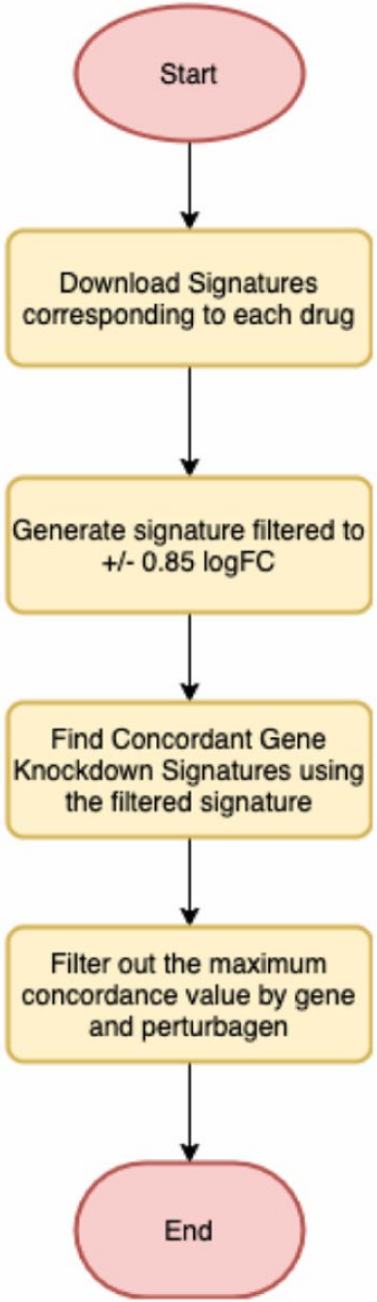
Biomedicine & Pharmacotherapy

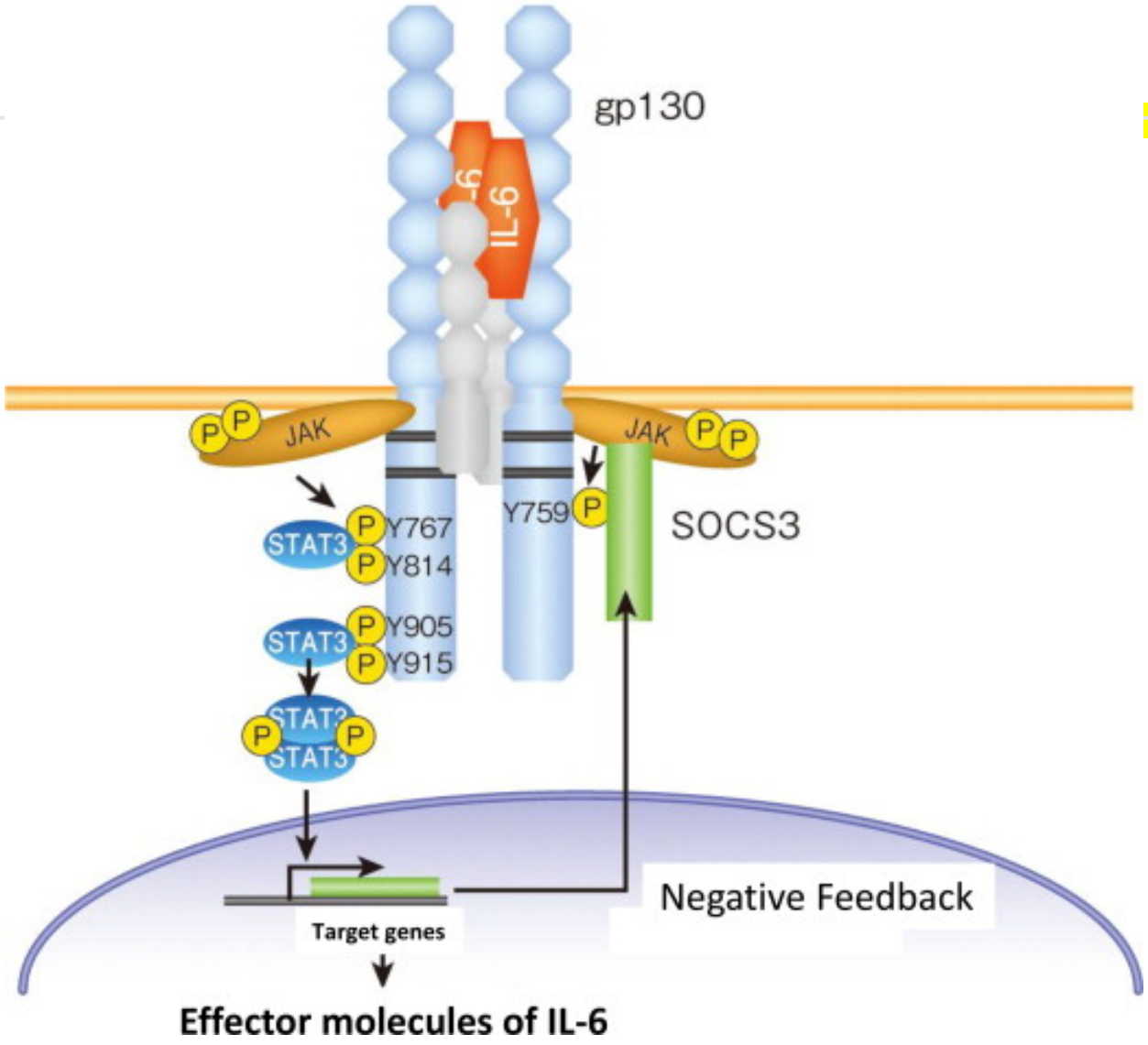
journal homepage: www.elsevier.com/locate/biopha

