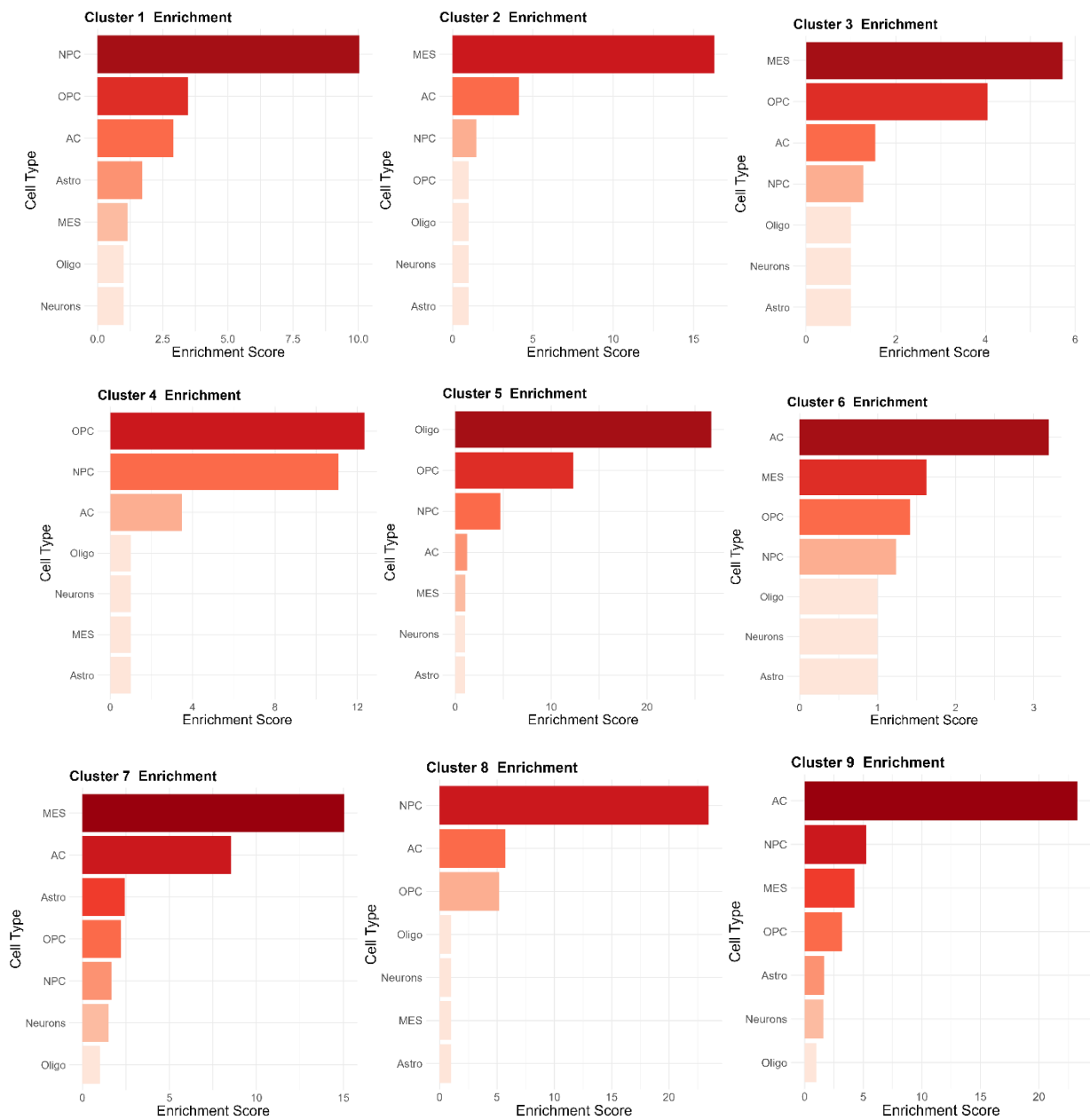
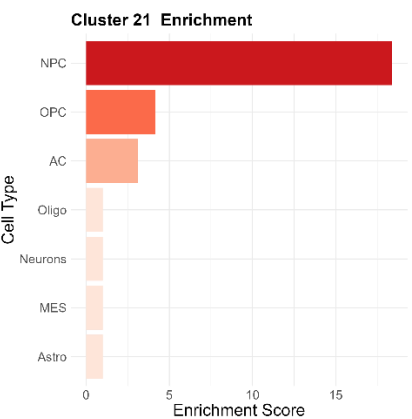
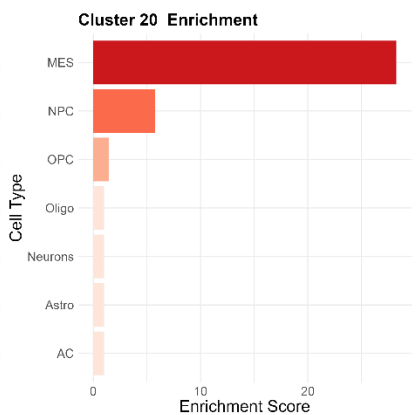
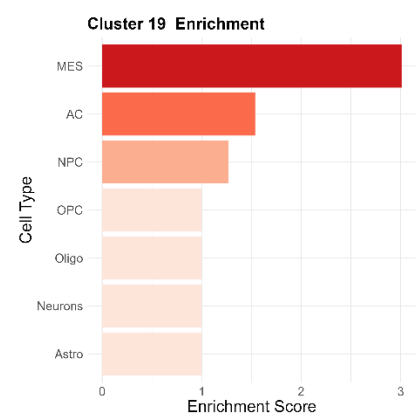
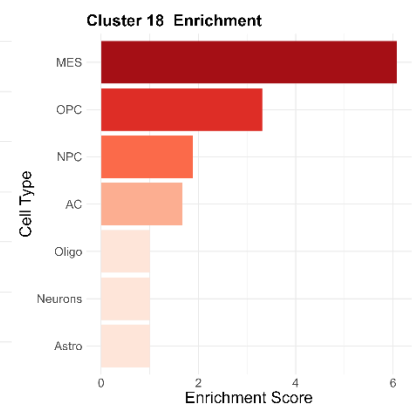
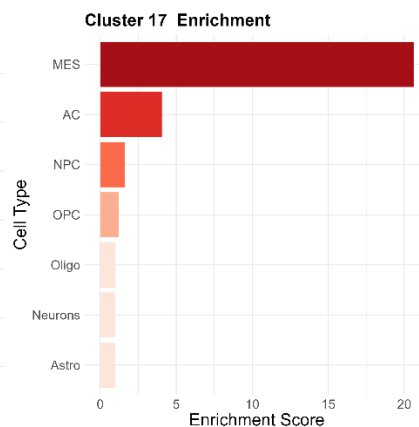
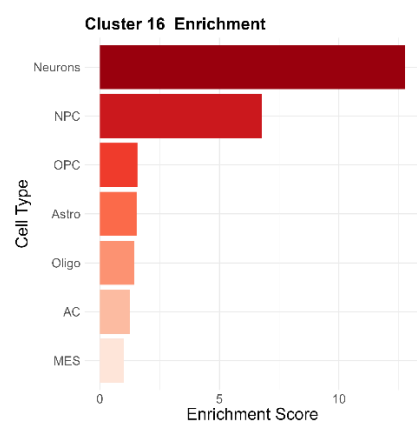
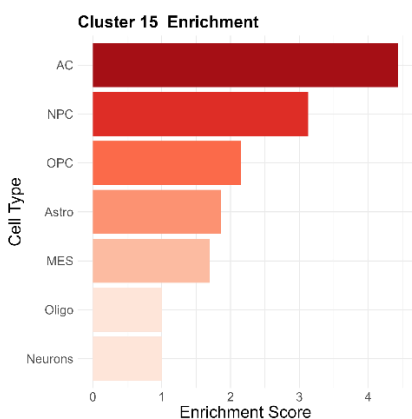
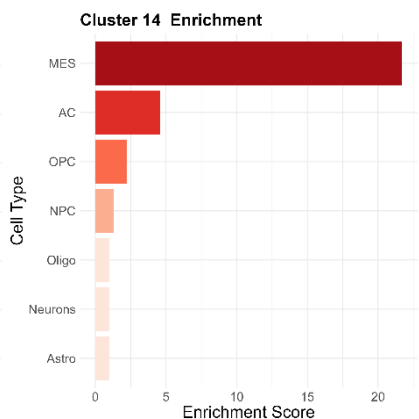
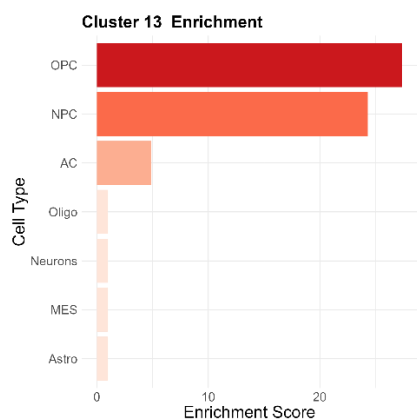
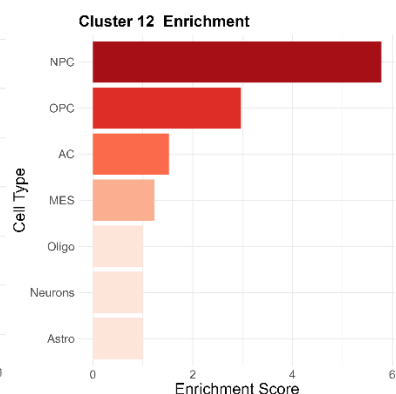
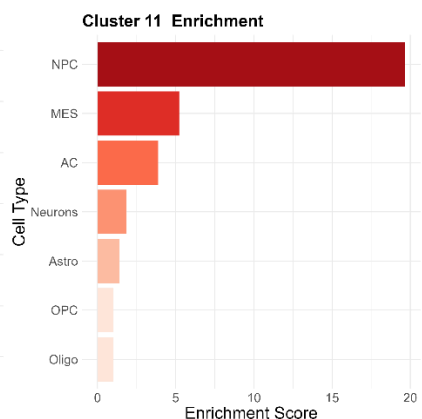
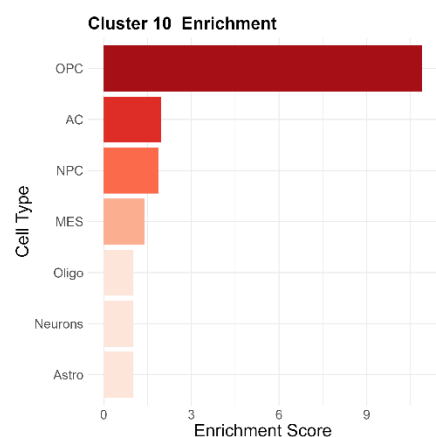
