Drugs and Bugs in Alzheimer's Disease

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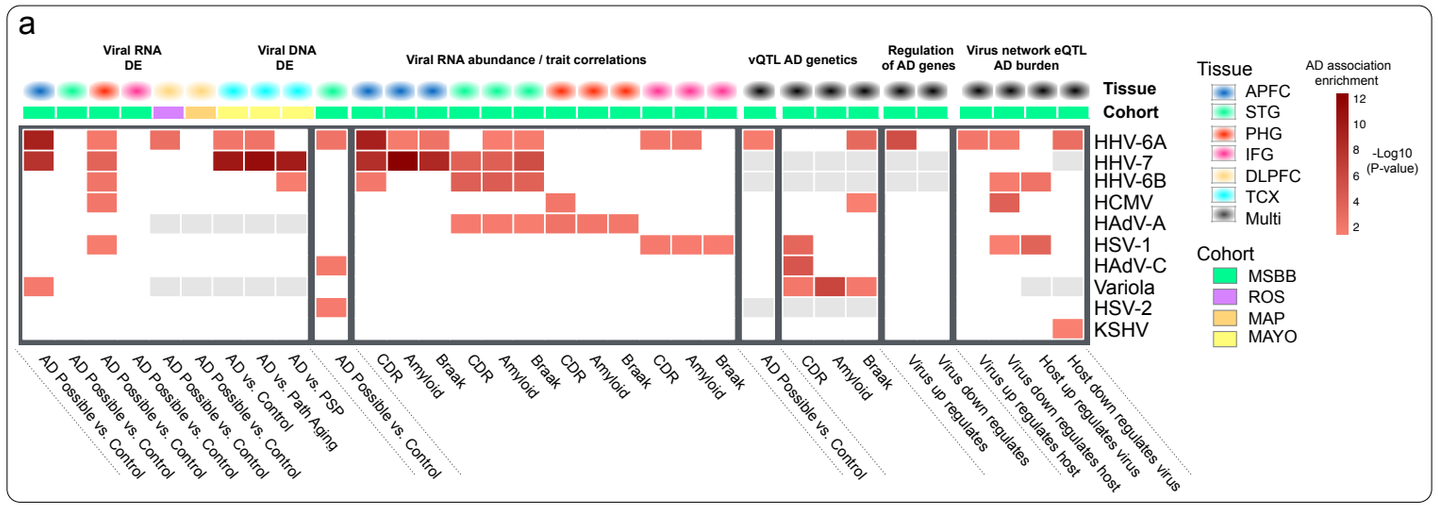
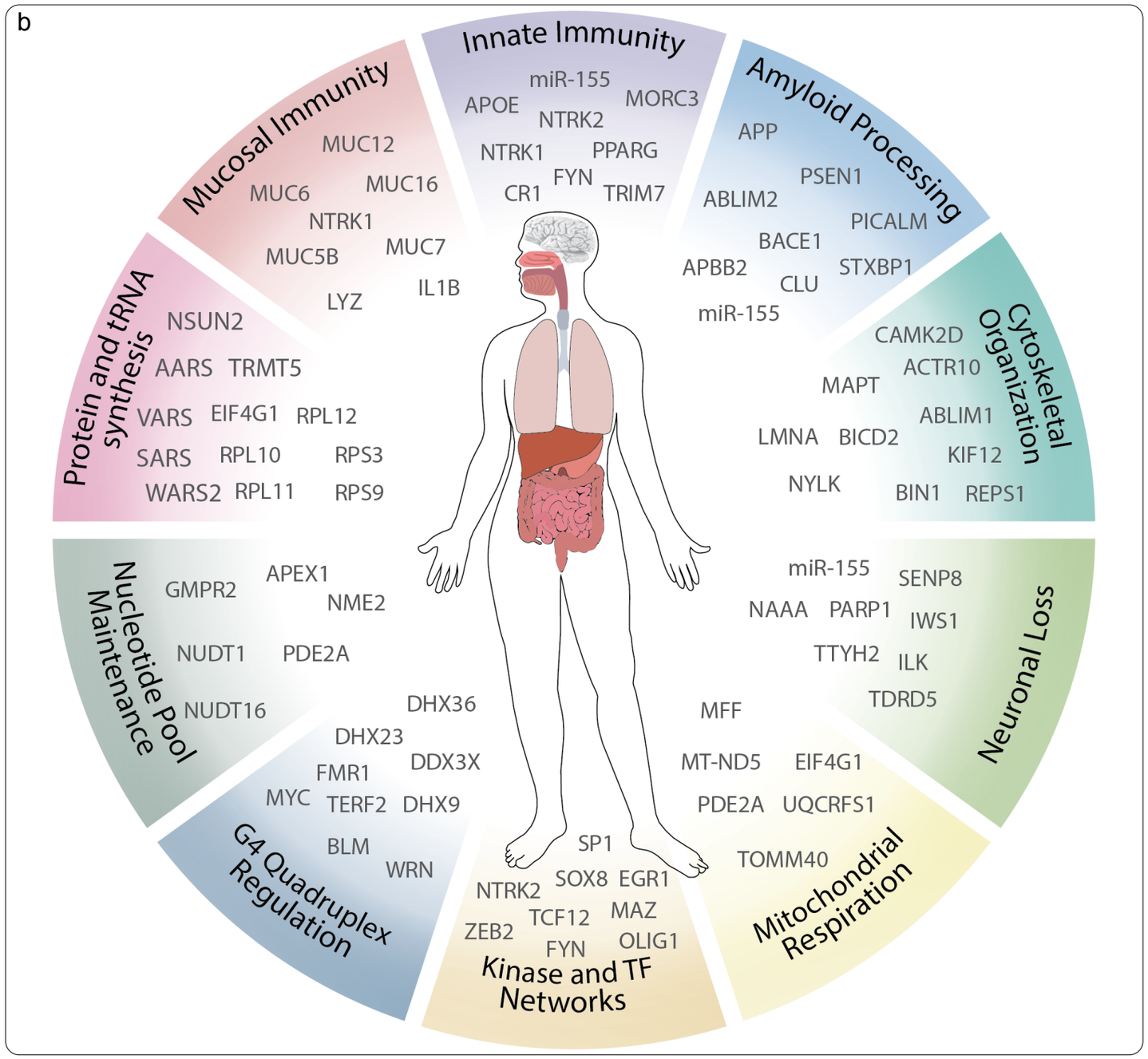
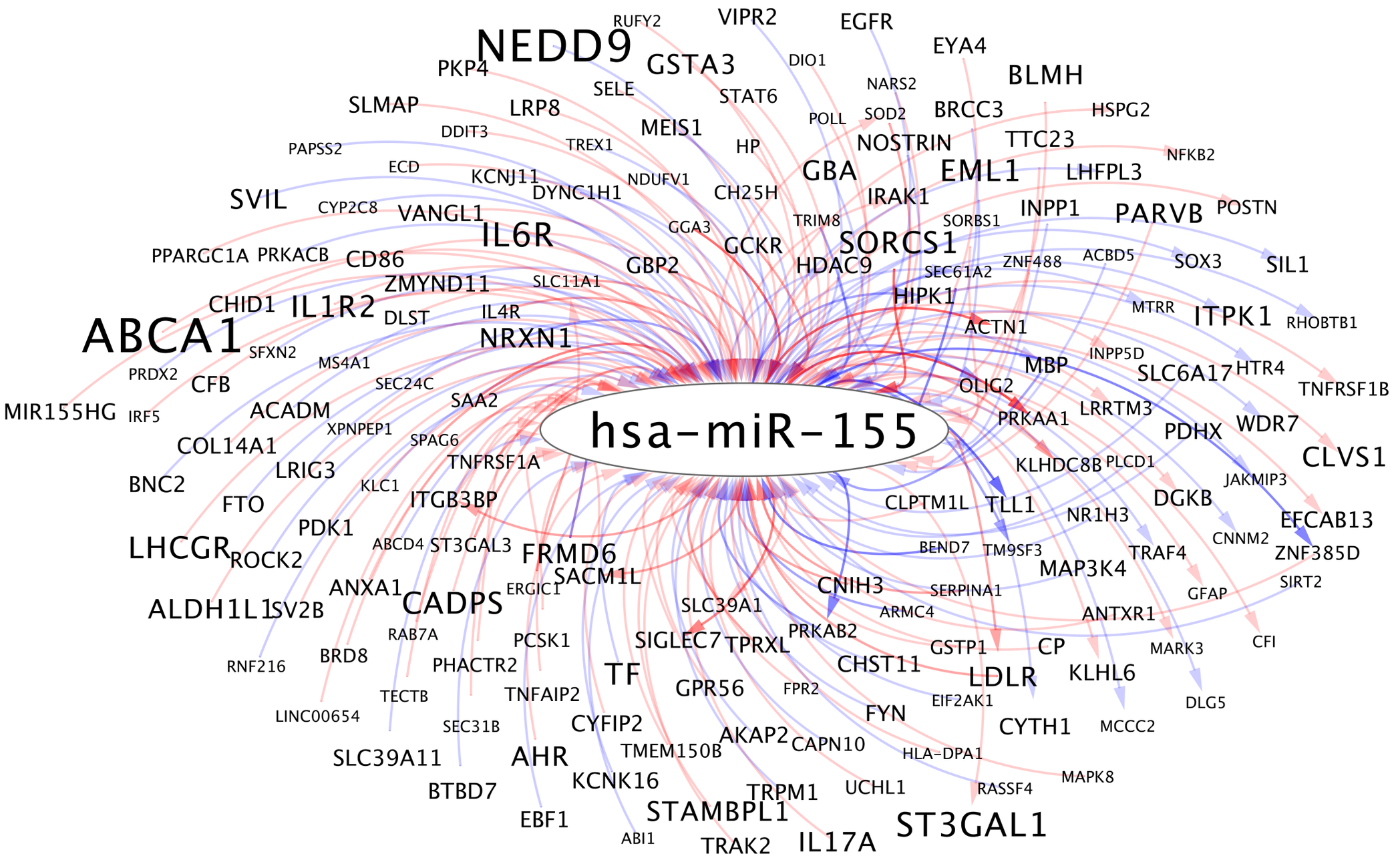




