The multikinase inhibitor RXDX-105 is effective against neuroblastoma *in vitro* and *in vivo*

SUPPLEMENTARY MATERIALS

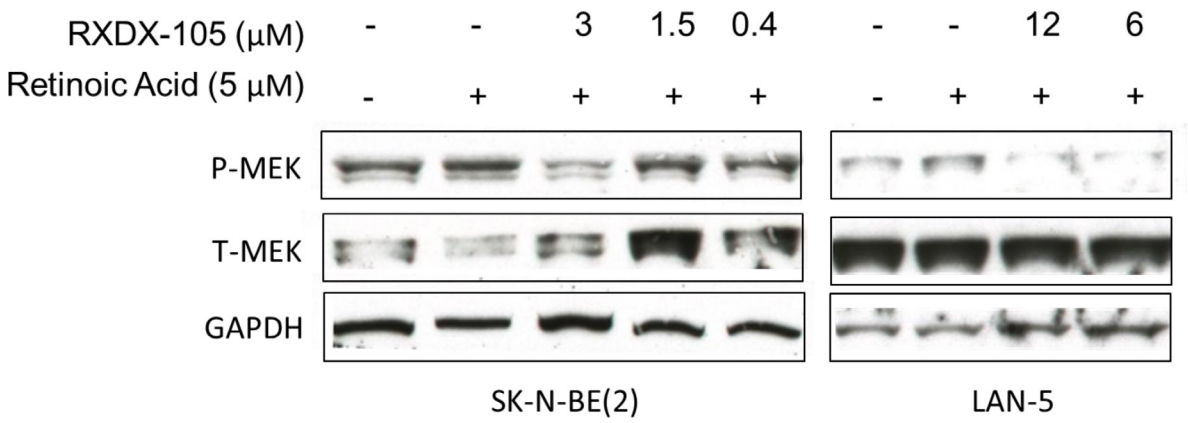
Supplementary Table 1: Biological and cytogenetic features of neuroblastoma

Cell line	MYCN Status	1p36 Del	3p26 del	11q23 del	17q21-qter unbal gain	ALK mutation	P53 mutation
CHP-134	Amplified	LOH p32.3-pter; Gain p34.3-p36.22; Loss p36.22-pter	Gain/AI p26.3	None	Gain q12-qter	WT	WT
IMR-32	Amplified	Loss p32.3-pter	Loss p12.3	cnLOH q23.1	Gain q21.2-qter	WT	WT
KELLY	Amplified	LOH p21.3-pter; Loss p36.32; Gain p36.33	Loss p26.2	Loss q23.3-qter	Gain q21.2-qter	F1174L	P177T
LA-N-5	Amplified	Loss p33-pter	None	None	Gain q21.2-qter	R1275Q	WT
SJ-NB-10	Amplified	Loss p32.2-pter	Gain p24.1-pter	cnLOH q23.1	Gain q22-qter	WT; amplified	WT
NGP	Amplified	cnLOH p32.3-pter	Gain p25.3-pter	Loss q22.1-qter	Gain q21.1-qter	WT	A159D, C141W
SK-N-AS	Non-amplified	Loss p36.22-36.32	Loss p14.2-pter	q13.4-qter	Gain q21.31-qter	WT	H168R
SK-N-BE(2)	Amplified	cnLOH p21.3-pter	Loss p14.2-pter	Gain/AI q13.1-qter	Gain q12-qter	WT	C135F
SK-N-SH	Non-amplified	None	None	None	Gain q21.31-qter	F1174L	WT

