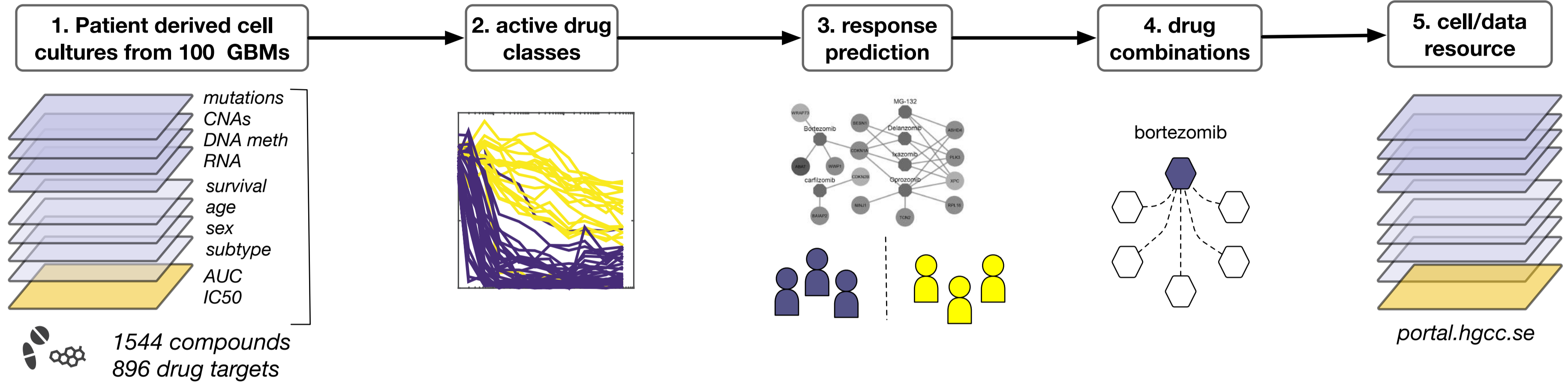
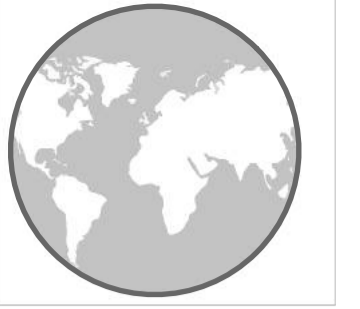
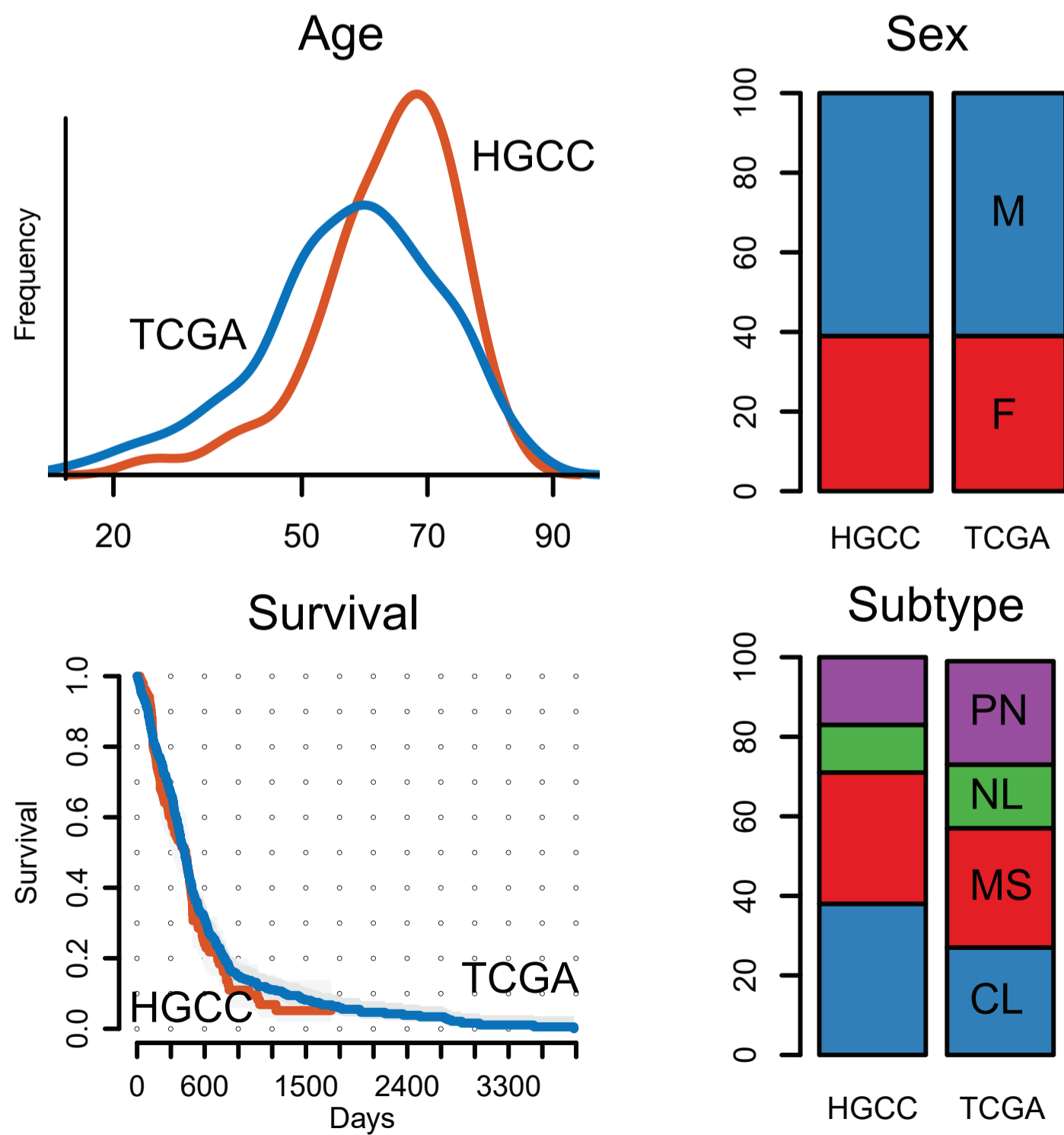