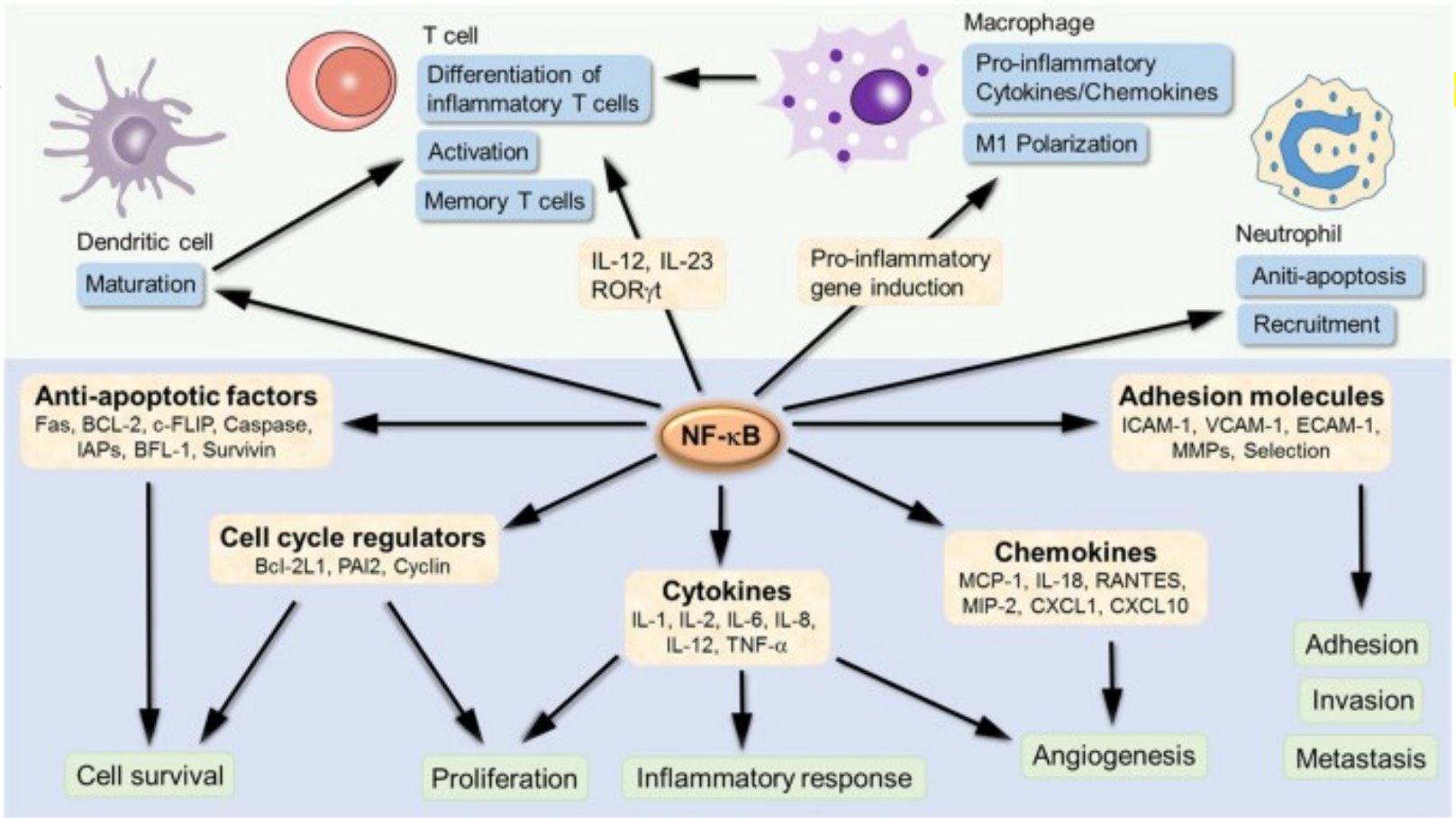
Original article

Fluoxetine as an anti-inflammatory therapy in SARS-CoV-2 infection

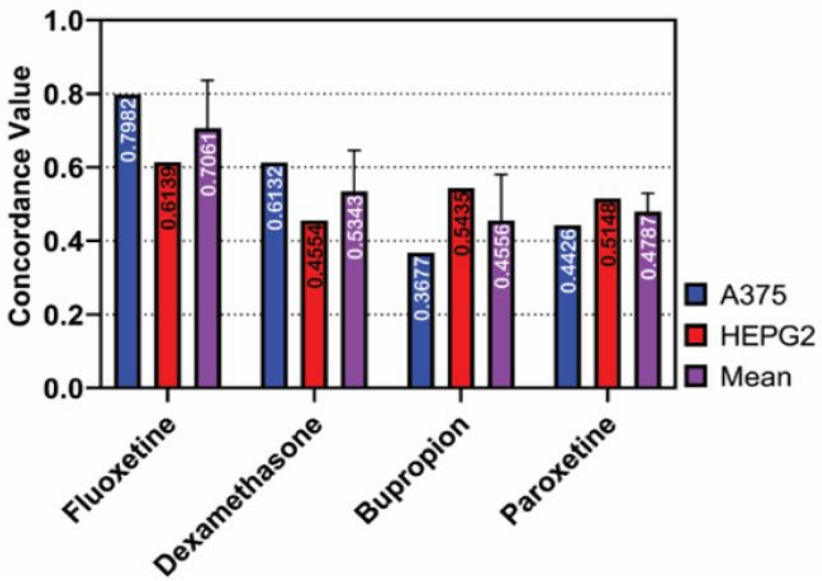
Justin Fortune Creeden [a,b,c,*], Ali Sajid Imami [a], Hunter M. Eby [a], Cassidy Gillman [c], Kathryn N. Becker [b], Jim Reigle [d,e], Elissar Andari [c], Zhixing K. Pan [f], Sinead M. O'Donovan [a], Robert E. McCullumsmith [a,g], Cheryl B. McCullumsmith [c]


Start
Download Signatures corresponding to each drug
Generate signature filtered to +/- 0.85 logFC
Find Concordant Gene Knockdown Signatures using the filtered signature
Filter out the maximum concordance value by gene and perturbagen
End

