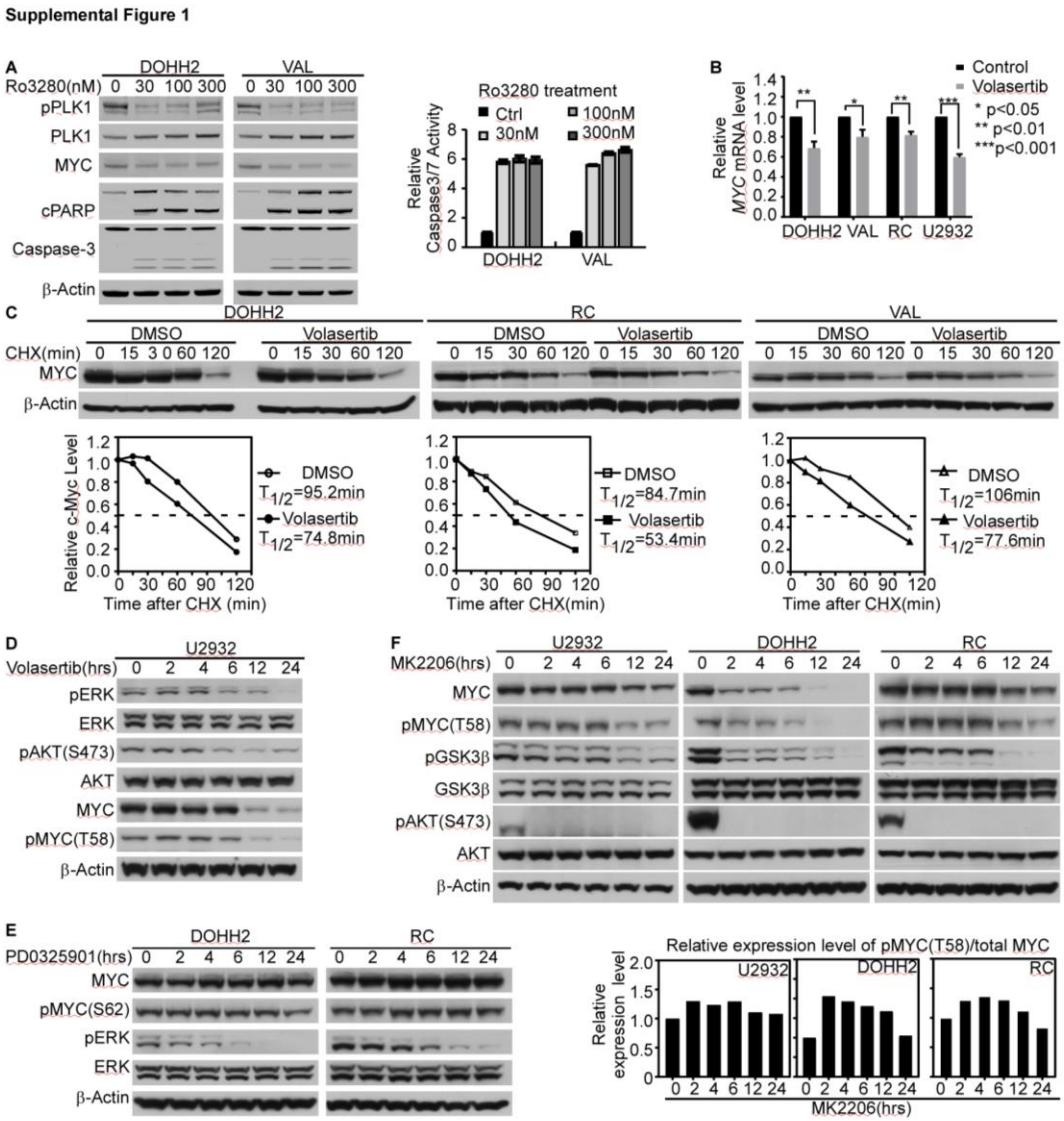
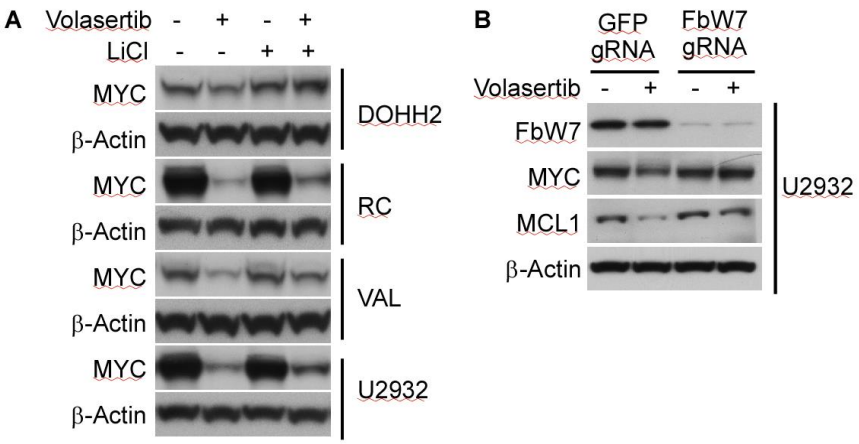
Supplemental figures and figure legends



Supplemental Figure 1. PLK1 is necessary to sustain an AKT-GSK3β-MYC circuit in DHL. (**A**) *Left*, western blot analyses demonstrate that treatment of the indicated DHL cells with the PLK1 inhibitor Ro3280 (24 hours) provokes reductions in MYC protein levels, PLK1 phosphorylation, and PARP cleavage. *Right panel*, Ro3280 treatment (24 hours) provokes apoptosis of DOHH2 and VAL DHL cells as judged by caspase-3/7 activation. (**B**) Volasertib treatment (20 nM, 24 hours) induces modest reductions changes of *MYC* mRNA levels in DHL cells. (**C**) Turnover of MYC protein in DHL cells (DOHH2, RC, and VAL) with either control DMSO or volasertib treatment (20 nM, 3 hours) +/- 15 minute pre-treatment with cycloheximide (CHX, 100 μg/ml). Lysates were prepared at the indicated times following the addition of CHX and probed with the indicated antibodies (*upper panels*) and MYC levels were quantified by LICOR, and were normalized to β-actin (*lower panels*). (**D**) Immunoblots documenting Volasertib-induced reductions in activation of ERK1/2 and AKT, and in pT58-MYC phosphorylation in U2932 DHL cells. (**E**) Efficient ERK1/2 inhibition in DHL cells (see pERK panel) by

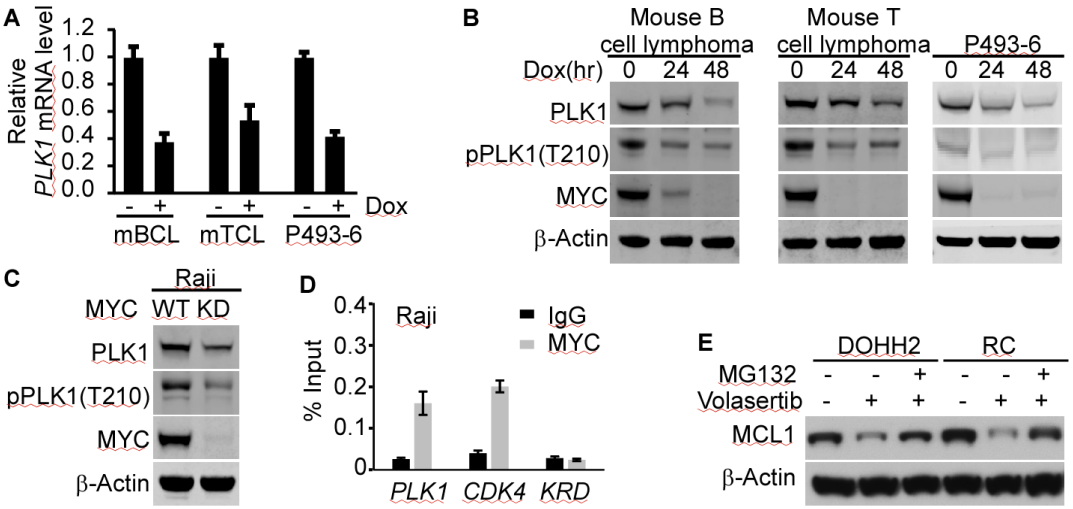
treatment with the inhibitor PD0325901 (10 nM) has no effect on MYC phosphorylation at S62 or on total levels of MYC protein in DHL cells. (**F**) Immunoblots documenting the repressive effects of efficient inhibition of AKT by MK2206 (see pS473-AKT panels) on levels of MYC, pT58-MYC, pGSK3β, and total GSK3β in the indicated DHL cells. Data shown in (**A-F**), are representative or means ± SD of at least 3 independent experiments.

Supplemental Figure 2



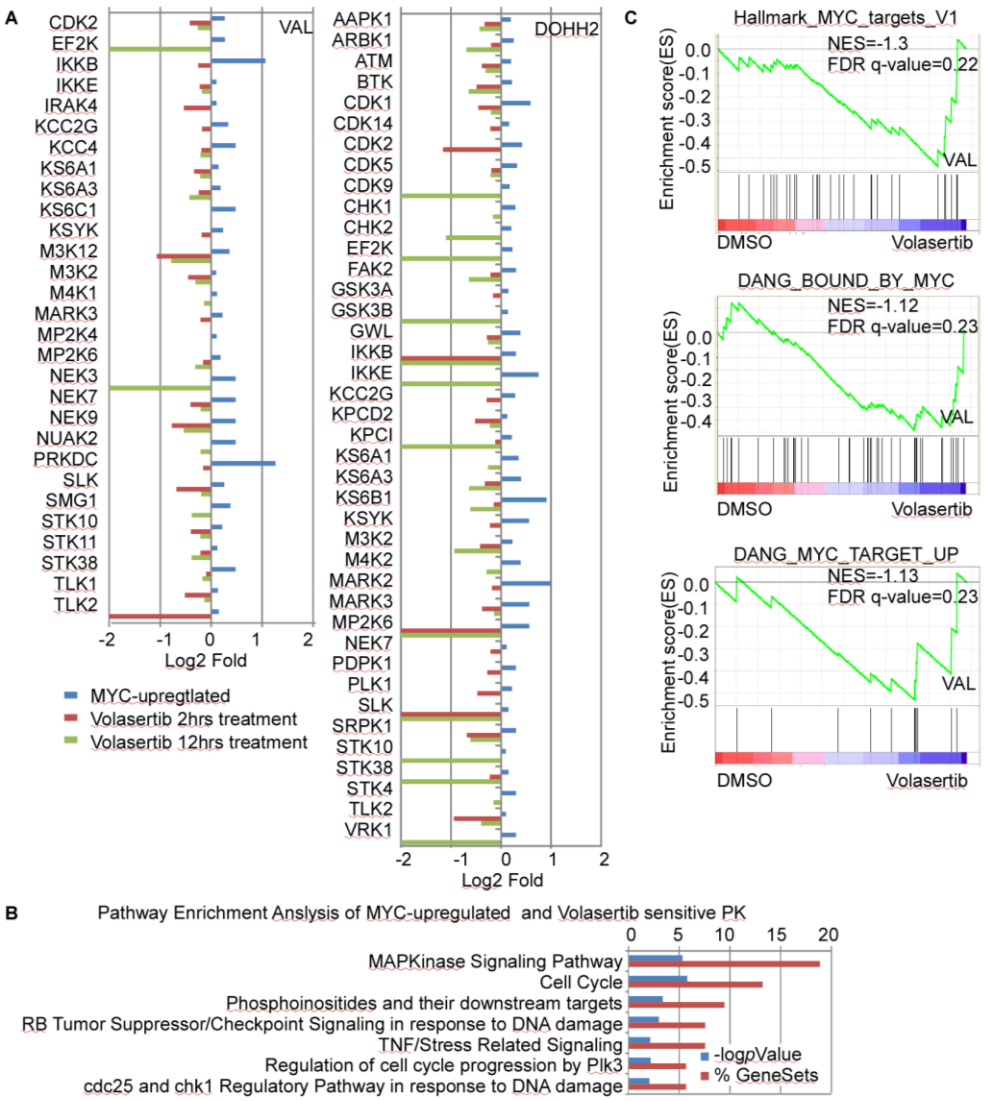
Supplemental Figure 2. Inhibition of GSK3β signaling or FBW7 impairs reductions of MYC protein provoked by Volasertib. (**A**) GSK3β inhibition provoked by lithium chloride (LiCl) treatment (10 mM) impairs Volasertib-induced reductions in MYC protein in DHL cells. **B**. Knockout of *FBW7* impairs Volasertib-induced reductions in MYC protein levels. Data shown in **A** and **B** are representative of at least 3 independent analyses.