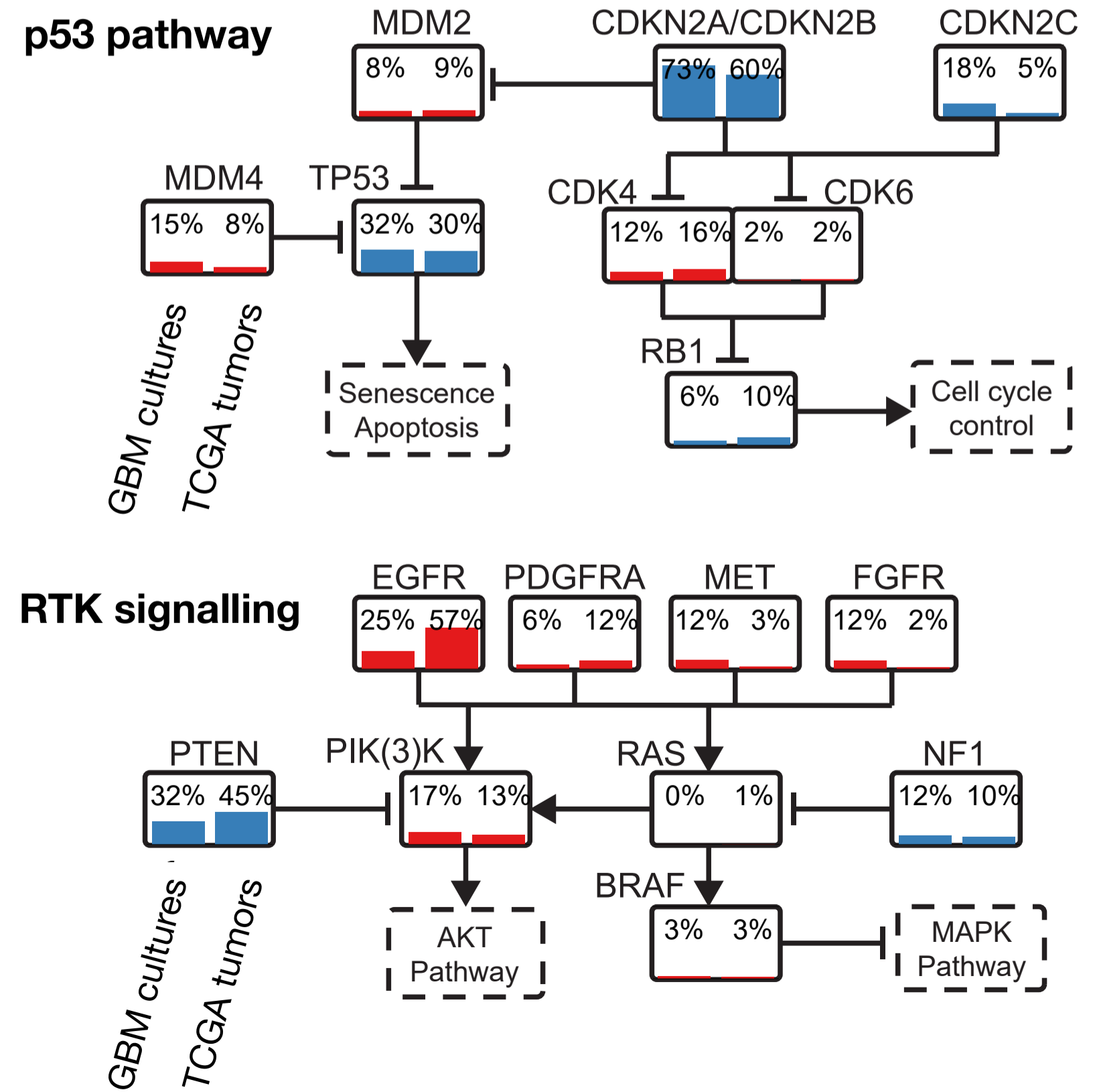
A

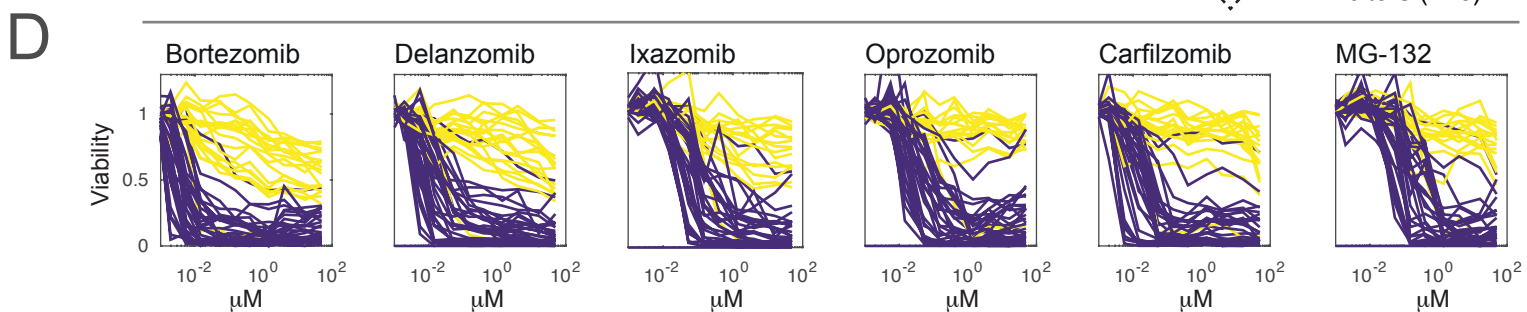
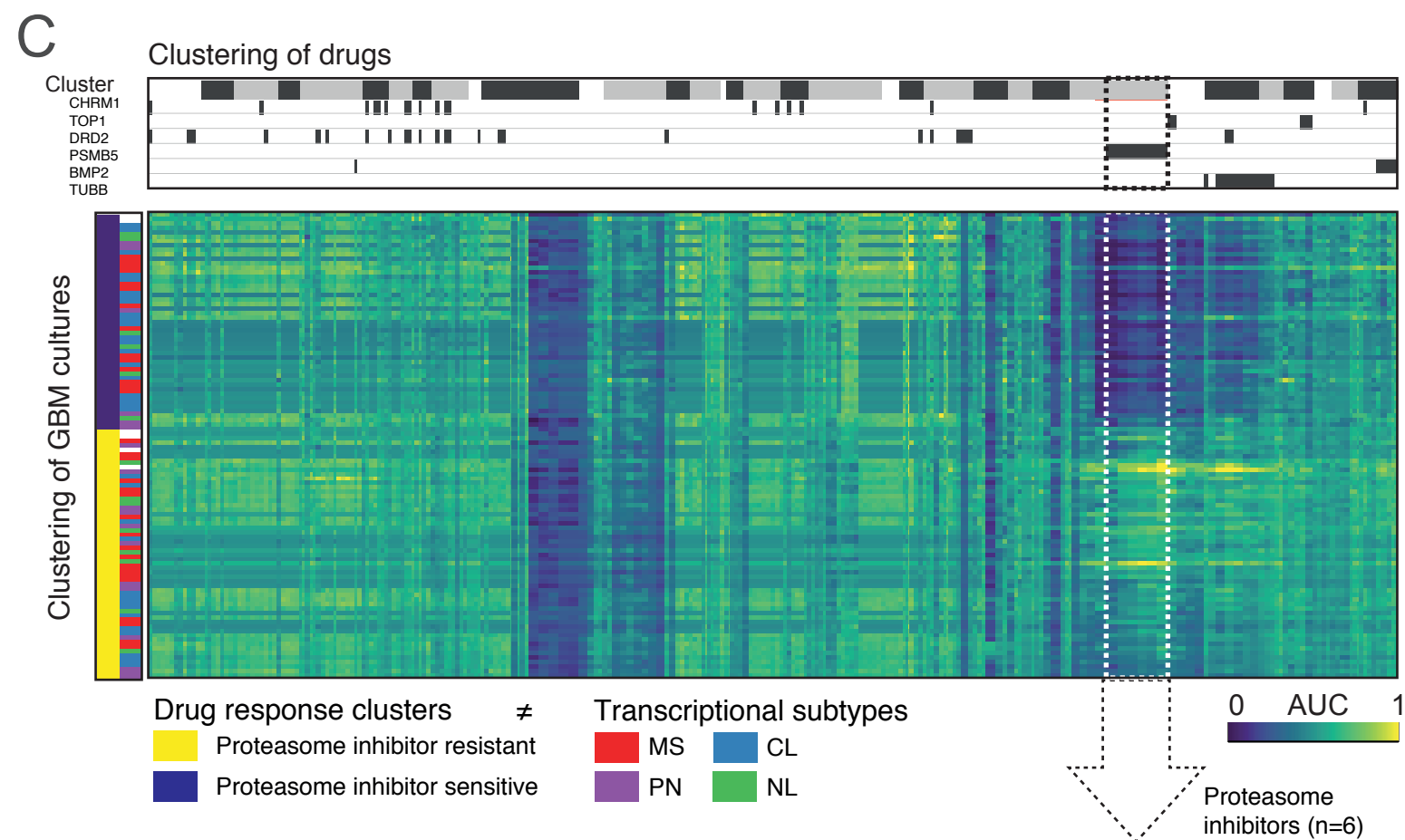
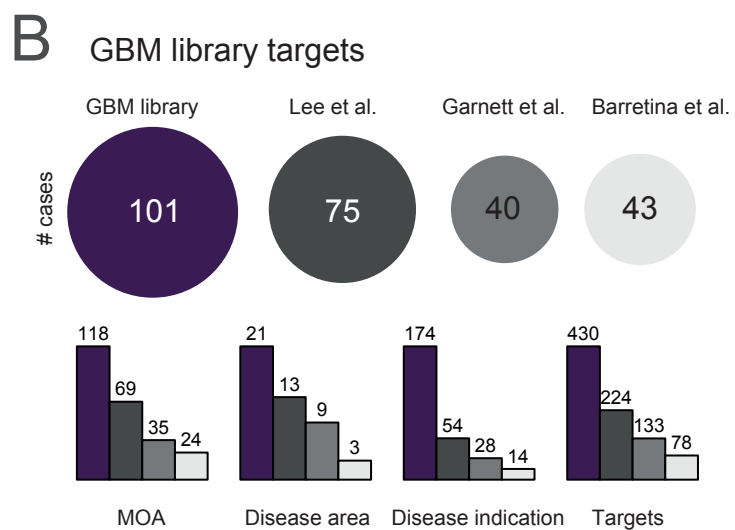
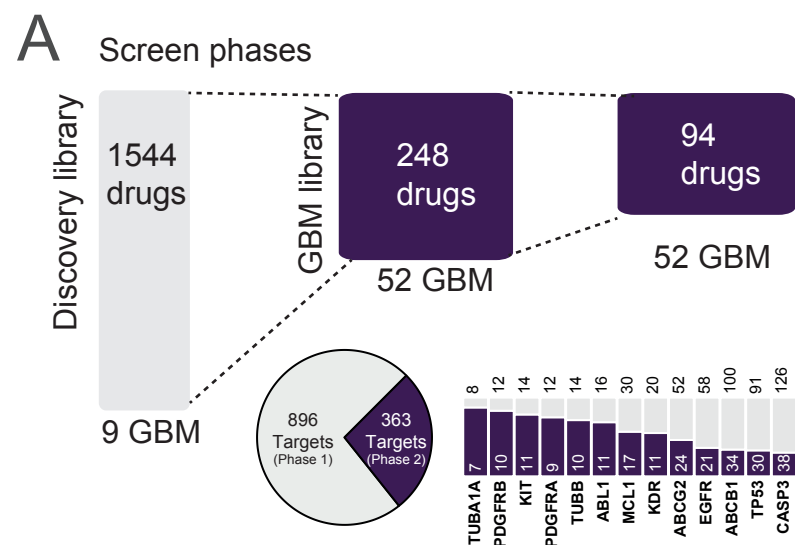