Host-Virus interaction networks in AD identify numerous potential therapeutic targets related to immune activation

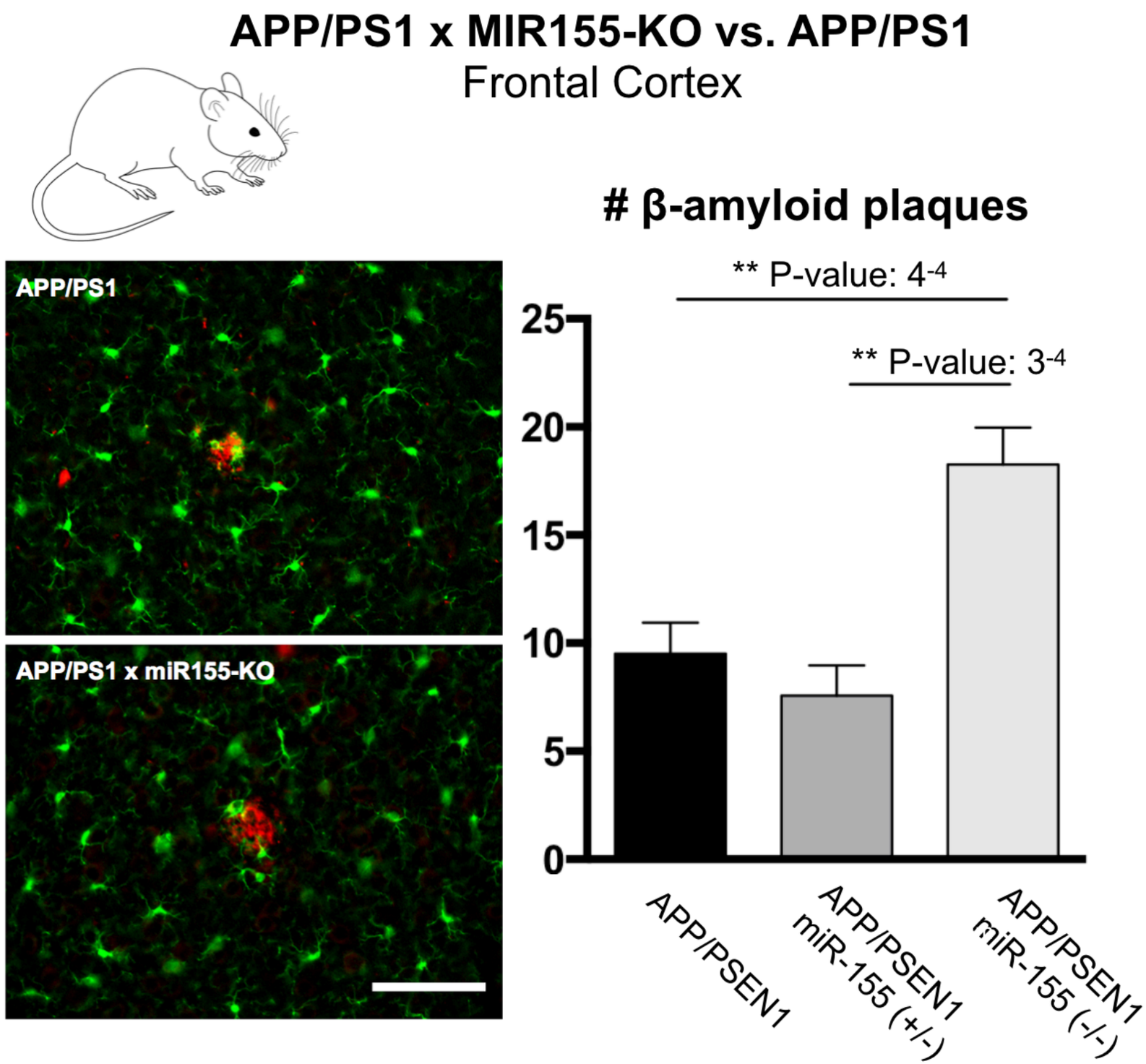
Readhead et al. *Neuron* 2018

miR-155 is suppressed by HHV-6A, a regulator of preclinical and clinical AD networks



