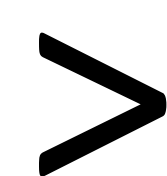


(1) Synopsis

S6K1 is implicated in the etiology of FXS, a genetic neuro-developmental disorder, and of TNBC, a highly aggressive cancer



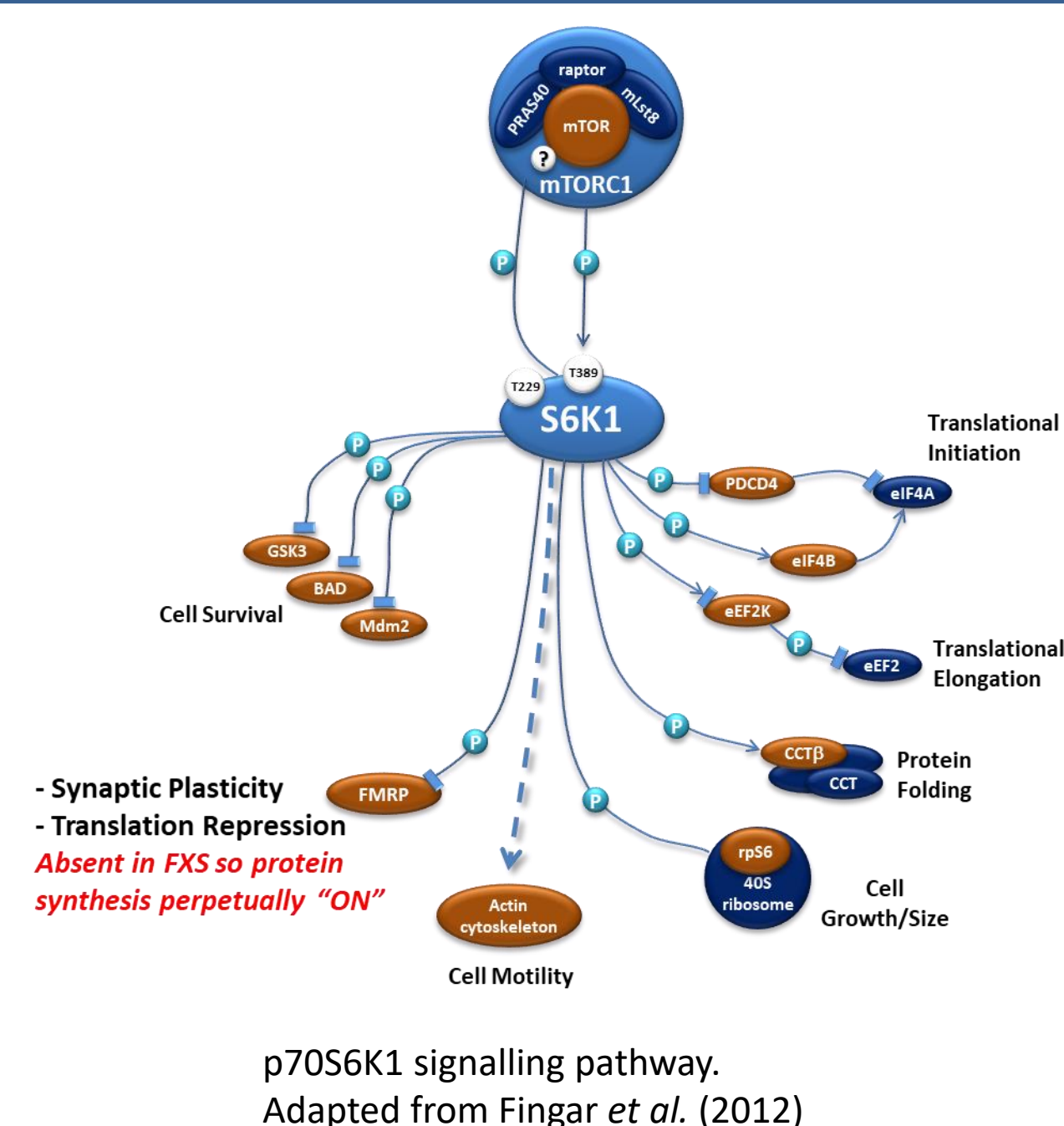
We set out to determine if small molecule S6K1 inhibitors, with the ability to reach the brain, could treat either disease