B

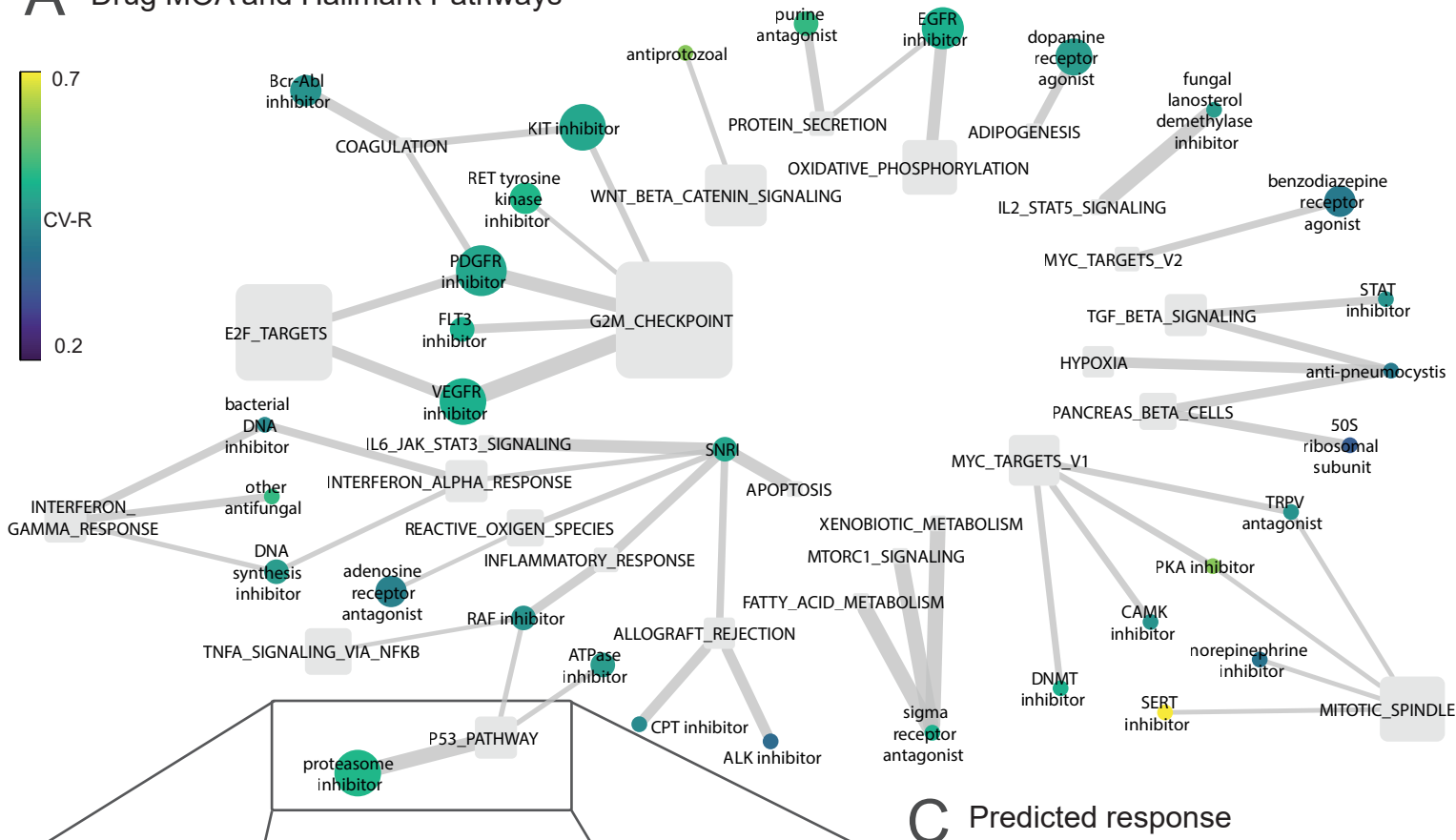


C

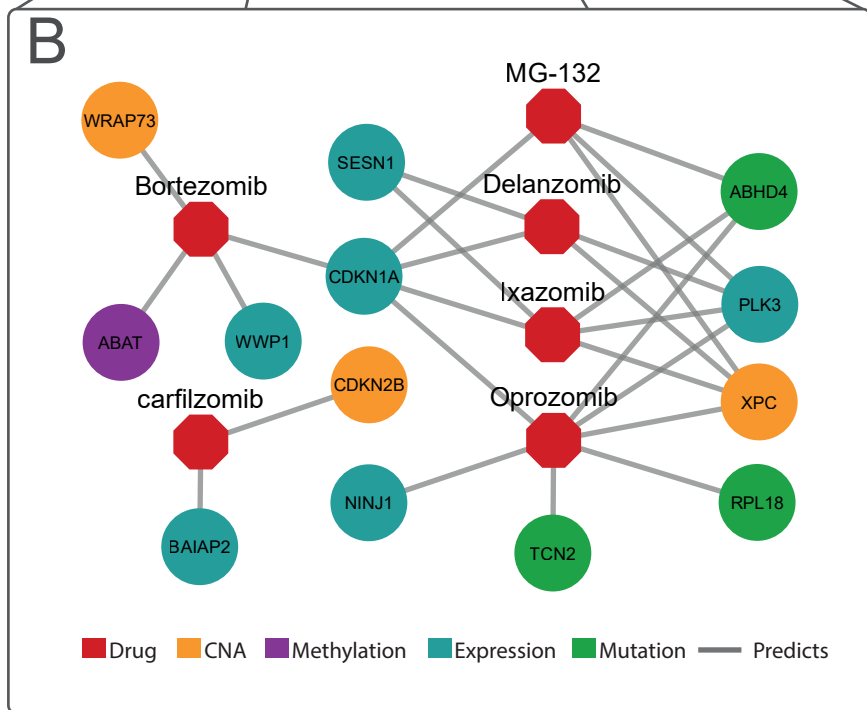




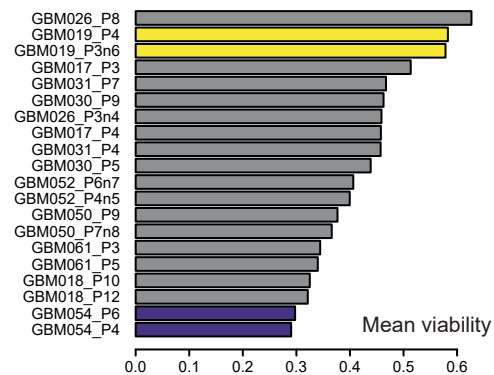
A Drug MOA and Hallmark Pathways



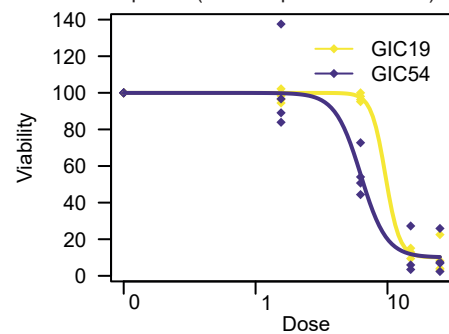
B



C Predicted response

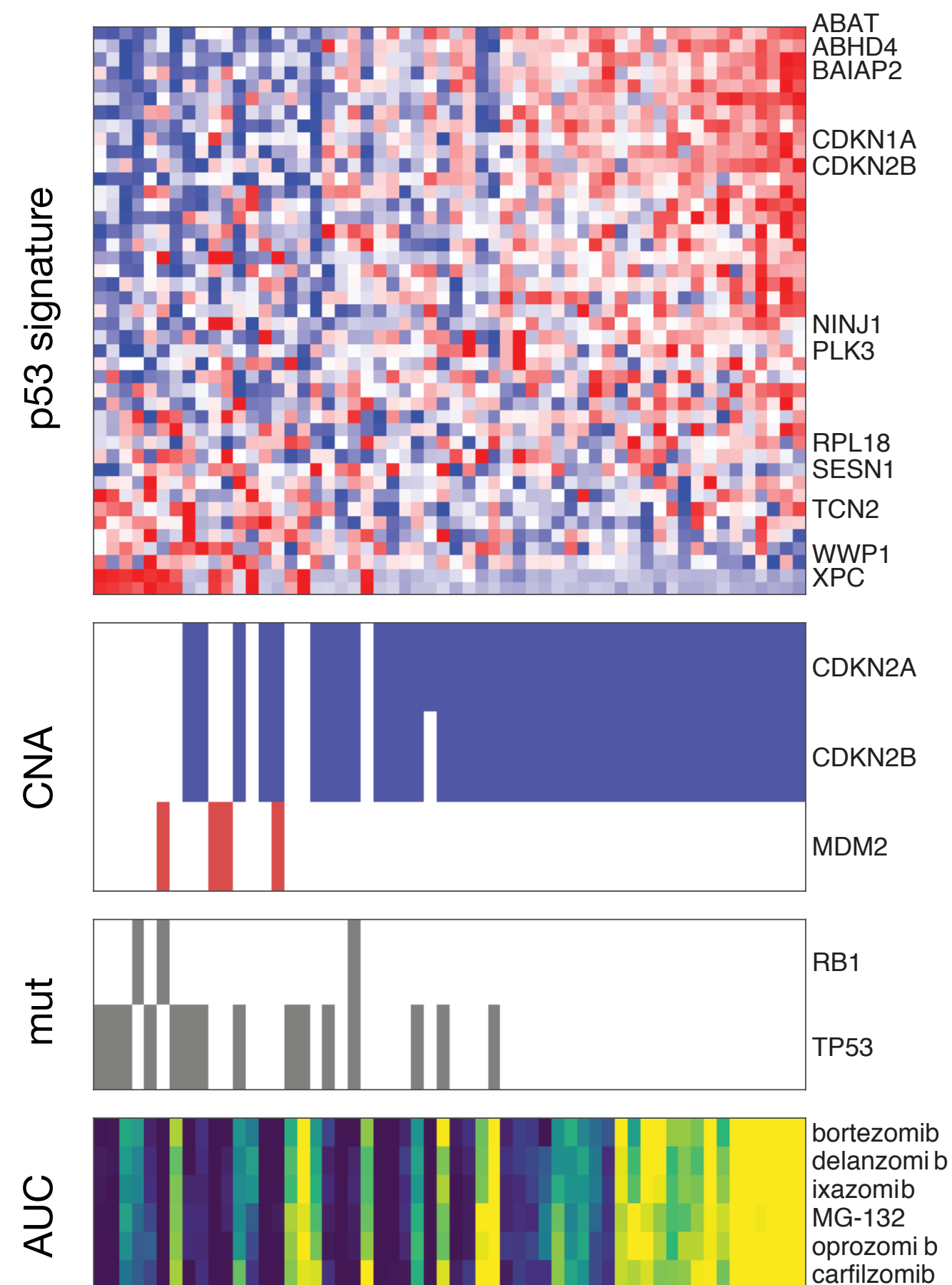


Validated response (ANOVA p-value<0.0001)

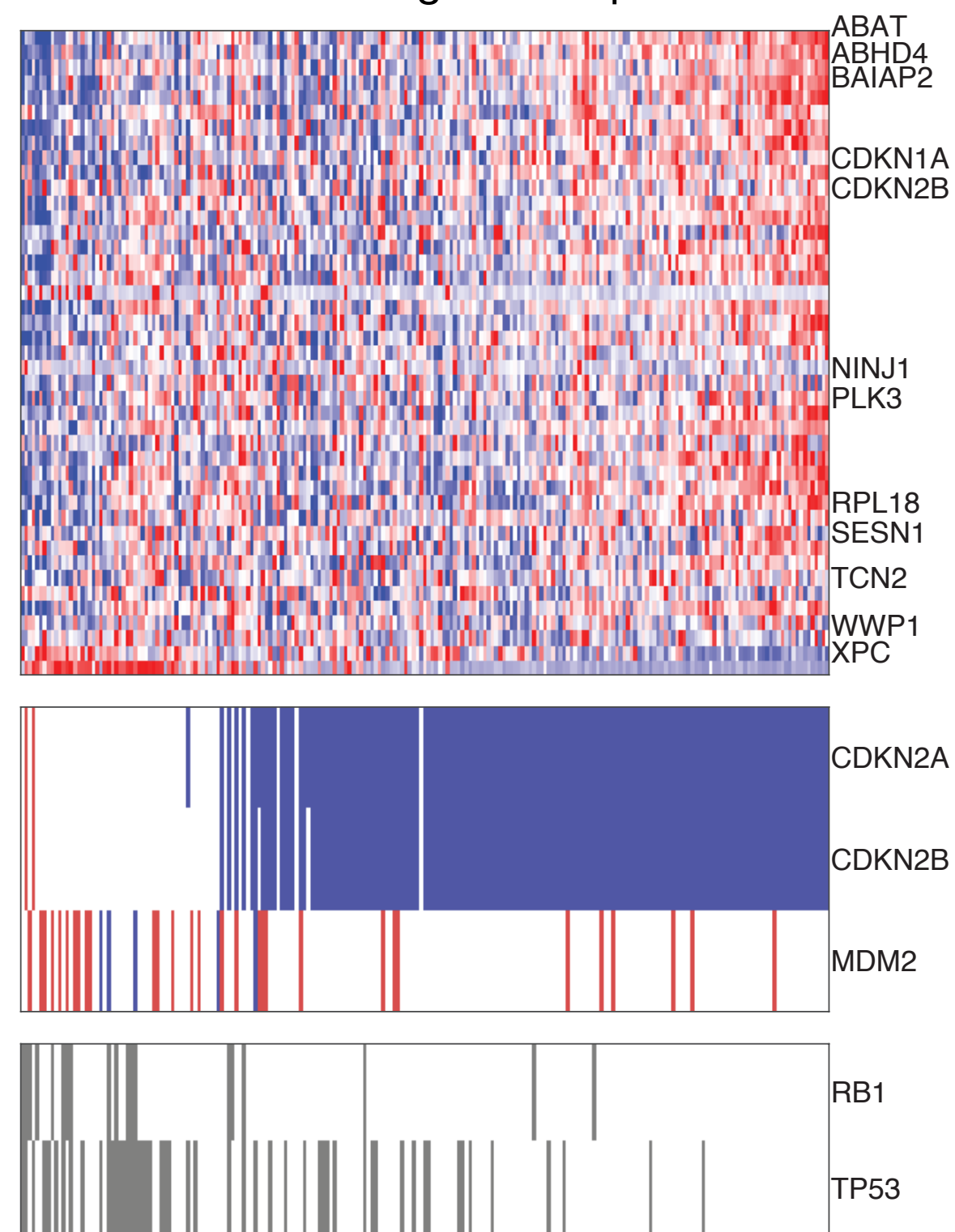
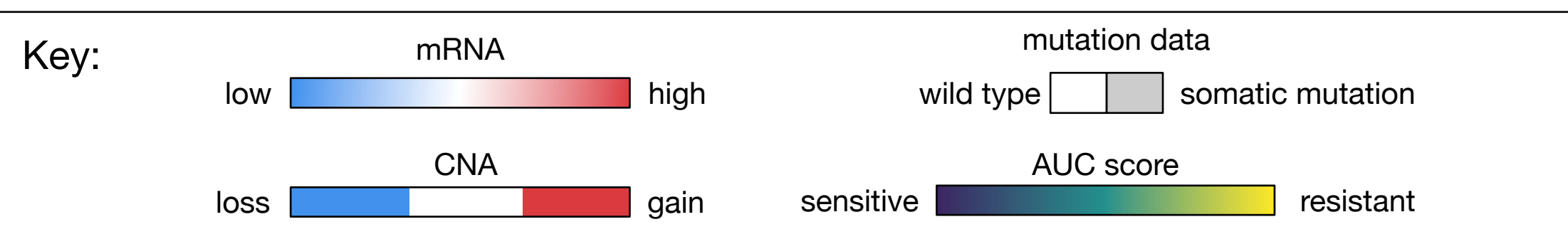
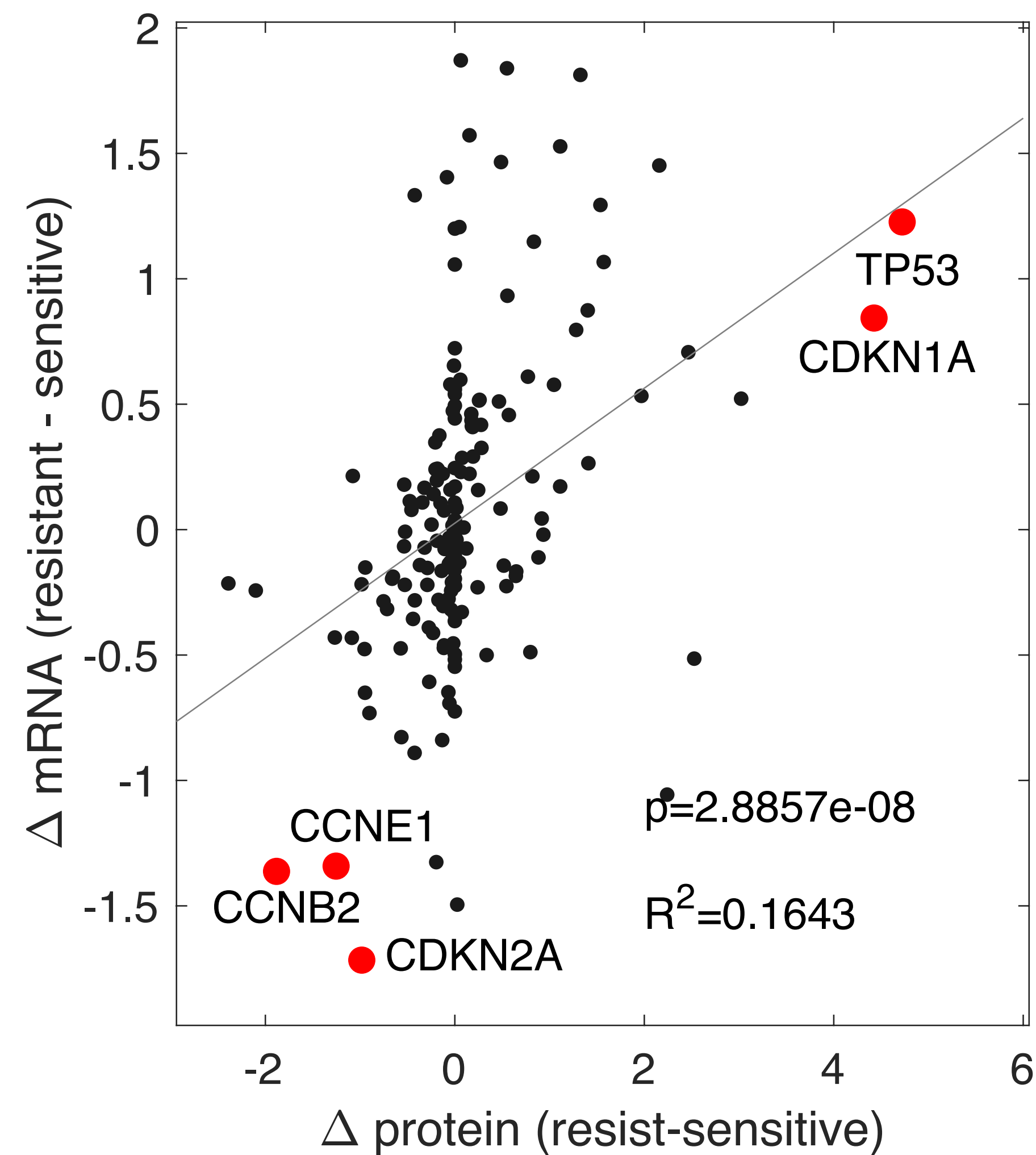