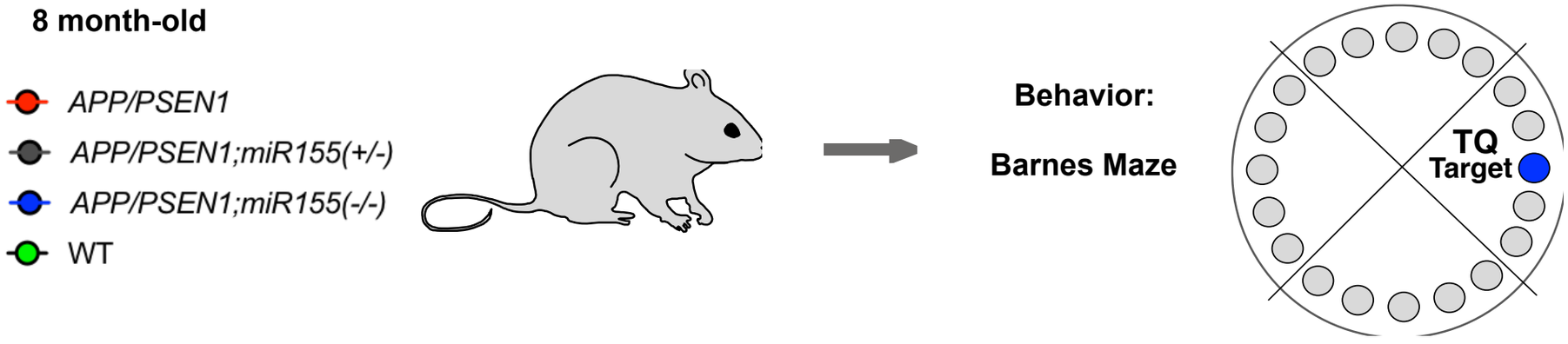
Readhead et al. *Neuron* 2018

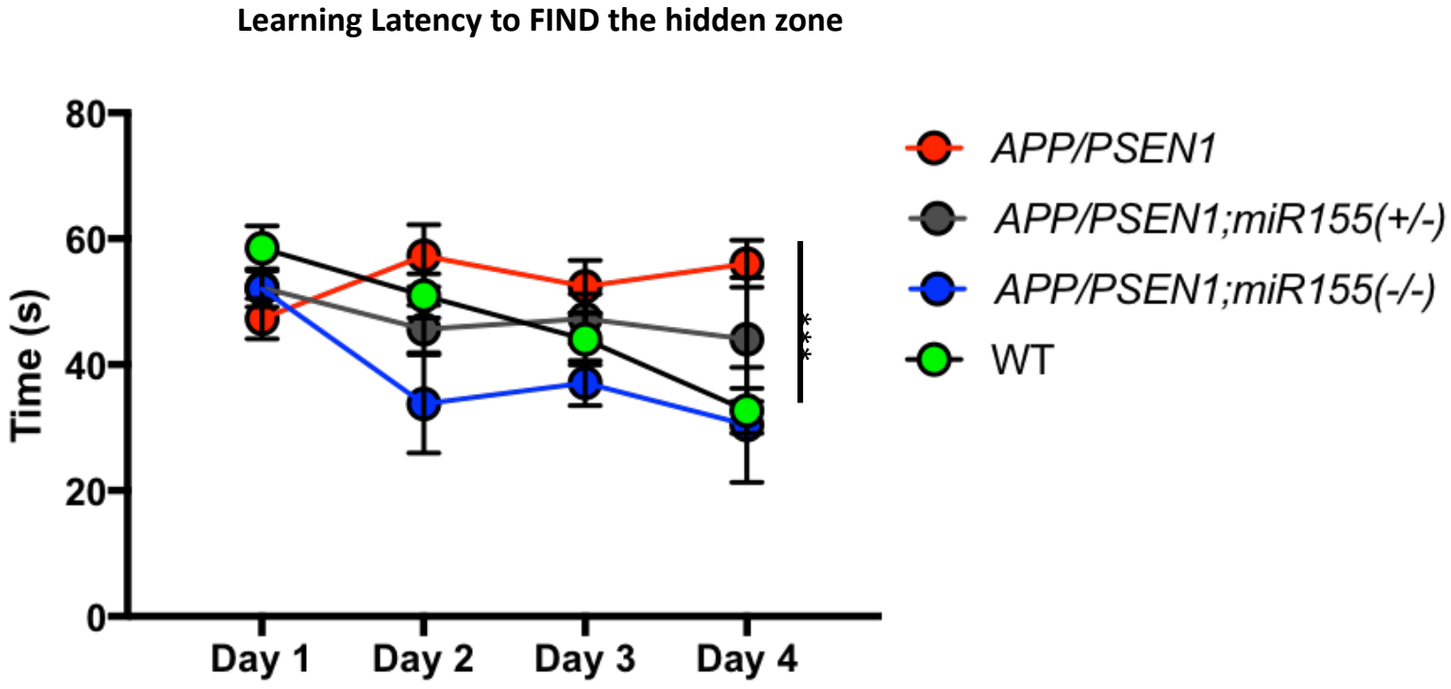
miR-155 is suppressed by HHV-6A, a regulator of preclinical and clinical AD networks and alters β-amyloid plaque and oligomer formation



Readhead et al. *Neuron* 2018

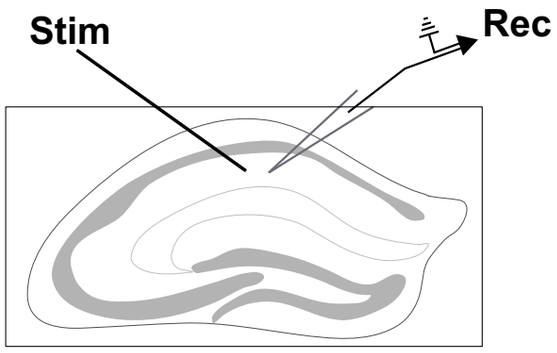
Constitutive absence of *miR-155* in *APP/PSEN1* mice improves learning and memory performances in Barnes maze test

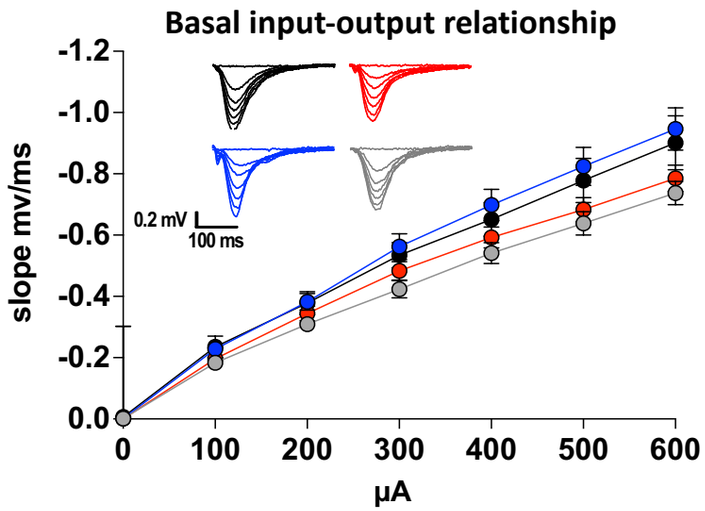


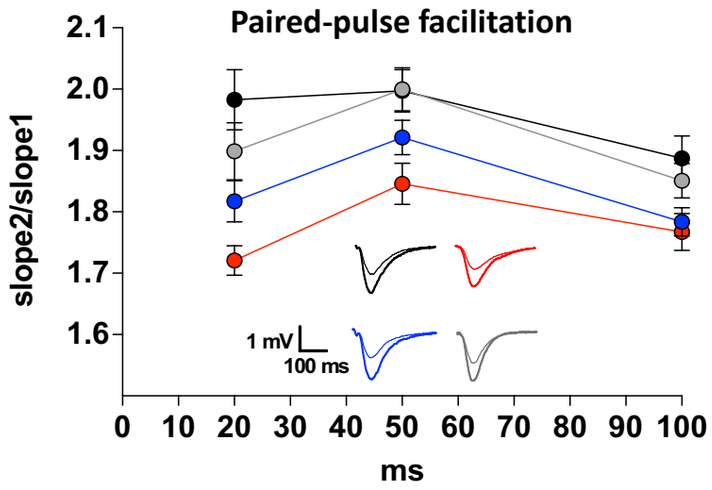


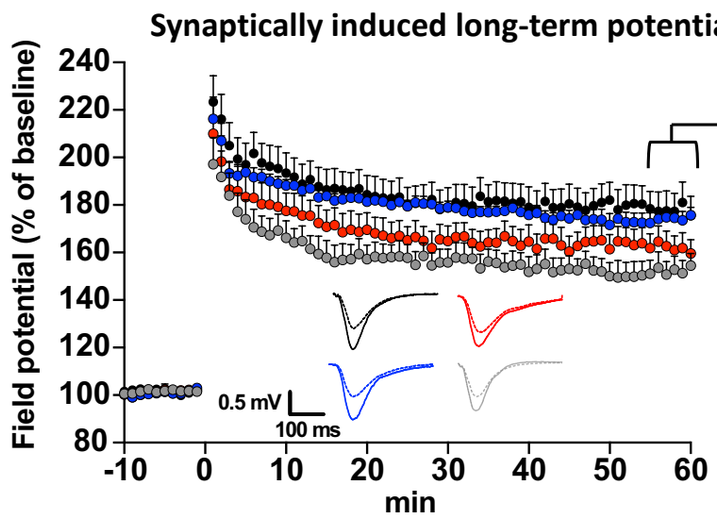
Unpublished work in progress

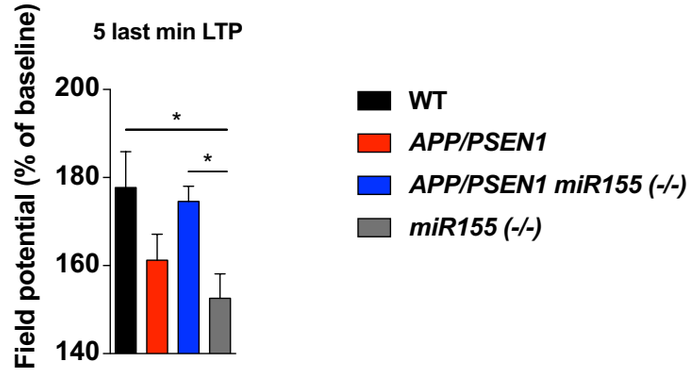
Absence of mir-155 mice ameliorates synaptic plasticity defects in APP/PSEN1 mice But induces defect of synaptic plasticity in WT mice