Supplemental Figure 3



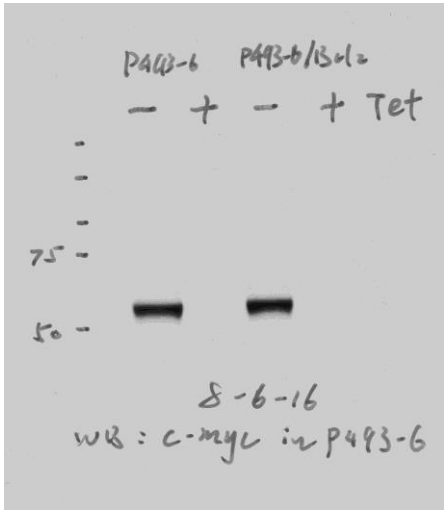
Supplemental Figure 3. MYC controls *PLK1* transcription in lymphoma cells. (**A**) *MYC* depletion suppresses *PLK1* mRNA levels in human B-lymphoma (P493-6) and mouse B and T lymphoma cells (mBCL, mTCL) bearing a tetracycline (Dox)-repressible *MYC* transgene. mRNAs were measured 24 hours after addition of Dox to these cells. (**B**) Immunoblots documenting that MYC depletion by Dox treatment of P493-6, mBCL or mTCL lymphoma cells triggers reductions in PLK1 protein levels and in the levels of active pT210-PLK1. (**C**) MYC knockout-knockdown in Raji BL by CRISPR/cas9 editing leads to marked reductions in PLK1 protein and phospho-PLK1 levels. (**D**) ChIP assays showing a significant increase in MYC recruitment to the E-box motif of *PLK1* as well as to the promoter region of the known MYC target *CDK4* in Raji BL cells. ChIP with immunoglobin G (IgG) isotype control antibody showed MYC binding was specific; *KRD* ChIP is a negative (i.e., a non-MYC regulated) control gene. (**E**) Volasertib-induced reductions in MCL-1 protein levels are blocked by pre-treatment with the proteasome inhibitor MG132. **A-E** are representative of, or the mean ± SD of, at least 3 independent experiments.

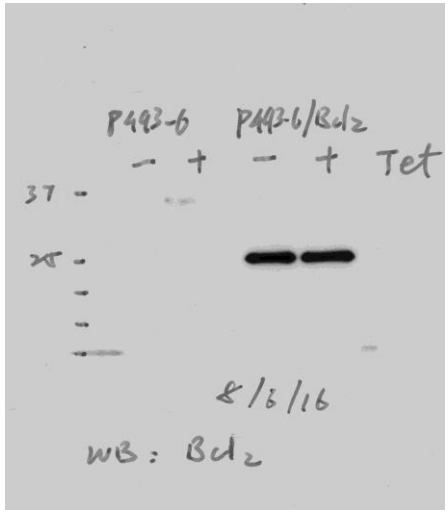
Supplemental Figure 4



Supplemental Figure 4. PLK1 inhibition disables the MYC-directed transcriptome and kinome in DHL. (**A**) Overlapping MYC-upregulated and volasertib-sensitive kinases in DHL. (**B**) Pathway enrichment analysis of MYC-upregulated and volasertib-sensitive protein kinases from (A). (**C**) GSEA analysis shows that changes in the ABPP profile provoked by volasertib treatment in VAL DHL cells are negatively related to the HALLMARK_MYC_TARGETS_V1 signature and CANG_BOUND_BY_MYC, and to DANG_MYC_TARGETS_UP gene sets from Molecular Signatures Database.

Fig. 1 A


P493-6
P493-6/Bcl2
– + – + Tet
75
50
8-6-16
WB: c-myc in P493-6


P493-6
P493-6/Bcl2
– + – + Tet
37
8/6/16
WB: Bcl2

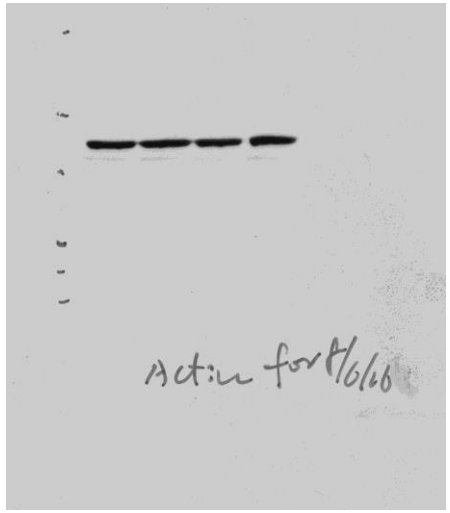
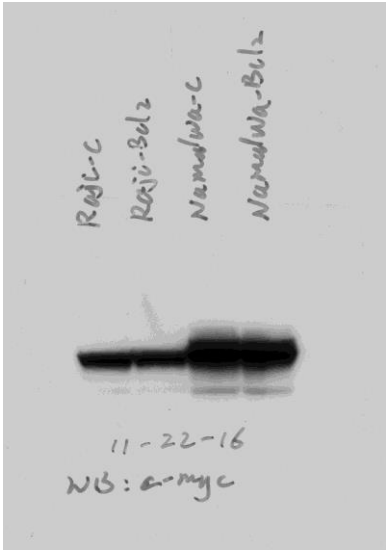
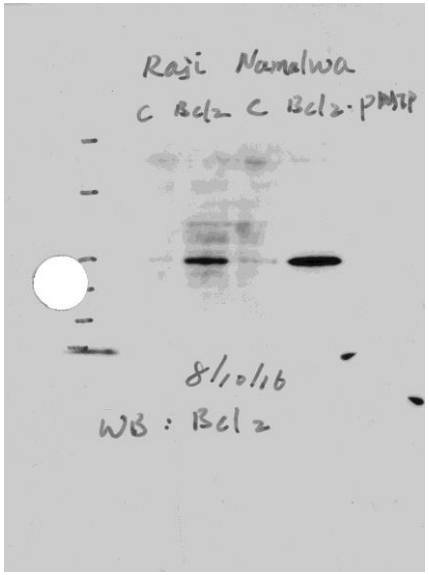

Actin for 8/6/16

Fig.1 B


Raji-C
Raji-Bcl2
Namalwa-C
Namalwa-Bcl2
11-22-16
WB: c-myc


Raji Namalwa
C Bcl2 C Bcl2-pMXP
8/10/16
WB: Bcl2

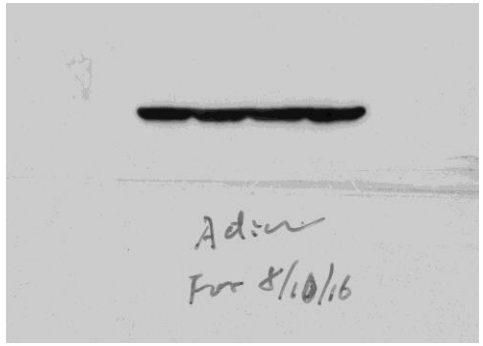
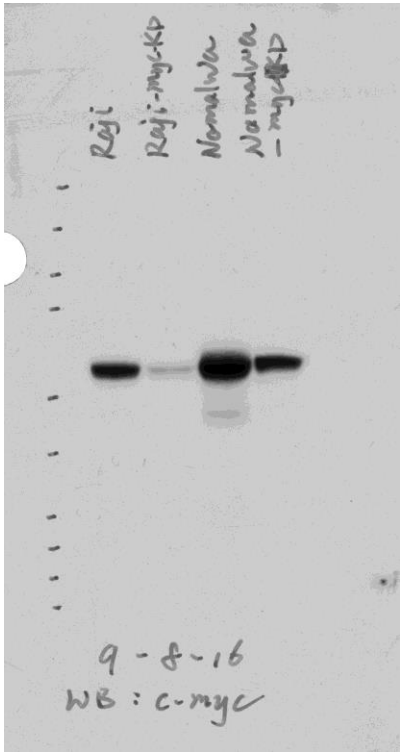
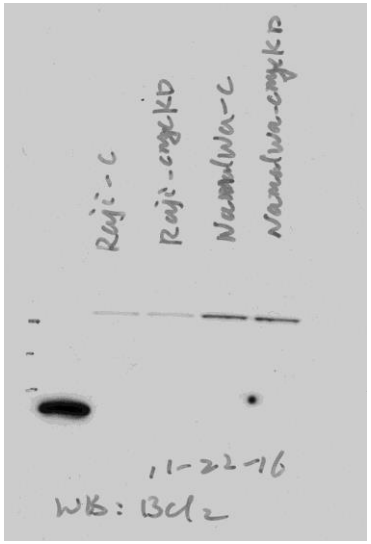

Actin
For 8/10/16

Fig. 1 C


Raji
Raji-myc-KD
Namalwa
Namalwa
-myc-KD
9-8-16
WB: c-myc


Raji-c
Raji-empty-KD
Namalwa-c
Namalwa-empty-KD
11-22-16
WB: Bcl2

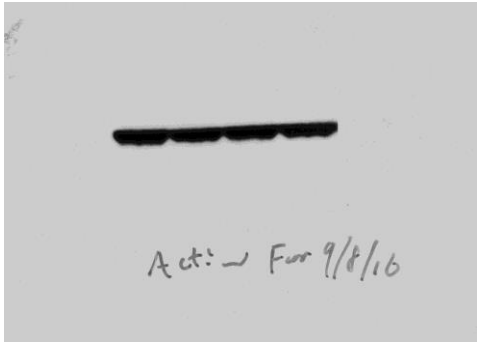
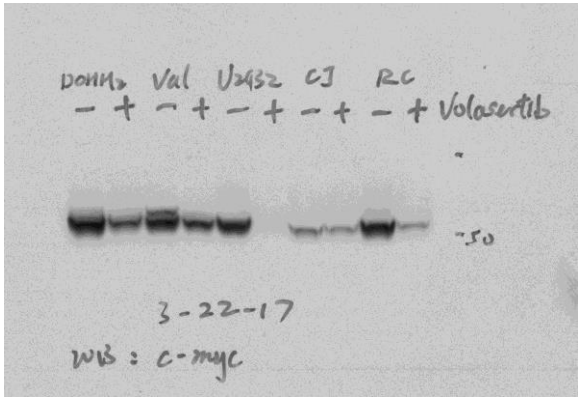

Actin Four 9/8/16

Fig.3 A


DOHH2 Val U2432 CJ RC
− + − + − + − + − + Volasertib
-50
3-22-17
WB : c-myc

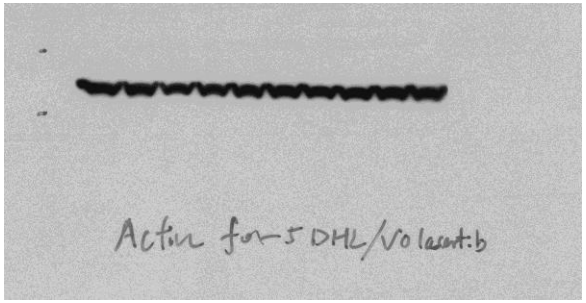
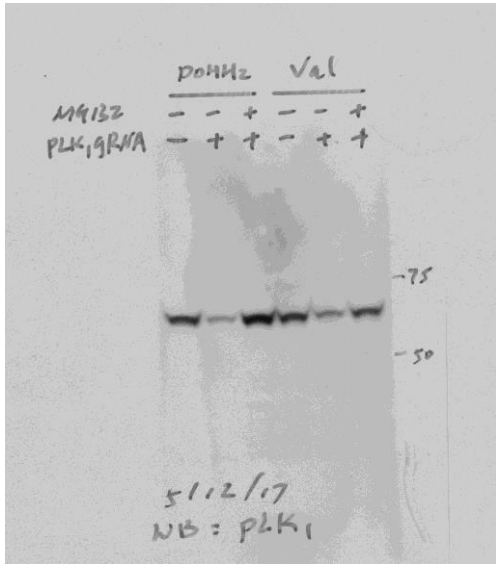
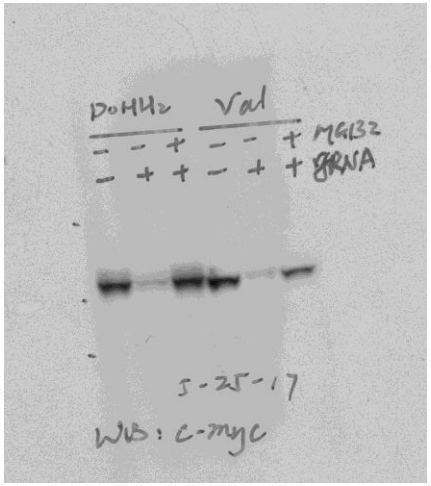