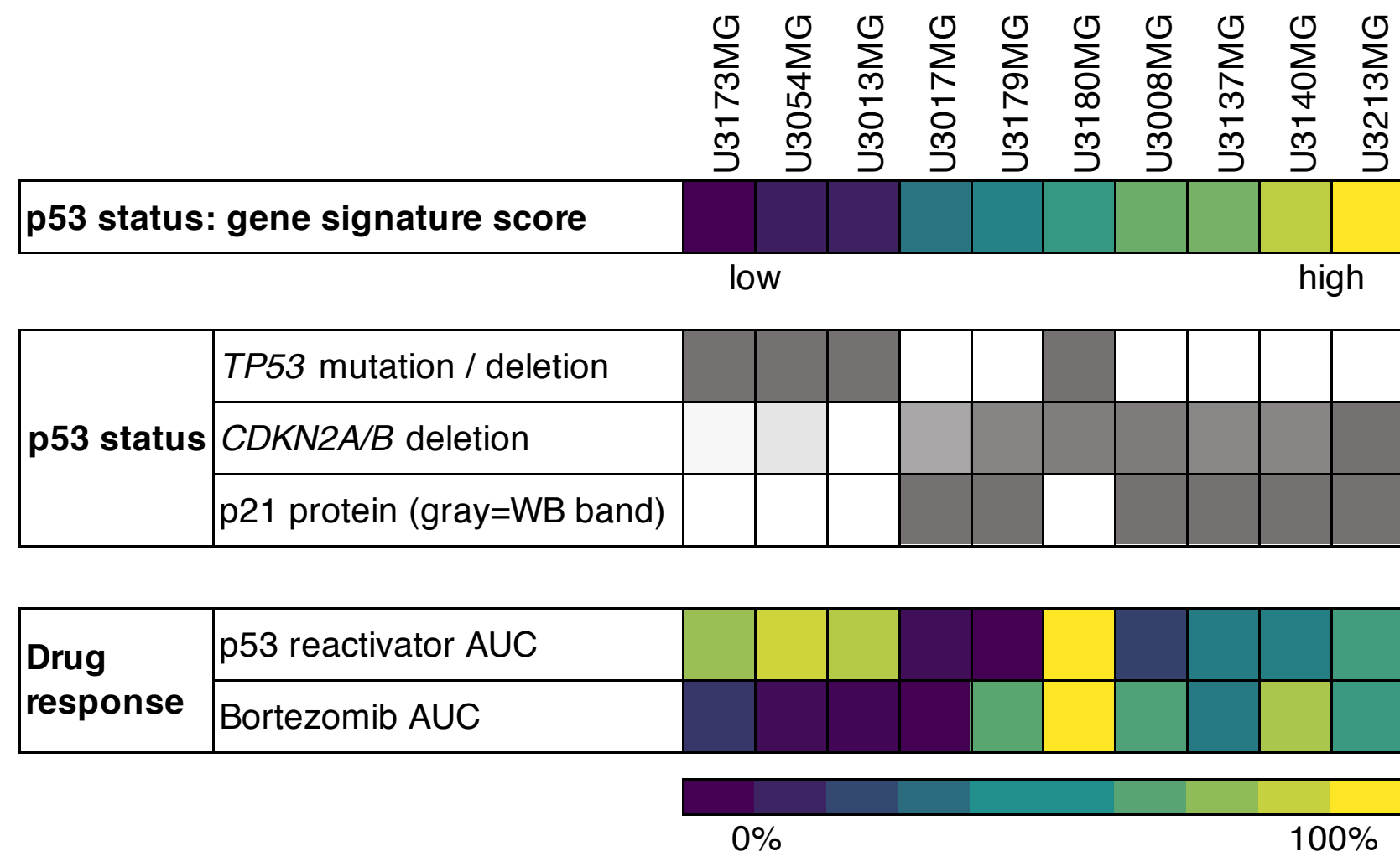
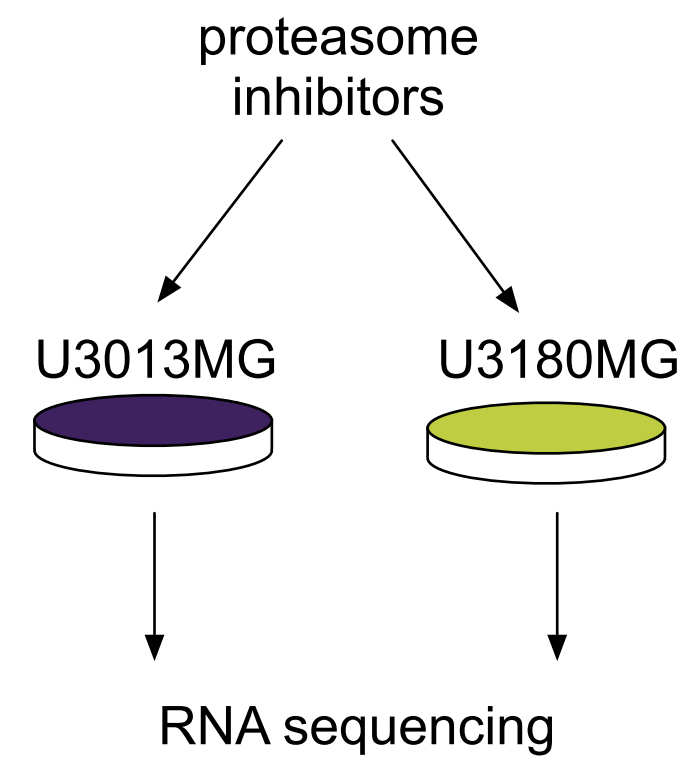
A