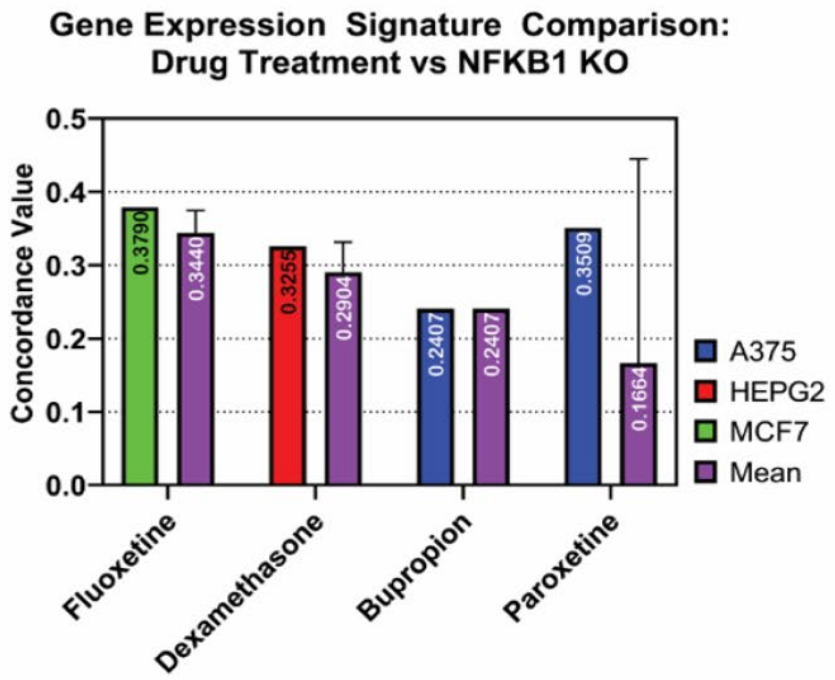

gp130
IL-6
JAK
JAK
P
Y759
SOCS3
STAT3
Y767
Y814
STAT3
Y905
Y915
STAT3
STAT3
Target genes
Negative Feedback
Effector molecules of IL-6


T cell
Differentiation of inflammatory T cells
Activation
Memory T cells
Macrophage
Pro-inflammatory Cytokines/Chemokines
M1 Polarization
Dendritic cell
Maturation
IL-12, IL-23
RORγt
Pro-inflammatory gene induction
Neutrophil
Aniti-apoptosis
Recruitment
Anti-apoptotic factors
Fas, BCL-2, c-FLIP, Caspase, IAPs, BFL-1, Survivin
NF-κB
Adhesion molecules
ICAM-1, VCAM-1, ECAM-1, MMPs, Selection
Cell cycle regulators
Bcl-2L1, PAI2, Cyclin
Cytokines
IL-1, IL-2, IL-6, IL-8, IL-12, TNF-α
Chemokines
MCP-1, IL-18, RANTES, MIP-2, CXCL1, CXCL10
Adhesion
Invasion
Metastasis
Cell survival
Proliferation
Inflammatory response
Angiogenesis

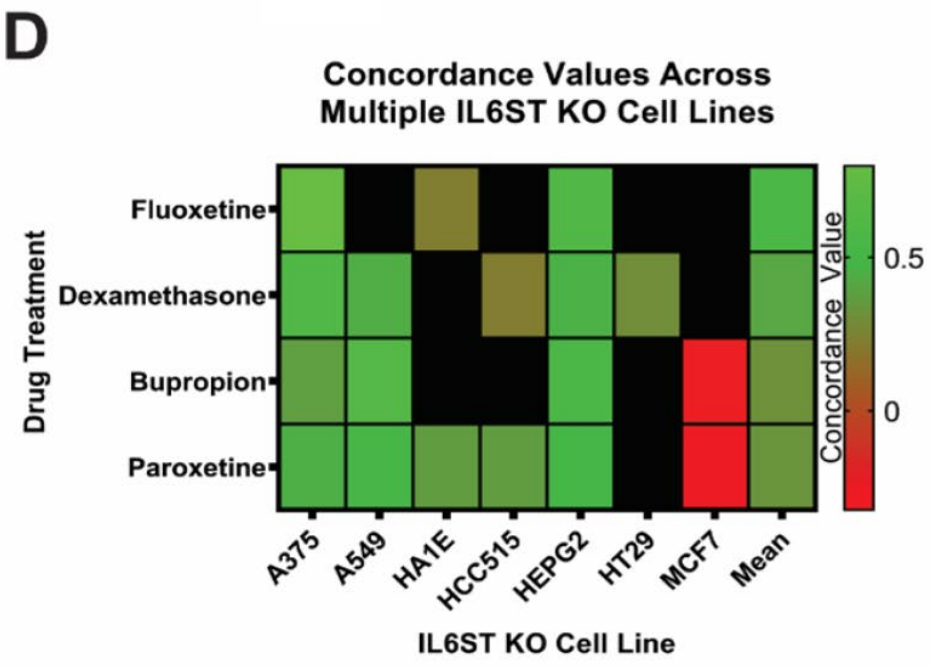
B


Gene Expression Signature Comparison:
Drug Treatment vs IL6ST KO
Concordance Value
1.0
0.8
0.6
0.4
0.2
0.0
0.7982
0.6139
0.7061
0.6132
0.4554
0.5343
0.3677
0.5435
0.4556
0.4426
0.5148
0.4787
Fluoxetine
Dexamethasone
Bupropion
Paroxetine
A375
HEPG2
Mean