Actin for SDHL/Volasertib

Fig. 3 B


DOHH2 Val
MG132 − − + − − +
PLK1gRNA − + + − + +
-75
-50
5/12/17
WB : PLK1


DOHH2 Val
− − + − − + MG132
− + + − + + gRNA
5-25-17
WB : c-myc

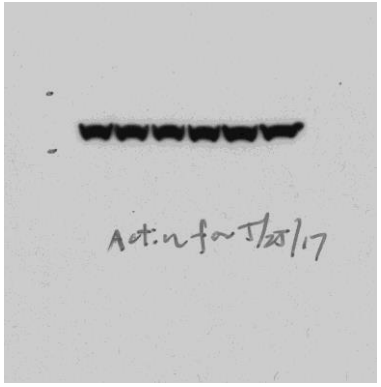
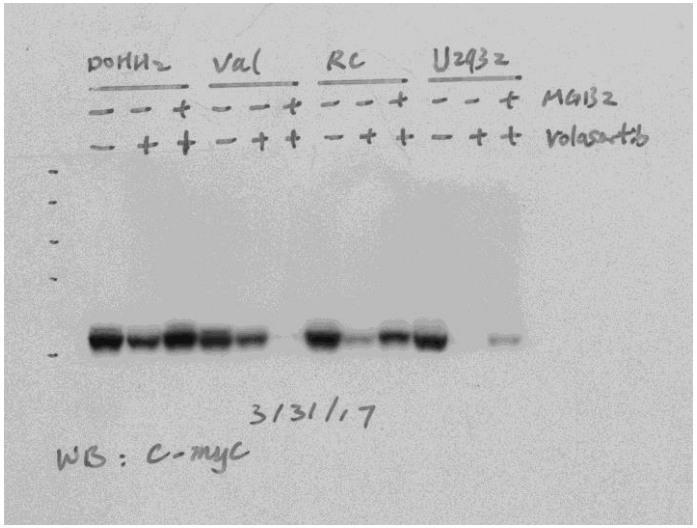
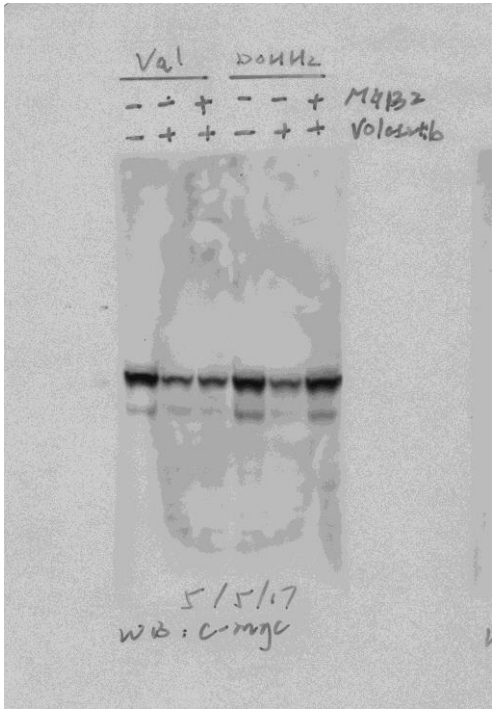
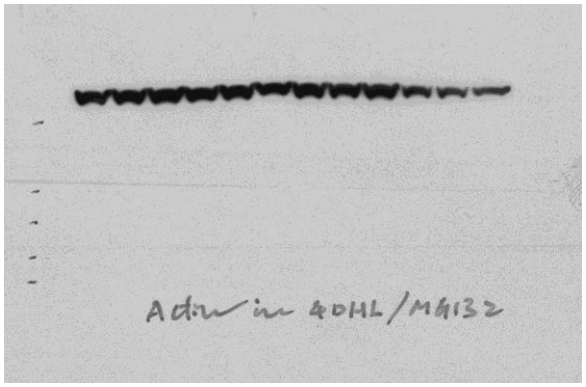

Actin for 5/25/17

Fig.3 C


DOHH2
Val
RC
U2932
MG132
Volasertib
3/31/17
WB : C-myc


Val
DOHH2
MG132
Volasertib
5/5/17
WB : C-myc


Actin in 4OHL/MG132

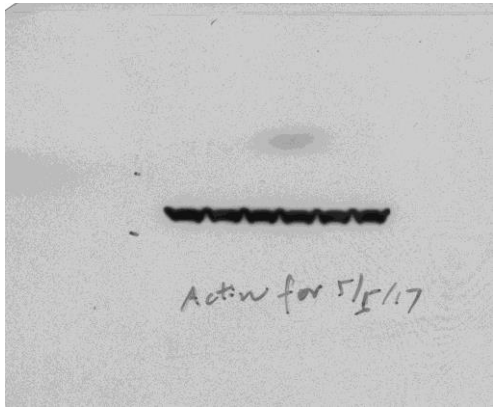
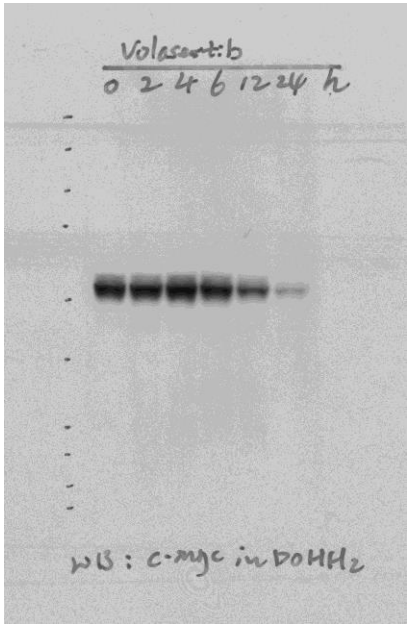
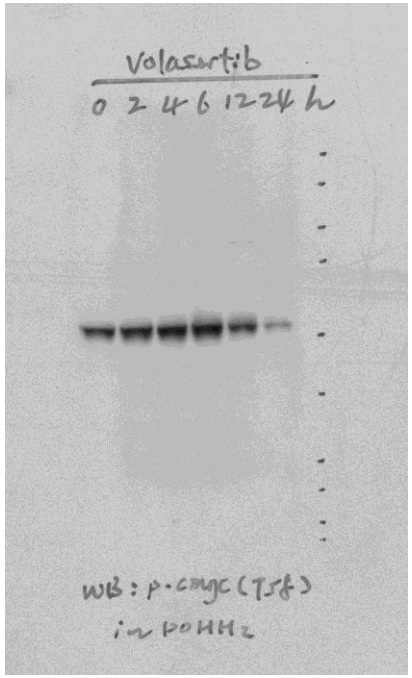

Actin for 5/5/17

Fig. 3 D


Volasertib
0 2 4 6 12 24 h
WB : c-myc in DOHH2


Volasertib
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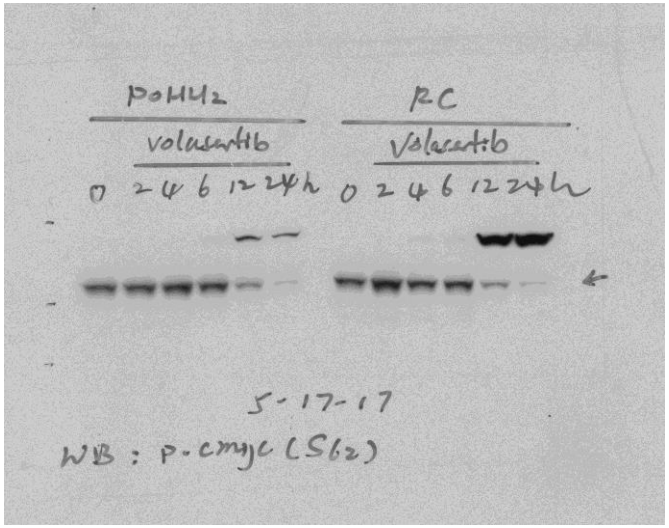
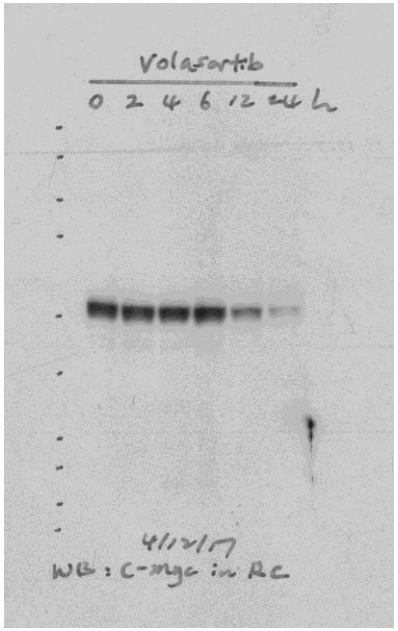
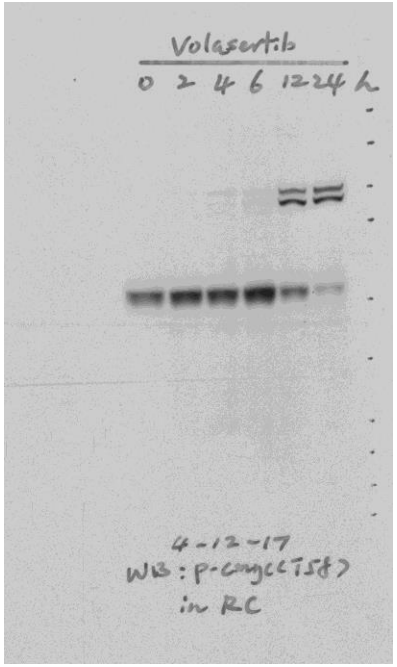
WB : p-cmyc (T58)
in DOHH2


DOHH2
RC
Volasertib
Volasertib
0 2 4 6 12 24 h
0 2 4 6 12 24 h
5-17-17
WB : p-cmyc (S62)


Volasertib
0 2 4 6 12 24 h
4/12/17
WB : C-myc in RC


Volasertib
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4-12-17
WB : p-cmyc (T58)
in RC

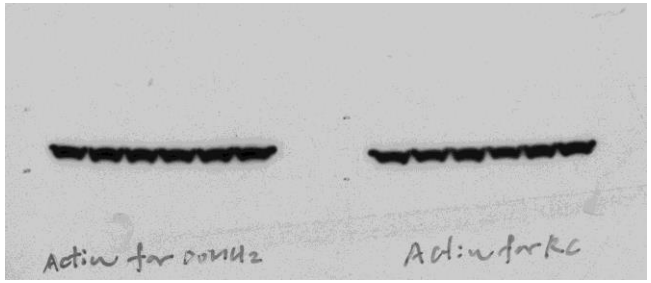
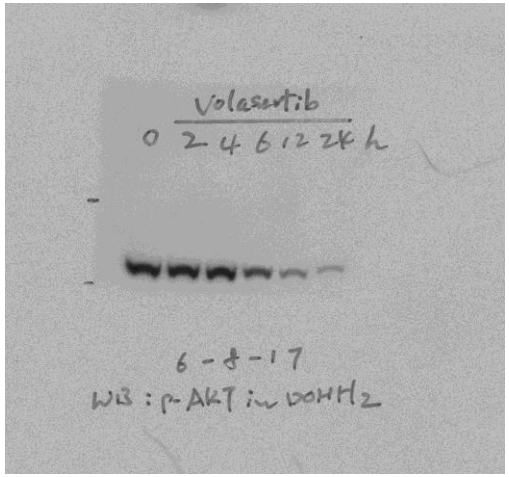
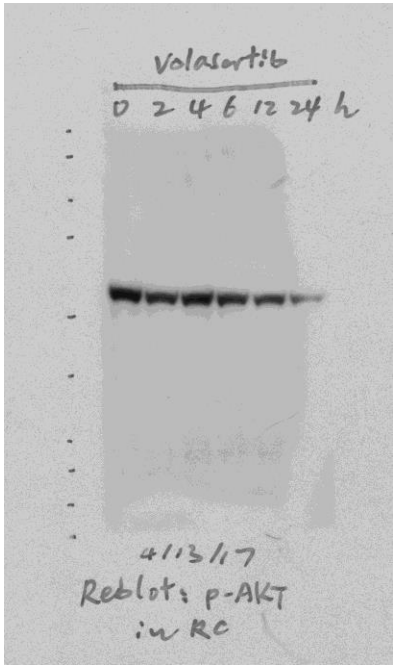
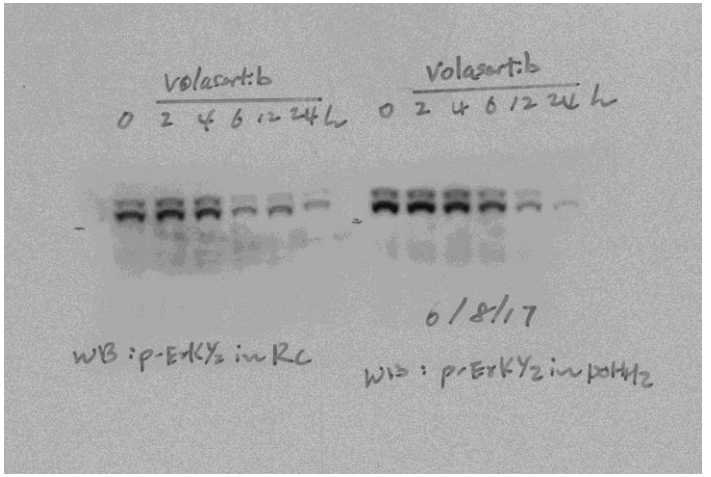
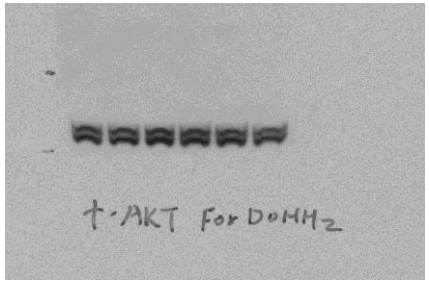