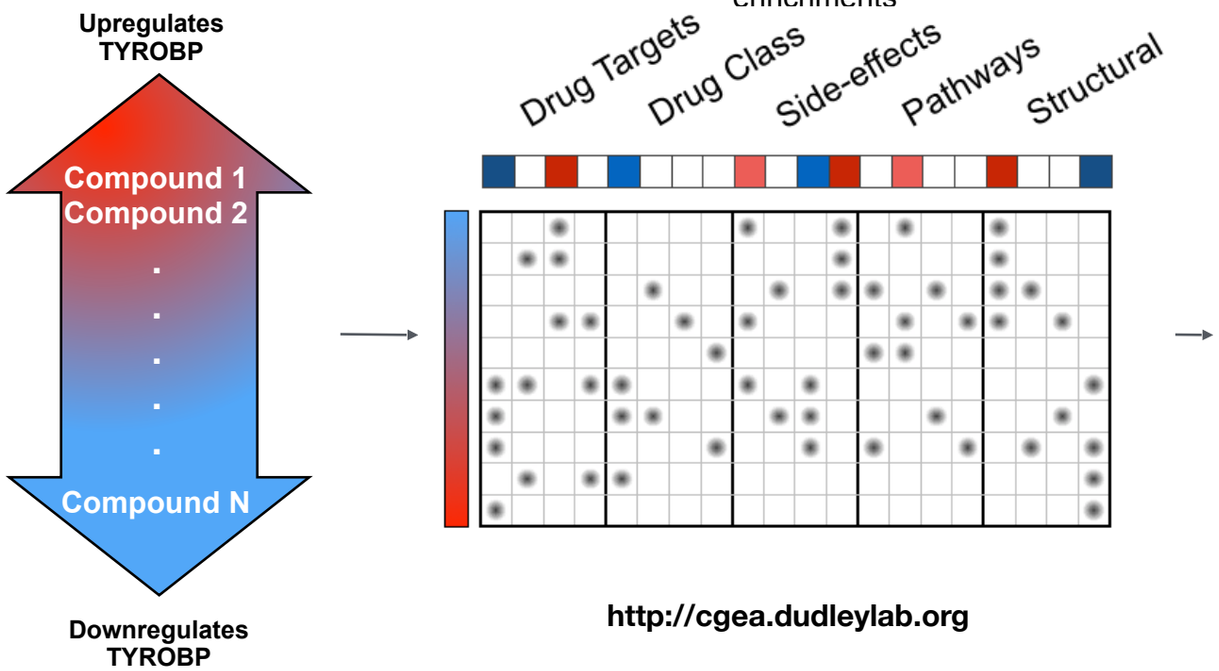




Unpublished work in progress

TYROBP repurposing use case

a



bi **Top CMAP compounds predicted to upregulate TYROBP**

compound	ATC Level 3
thioguanosine	ANTIMETABOLITES
clorgiline	
methapyrilene	ANTIHISTAMINES FOR SYSTEMIC USE
estradiol	ESTROGENS
procainamide	ANTIARRHYTHMICS, CLASS I AND III
apigenin	
atropine	BELLADONNA AND DERIVATIVES, PLAIN
minaprine	ANTIDEPRESSANTS
clemizole	
salsolinol	
luteolin	
moxisylyte	PERIPHERAL VASODILATORS
alfuzosin	DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY
tranylcypromine	ANTIDEPRESSANTS
vinpocetine	PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS

C

Drug targets enriched in compounds that regulate TYROBP

Predicted Targets	Name
CHRND	cholinergic receptor, nicotinic, delta (muscle)
RIPK1	receptor (TNFRSF)-interacting serine-threonine kinase 1
KCNN2	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2
KYNU	kynureninase
CCR8	chemokine (C-C motif) receptor 8
CHKA	choline kinase alpha
ENPEP	glutamyl aminopeptidase (aminopeptidase A)
SELP	selectin P (granule membrane protein 140kDa, antigen CD62)
ADRA1B	adrenoceptor alpha 1B
CTSD	cathepsin D
AOC3	amine oxidase, copper containing 3

bii **Top CMAP compounds predicted to downregulate TYROBP**

compound	ATC Level 3
myosmine	
imatinib	OTHER ANTINEOPLASTIC AGENTS
benzathine benzylpenicillin	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
diphenylpyraline	ANTIHISTAMINES FOR SYSTEMIC USE
SC-58125	
lasalocid	
methyldopate	ANTIADRENERGIC AGENTS, CENTRALLY ACTING
harpagoside	
ketotifen	ANTIHISTAMINES FOR SYSTEMIC USE
cloxacillin	BETA-LACTAM ANTIBACTERIALS, PENICILLINS

Unpublished work in progress

Compounds that modulate TYROBP are enriched for drug targets that link to AD

Symbol	Name	Notes
CHRND	cholinergic receptor, nicotinic, delta (muscle)	
RIPK1	receptor (TNFRSF)-interacting serine-threonine kinase 1	Mediates AB induced TNF production by microglia in vitro (Zhou, 2014 for review)
KCNN2	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2	
KYNU	kynureninase	
CCR8	chemokine (C-C motif) receptor 8	Monocyte chemotaxis and localization of activated T-cells
CHKA	choline kinase alpha	
ENPEP	glutamyl aminopeptidase (aminopeptidase A)	
SELP	selectin P (granule membrane protein 140kDa, antigen CD62)	
ADRA1B	adrenoceptor alpha 1B	
CTSD	cathepsin D	Risk gene for AD (Schuur, 2011)
AOC3	amine oxidase, copper containing 3	

* Targets enriched (FDR < 0.1) in CMAP compounds ranked according to TYROBP expression

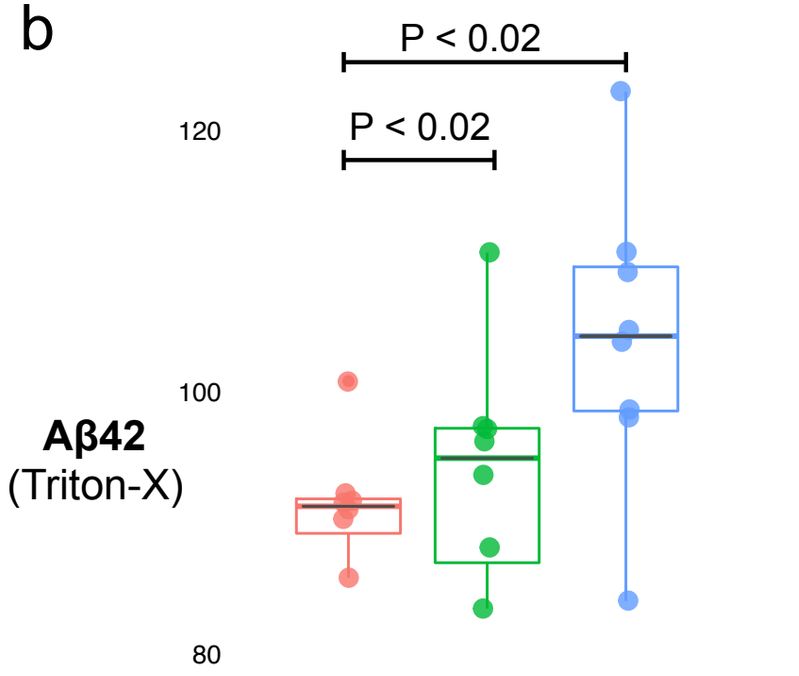
Unpublished work in progress

APP/PSEN1 x SP1-KO vs. APP/PSEN1 RNA-sequencing Frontal Cortex

a Differential gene expression

Symbol	Name	logFC	FDR
Amhr2	anti-Mullerian hormone type 2 receptor	3.60	3.52e-08
Sp1	trans-acting transcription factor 1	-0.90	4.25e-08
Pfn1	profilin 1	0.42	2.84e-03
Ppp1r9b	protein phosphatase 1, regulatory subunit 9B	0.26	5.02e-03
Mrps34	mitochondrial ribosomal protein S34	0.44	8.35e-03
Ptms	parathymosin	0.40	1.05e-02
Hist2h4	histone cluster 2, H4	0.56	1.05e-02
Hepacam	hepatocyte cell adhesion molecule	0.53	1.05e-02
Hnrnpa0	heterogeneous nuclear ribonucleoprotein A0	0.31	1.05e-02
Hnrnph3	heterogeneous nuclear ribonucleoprotein H3	0.74	1.05e-02