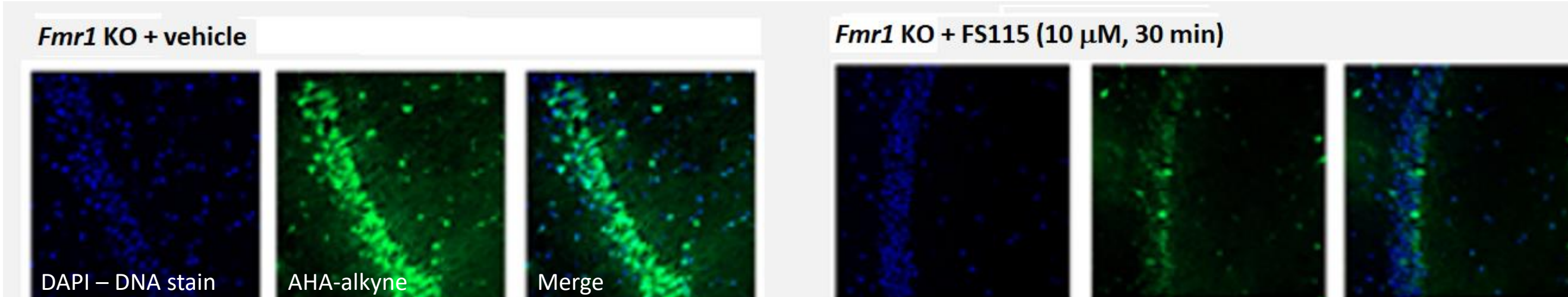
Lead FS115, a proprietary oral brain penetrant S6K1 inhibitor, shows robust efficacy in models of either disease

(2) The role of S6K1 in FXS and TNBC

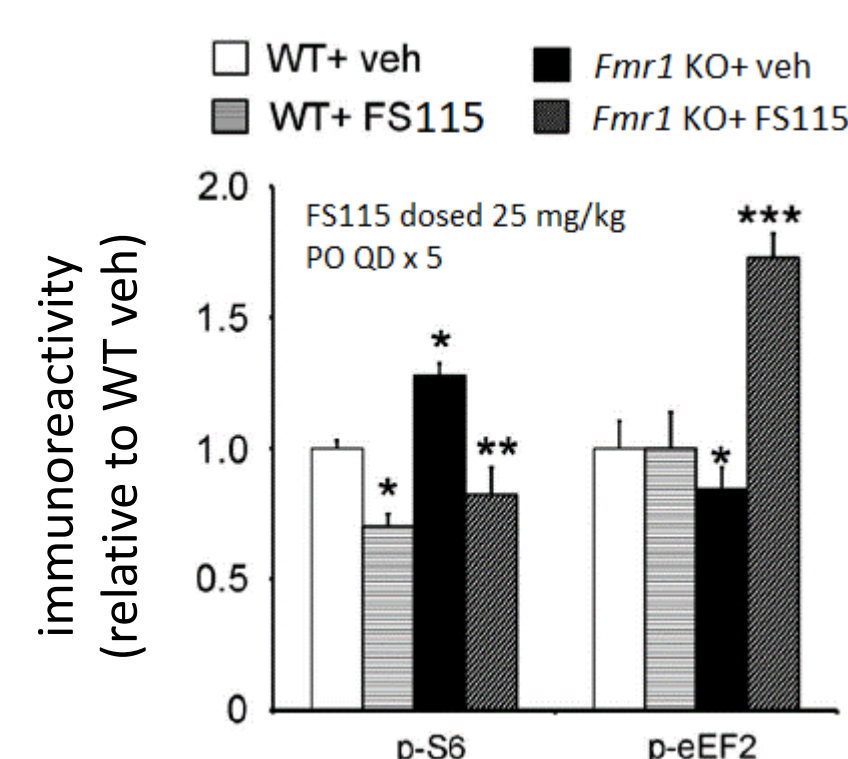
- S6 Kinase 1 (S6K1 or p70S6K1) is a Ser/Thr protein kinase of the AGC family
- An effector of the PI3K pathway and master regulator of protein translation
- In FXS, S6K1 drives excessive protein production in the brain; genetic S6K1 KO in a FXS model mouse is corrective¹
- S6K1 drives local relapse and distant metastasis in models of TNBC^{2,3}