C

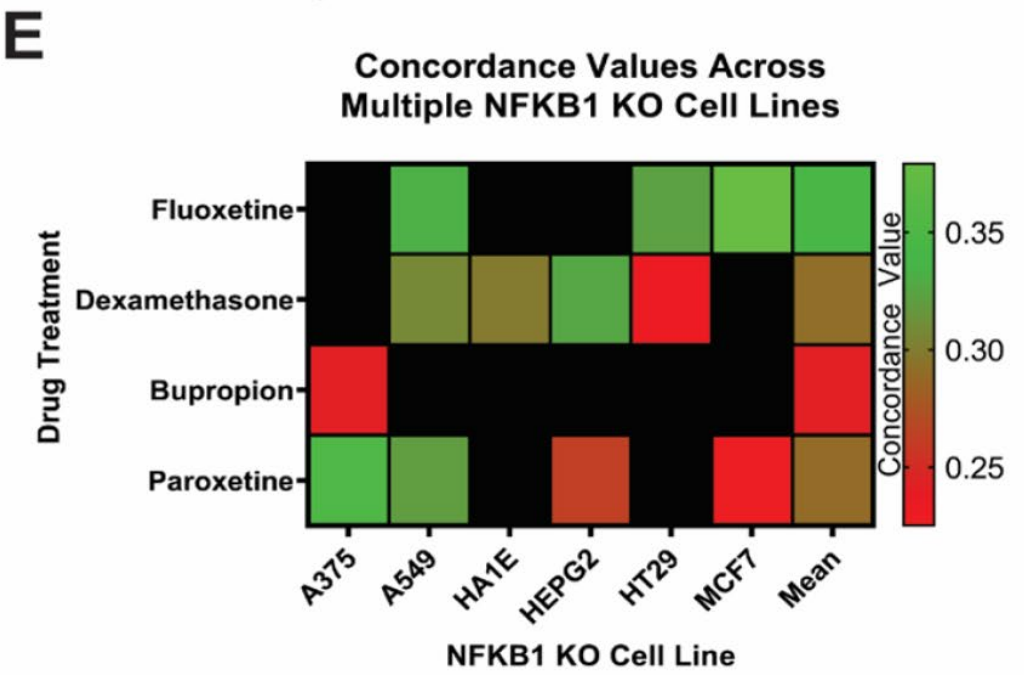

Gene Expression Signature Comparison:
Drug Treatment vs NFKB1 KO
Concordance Value
0.5
0.4
0.3
0.2
0.1
0.0
0.3790
0.3440
0.3255
0.2904
0.2407
0.2407
0.3509
0.1664
Fluoxetine
Dexamethasone
Bupropion
Paroxetine
A375
HEPG2
MCF7
Mean