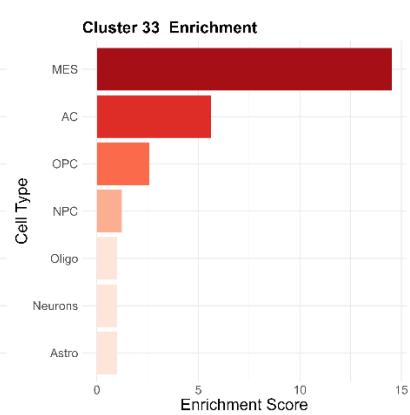
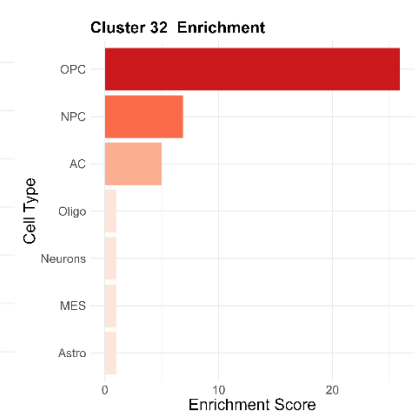
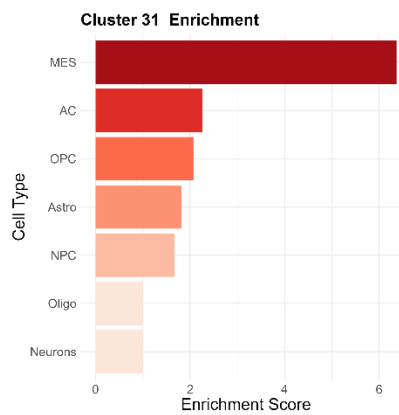
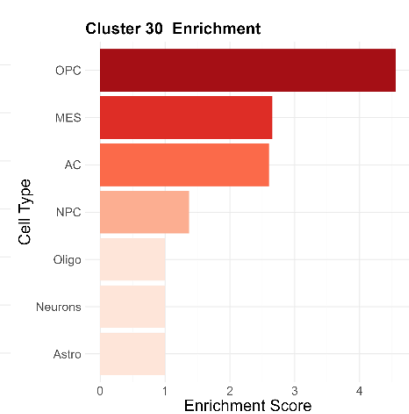
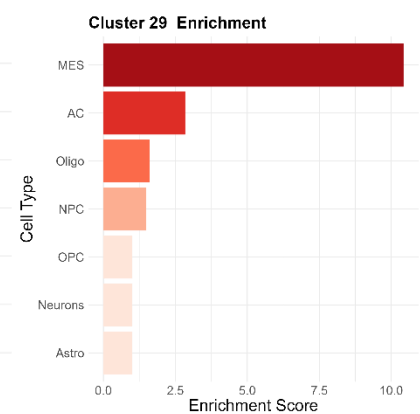
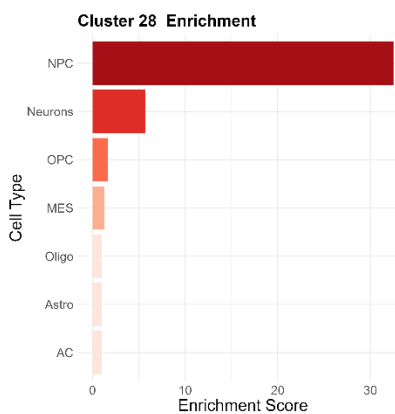
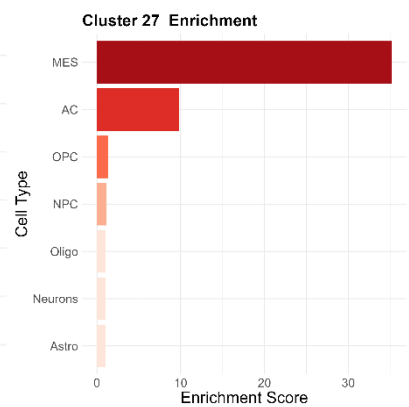
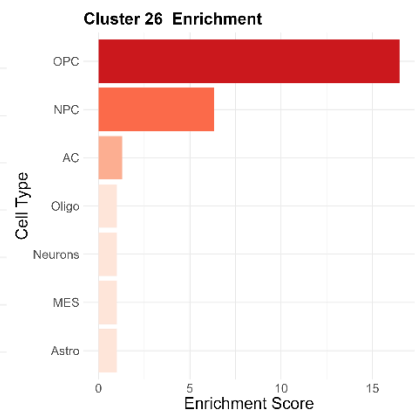
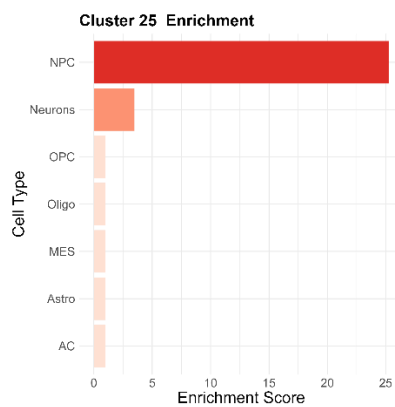
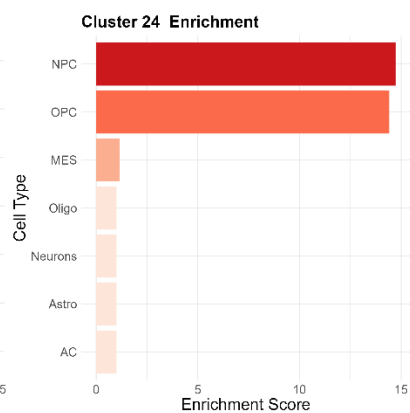
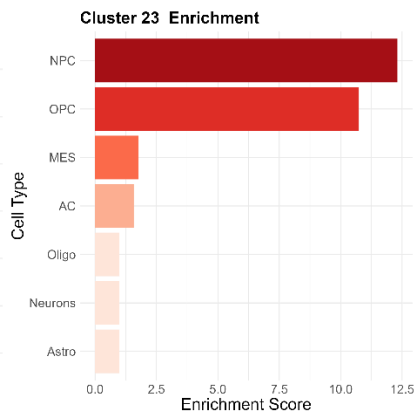
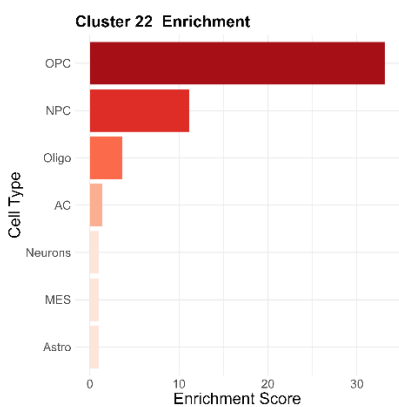