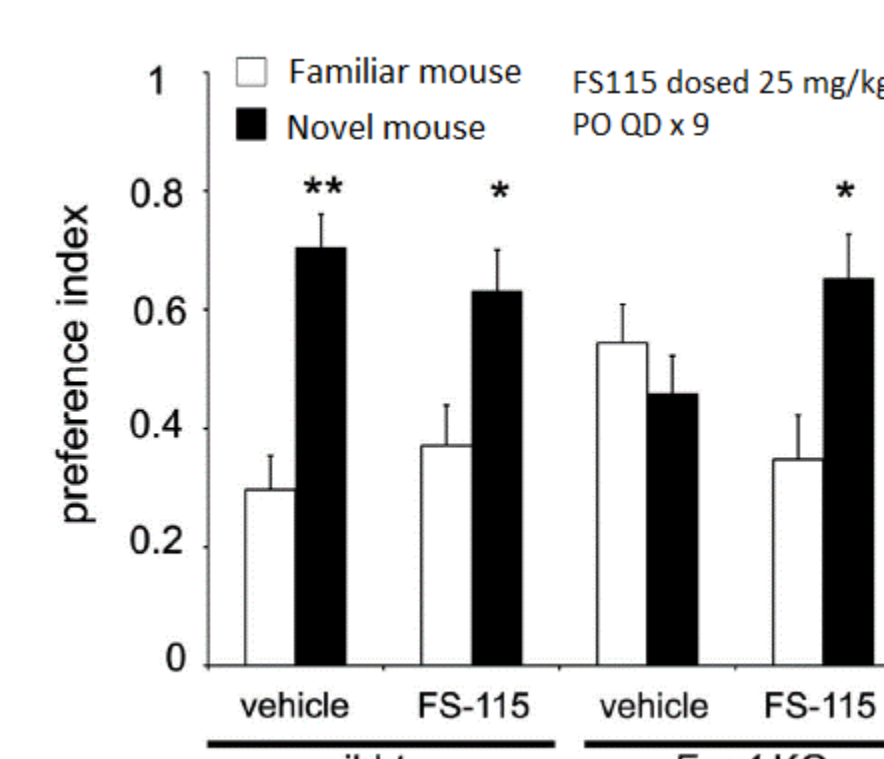
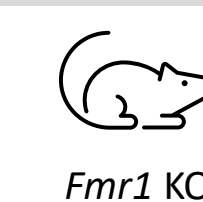
(4) Results – FS115 corrects pathology in FXS model mice⁴



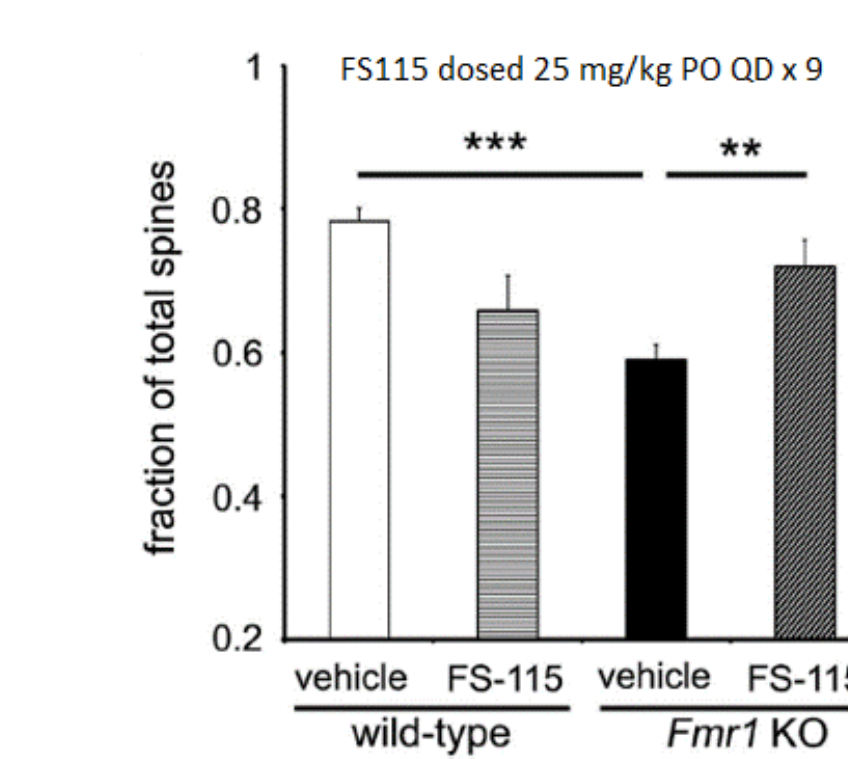
Reduction of excessive protein synthesis in hippocampal slices