b



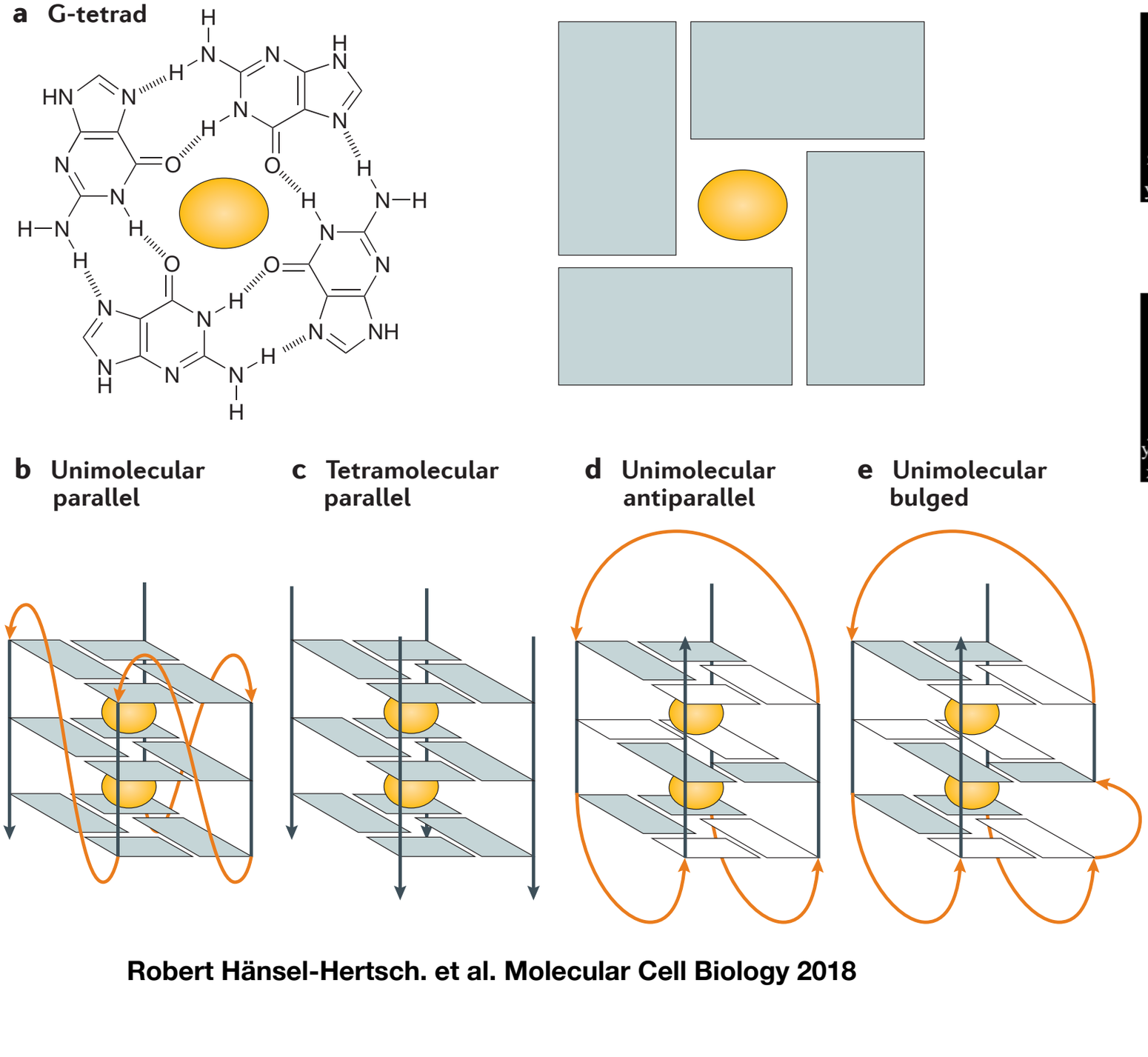
c Causal Inference Testing (CIT)

- ☑ SP1 and Aβ42 are associated
- ☑ SP1 and Aβ42-genes are associated
- ? SP1 associated with Aβ42-genes | Aβ42
- ? SP1 independent of Aβ42 | Aβ42-genes

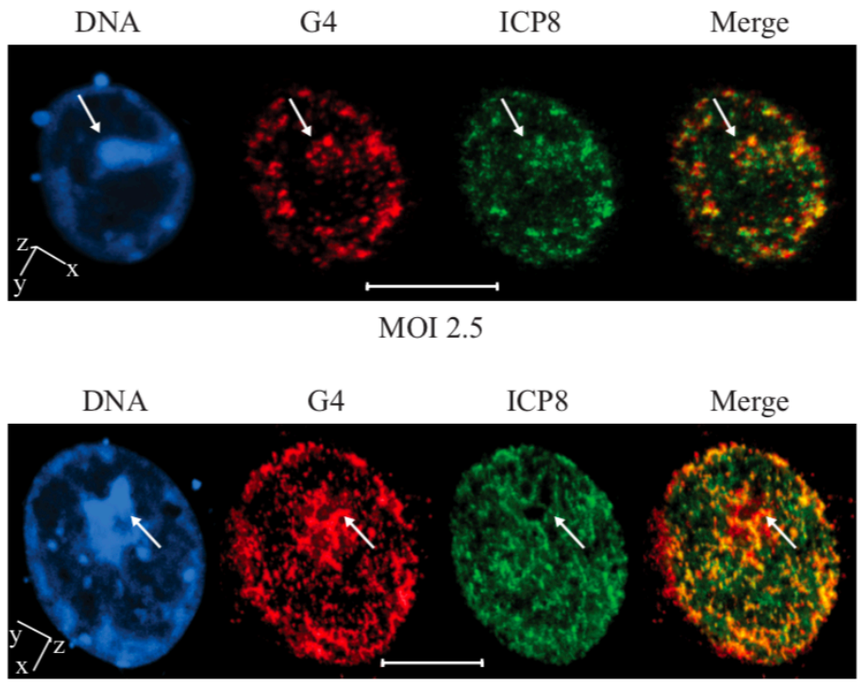
d

Symbol	Name	CIT (FDR)	Cor with SP1 dosage	Cor with Aβ42
Ppp1r9b	protein phosphatase 1, regulatory subunit 9B	9.99e-04	-0.71	0.71
Lrrk2	leucine-rich repeat kinase 2	9.99e-04	0.69	-0.67
Mettl7a1	methyltransferase like 7A1	9.99e-04	0.63	-0.76
Slc25a25	solute carrier family 25 (mitochondrial carrier, phosphate carrier), member 25	9.99e-04	0.73	-0.64
Edrf1	erythroid differentiation regulatory factor 1	9.99e-04	0.63	-0.80
Chd3	chromodomain helicase DNA binding protein 3	9.99e-04	-0.63	0.59
A230050P20Rik	RIKEN cDNA A230050P20 gene	9.99e-04	-0.71	0.58
Lgals9	lectin, galactose binding, soluble 9	9.99e-04	-0.71	0.58
Nbas	neuroblastoma amplified sequence	2.00e-03	0.72	-0.68
Tmem191c	transmembrane protein 191C	2.00e-03	-0.78	0.64