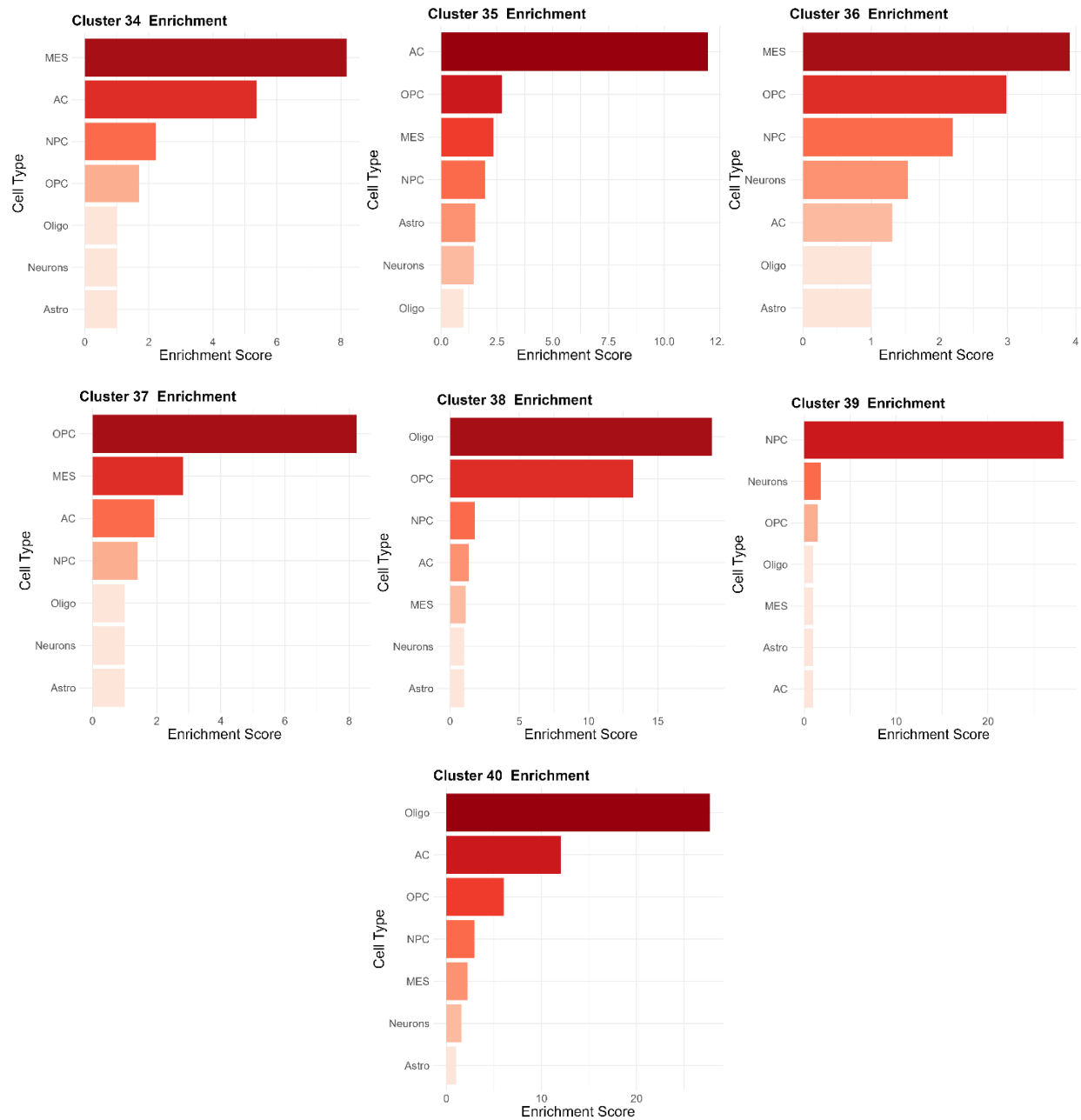
Network Analyses of Brain Tumor Patients' Multiomic Data Reveals Pharmacological Opportunities to Alter Cell State Transitions