HGCC cultures

**B**

TCGA surgical samples

**C**

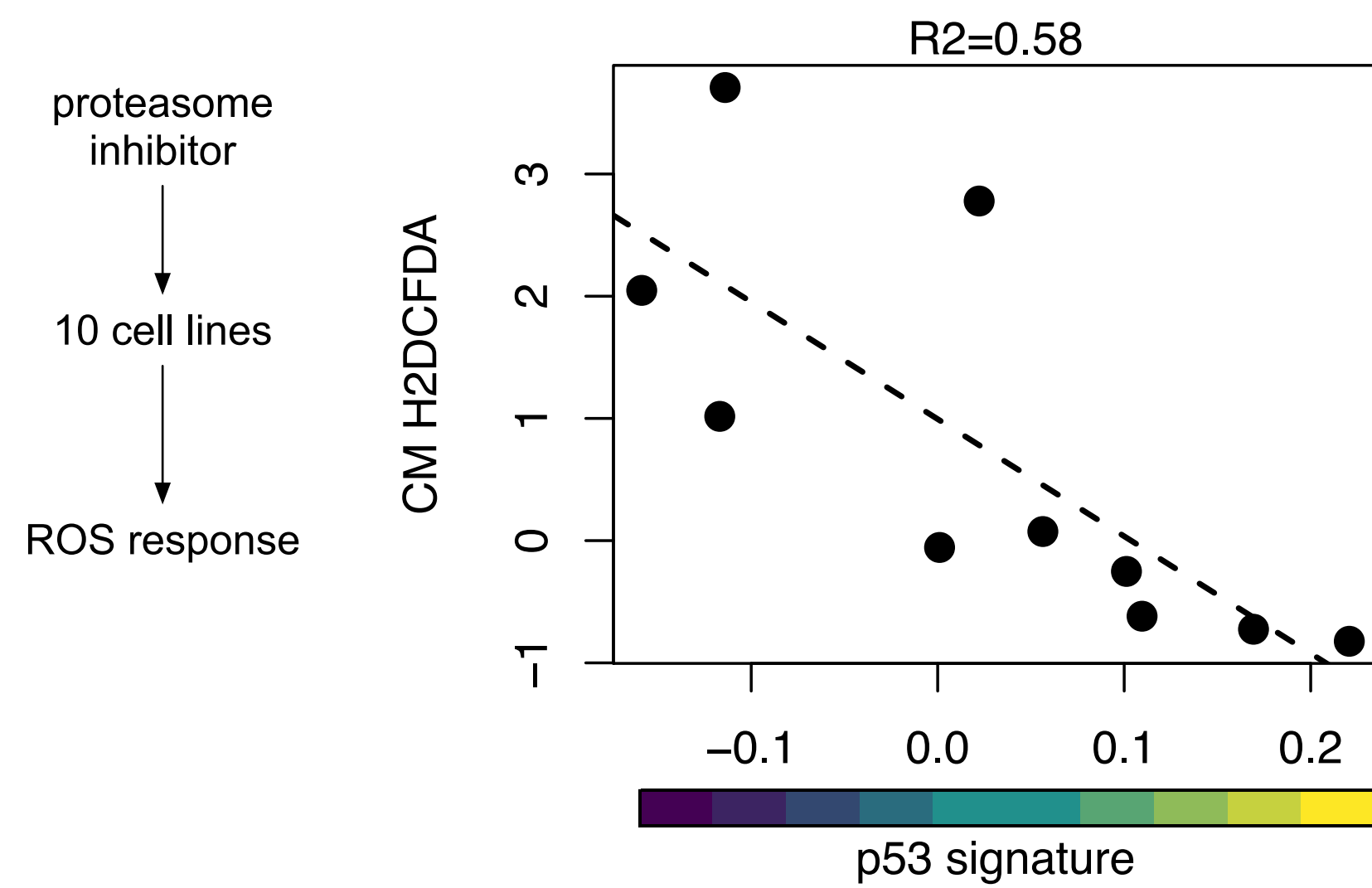
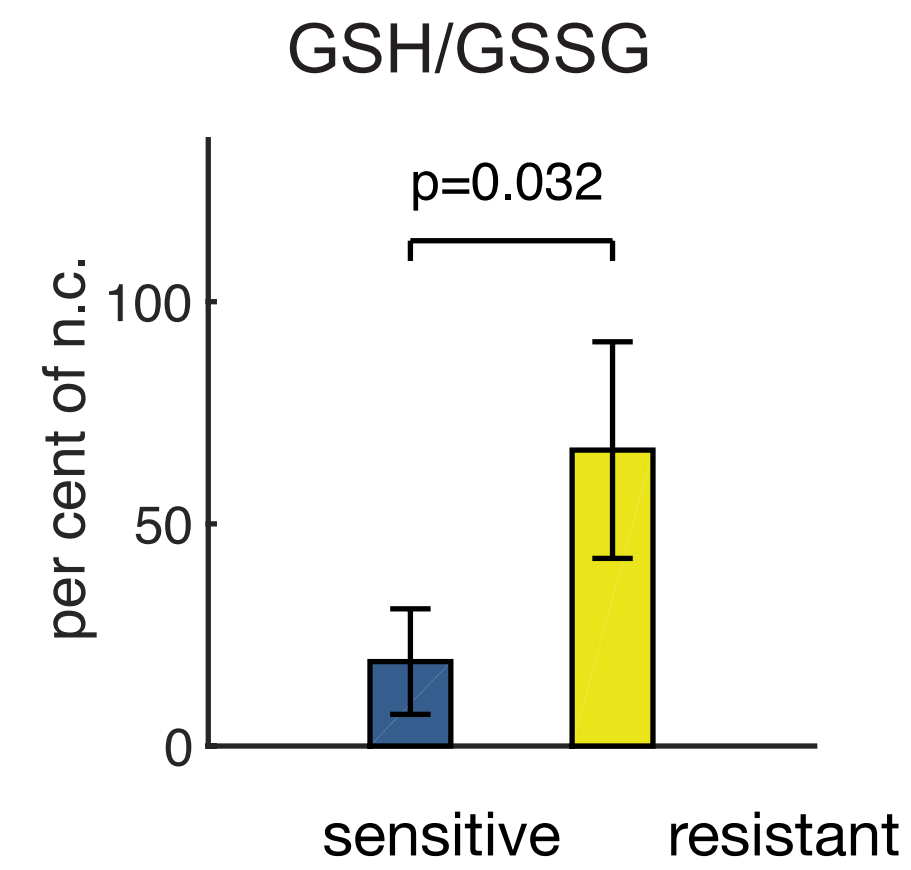
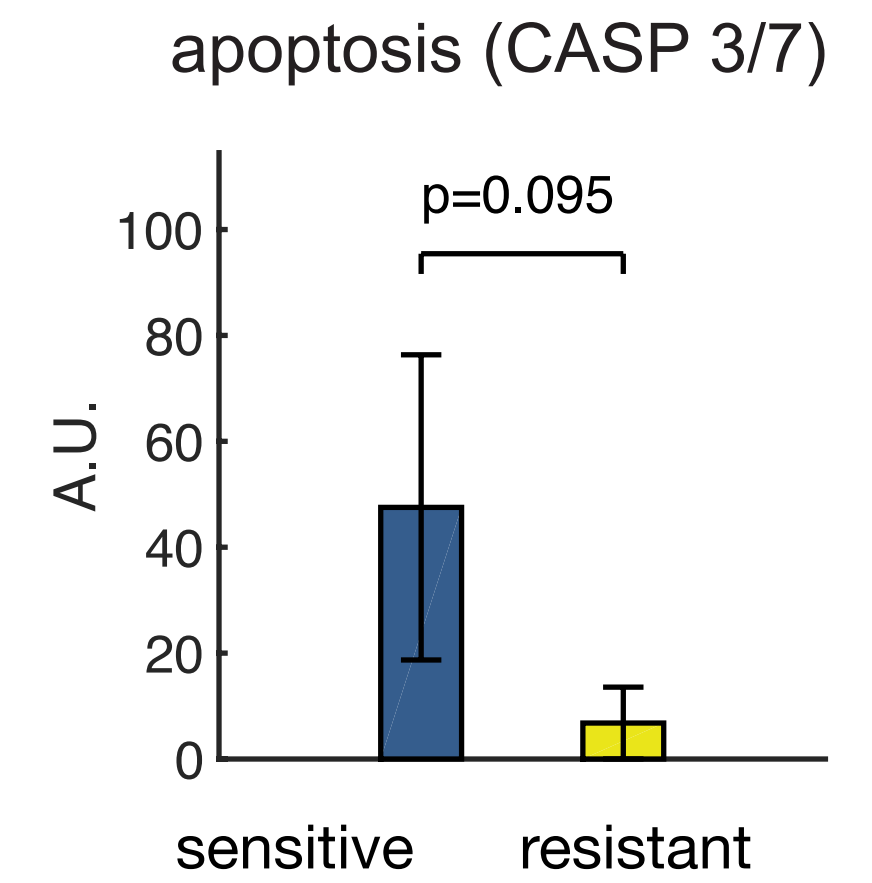
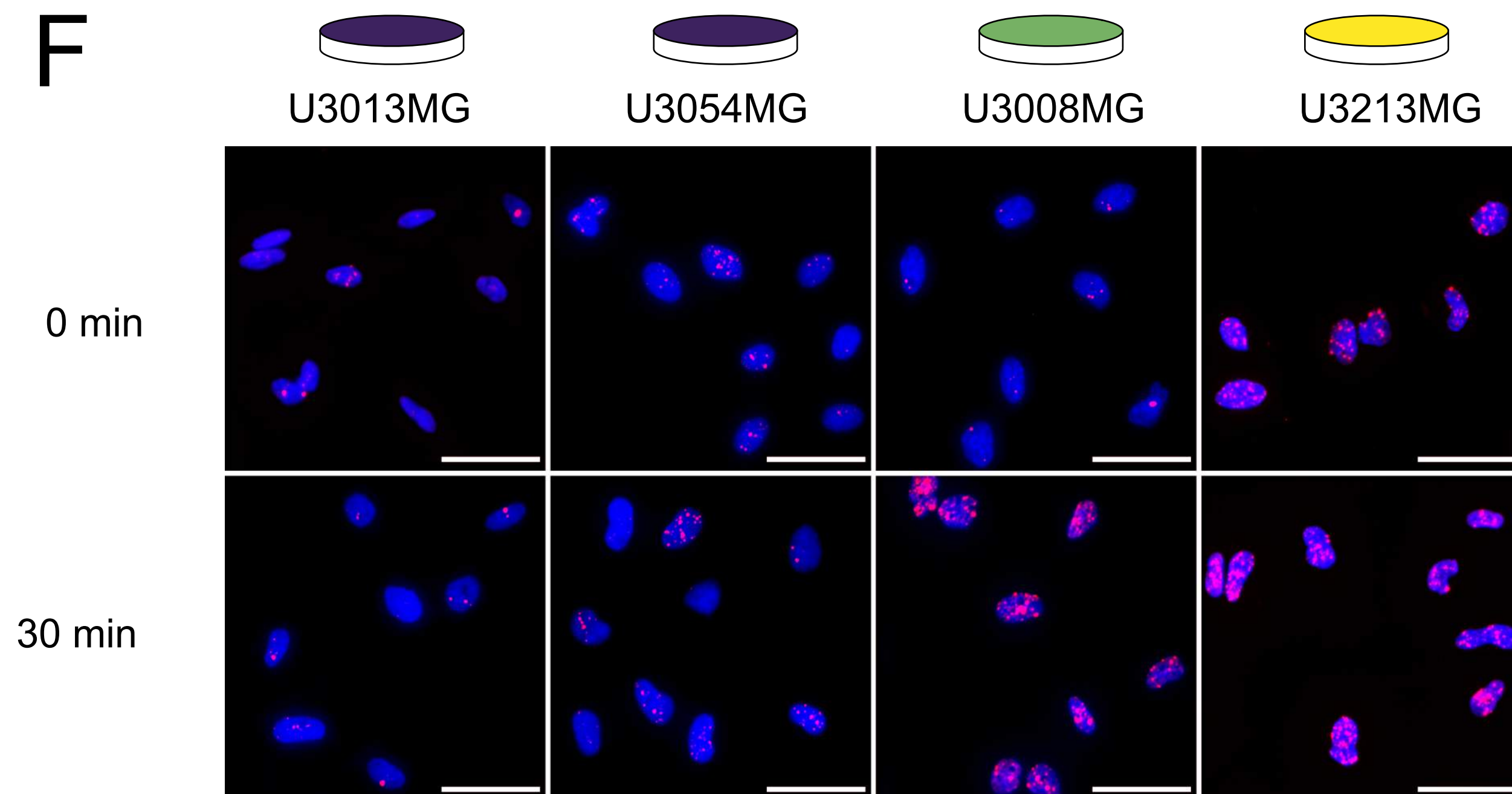
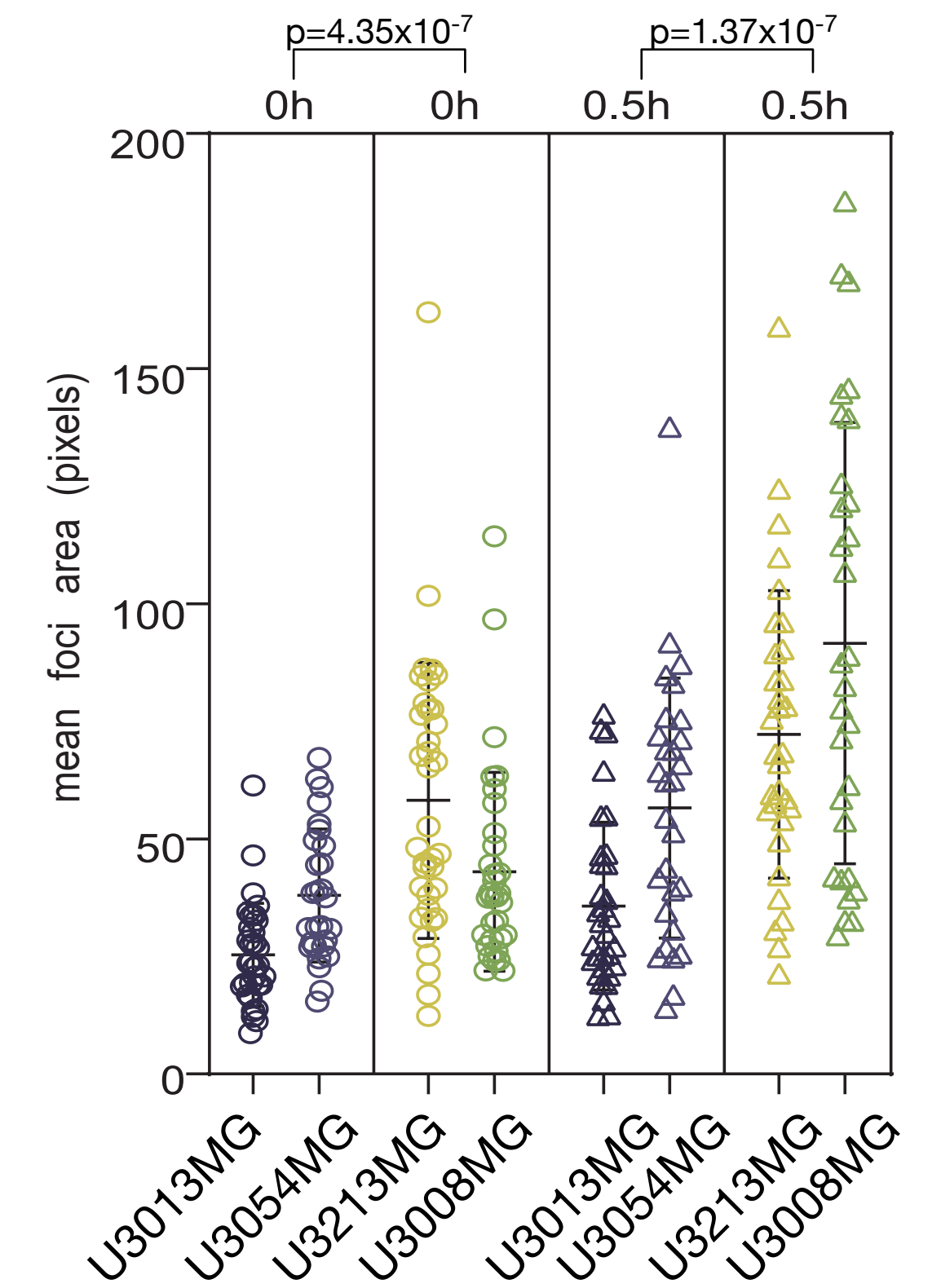
A**B****COMMON PATHWAYS (U3013 AND U3180)** **FDR q value**