Actin for DOHH2
Actin for RC

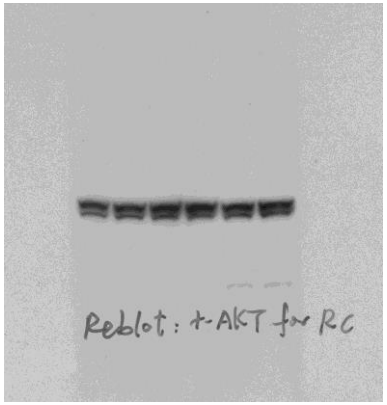
Fig.3 D


Volasertib
0 2 4 6 12 24 h
6-8-17
WB: p-AKT in DOHH2


Volasertib
0 2 4 6 12 24 h
4/13/17
Reblot: p-AKT
in RC


Volasertib
0 2 4 6 12 24 h
Volasertib
0 2 4 6 12 24 h
WB: p-ErkY2 in RC
6/8/17
WB: p-ErkY2 in DOHH2


t-AKT For DOHH2


Reblot: t-AKT for RC

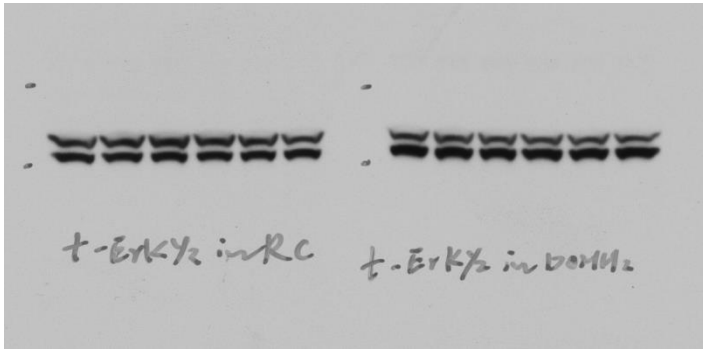
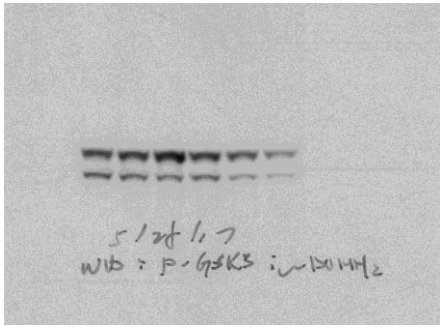
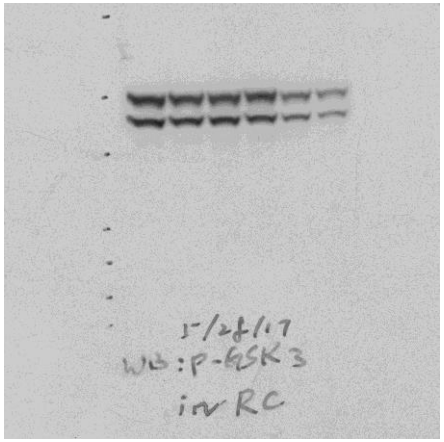
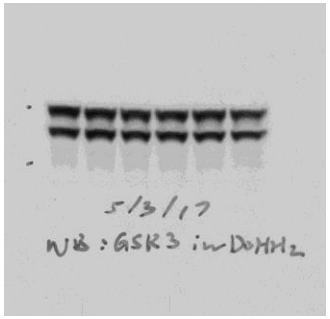

t-ErkY2 in RC
t-ErkY2 in DOHH2

Fig.3 D


5/24/17
WB : P-GSK3 in DMH2


5/24/17
WB: P-GSK3
in RC


5/3/17
WB: GSK3 in DMH2

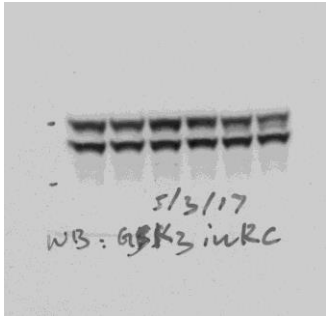
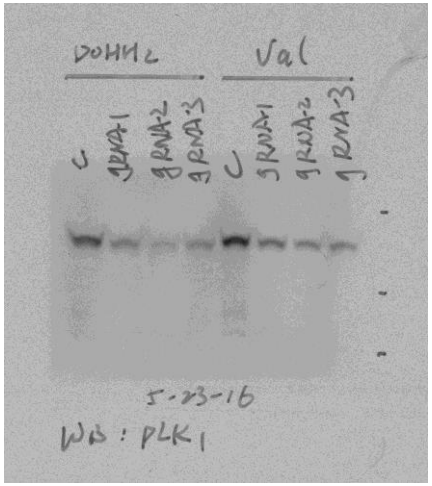
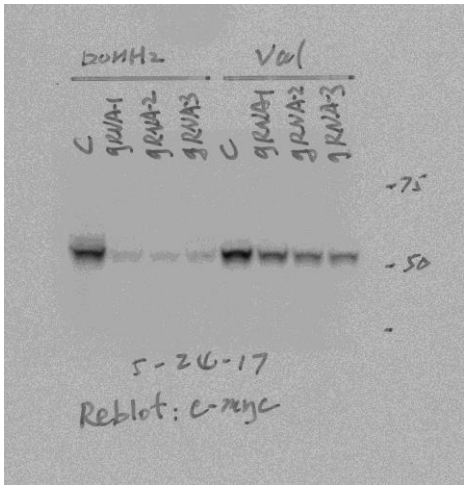
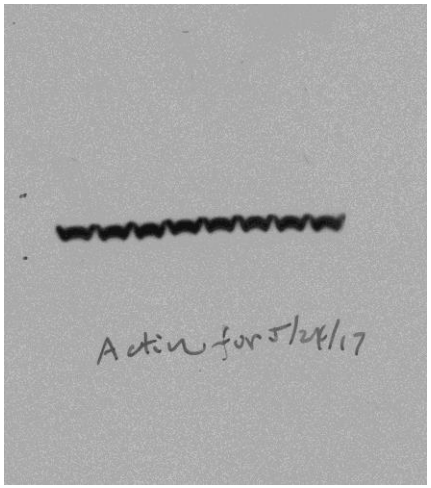
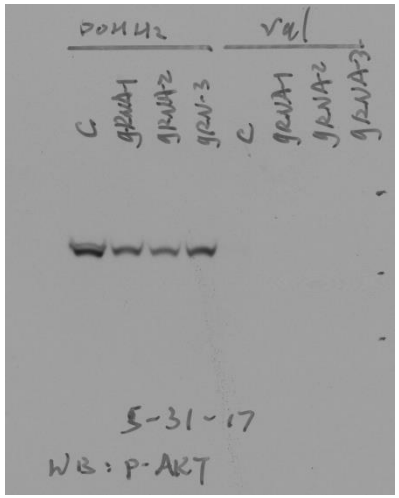

5/3/17
WB: GSK3 in RC

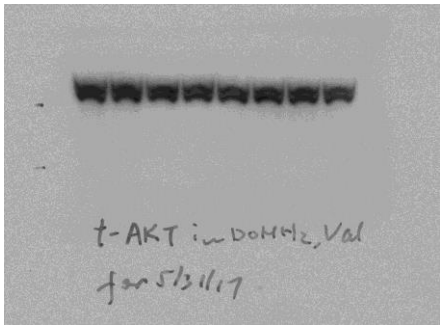
Fig.3 E

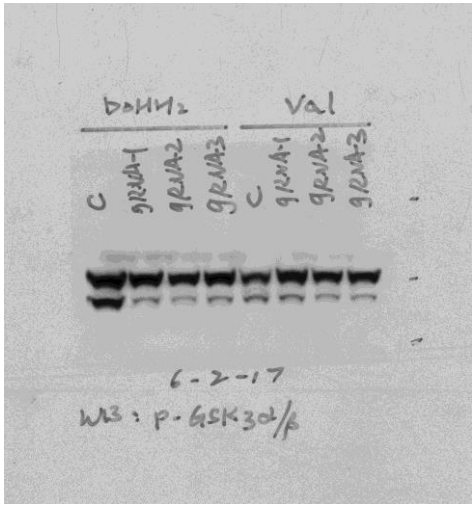

DOHH2
Val
C
gRNA-1
gRNA-2
gRNA-3
5-23-16
WB: PLK1


DOHH2
Val
C
gRNA-1
gRNA-2
gRNA-3
-75
-50
5-26-17
Reblot: c-myc


Actin for 5/26/17


DOHH2
Val
C
gRNA-1
gRNA-2
gRNA-3
5-31-17
WB: p-AKT


t-AKT in DOHH2, Val
for 5/31/17


DOHH2
Val
C
gRNA-1
gRNA-2
gRNA-3
6-2-17
WB: p-GSK3α/β

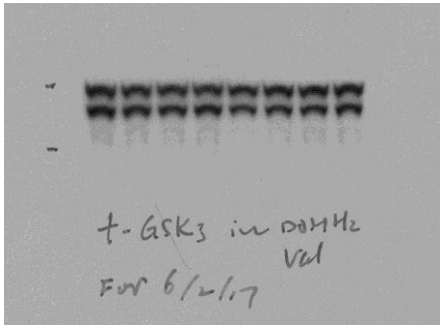
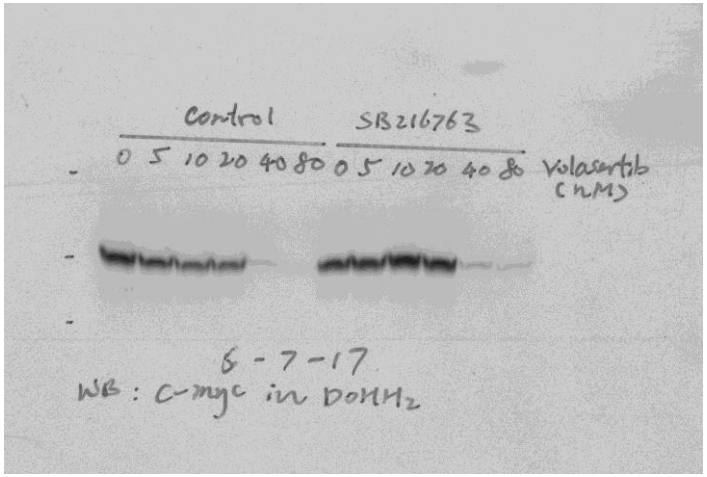
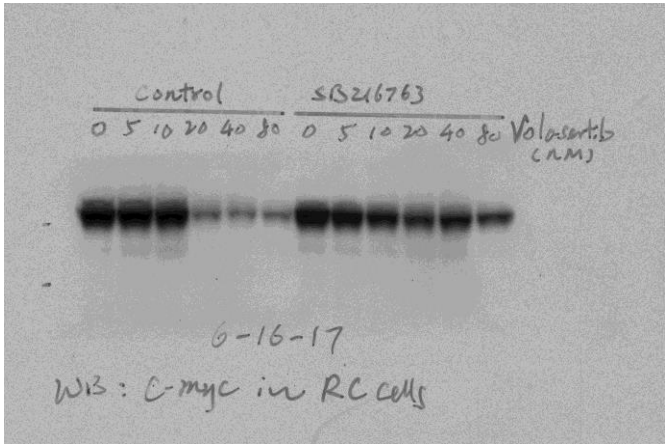
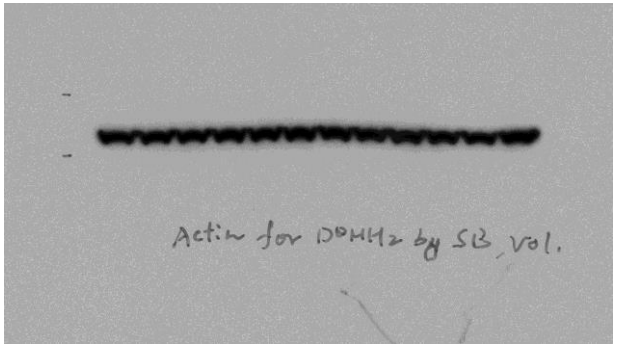

t-GSK3 in DOHH2
Val
For 6/2/17

Fig.3 F


Control
SB216763
0 5 10 20 40 80 0 5 10 20 40 80 Volasertib (nM)
6-7-17
WB: C-myc in DOHH2


Control
SB216763
0 5 10 20 40 80 0 5 10 20 40 80 Volasertib (nM)
6-16-17
WB: C-myc in RC cells


Actin for DOHH2 by SB_Vol.