D



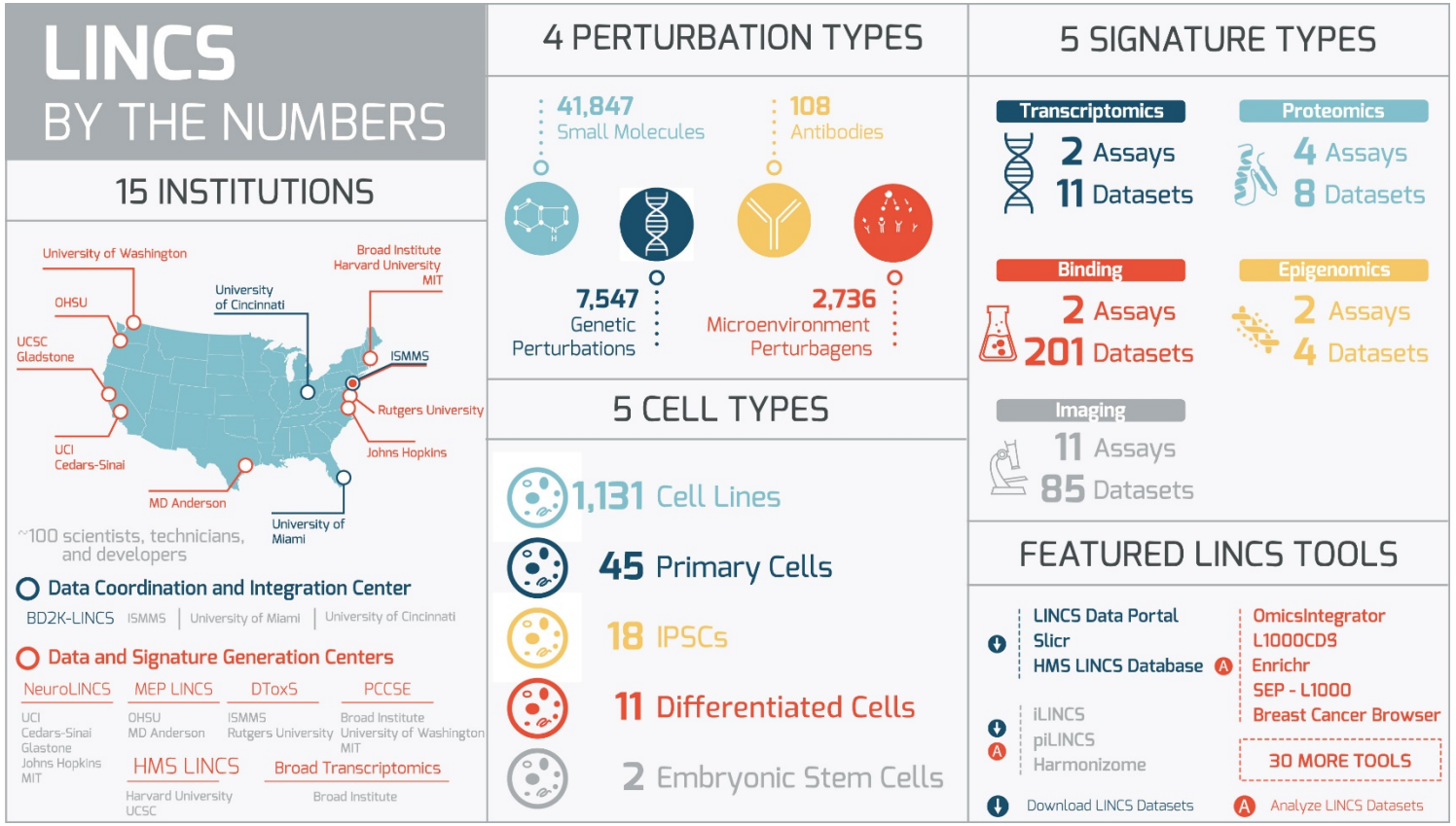
	A375	A549	HA1E	HCC515	HEPG2	HT29	MCF7	Mean	SD	N
Fluoxetine	0.7982		0.2262		0.6139			0.5461	0.291965118	3
Dexamethasone	0.6132	0.4371		0.2196	0.4554	0.293		0.40366	0.153155144	5
Bupropion	0.3677	0.6458			0.5435		-0.3232	0.30845	0.436480549	4
Paroxetine	0.4426	0.5236	0.3597	0.3616	0.5148		-0.2591	0.323866667	0.294280313	6

E



	A375	A549	HA1E	HEPG2	HT29	MCF7	Mean	SD	N
Fluoxetine		0.3313			0.3218	0.379	0.344033333	0.030652297	3
Dexamethasone		0.3067	0.2979	0.3255	0.2313		0.29035	0.041015241	4
Bupropion	0.2407						0.2407	0	1
Paroxetine	0.3509	0.3189		0.2615		0.2252	0.289125	0.056427675	4

The Library of Integrated Network-based Cellular Signatures (LINCS)



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NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

Fluoxetine to Reduce Intubation and Death After COVID19 Infe

The safety and scientific validity of this study is the responsibility of the study sponsor an investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your hea care provider before participating. Read our disclaimer for details.

Sponsor:

University of Toledo Health Science Campus

Information provided by (Responsible Party):

Cheryl Mccullumsmith, University of Toledo Health Science Campus

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

Autism Oxytocin Brain Project

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Sponsor:

Emory University

Collaborator:

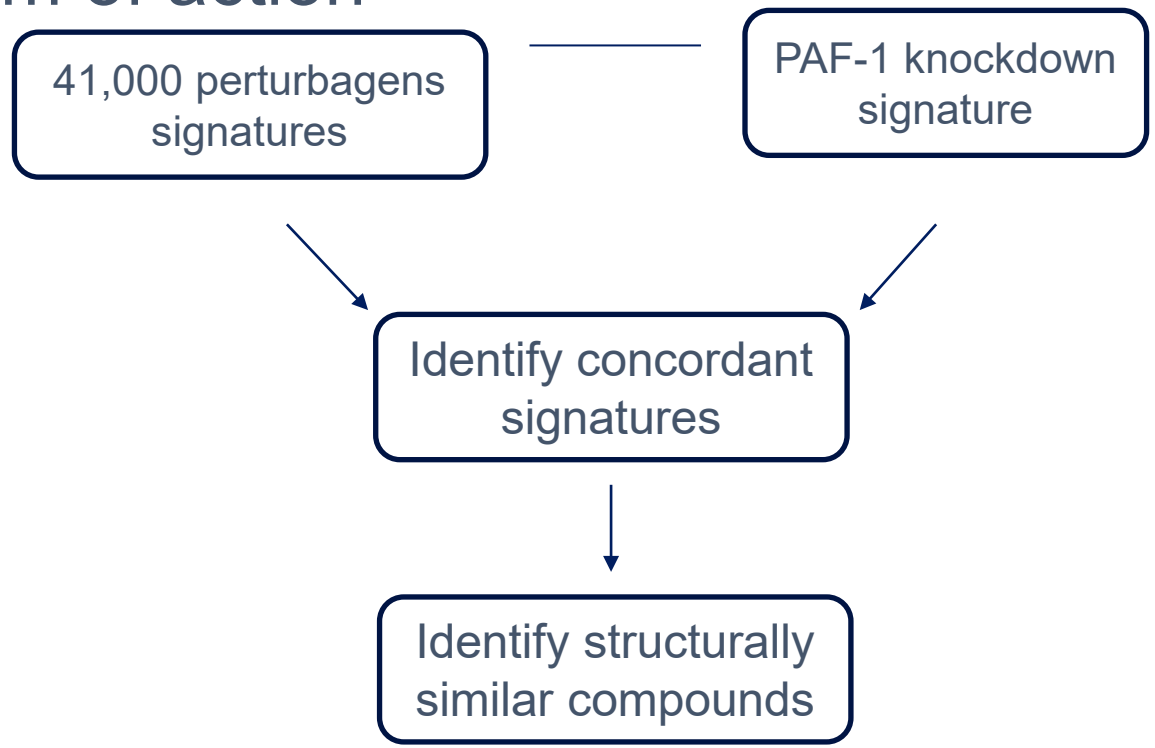
National Institute of Mental Health (NIMH)

Information provided by (Responsible Party):

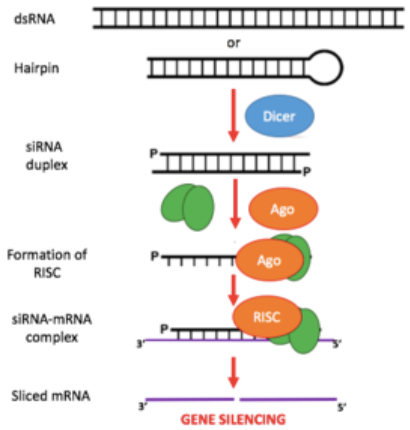
Elissar Andari, Emory University

Structure-Activity Relationship (SAR)

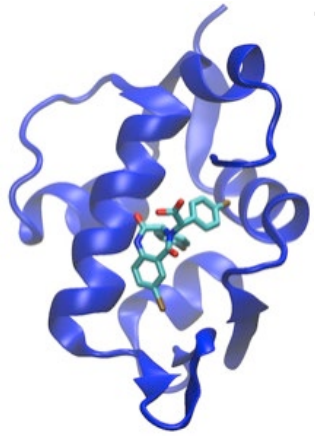
- Using shared biological activity (e.g. gene expression profiles) and similar structural moieties to identify a common mechanism of action