SUPPLEMENTARY INFORMATION

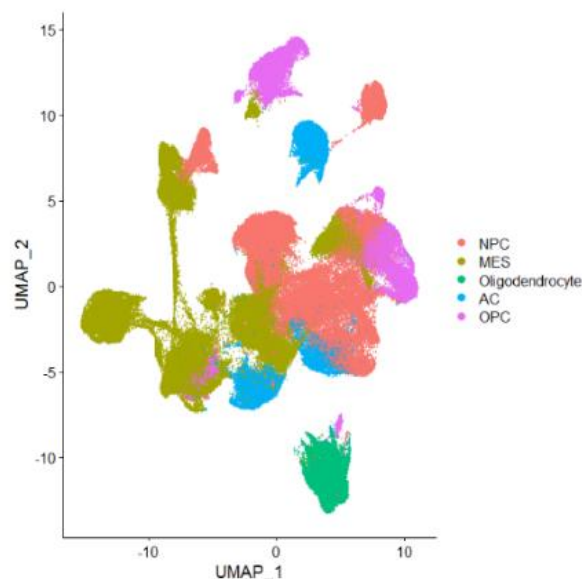








Supplementary Figure 1 (S1). Single Cell Cluster Enrichment. Clusters were labeled using meta-modules as defined by Neftel et al. (2019) [1] and Wang et al (2021) [2]. A hypergeometric test was used to evaluate whether each meta-module was overrepresented in each cluster and clusters were labeled with the most overrepresented meta-module ($-\log(p\text{-value})$).



Supplementary Figure 2 (S2). UMAP of snRNA-seq Data.

Species	Logic
ABL1	= (!ATM & !CDK1 & !CDK2 & !FYN & !LCK & !PAK2 & !PRKCA & !PRKDC & !RFX1 & SRC) (!ATM & !CDK1 & !CDK2 & !FYN & !LCK & !PAK2 & !PRKCA & !PRKDC & RFX1) (!ATM & !CDK1 & !CDK2 & !FYN & !LCK & !PAK2 & !PRKCA & PRKDC) (!ATM & !CDK1 & !CDK2 & !FYN & !LCK & !PAK2 & PRKCA) (!ATM & !CDK1 & !CDK2 & !FYN & !LCK & PAK2) (!ATM & !CDK1 & !CDK2 & !FYN & LCK) (!ATM & !CDK1 & !CDK2 & FYN) (!ATM & !CDK1 & CDK2) (!ATM & CDK1) (ATM)
ATR	ABL1
EGFR	(ABL1 AR EGF FGF2 FYN HGF IRF1 JUN JUNB NFKB1 RARA RELA)
AGT	(!FOS & HIF1A) (FOS)
AHR	AHR
AKT1	(AR ATM AURKA FGF2 LCK PRKDC RAC1 SRC TBK1 TNF) & (!TP53 !PPP2CA)
AKT2	(SRC INSR PRKDC TBK1) & (!PPP2CA !PTEN)
AKT3	(!MAP3K7 & !PPP2CA & !PRKCZ & !PRKDC & !PTEN & !PTK2B & !SRC & TBK1) (!MAP3K7 & !PPP2CA & !PRKCZ & !PRKDC & !PTEN

	& !PTK2B & SRC) (!MAP3K7 & !PPP2CA & !PRKCZ & !PRKDC & !PTEN & PTK2B) (!MAP3K7 & !PPP2CA & !PRKCZ & !PRKDC & PTEN) (!MAP3K7 & !PPP2CA & !PRKCZ & PRKDC) (!MAP3K7 & !PPP2CA & PRKCZ) (MAP3K7 & !PPP2CA)
AR	AR
ARAF	PAK1
ARNT	ARNT
ATM	(!ATR & !CDK5 & !E2F1 & !EGF & !FOXO3 & !PPP2CA & !RPS6KA2 & TNF) (!ATR & !CDK5 & !E2F1 & !EGF & !FOXO3 & !PPP2CA & RPS6KA2) (!ATR & !CDK5 & !E2F1 & !EGF & FOXO3 & !PPP2CA) (!ATR & !CDK5 & !E2F1 & EGF & !PPP2CA) (!ATR & !CDK5 & E2F1 & !PPP2CA) (!ATR & CDK5 & !PPP2CA) (ATR & !PPP2CA)
AURKA	(!E2F1 & PRKACA) (E2F1)
BCL6	BCL6
BDNF	TNF
BRAF	(!AKT1 & !AKT2 & !AKT3 & !PAK4 & PPP2CA) (!AKT1 & !AKT2 & !AKT3 & PAK4)
BUB1	CDK1
CAMK2B	CAMKK1
CAMKK1	(!CDK6 & CDK5) (CDK6)
CDK1	(E2F1 & E2F4) & (FOS SP1 !TP53 !GSK3B !PIN1 !MAPK1)
CDK2	(!AKT1 & !AKT3 & !MAPK3 & MITF & !TGFB1) (!AKT1 & !AKT3 & MAPK3 & !TGFB1) (!AKT1 & AKT3 & !TGFB1) (AKT1 & !TGFB1)
CDK4	(!FOS & !GSK3B & !JUN & !MAX & !MYC & !NFKB1 & !RELA & STAT3 & !YES1) (!FOS & !GSK3B & !JUN & !MAX & !MYC & !NFKB1 & RELA & !YES1) (!FOS & !GSK3B & !JUN & !MAX & !MYC & NFKB1 & !YES1) (!FOS & !GSK3B & !JUN & !MAX & MYC & !YES1) (!FOS & !GSK3B & !JUN & MAX & !YES1) (!FOS & !GSK3B & JUN & !YES1) (FOS & !GSK3B & !YES1)
CDK6	(!GSK3B & !MAX & !MYC & RELA & !SP1) (!GSK3B & !MAX & MYC & !SP1) (!GSK3B & MAX & !SP1)
CDK5	FYN
CDK9	AKT1 & MAPK3
CEBPA	CEBPA