in vivo

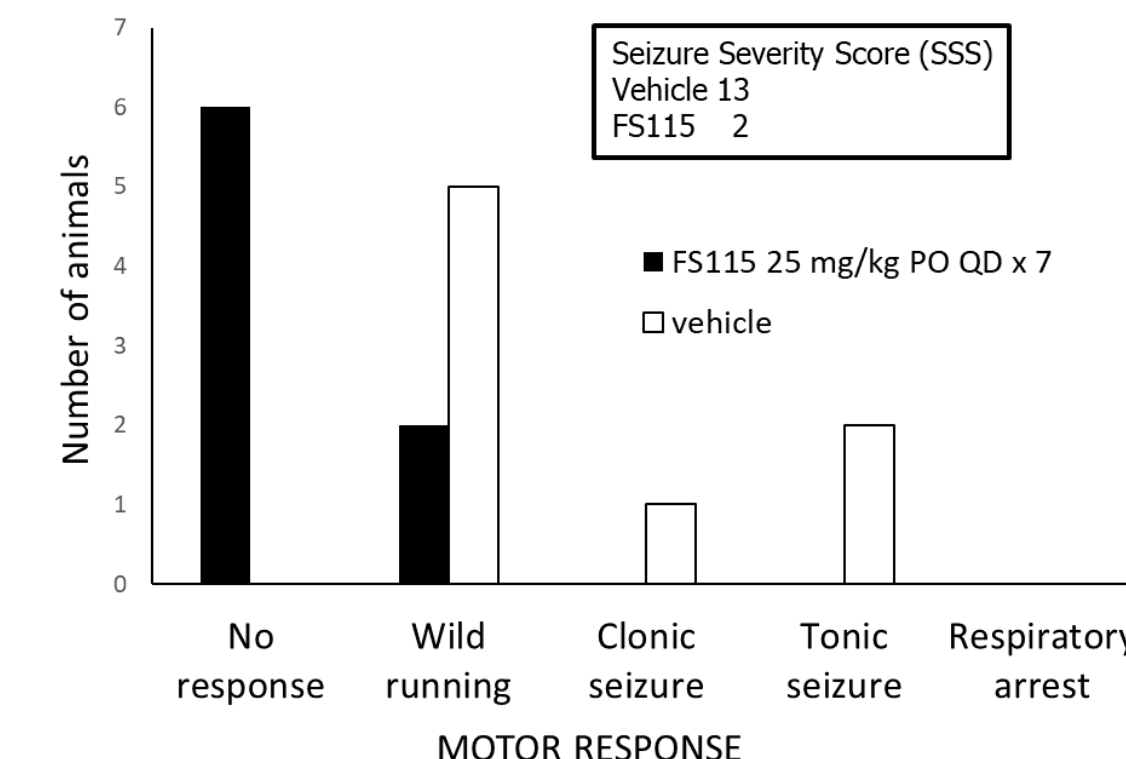


Modulation of biomarkers downstream of S6K1 in brain



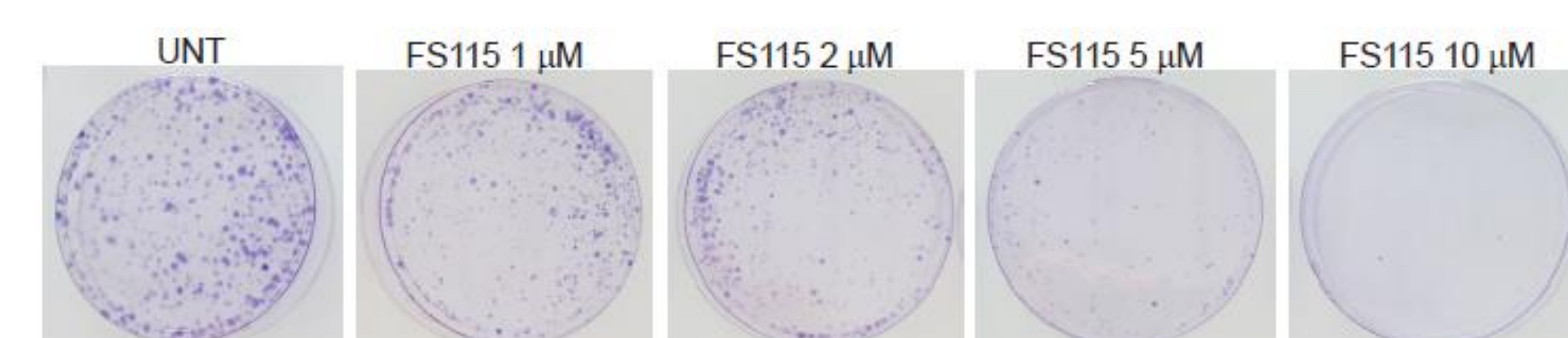
Restoration of "stubby" mature neuronal spine morphology