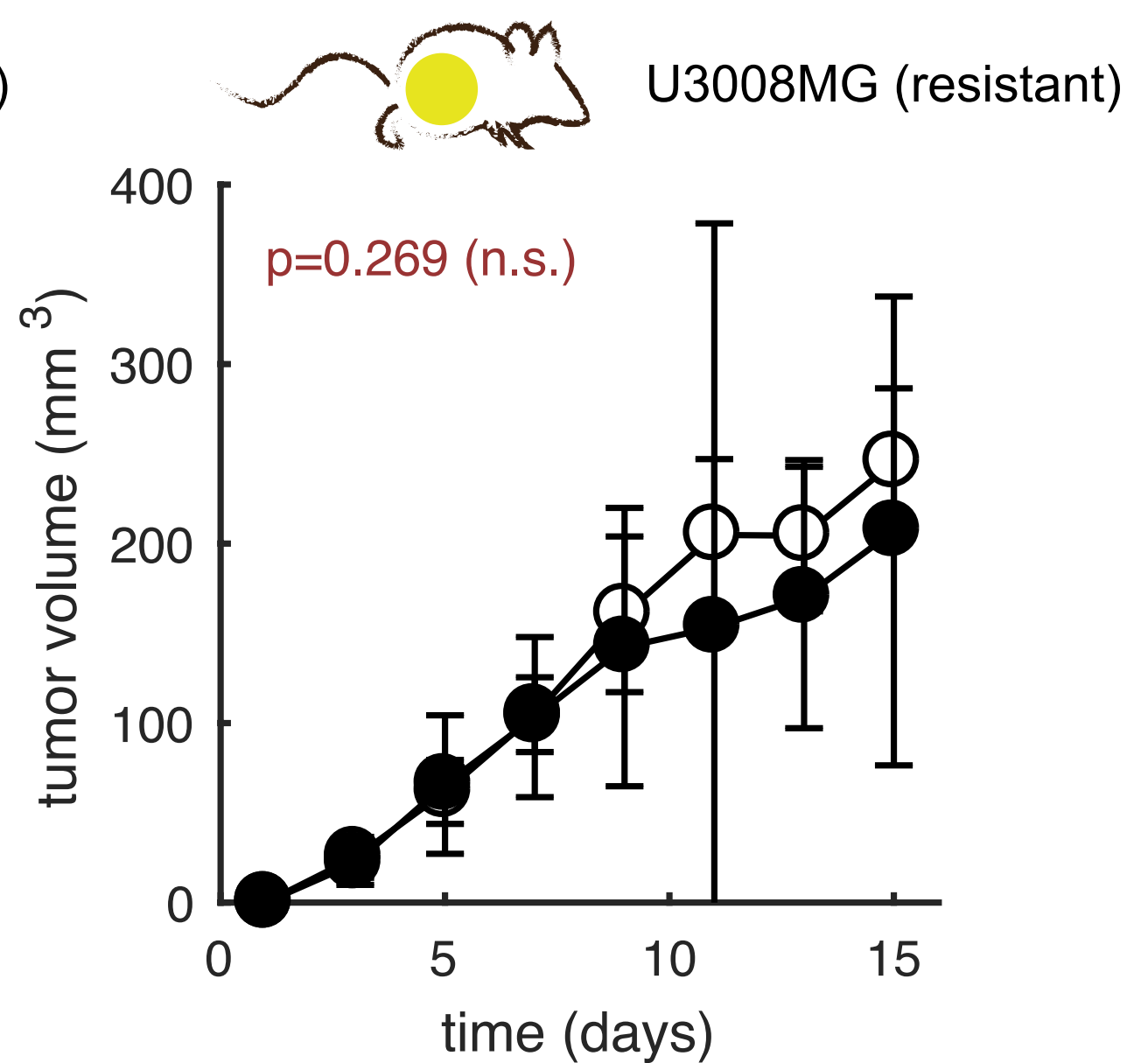
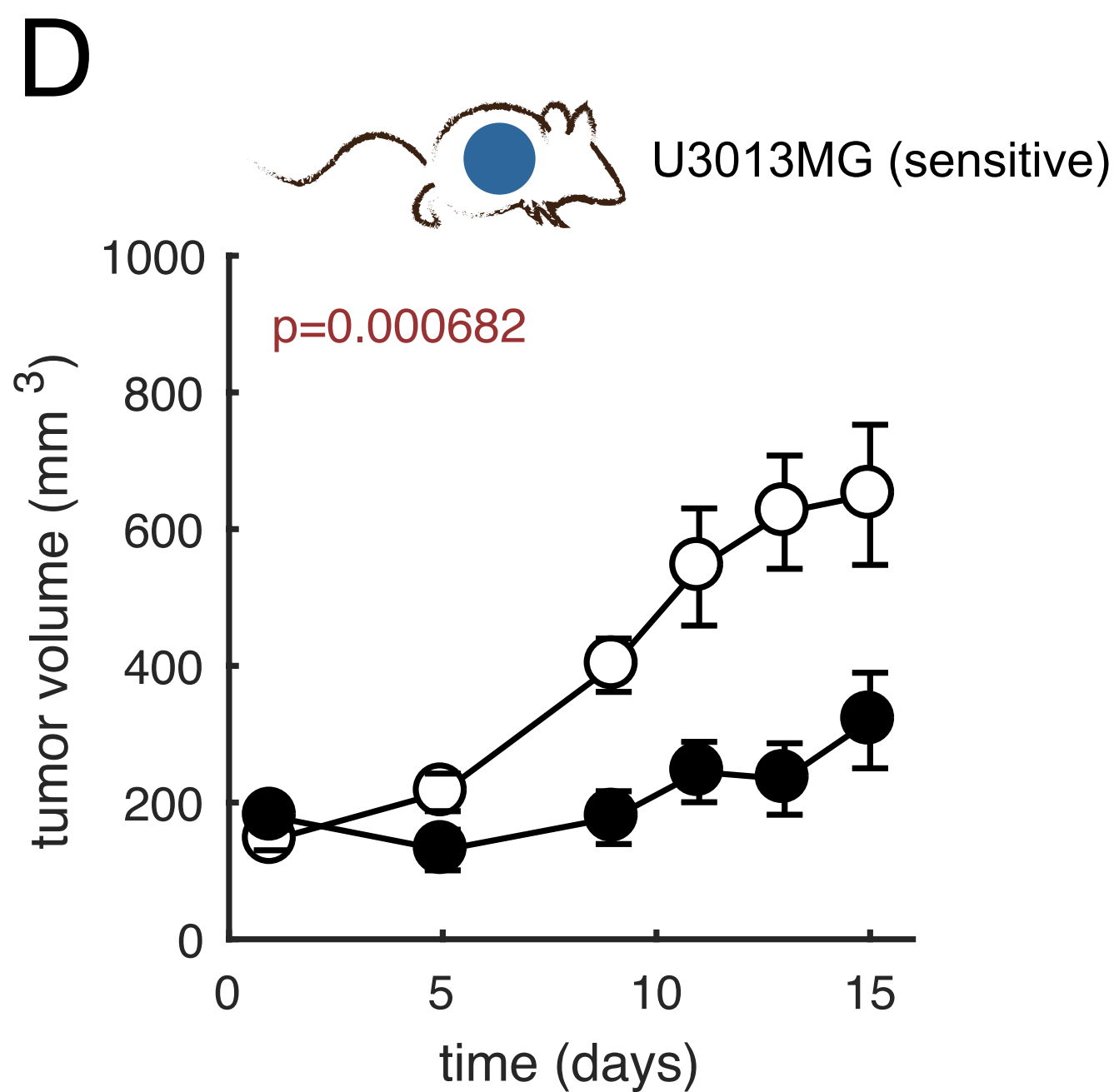
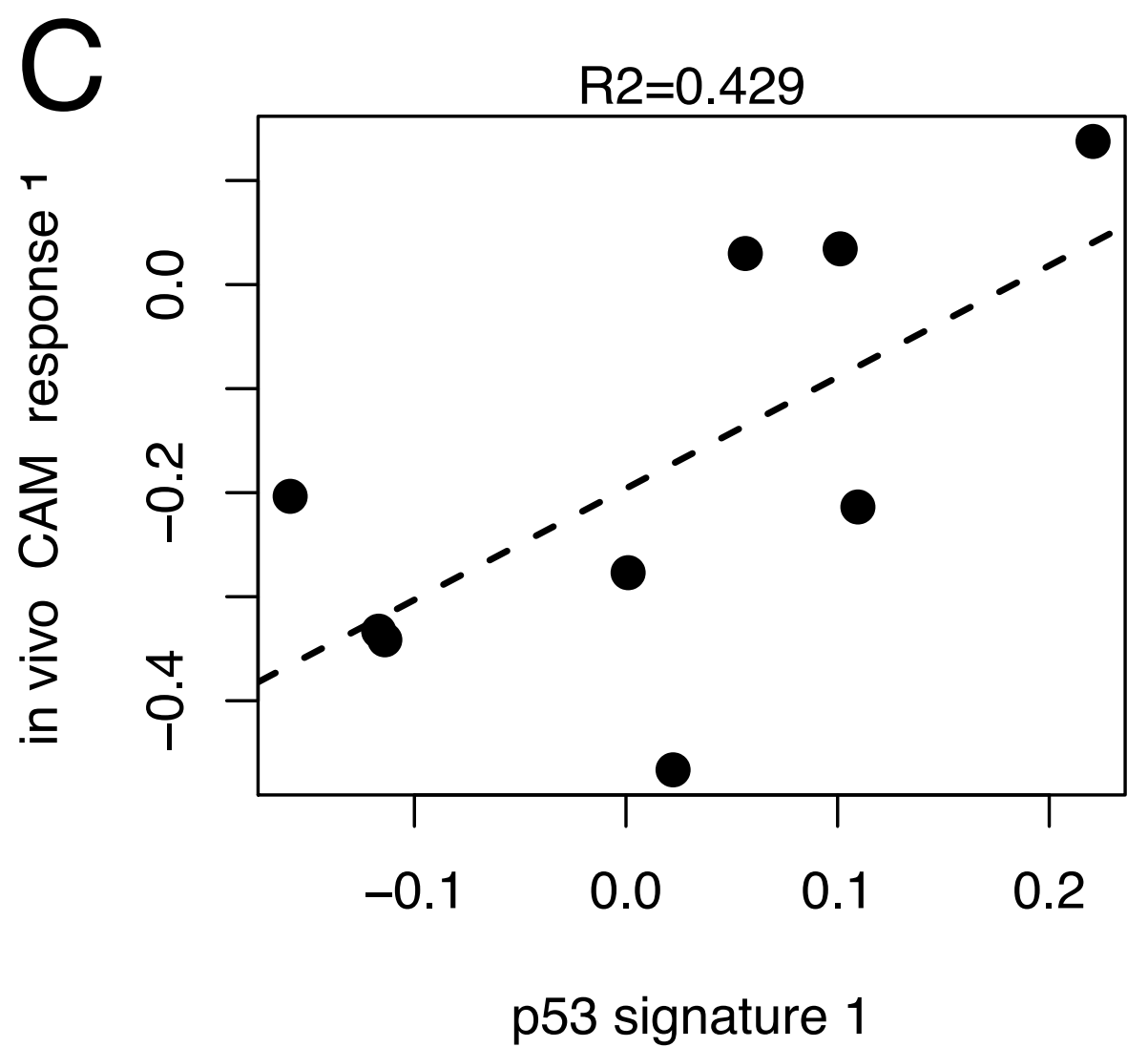
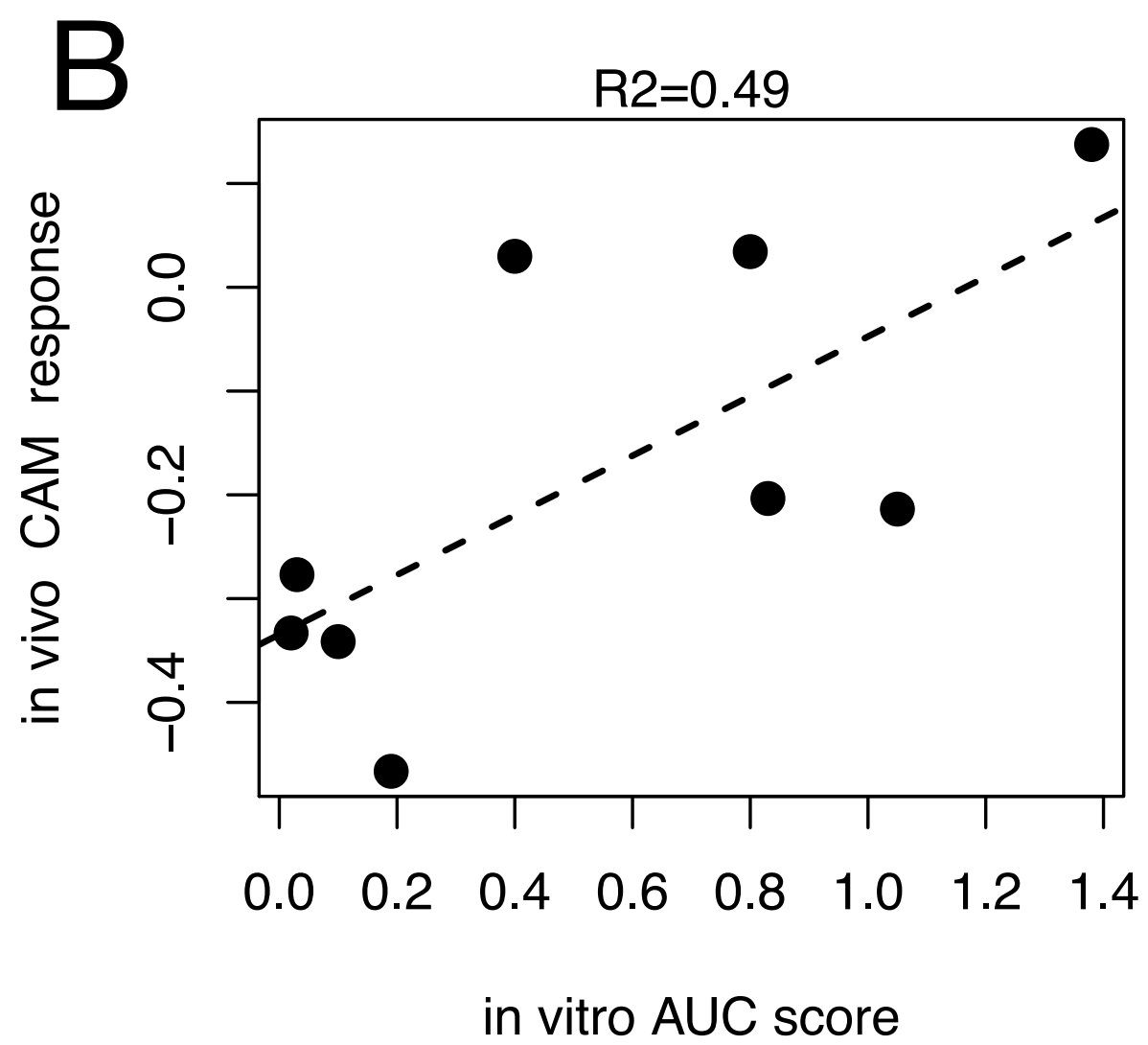
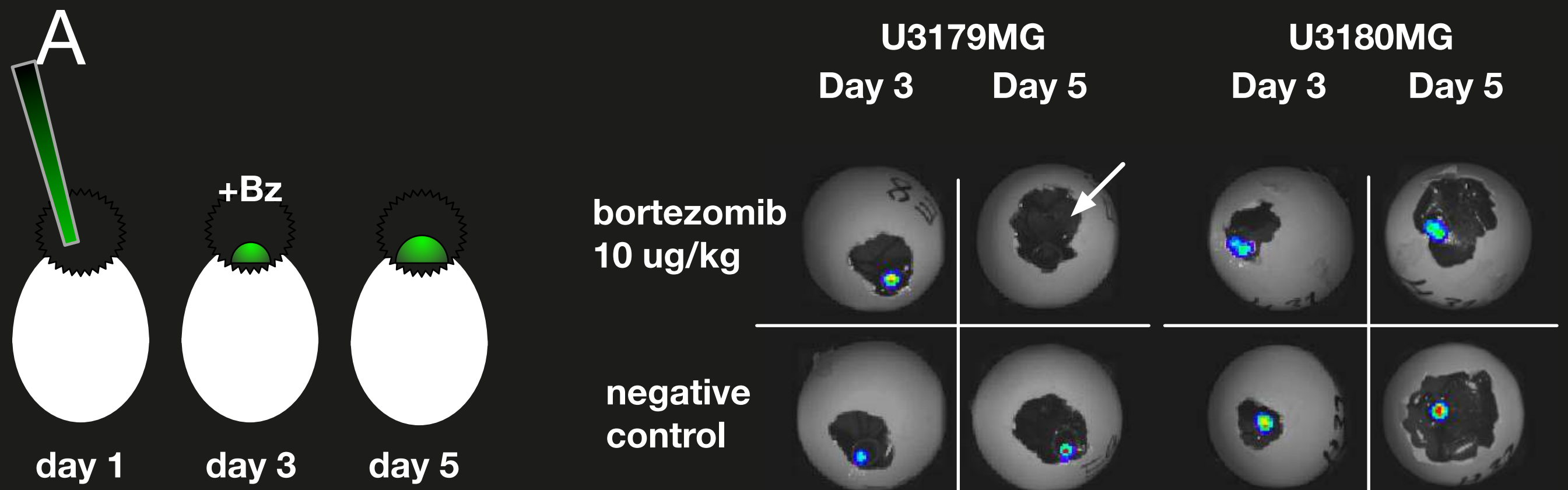
Unfolded protein response	up	6.12E-15
Reactive oxygen species	up	2.08E-11
p53 pathway	up	2.25E-11
MTORC1 signalling	up	1.00E-16