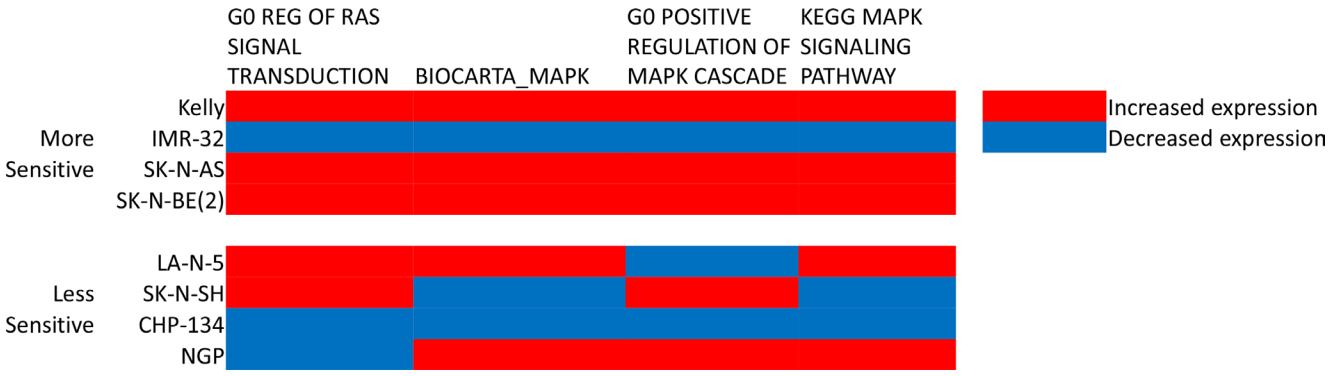
Adapted from Harenza *et. al*. [25].

Supplementary Table 2: IC50 values for inhibition of cell proliferation

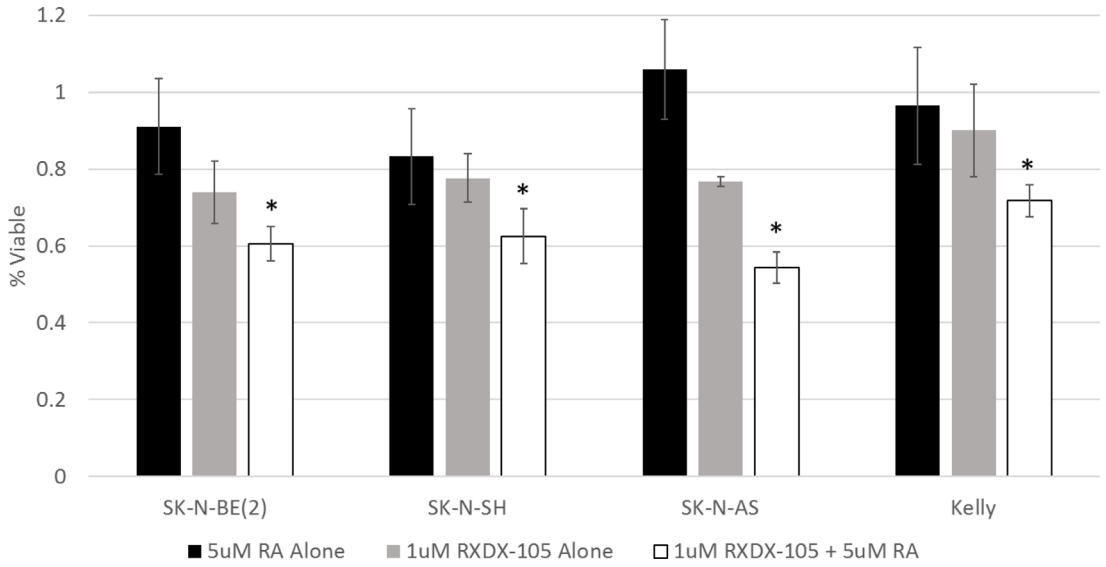
Cell line	IC 50 [μM]
Kelly	3.5
IMR-32	4.3
SK-N-AS	5.6
SK-N-BE(2)	7.8
LA-N-5	9.9
SK-N-SH	10.4
LA-155-N	12.1
LA-N-1	12.4
CHP-134	15.1
SJ-NB-10	15.4
NGP	15.9