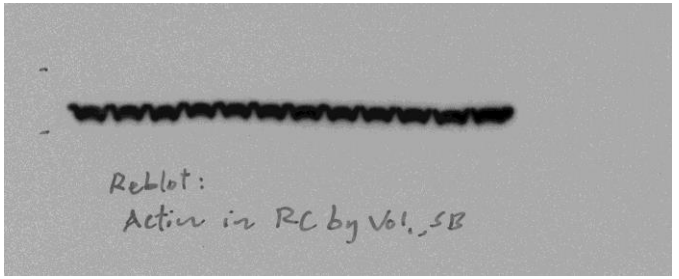
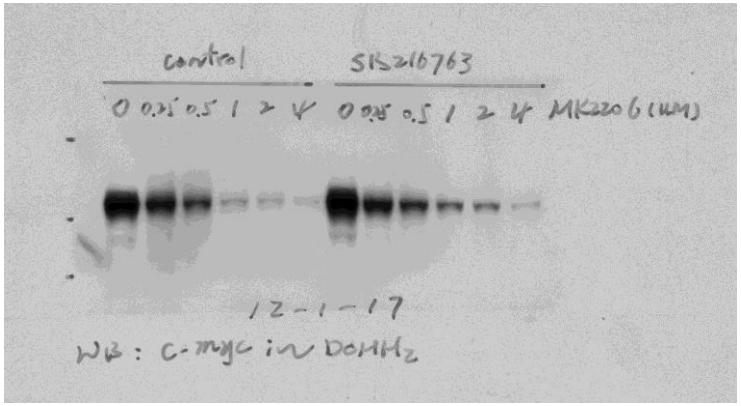
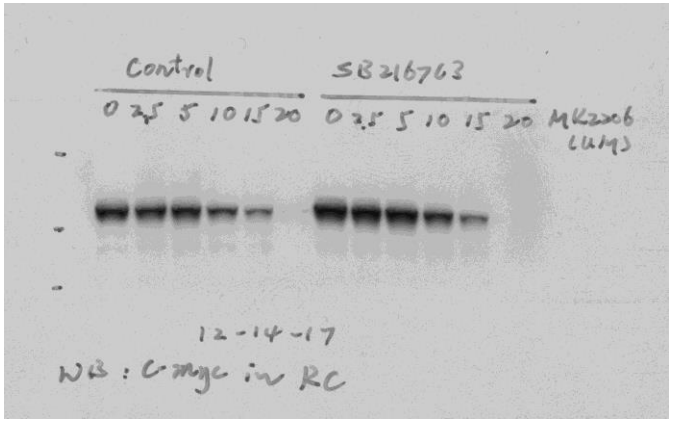
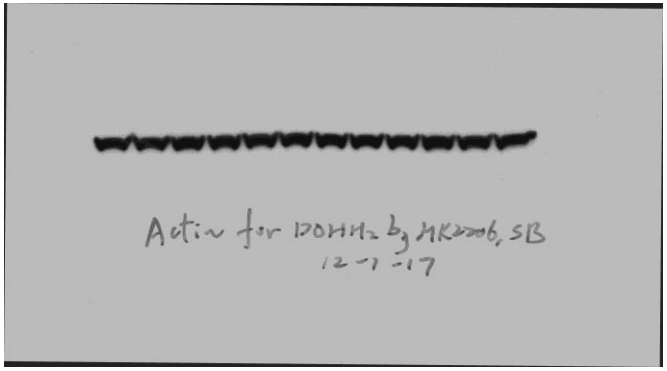

Reblot:
Actin in RC by Vol._SB

Fig.3 G


control
SB216763
0 0.25 0.5 1 2 4 0 0.25 0.5 1 2 4 MK2206 (uM)
12-1-17
WB : C-myc in DOHH2


Control
SB216763
0 2.5 5 10 15 20 0 2.5 5 10 15 20 MK2206 (uM)
12-14-17
WB : C-myc in RC


Actin for DOHH2 by MK2206, SB
12-1-17

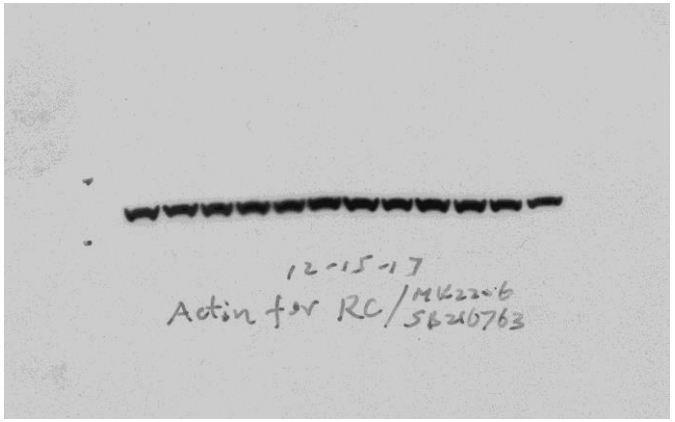
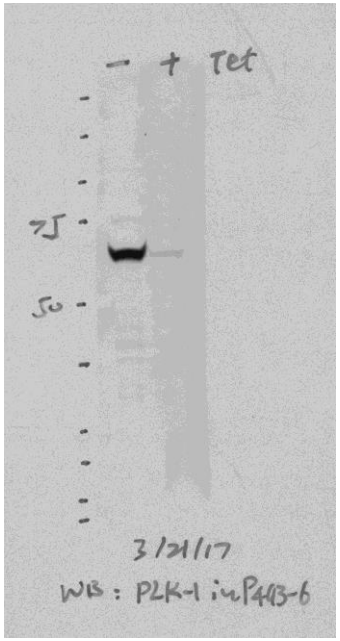
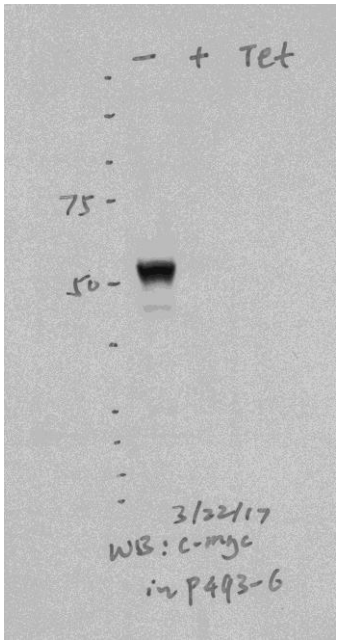

12-15-17
Actin for RC/MK2206
SB216763

Fig.4 A


– + Tet
75
50
3/21/17
WB: PLK-1 in P493-6


– + Tet
75
50
3/22/17
WB: c-myc
in P493-6

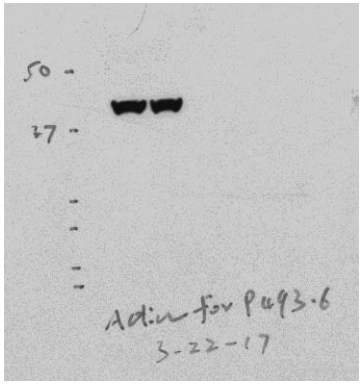
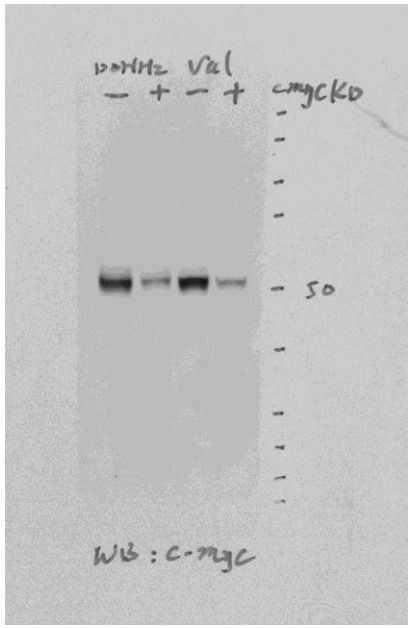
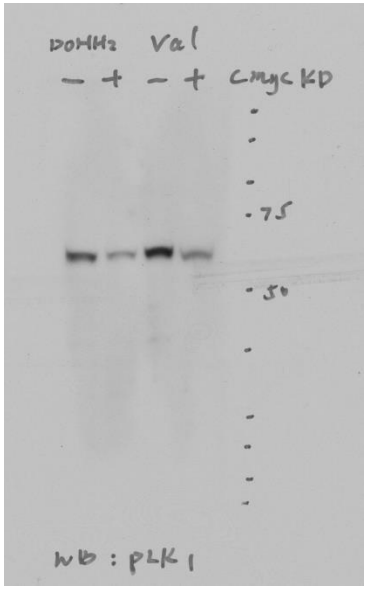