G2M checkpoint	down	9.25E-11
E2F targets	down	3.66E-05
mitotic spindle	down	4.50E-04
Epithelial to mesenchymal transition	down	8.30E-04

DIFFERENTIAL PATHWAYS (U3180MG VS U3013MG)

Reactive oxygen species pathway	diff	5.15E-02
DNA repair	diff	7.43E-02
G2M checkpoint	diff	1.81E-01

C**D****E****F****G**

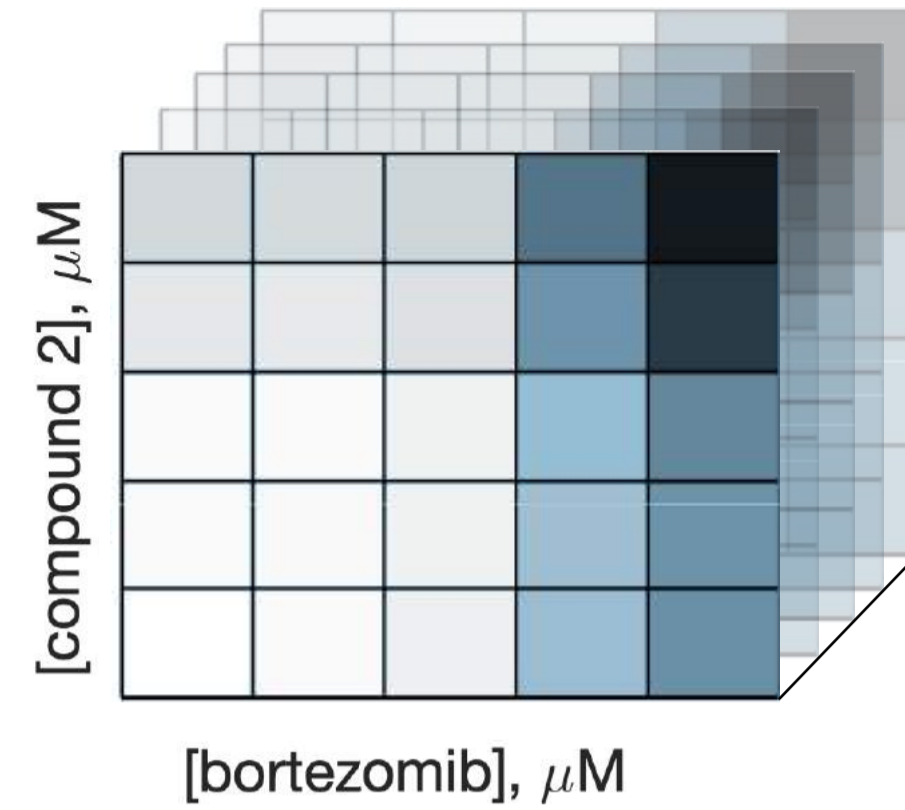


- Tumor size, vehicle treated
- Tumor size, bortezomib treated

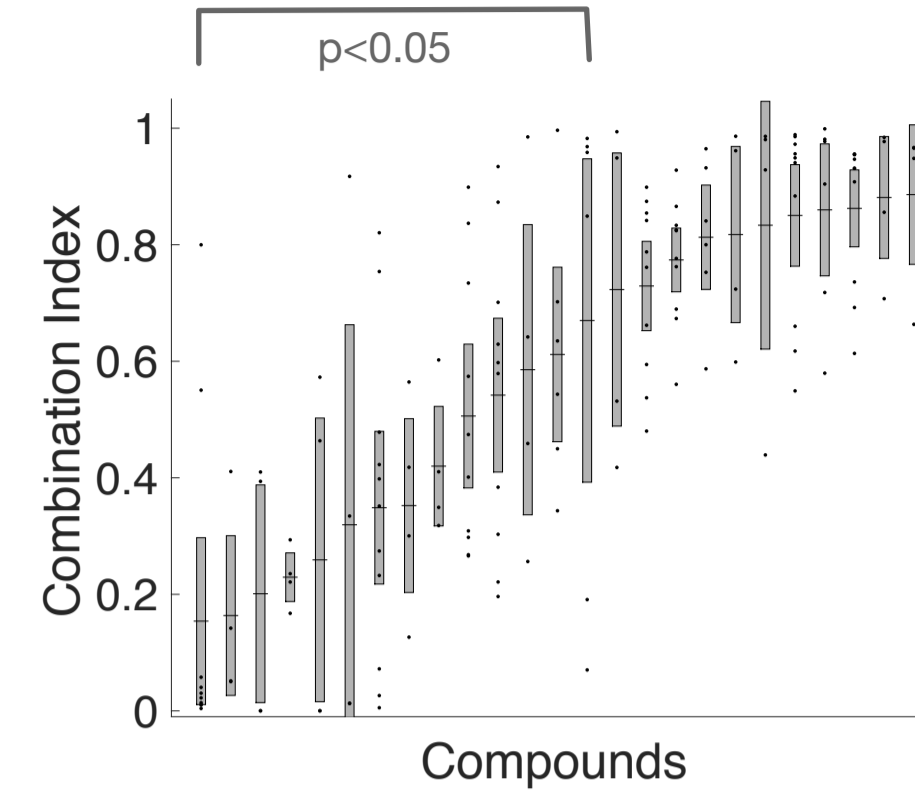
A Candidate combinations

bortezomib	
25 candidates	
(i) p53 reactivators	(n=5)
(ii) apoptosis modulators	(n=3)
(iii) cell signaling	(n=5)
(iv) anti-correlating	(n=3)
(v) redox	(n=5)
(vi) up-regulated	(n=4)