G-quadruplex secondary structures associate with normal gene regulatory activity and viral replication

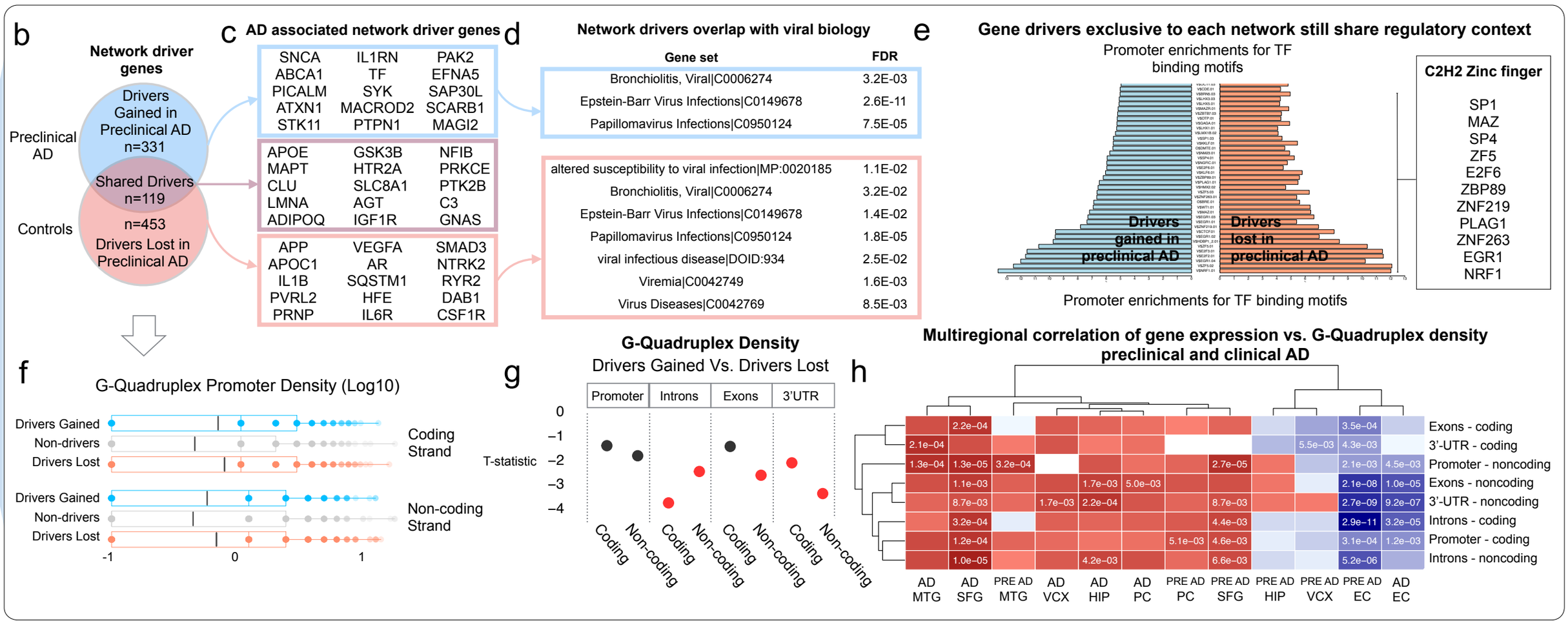


Robert Hänsel-Hertsch. et al. Molecular Cell Biology 2018



Artusi et al. Nucleic Acids Research, 2016, Vol. 44, No. 21

Association between changes in G-quadruplex promoter density and network driver gain/loss



Readhead et al. *Neuron* 2018

A core extended naphtalene diimide G-quadruplex ligand potently inhibits herpes simplex virus 1 replication

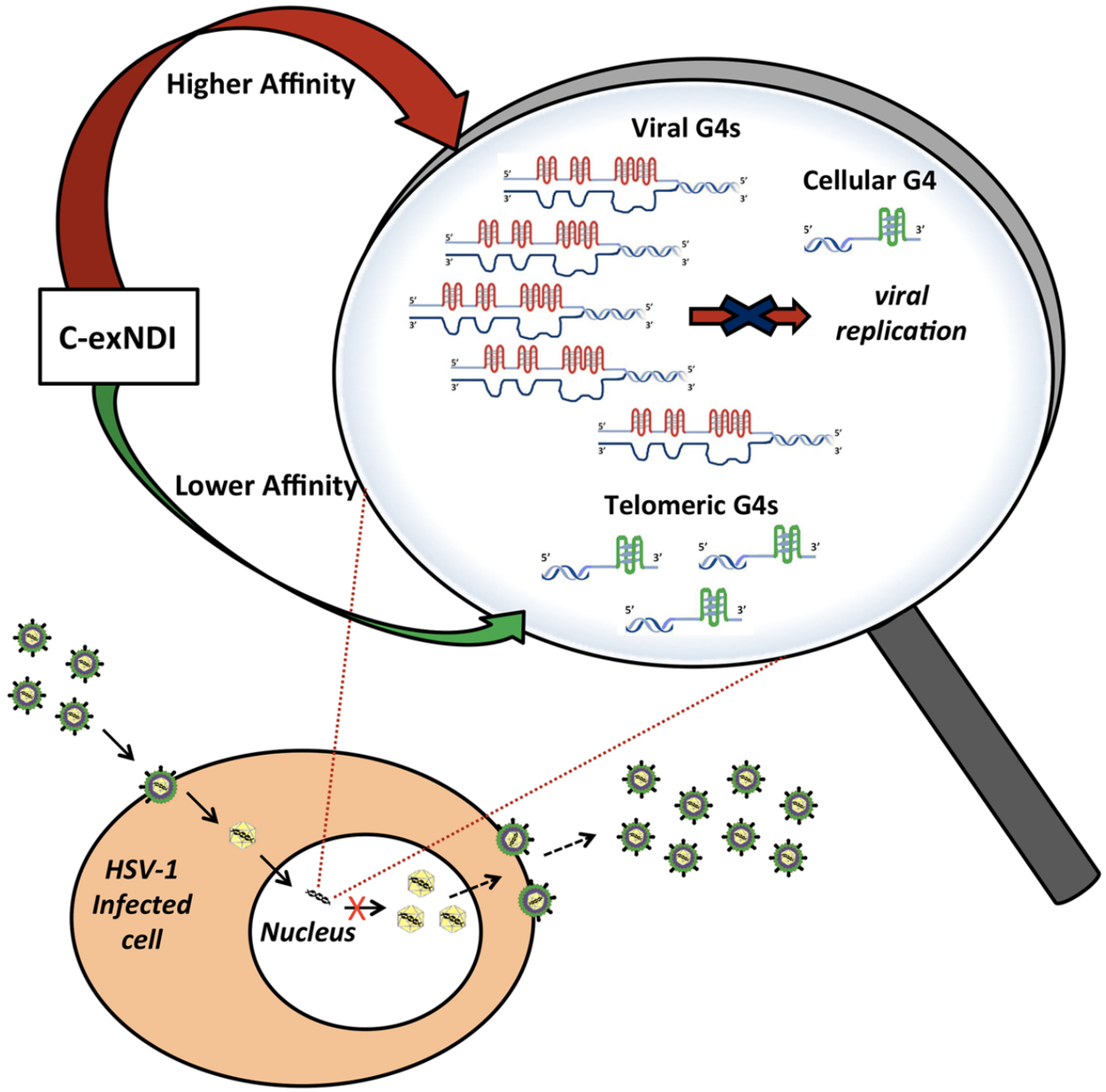


Figure 5. Scheme of the proposed c-exNDI mechanism of anti-HSV-1 activity.