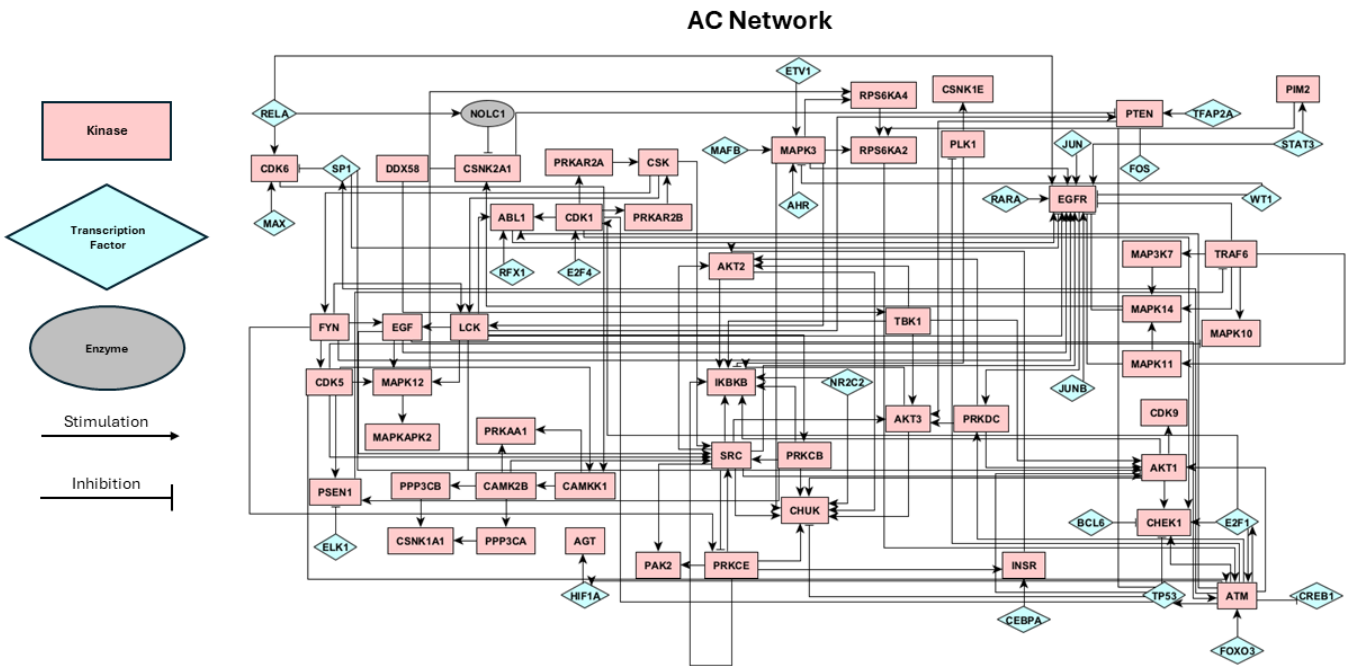
CHEK1	(AKT1 ATM ATR CDK1 E2F1 CDK2 MAP3K8) & (!BCL6 !PPP2CA !TP53)
CHEK2	CDK9 & PPP2CA
CHUK	(!AKT1 & !AKT2 & !AKT3 & !MAPK3 & !NR2C2 & !PRKCB & !PRKCE & SRC & !TP53) (!AKT1 & !AKT2 & !AKT3 & !MAPK3 & !NR2C2 & !PRKCB & PRKCE & !TP53) (!AKT1 & !AKT2 & !AKT3 & !MAPK3 & !NR2C2 & PRKCB & !TP53) (!AKT1 & !AKT2 & !AKT3 & !MAPK3 & NR2C2 & !TP53) (!AKT1 & !AKT2 & !AKT3 & MAPK3 & !TP53) (!AKT1 & !AKT2 & AKT3 & !TP53) (!AKT1 & AKT2 & !TP53) (AKT1 & !TP53)
CREB1	IATM
CREBBP	(!NFKB1 & !RUNX2 & !SMAD3 & SMAD4 & !YY1) (!NFKB1 & !RUNX2 & SMAD3 & !YY1) (!NFKB1 & RUNX2 & !YY1) (NFKB1 & !YY1)
CSK	(!CREBBP & !PRKAR2A & !PRKAR2B & VEGFA) (!CREBBP & !PRKAR2A & PRKAR2B) (!CREBBP & PRKAR2A) (CREBBP)
CSNK1E	PLK1
CSKN1A1	(!PPP3CA & PPP3CB) (PPP3CA)
CSNK2A1	(MAPK14 & !NOLC1)
DAPK1	!RPS6KA3
DDX58	!CSNK2A1
DYRK2	ATM
E2F1	ATM
EGF	(!FYN & LCK) (FYN)
E2F4	E2F4
EGR1	EGR1
ELK1	ELK1
ETV1	ETV1
FGF2	(HIF1A STAT1 TNF) & (!TP53 !SRC)
FOS	FOS
FOXO1	FOXO1
FOXO3	FOXO3
FYN	CSK
GRK5	CDK1
GSK3A	PRKCZ
GSK3B	(!AKT1 & !AKT2 & !AKT3 & MAPK1 & !PRKACA & !PRKCA & !PRKCZ & !RPS6KA5)
HGF	OSM & !PTEN
IGF1R	!TP53
HIF1A	ATM

IKBKB	(!AKT1 & !AKT2 & !AKT3 & !NR2C2 & !PLK1 & !PRKCA & !PRKCB & !PRKCE & !PRKCZ & !SRC & TBK1) (!AKT1 & !AKT2 & !AKT3 & !NR2C2 & !PLK1 & !PRKCA & !PRKCB & !PRKCE & !PRKCZ & SRC) (!AKT1 & !AKT2 & !AKT3 & !NR2C2 & !PLK1 & !PRKCA & !PRKCB & !PRKCE & PRKCZ) (!AKT1 & !AKT2 & !AKT3 & !NR2C2 & !PLK1 & !PRKCA & !PRKCB & PRKCE) (!AKT1 & !AKT2 & !AKT3 & !NR2C2 & !PLK1 & !PRKCA & PRKCB) (!AKT1 & !AKT2 & !AKT3 & !NR2C2 & !PLK1 & PRKCA) (!AKT1 & !AKT2 & !AKT3 & NR2C2 & !PLK1) (!AKT1 & !AKT2 & AKT3 & !PLK1) (!AKT1 & AKT2 & !PLK1) (AKT1 & !PLK1)
IL1B	(!FOS & !JUN & !NFKB1 & !RELA & !STAT1 & STAT3) (!FOS & !JUN & !NFKB1 & !RELA & STAT1) (!FOS & !JUN & !NFKB1 & RELA) (!FOS & !JUN & NFKB1) (!FOS & JUN) (FOS)
INSR	(!CEBPA & PRKCE) (CEBPA)
IRF1	IRF1
JUNB	JUNB
JUN	JUN
LCK	FYN & MAPK3) (!CSK)
MAFB	MAFB
MAP2K1	(EGFR MAP3K7 PAK2 RAC1) & (!CDK1 !PPP2CA)
MAP3K7	(!PPP2CA) (TRAF6)
MAP3K8	AKT1
MAPK1	(FGF2 YES1 IL1B PRKCA !SGK1) & (!HGF)
MAPK10	!CDK5 & TRAF6
MAPK12	(LCK & EGF & CDK5) (PDPK1 & PGR)
MAPK11	PAK1 & TRAF6
MAPK13	PGR
MAPK14	MAP3K7 & MAPK11 & TRAF6
MAPK8	(PRKAA1 PRKAA2 PRKDC PRKCZ) & (MAP2K1 & MAP3K7) & (HGF TNF BDNF) & (RAC1 TGFB2 PTK2B)
MAPK3	(MAPK1 & (AHR FGF2 ETV1 MAFB) & (!WT1))
MAPKAPK2	(!MAPK12 & TNF) (MAPK12)
MAX	MAX
MITF	MITF
MYC	MYC
NFATC1	NFACT1