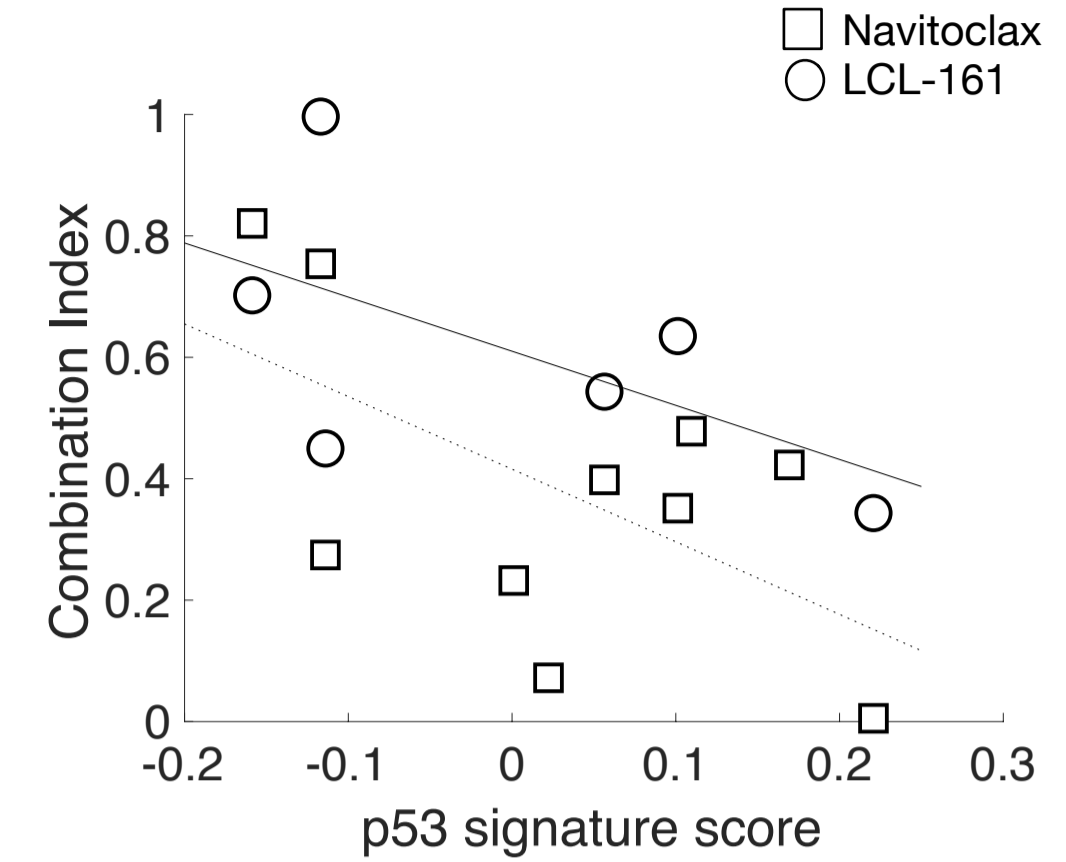
B Combination Index (CI) in multiple GBM cultures



C Endpoint 1: average CI



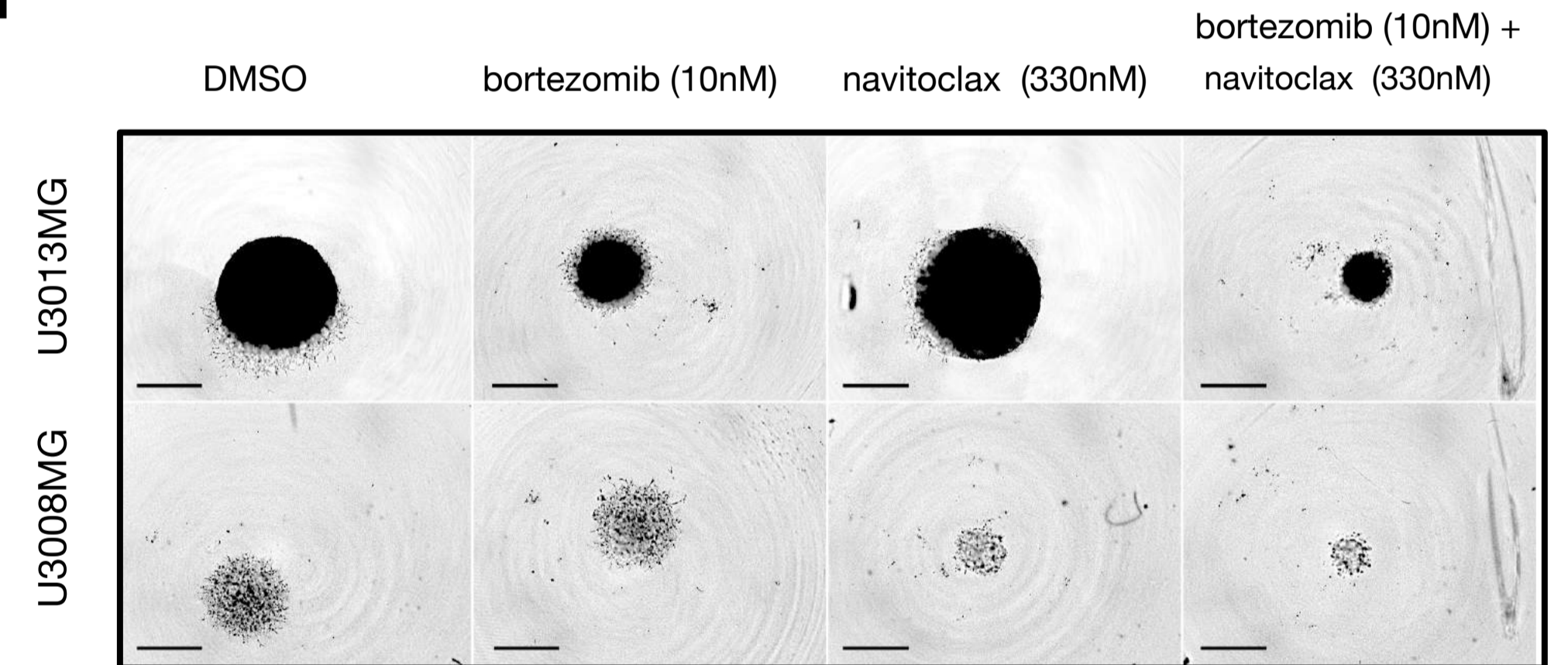
D Endpoint 2: p53 dependent CI



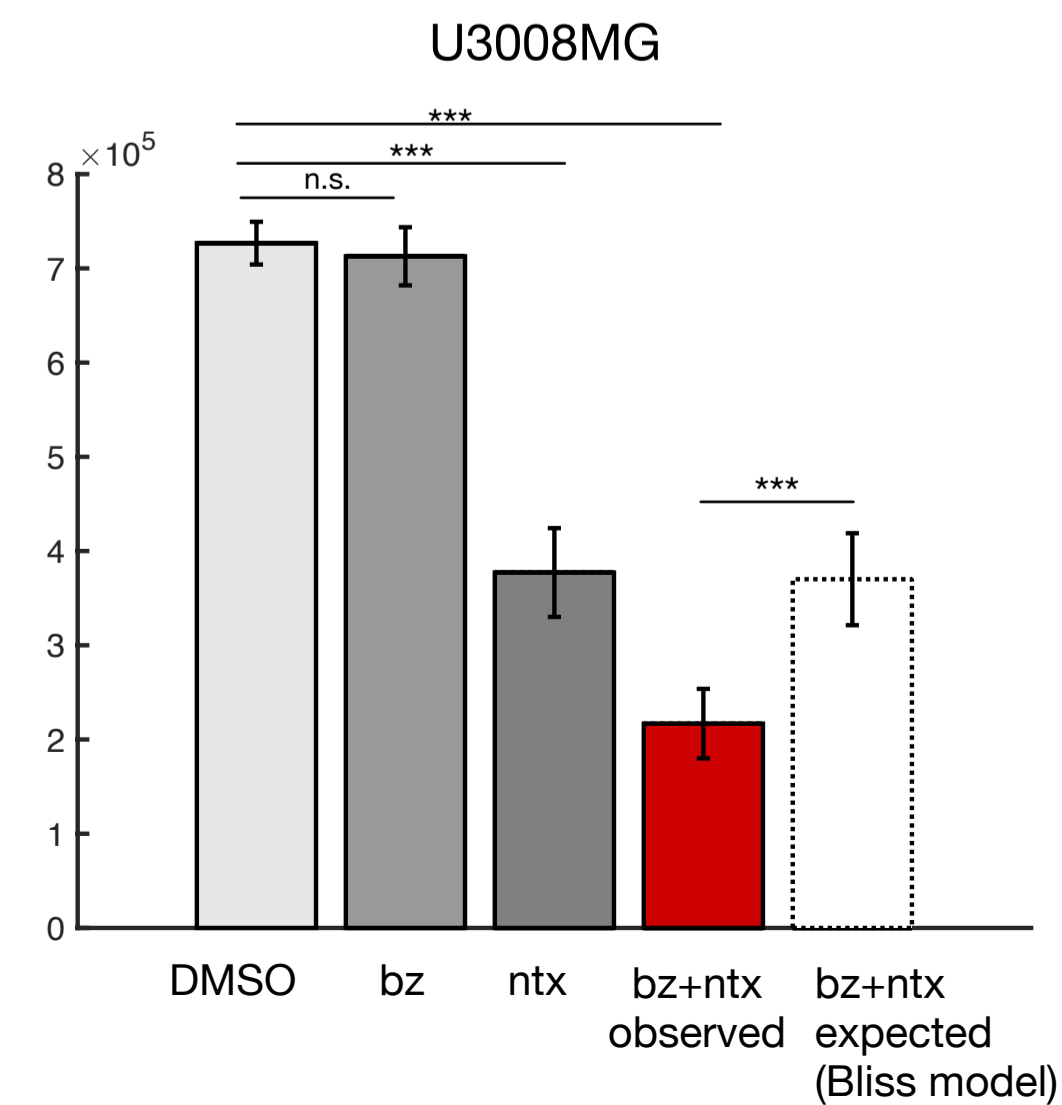
E

Drug		AUC < 1	CI < 1	p53 dependent CI		
(i)	MDM2/TP53	PM2	p=0	0.17±0.37	p=0	
	MDM2/TP53	AMG232	p=0.01	0.67±0.39	p=0.08	↘ p=0
	MDM2/TP53	VIP116	p=0	0.72±0.37	n.s.	
	TP53	PRIMA1	n.s.	0.81±0.39	n.s.	
	MDM2/TP53	nutlin-3	n.s.	0.86±0.39	n.s.	↘ p=0.036
(ii)	BCL2	navitoclax	p=0.05	0.42±0.37	p=0	↘ p=0.0086
	BCL2L1	WEHI-539	p=0	0.59±0.41	p=0.03	
	BIRC2, XIAP	LCL-161	p=0.03	0.61±0.39	p=0.03	↘ p=0.081
(iii)	CDK2	milciclib	p=0.09	0.51±0.37	p=0	
	MTOR	torin-2	p=0	0.17±0.41	p=0	↗ p=0.028
	EGFR	gefitinib	p=0	0.53±0.37	p=0	
	ERK	XMD8-96	n.s.	0.35±0.41	p=0	
	MET	volitinib	n.s.	0.85±0.41	n.s.	
(iv)	CACNA1B	cilnidipine	n.s.	0.18±0.41	p=0	
	-	nocodazole	p=0	0.23±0.41	p=0	
	-	spectinomycin	no	0.35±0.41	p=0	↘ p=0.049
(v)	-	pterostilbene	n.s.	0.3±0.41	p=0	↘ p=0.0045
	GSTA2	chloroquine	p=0	0.41±0.41	p=0	
	-	costunolide	p=0	0.85±0.37	n.s.	
	-	niclosamide	p=0	0.77±0.37	n.s.	
	ATP6V1A	bafilomycin A1	n.s.	0±19.35	n.s.	
(vi)	CDK9	alvocidib	p=0	0.86±0.37	n.s.	
	KMO	Ro61-8048	n.s.	0.76±0.41	n.s.	↘ p=0.0043
	PAK	FRAX486	p=0	0.89±0.41	n.s.	
	UGCG	DL-PDMP	n.s.	0.84±0.41	n.s.	

F



G



H