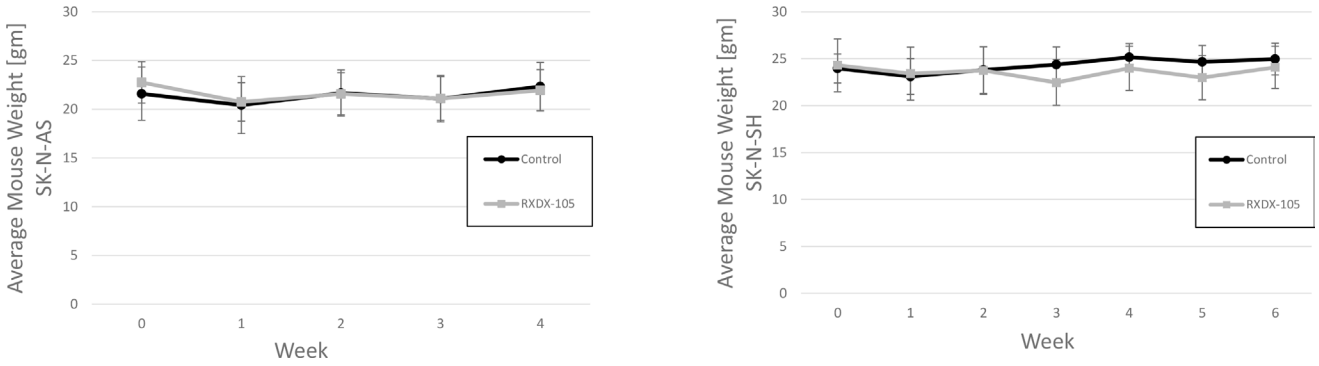
Supplementary Figure 1: RXDX-105 inhibits target kinases and intracellular signaling pathways. Neuroblastoma cell lines were treated with either vehicle or decreasing doses of RXDX-105 for 24 hours in combination with 5 μM 13-*cis*-retinoic acid. Cells were lysed and Western blots were performed to assess MEK expression and phosphorylation. GAPDH expression is shown as a loading control.



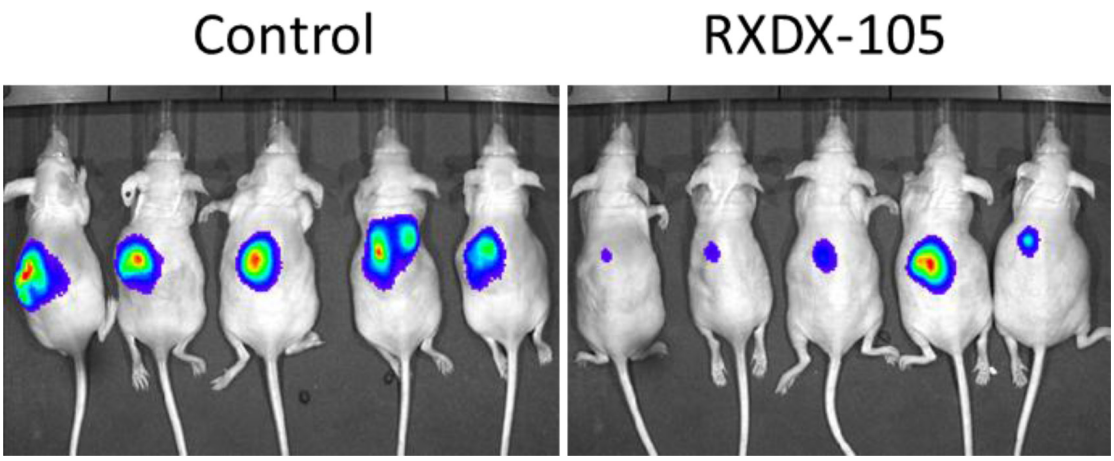
Supplementary Figure 2: Sensitivity to RXDX-105 is related to RAS-MAPK gene expression. Neuroblastoma cell line gene expression from [25] was assessed to evaluate for differences in gene pathway expression using pathways from the Molecular Signatures Database [36] underlying relative cell line sensitivities to RXDX-105. Cell lines with IC50 values less than 8 μM were considered more sensitive, while cell lines with IC50 values above 8 μM were considered less sensitive. Increased pathway gene expression is shown in red, while decreased pathway gene expression is shown in blue.



Supplementary Figure 3: RXDX-105 efficacy is enhanced when combined with 13-*cis*-retinoic acid. A panel of neuroblastoma cell lines were treated with 1 µM RXDX-105 alone or in combination with 5 µM 13-*cis*-retinoic acid for 72 hours and cell viability was assessed with an alamarBlue™ assay. Cell viability with each condition is shown.



Supplementary Figure 4: Mouse weight during RXDX-105 treatment. Mice being treated with RXDX-105 or vehicle control were weighed weekly during treatment and weights were plotted on graphs.



Supplemental Figure 5: RXDX-105 inhibits tumor xenograft growth. Bioluminescent images of orthotopic neuroblastoma xenograft tumors in mice treated for six weeks with vehicle alone (left) or with RXDX-105 (right).