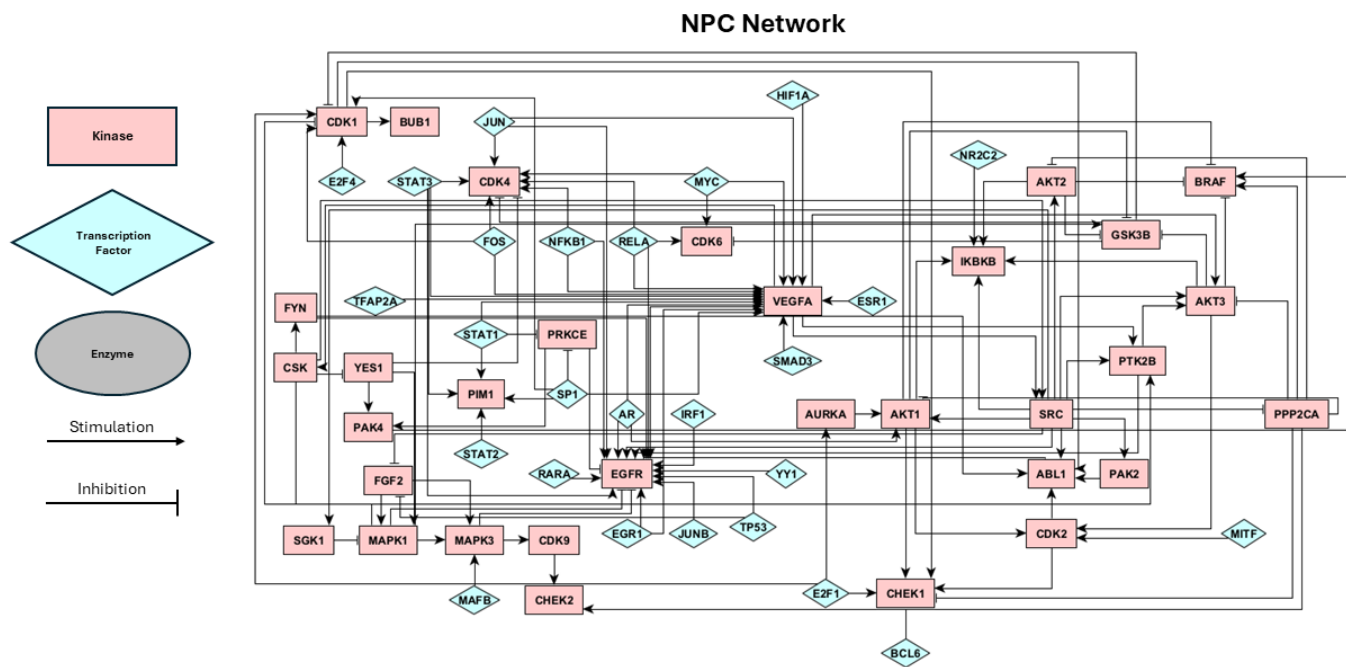
NFKB1	NFKB1
NOLC1	RELA
NR2C2	NR2C2
OSM	STAT3
PAK1	PDPK1
PAK2	(!PRKCE & !SRC & TGFB1) (!PRKCE & SRC) (PRKCE)
PAK4	(!PRKCE & YES1) (PRKCE)
PDPK1	PTEN & IGF1R
PGR	PGR
PIM1	(!PRKACA & !SP1 & !STAT1 & !STAT2 & STAT3) (!PRKACA & !SP1 & !STAT1 & STAT2) (!PRKACA & !SP1 & STAT1) (!PRKACA & SP1) (PRKACA)
PIM2	(!PRKACA & STAT3) (PRKACA)
PIM3	STAT5A
PIN1	!DAPK1
PLK1	!ATM
PPARG	PPARG
PPP2CA	(!CREB1 & !SRC & TGFB2) (CREB1 & !SRC)
PPP3CA	CAMK2B
PPP3CB	CAMK2B
PRKAA1	(!CAMK2B & !CAMKK1 & MAP3K7) (!CAMK2B & CAMKK1) (CAMK2B)
PRKAA2	MAP3K7
PRKACA	(!AKT3 & !PPP2CA & RPS6KA5) (AKT3 & !PPP2CA)
PRKAR2A	CDK1
PRKAR2B	CDK1
PRKCA	IL1B & !PPP2CA
PRKCB	LCK
PRKCE	FYN & !SP1 & !STAT1
PRKCZ	!PPP2CA
PRKD1	PDPK1
PRKDC	(!ATR & !EGFR & ATM) (!ATR & EGFR) (ATR)
PSEN1	(!CDK5 & !ELK1 & PRKCB) (CDK5 & !ELK1)
PTEN	(TFAP2A (TP53 & LCK) (TP53 & PRKCA) (PRKCA & LCK)) & (!FOS !CSNK2A1)
PTK2B	(!CSK & !SRC & VEGFA) (!CSK & SRC) (CSK)
RAC1	(!ABL1 & !EGFR & !FYN & !HGF & PTK2B & !TP53) (!ABL1 & !EGFR & !FYN & HGF & !TP53) (!ABL1 & !EGFR & FYN & !TP53) (!ABL1 & EGFR & !TP53) (ABL1 & !TP53)
RARA	RARA