50
37
Actin for P493-6
3-22-17

Fig.4 B


DOHH2 Val
– + – + cmycKD
50
WB: c-myc


DOHH2 Val
– + – + cmycKD
75
50
WB: PLK1

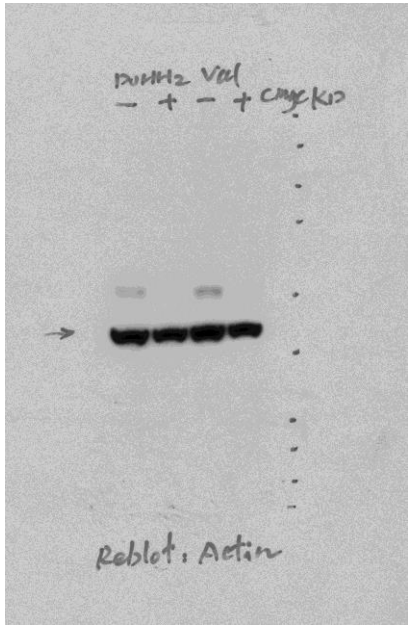
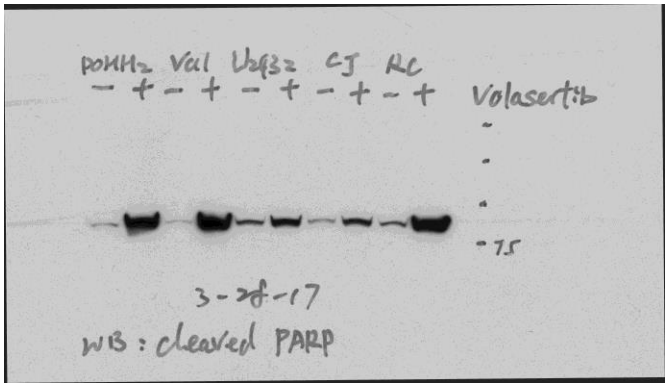
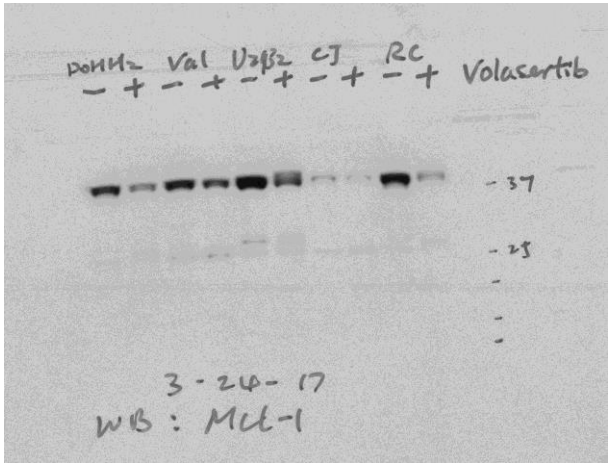
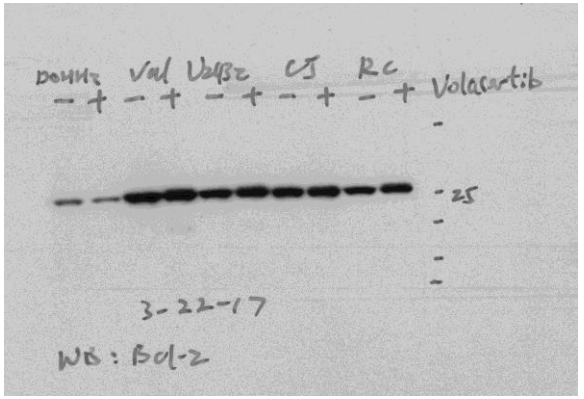
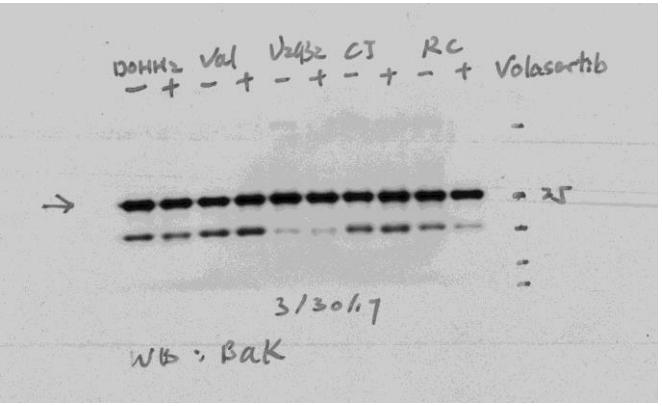

DOHH2 Val
– + – + cmycKD
Reblot: Actin

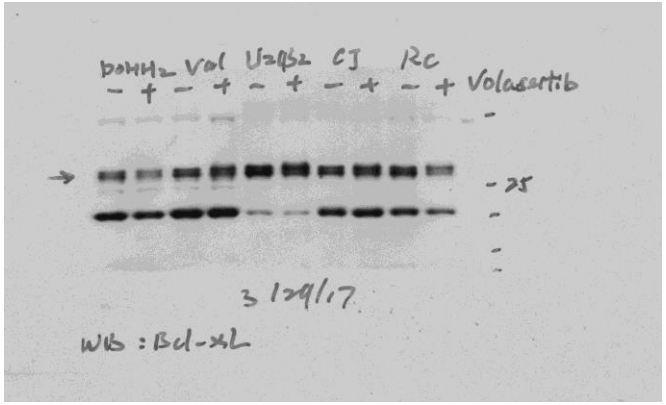
Fig.5 C

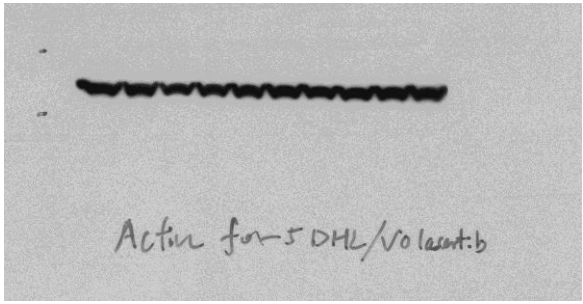

DOHH2 Val U2αβ2 CJ RC Volasertib
− + − + − + − + − +
75
3-28-17
WB: cleaved PARP


DOHH2 Val U2αβ2 CJ RC Volasertib
− + − + − + − + − +
37
25
3-24-17
WB: Mcl-1


DOHH2 Val U2αβ2 CJ RC Volasertib
− + − + − + − + − +
25
3-22-17
WB: Bcl-2


DOHH2 Val U2αβ2 CJ RC Volasertib
− + − + − + − + − +
25
3/30/17
WB: BaK


DOHH2 Val U2αβ2 CJ RC Volasertib
− + − + − + − + − +
25
3/29/17
WB: Bcl-xL


Actin for 5 DHL/Volasertib

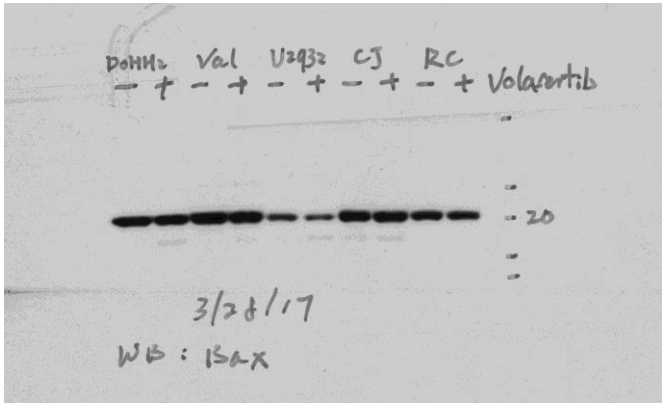
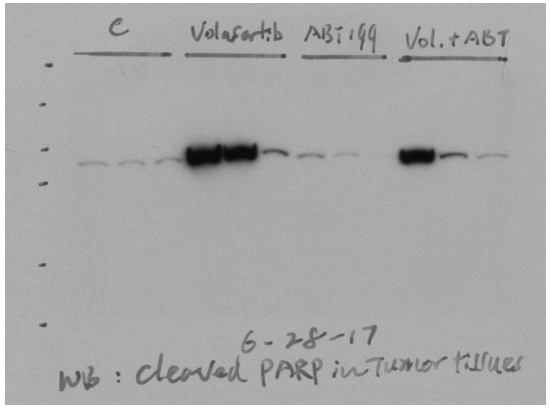
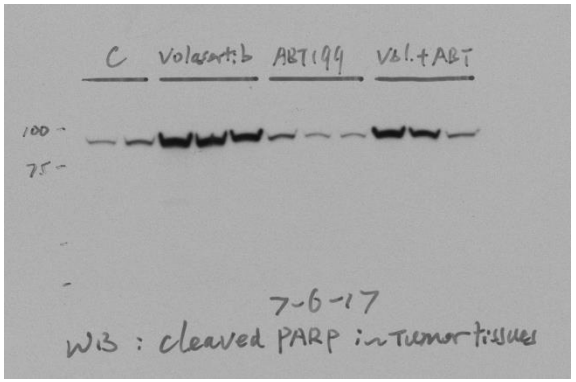
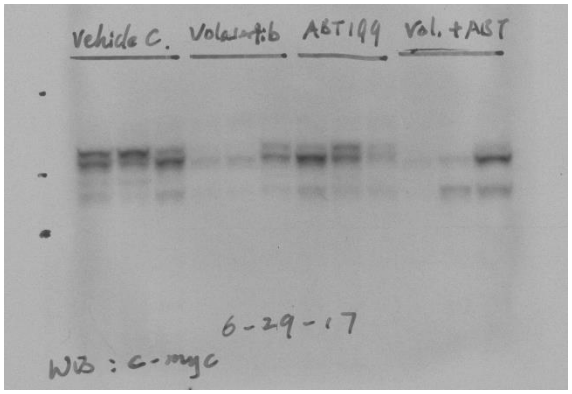
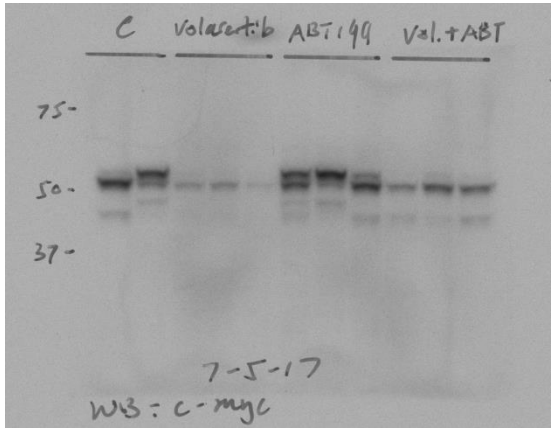

DOHH2 Val U2αβ2 CJ RC Volasertib
− + − + − + − + − +
20
3/28/17
WB: BAX

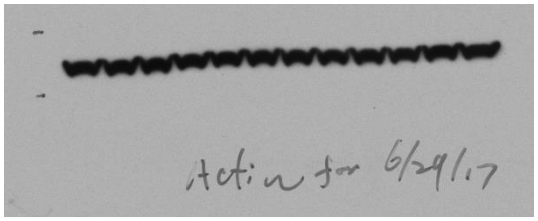
Fig. 7E


C
Volasertib
ABT199
Vol.+ABT
6-28-17
WB : cleaved PARP in Tumor tissues


C
Volasertib
ABT199
Vol.+ABT
100
75
7-6-17
WB : cleaved PARP in Tumor tissues


Vehicle C.
Volasertib
ABT199
Vol.+ABT
6-29-17
WB : c-myc


C
Volasertib
ABT199
Vol.+ABT
75
50
37
7-5-17
WB : c-myc


Actin for 6/29/17

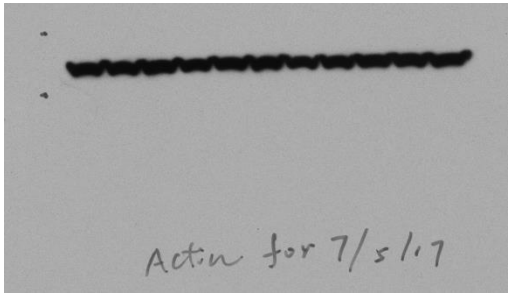
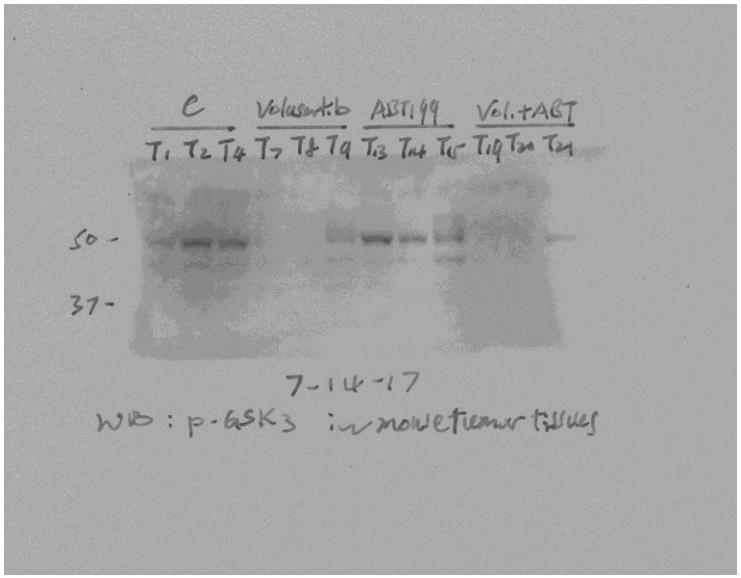
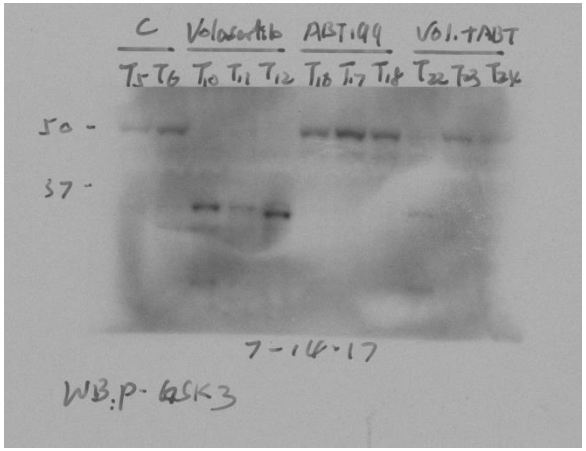
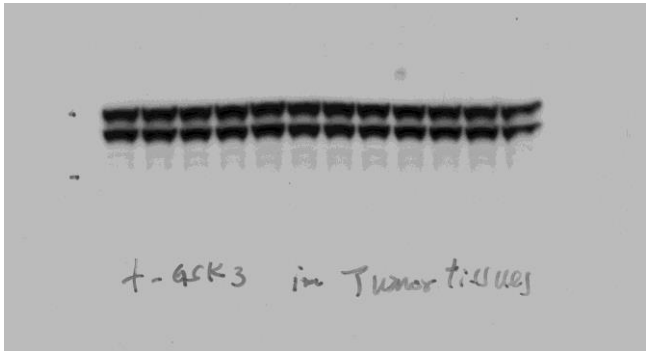
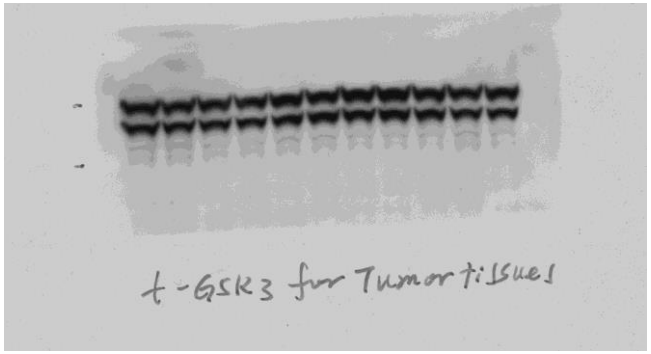