Defining the "opposite phenotype" using Generative Adversarial Networks (GAN)

man with glasses − man without glasses + woman without glasses

=

woman with glasses

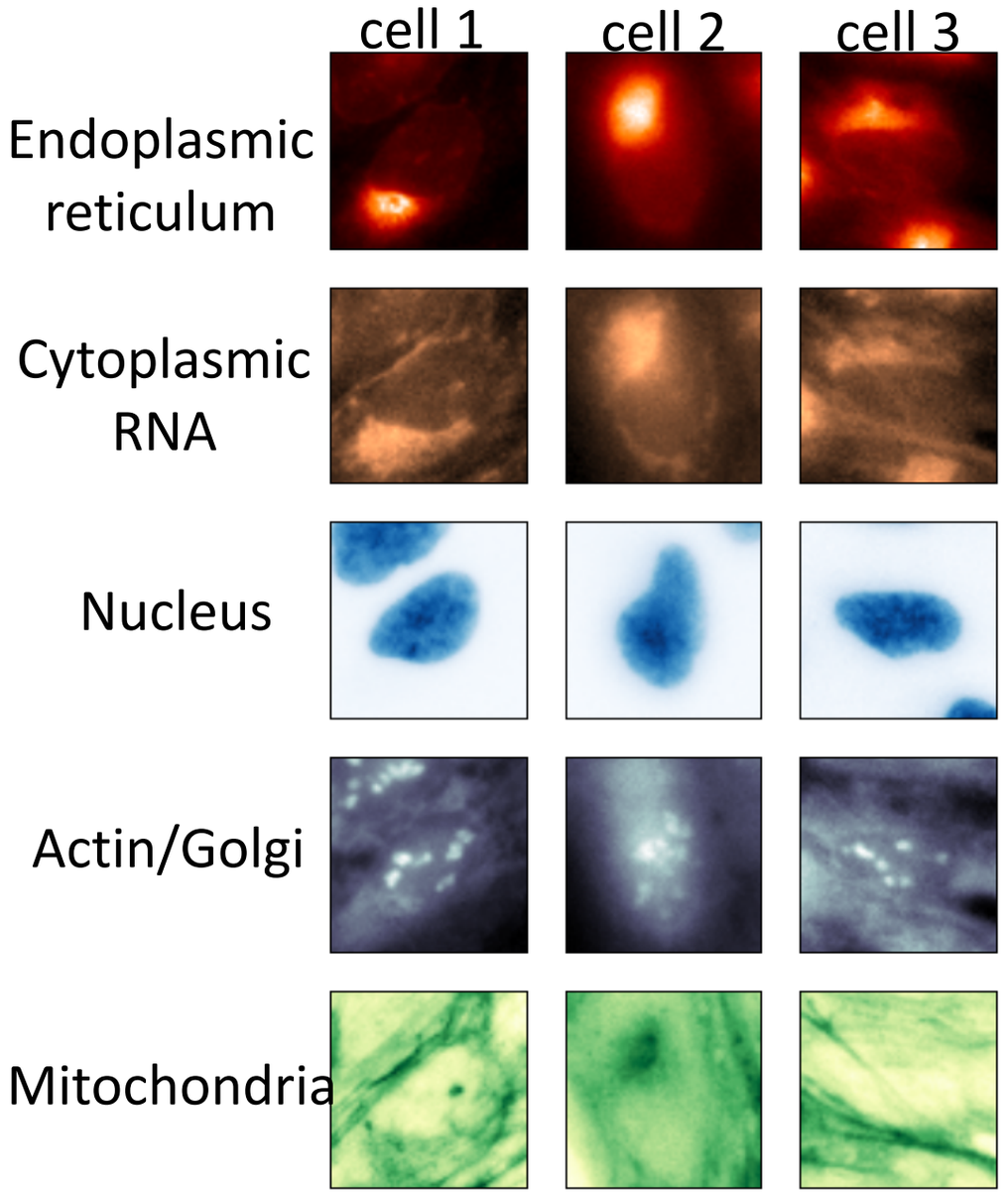
Rationale for drug discovery:

$v_{wthout\ phenotype} - v_{with\ phenotype}$
$\approx$ action reversing the phenotype

Unpublished work in progress

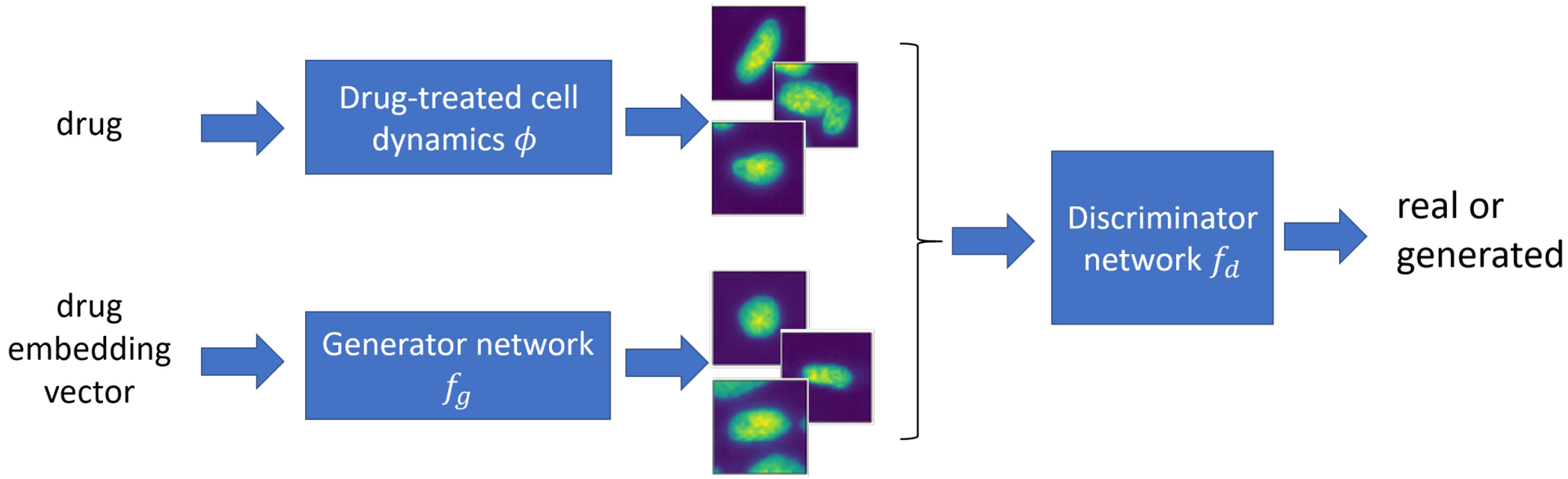
Data source: drug-treated image “patches”

- On average 4 repeats per treatment
- 6 images form each repeat
- 10~50 cells from 1 images
- 2 TB of image patches (64x64)



Cell Painting Assay data from Bray et al. Gigascience. 2017 Dec 1;6(12):1-5.

Using a conditional GAN to model high-throughput imaging data



Rationale for characterizing drug treated cell dynamics:

$\phi \approx f_g$ if f_d cannot tell the difference

Unpublished work in progress

Cellular phenotypes generated by GAN

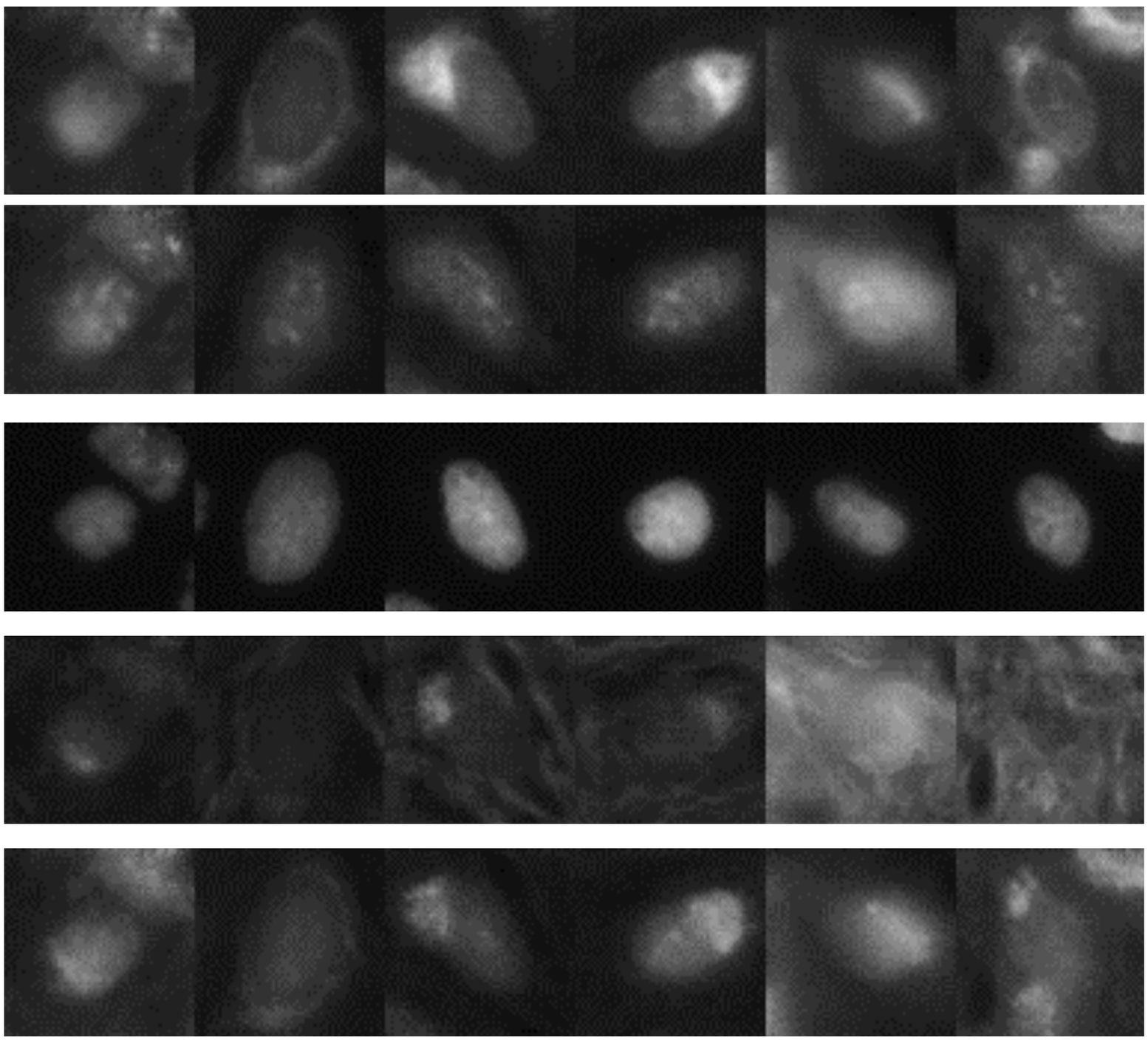
Endoplasmic reticulum

Cytoplasmic RNA

Nucleus

Actin/Golgi

Mitochondria



25 epochs

Thank you for your attention!

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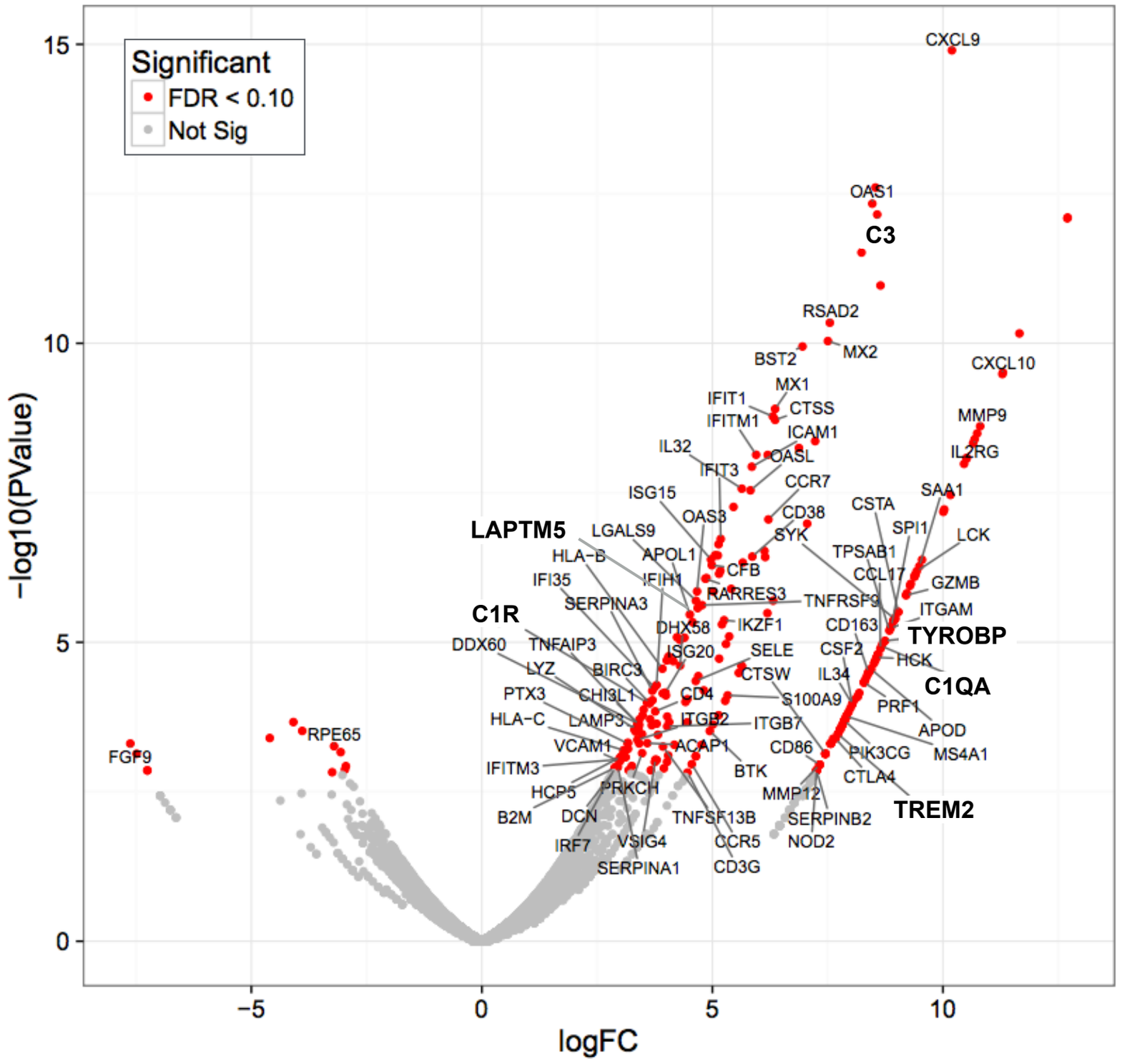
Mount Sinai


Significant
FDR < 0.10
Not Sig
15
10
5
0
−log10(PValue)
−5
0
5
10
logFC
CXCL9
OAS1
C3
RSAD2
MX2
BST2
CXCL10
MX1
IFIT1
CTSS
IFITM1
ICAM1
MMP9
IL32
OASL
IL2RG
IFIT3
CCR7
SAA1
ISG15
CD38
CSTA
OAS3
SYK
SPI1
LCK
LAPTM5
LGALS9
TPSAB1
HLA-B
APOL1
CFB
CCL17
GZMB
IFI35
IFIH1
RARRES3
TNFRSF9
ITGAM
SERPINA3
C1R
DHX58
IKZF1
CD163
TYROBP
DDX60
TNFAIP3
ISG20
SELE
CSF2
HCK
LYZ
BIRC3
CTSW
IL34
C1QA
PTX3
CHI3L1
CD4
S100A9
PRF1
HLA-C
LAMP3
ITGB2
ITGB7
APOD
RPE65
VCAM1
ACAP1
CD86
PIK3CG
MS4A1
FGF9
IFITM3
BTK
CTLA4
HCP5
PRKCH
MMP12
TREM2
B2M
DCN
TNFSF13B
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IRF7
VSIG4
CCR5
NOD2
SERPINA1
CD3G