RFX1	RFX1
RELA	RELA
RPS6KA2	(!MAPK3 & PIM2 & RPS6KA4) (MAPK3 & RPS6KA4)
RPS6KA3	(!FOXO1 & FYN) (FOXO1);
RPS6KA4	(!MAPK12 & MAPK3) (MAPK12)
RPS6KA5	(!MAP2K1 & MAPK1) (MAP2K1)
RUNX2	RUNX2
SGK1	SRC
SMAD3	SMAD3
SMAD4	SMAD4
SP1	!ATM
SRC	(!CAMK2B & !CDK5 & !CSK & !EGF & !PRKCB & !PRKCE & VEGFA) (!CAMK2B & !CDK5 & !CSK & !EGF & !PRKCB & PRKCE) (!CAMK2B & !CDK5 & !CSK & !EGF & PRKCB) (!CAMK2B & !CDK5 & !CSK & EGF) (!CAMK2B & !CDK5 & CSK) (!CAMK2B & CDK5) (CAMK2B)
STAT1	STAT1
STAT2	STAT2
STAT3	STAT3
STAT5A	MAPK8
TBK1	DDX58
TFAP2A	TFAP2A
TFRC	(!ARNT & !HIF1A & MAX) (!ARNT & HIF1A) (ARNT)
TGFB1	(!EGR1 & !FOS & !HIF1A & !JUN & !NFKB1 & !RELA & USF1 & !YY1) (!EGR1 & !FOS & !HIF1A & !JUN & !NFKB1 & RELA & !YY1) (!EGR1 & !FOS & !HIF1A & !JUN & NFKB1 & !YY1) (!EGR1 & !FOS & !HIF1A & JUN & !YY1) (!EGR1 & !FOS & HIF1A & !YY1) (!EGR1 & FOS & !YY1) (EGR1 & !YY1)
TGFBR2	PDPK1
TNF	(!CREBBP & !FOS & !JUN & !NFATC1 & !NFKB1 & !PTEN & RELA & !SP1) (!CREBBP & !FOS & !JUN & !NFATC1 & NFKB1 & !PTEN & !SP1) (!CREBBP & !FOS & !JUN & NFATC1 & !PTEN & !SP1) (!CREBBP & !FOS & JUN & !PTEN & !SP1) (!CREBBP & FOS & !PTEN & !SP1) (CREBBP & !PTEN & !SP1)
TP53	TP53
TRAF6	!PSEN1

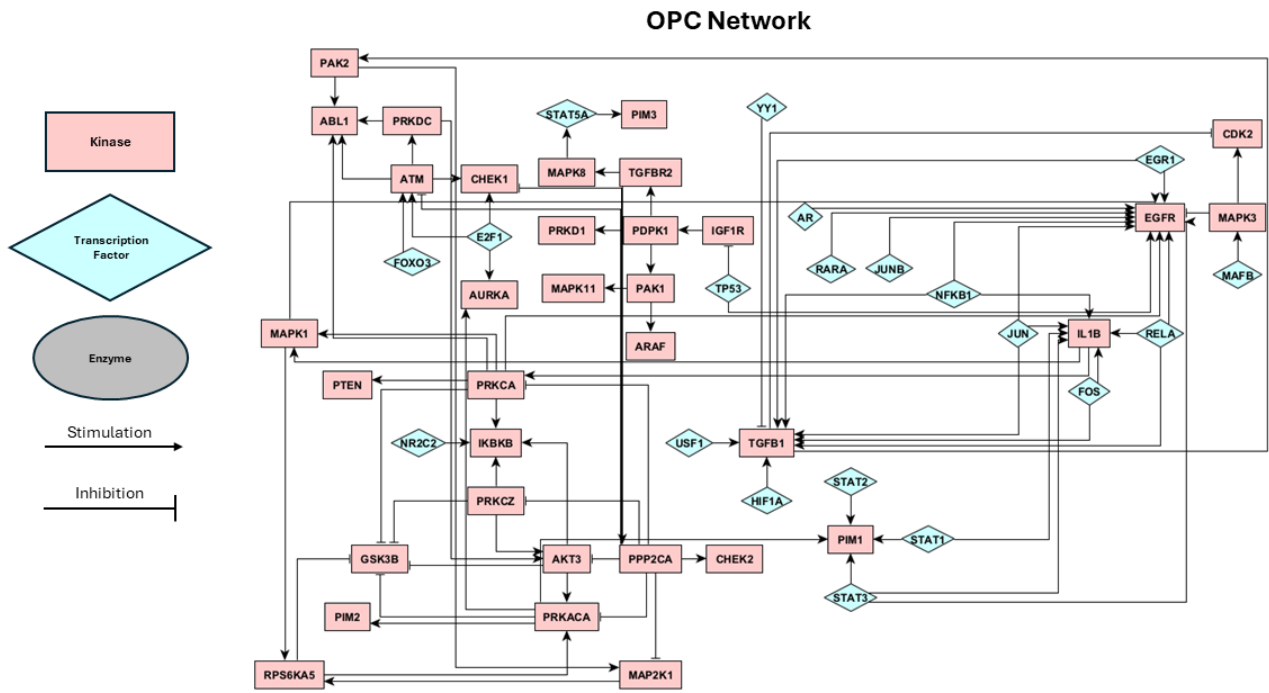
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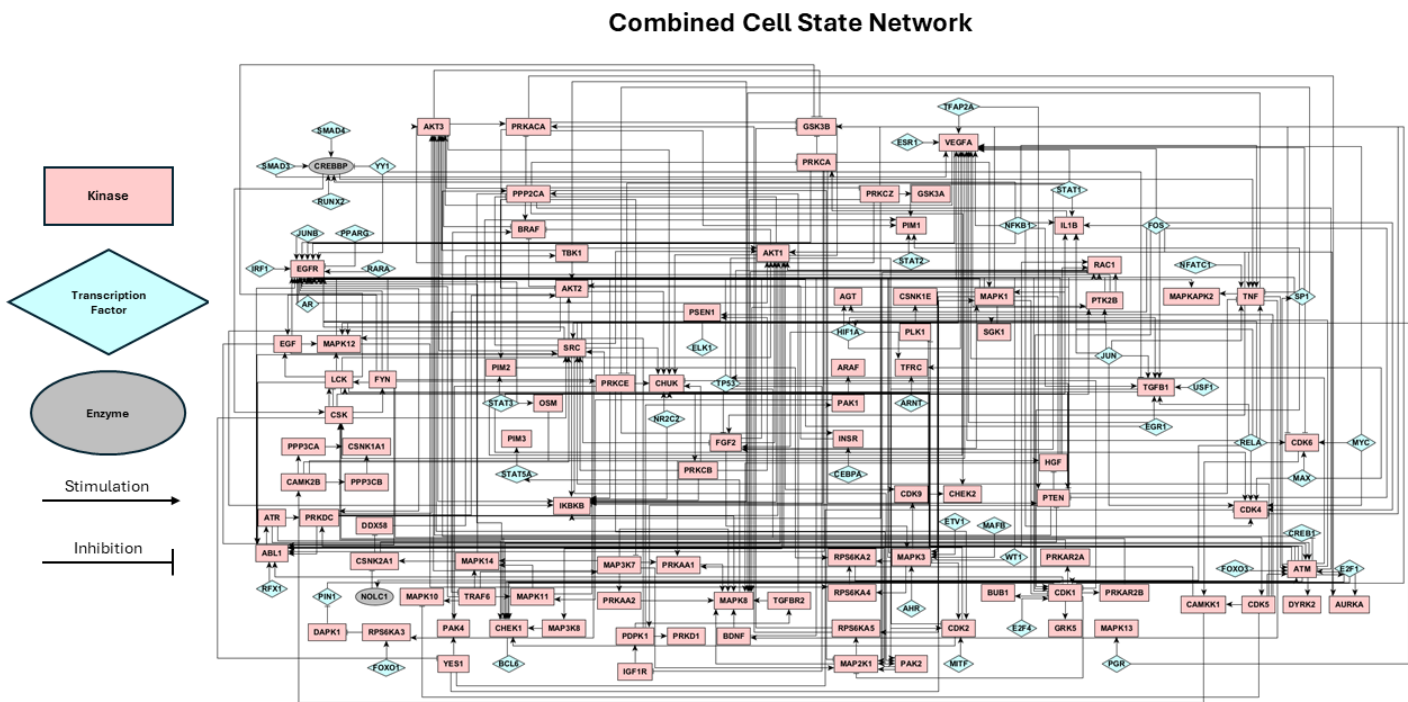
c)



d)



e)