Actin for 7/5/17

Fig.7E

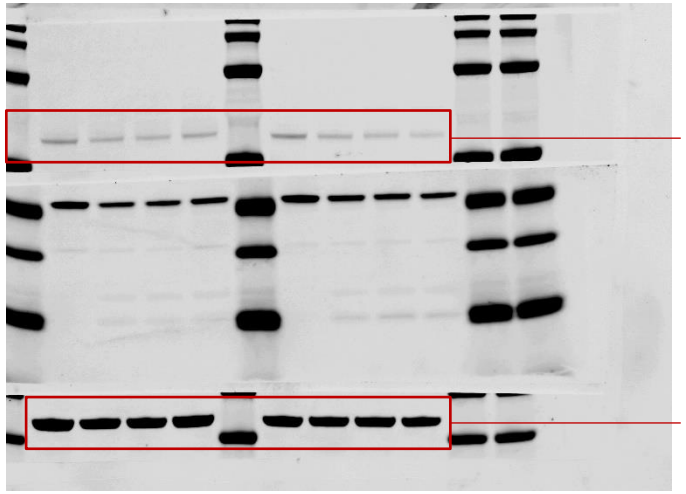

C
Volasertib
ABT199
Vol.+ABT
T1 T2 T4 T7 T8 T9 T13 T14 T16 T19 T20 T24
50 -
37 -
7-14-17
WB : p-GSK3 in xenotransplantation tissues

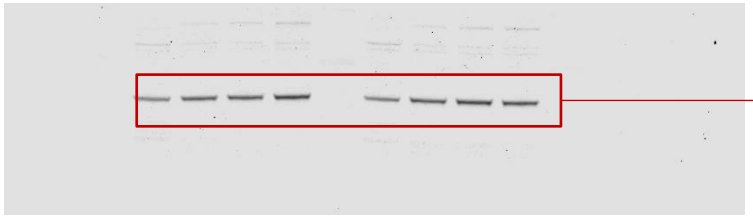

C
Volasertib
ABT199
Vol.+ABT
T5 T6 T10 T11 T12 T18 T17 T21 T22 T23 T24
50 -
37 -
7-14-17
WB:p-GSK3