Social novelty model: correction of social development deficit

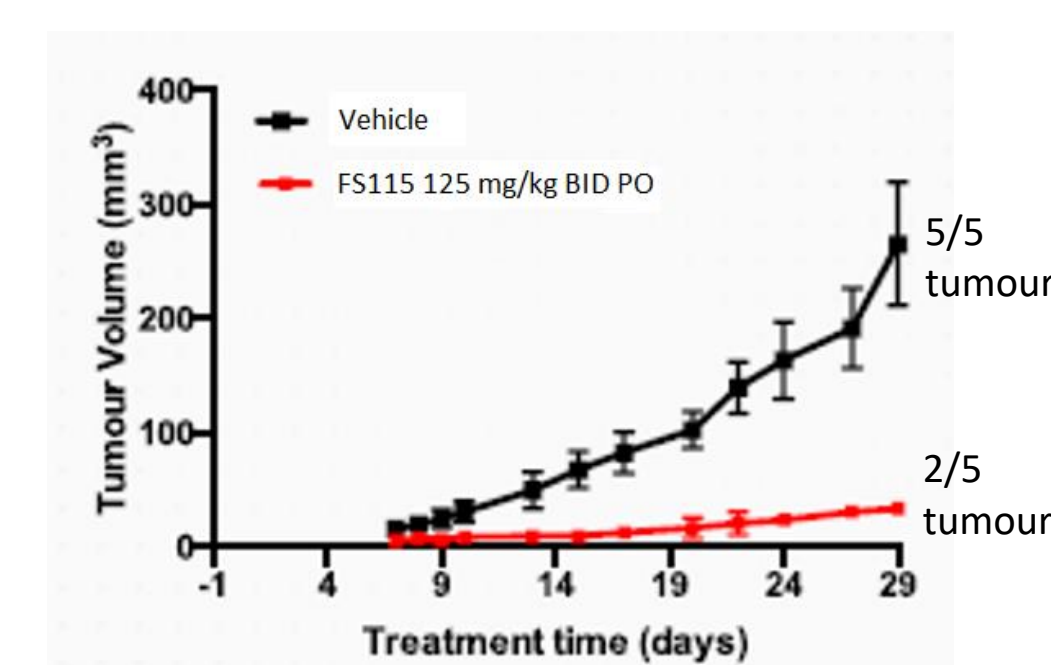


Suppression of audiogenic seizures

(5) Results - FS115 is effective in models of TNBC⁵

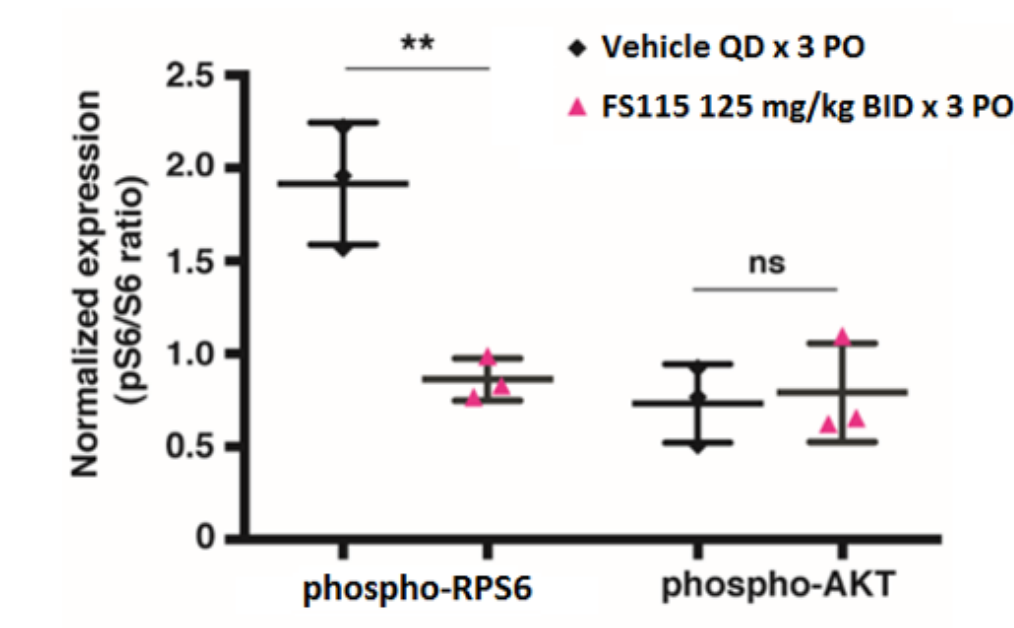


Suppressed survival of MDA-MB-231 cells in colony assay

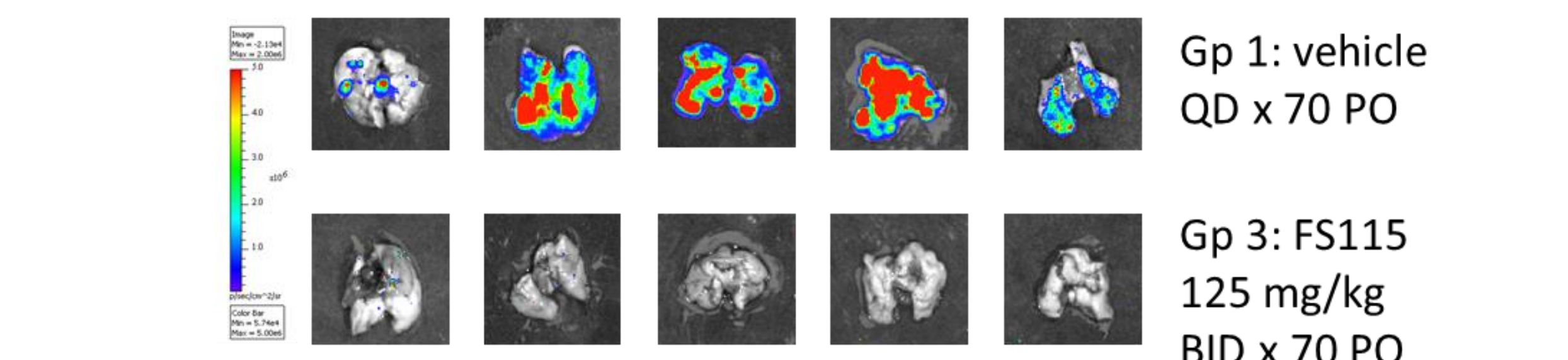