Supplementary Figure 4 (S4). COSMOS PPINs. The PPINs of the four individual cell states (a-d) and the final combined network (e). Pink rectangles indicate kinases and blue diamonds indicate transcription factors. Activating/Stimulating interactions are depicted by arrows and inhibitory interactions are depicted by T-bars.

a) Multinomial Regression

Primary Tumors				Recurrent Tumors			
Phenotype	Sensitivity	Specificity	Balanced Accuracy	Phenotype	Sensitivity	Specificity	Balanced Accuracy
AC	1.0	0.72	86.0%	AC	1.0	0.7	84.9%
	1.0	0.51	75.5%		0.0	0.46	23%
	1.0	0.42	74.5%		1.0	0.42	70.1%
MES	0.97	0.99	98.3%	MES	0.98	0.99	98.5%
	0.73	0.99	86.4%		0.64	0.9	77.2%
	0.71	0.95	83.3%		0.6	0.96	78.3%
NPC	0.41	0.99	70.2%	NPC	0.38	0.99	68.9%
	0.22	0.98	60.8%		0.14	0.99	55.1%
	0.14	0.98	56.8%		0.22	0.98	59.1%
OPC	0.0	1.0	50.0%	OPC	0.0	1.0	50.0%
	0.0	1.0	50.0%		0.0	1.0	50.0%
	0.0	1.0	50.0%		0.0	1.0	50.0%

Original Data

Data +10% Noise

Data +20% Noise

b) K-Nearest Neighbor (KNN)

Primary Tumors				Recurrent Tumors			
Phenotype	Sensitivity	Specificity	Balanced Accuracy	Phenotype	Sensitivity	Specificity	Balanced Accuracy
AC	1.0	0.88	94.0%	AC	1.0	0.82	91.1%
	1.0	0.64	82.0%		0.0	0.62	31.0%
	1.0	0.58	79.0%		1.0	0.57	78.3%
MES	0.96	0.99	98.3%	MES	1.0	0.99	99.5%
	0.80	0.98	88.7%		0.78	0.86	82.0%
	0.69	0.97	84.7%		0.77	0.98	87.4%
NPC	0.83	0.98	90.8%	NPC	0.76	0.99	87.8%
	0.43	0.98	70.6%		0.32	0.99	64.6%
	0.46	0.97	72.0%		0.35	0.99	66.6%
OPC	0.0	1.0	50.0%	OPC	0.0	1.0	50.0%
	0.0	1.0	50.0%		0.0	1.0	50.0%
	0.0	1.0	50.0%		0.0	1.0	50.0%

Original Data

Data +10% Noise

Data +20% Noise

c) Random Forest (RF)

Primary Tumors				Recurrent Tumors			
Phenotype	Sensitivity	Specificity	Balanced Accuracy	Phenotype	Sensitivity	Specificity	Balanced Accuracy
AC	0.0	0.99	49.5%	AC	0.0	0.95	47.3%
	0.0	0.97	48.5%		0.0	0.91	45.5%
	0.33	0.96	64.7%		0.0	0.92	45.5%
MES	0.98	0.93	95.5%	MES	0.98	0.94	96.9%
	0.98	0.91	94.4%		0.98	0.96	98.0%
	0.93	0.89	90.9%		0.76	0.92	83.6%
NPC	0.98	0.95	96.7%	NPC	0.98	0.99	98.5%
	0.89	0.97	93.1%		0.92	0.99	95.2%
	0.76	0.92	84.0%		0.78	0.97	87.9%
OPC	0.0	1.0	50.0%	OPC	0.27	1.0	63.6%
	0.25	0.99	62.0%		0.18	1.0	59.1%
	0.25	0.96	60.4%		0.27	0.96	61.7%

■ Original Data
■ Data +10% Noise
■ Data +20% Noise

d) XGBoost

Primary Tumors				Recurrent Tumors			
Phenotype	Sensitivity	Specificity	Balanced Accuracy	Phenotype	Sensitivity	Specificity	Balanced Accuracy
AC	0.0	0.91	45.6%	AC	0.0	0.83	41.6%
	0.67	0.86	76.3%		0.0	0.76	38.0%
	0.67	0.81	73.8%		0.0	0.74	37.1%
MES	0.98	1.0	99.1%	MES	0.98	0.99	98.2%
	0.93	0.93	93.2%		0.80	0.78	78.7%
	0.81	0.91	86.1%		0.75	0.92	83.6%
NPC	0.89	0.95	92.3%	NPC	0.81	0.99	89.8%
	0.76	0.98	87.0%		0.51	0.94	72.4%
	0.70	0.94	82.1%		0.67	0.91	79.2%
OPC	0.0	1.0	50.0%	OPC	0.0	1.0	50.0%
	0.0	1.0	50.0%		0.0	1.0	50.0%
	0.0	1.0	50.0%		0.0	1.0	50.0%

■ Original Data
■ Data +10% Noise
■ Data +20% Noise

Supplementary Figure 5 (S5). Machine Learning Results. The sensitivity, specificity, and balanced accuracy for each machine learning model. Results are divided into two tables, one for primary tumors and one for recurrent tumors. Results from the original GLASS data is shown in red, while results from the data with 10% and 20% noise are shown in light and dark blue, respectively.

ADDITIONAL SUPPLEMENTARY FILES

Additional File 1: Differentially_Expressed_Genes.xlsx. This file contains the lists of differentially expressed genes in each of the four dominant cell states of glioblastoma. Each cell state is a separate sheet in this order: MES, NPC, OPC, AC.

Additional File 2: Differentially_Expressed_Phosphoproteins.xlsx. This file contains the lists of differentially expressed phosphoproteins in each of the four dominant cell states of glioblastoma. Each cell state is a separate sheet in this order: MES, NPC, OPC, AC.

Additional File 3: COSMOS_PPI.xlsx This file contains information regarding the PPINs for each of the four dominant cell states, as well as the final integrated network (5 total). Each network has two sheets associated with it. Sheets with the suffix “ATT” describe the attributes of the nodes of the PPIN, including the protein name and activity. Sheets with the suffix “SIF” describe the interaction between nodes, which is whether the interaction is activating or inhibiting.

References

1. Neftel, C., et al., *An Integrative Model of Cellular States, Plasticity, and Genetics for Glioblastoma*. Cell, 2019. **178**(4): p. 835-849.e21.
2. Wang, L.-B., et al., *Proteogenomic and metabolomic characterization of human glioblastoma*. Cancer Cell, 2021. **39**(4): p. 509-528.e20.