Connectivity Between Target Knockdown and Chemical Inhibition Signatures

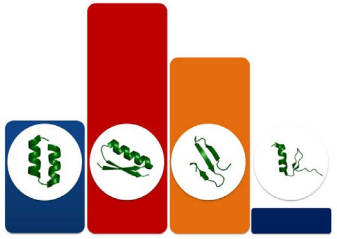


AND

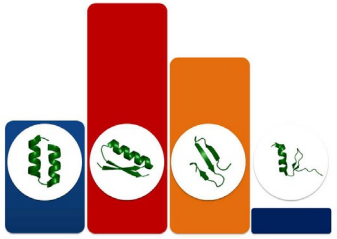


Knockdown Signature at the Transcriptional/Protein Level

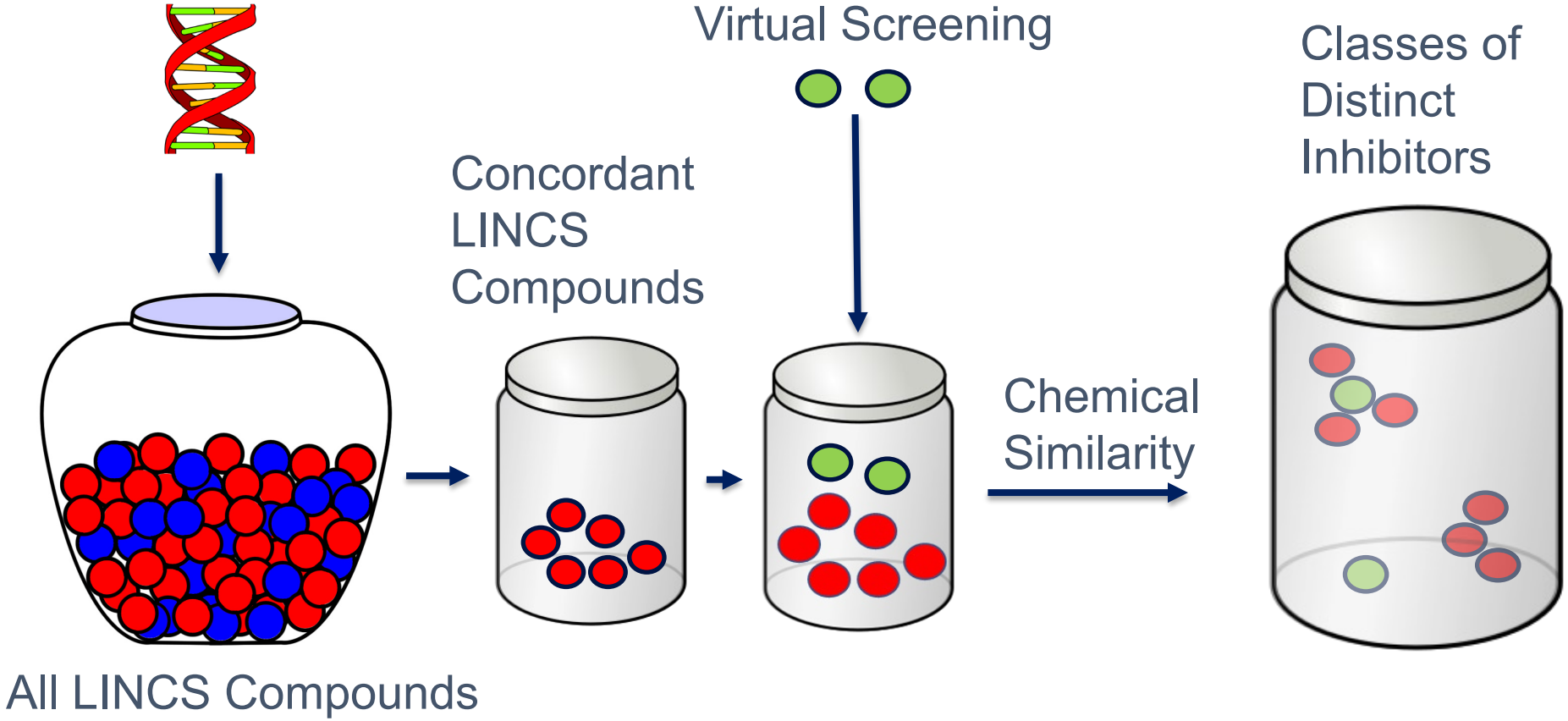
Signature of Chemical Inhibition at the Transcriptional/Protein Level



Concordance



Gene Target
Knockdown Signature



Resources!

- Webinars: https://www.utoledo.edu/med/depts/neurosciences/calendar1.htmlI am not a bioinformaticist
- LINCS: https://lincsproject.org/
- Kaleidoscope: https://kalganem.shinyapps.io/BrainDatabases/

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James Meador-Woodruff

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ABC, NIMH

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MH087752 (REM)
MH094445 (REM)
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LIFE Foundation

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