Inhibition of orthotopic MDA-MB-231 tumour initiation

in vivo

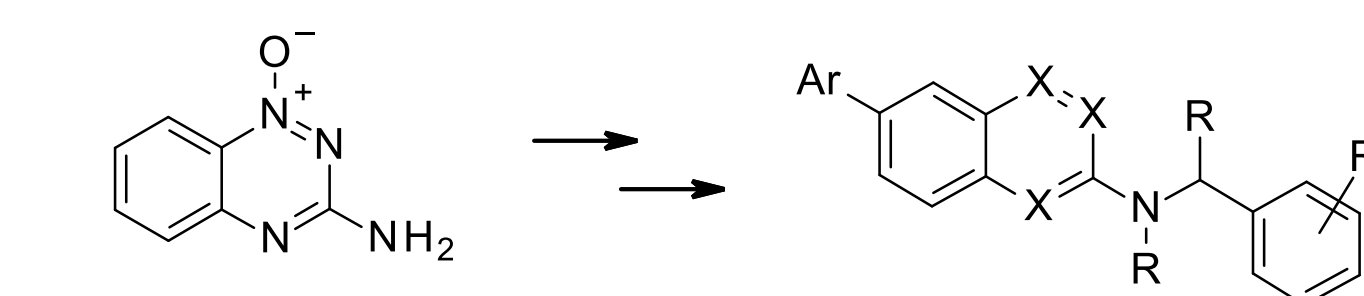


Inhibition of downstream p-RPS6 in MDA-MB-231 tumour; No p-Akt ↑



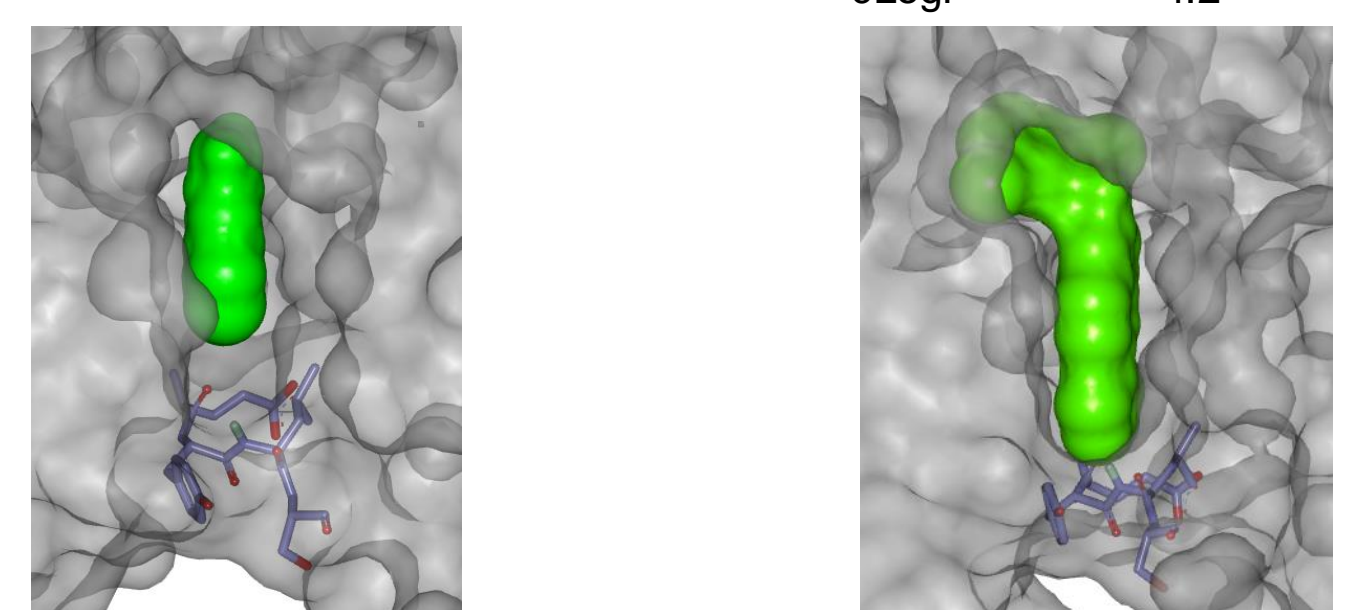
Prevention of MDA-MB-231 lung metastases after 70 days dosing

(3) FS115 – an oral brain penetrant S6K1 inhibitor



Fragment p70S6K1: 25% inh. at 200 μM

FS115 p70S6K1 IC₅₀ 0.035 μM
PSA < 70
cLogP 4.2



Compounds docked into p70S6K1 (PDB 4L31)

Assay	FS115
p70S6K1 IC ₅₀ (μM)	0.035
p70S6K2 IC ₅₀ (μM)	2.06
AKT2 IC ₅₀ (μM)	23.8
Kinase panel selectivity	12% ^a
Mouse PK	
F (%)	> 95
Cl (mL/min/kg)	25
Vd _{ss} (L/kg)	1.6
t _{1/2} PO (h)	1.6
Brain:plasma (2.6 h)	4.0
^a inhibited by ≥ 50% at 0.5 μM	