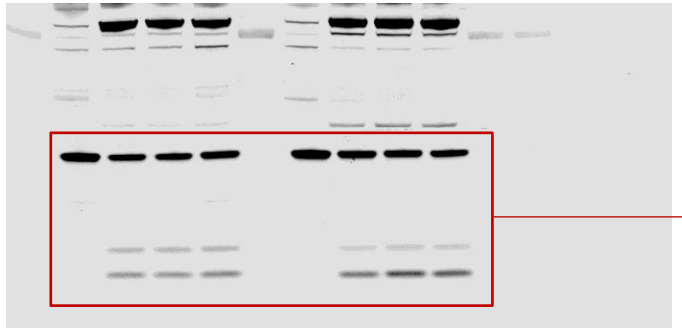

t-GSK3 in Tumor tissues

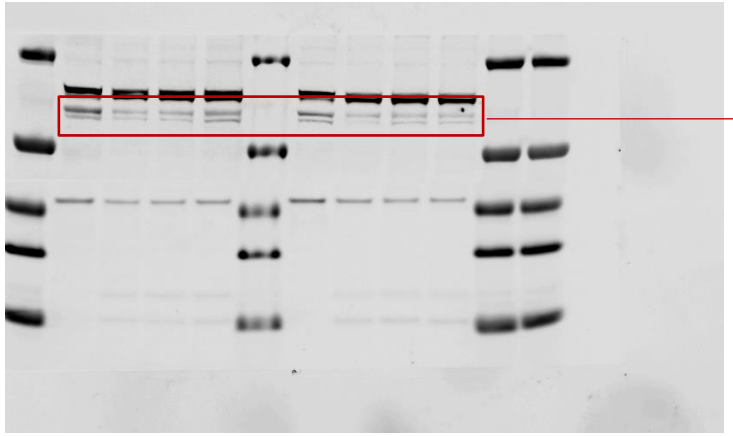

t-GSK3 for Tumor tissues

Supplementary Figure 1A

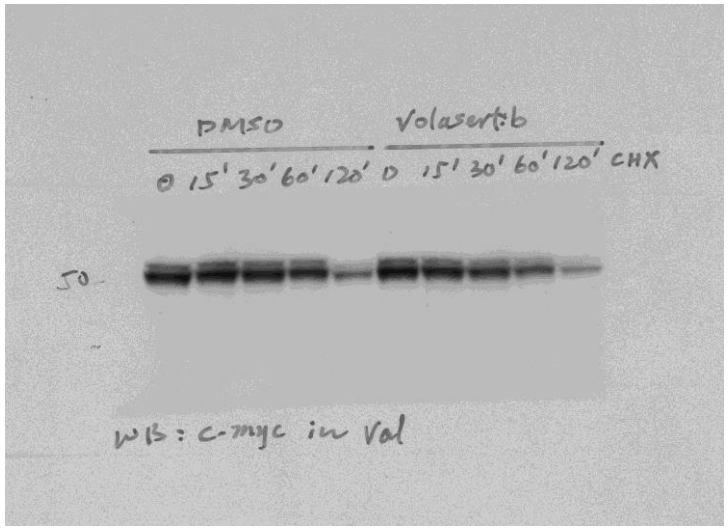


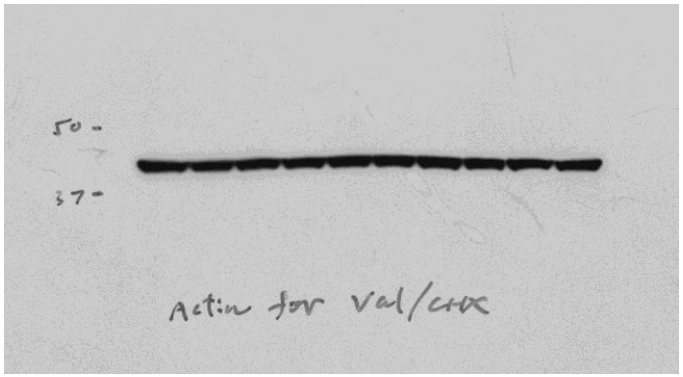




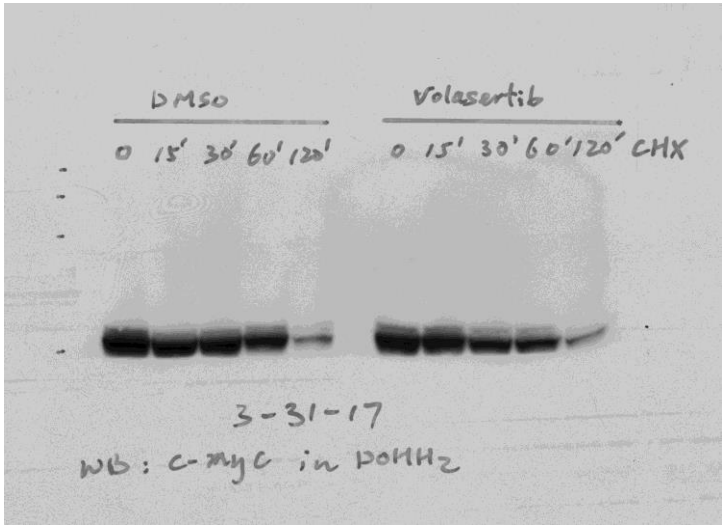


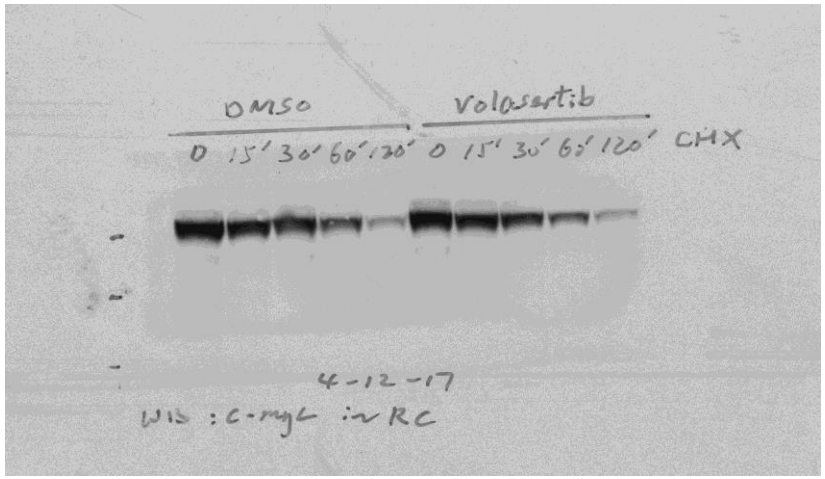
Supplementary Fig.1 C

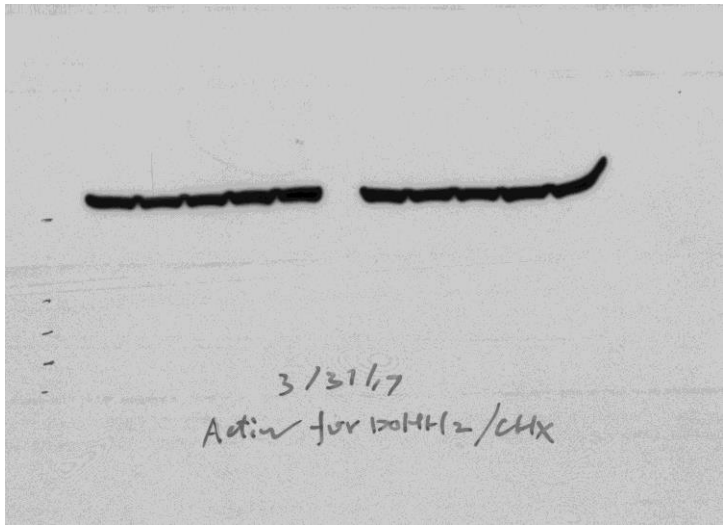


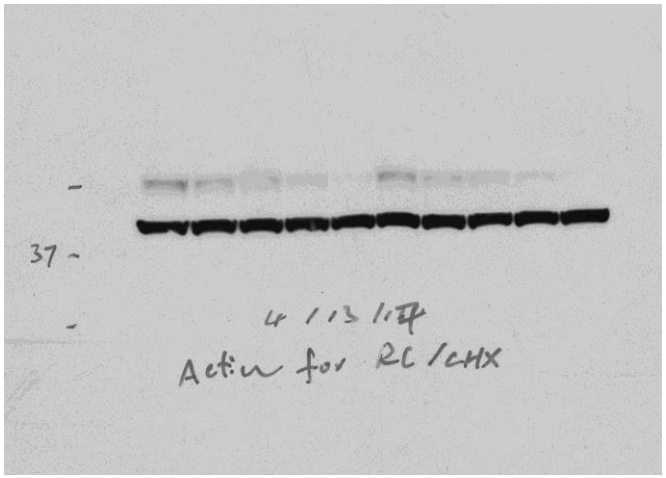


Supplementary Fig.1 C

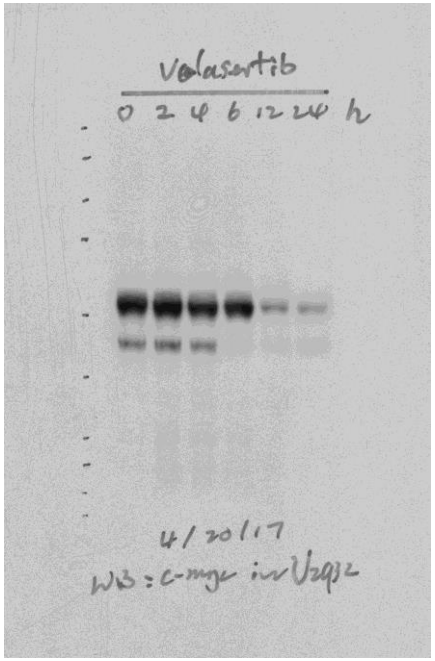


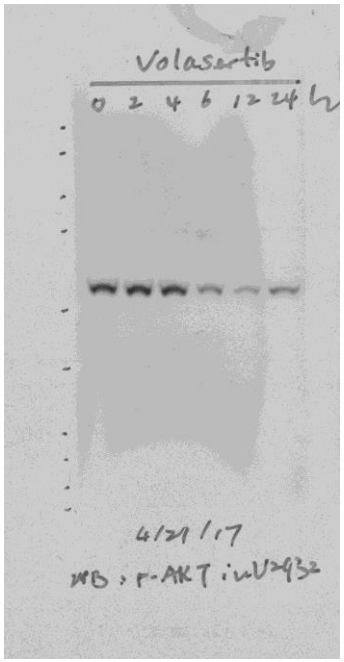


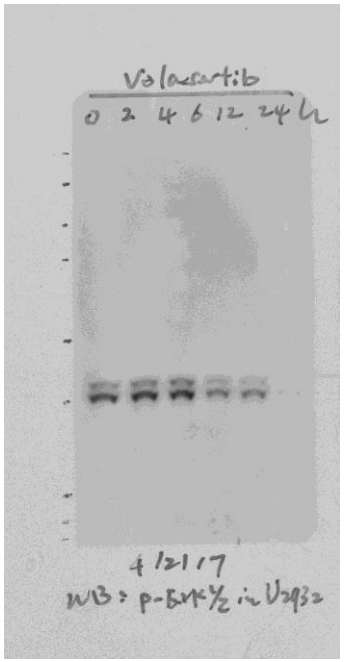


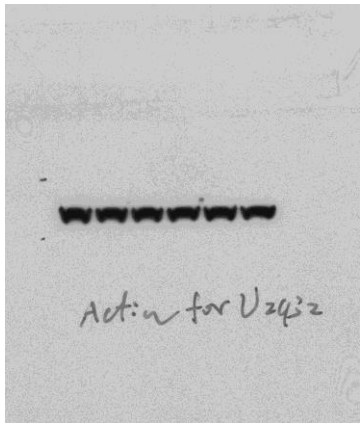


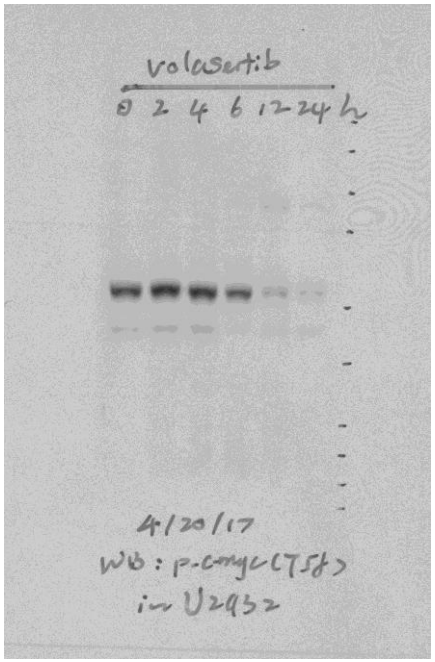
Supplementary Fig.1 D

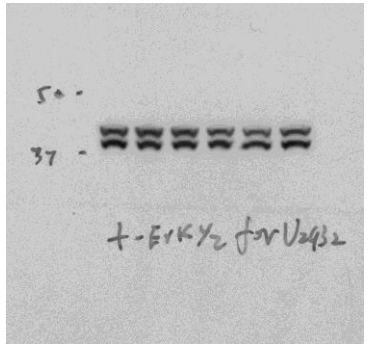




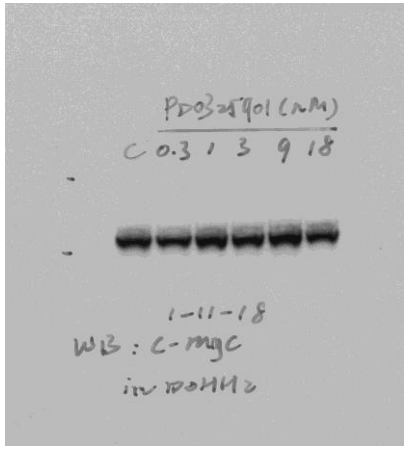


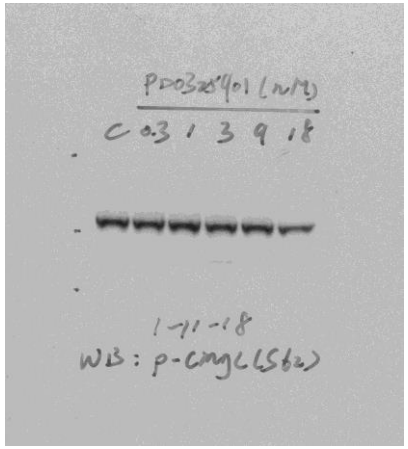


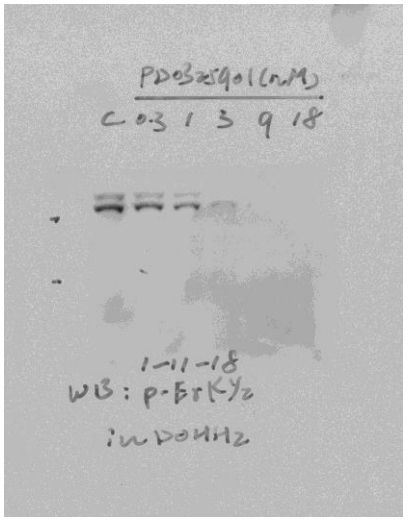


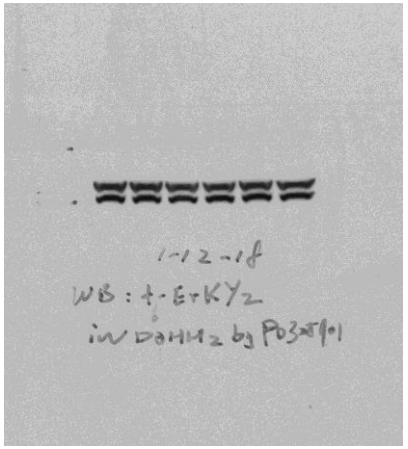


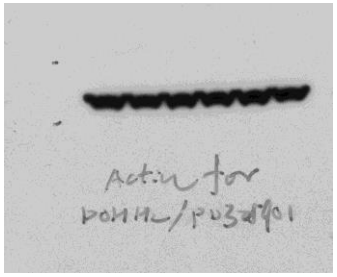
Supplementary Fig.1 E

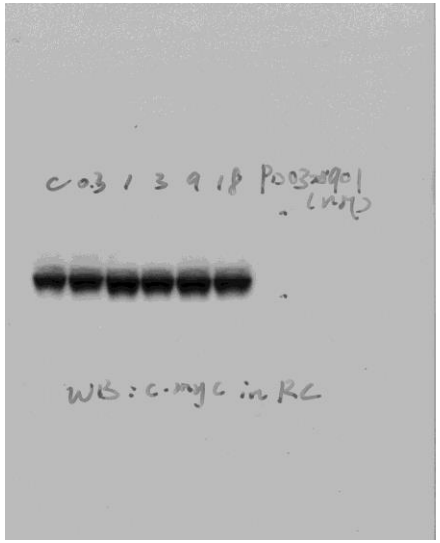


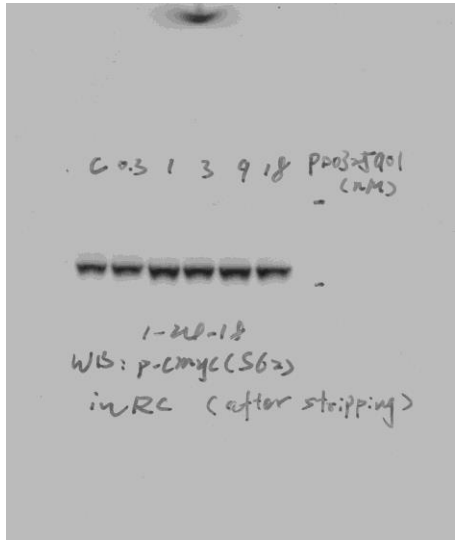


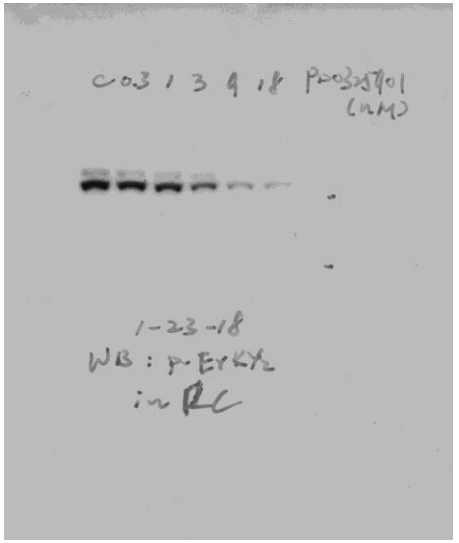


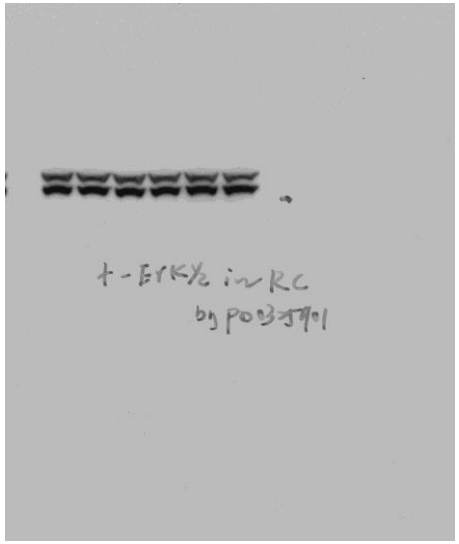




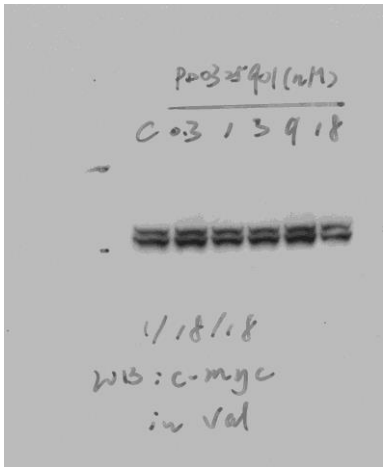


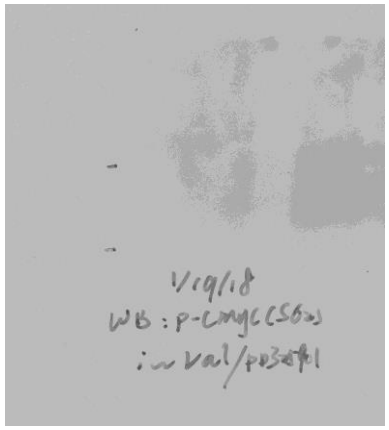


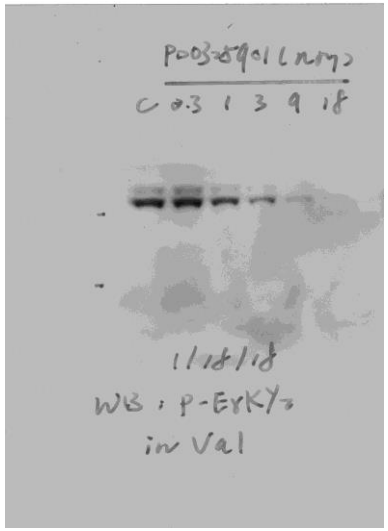


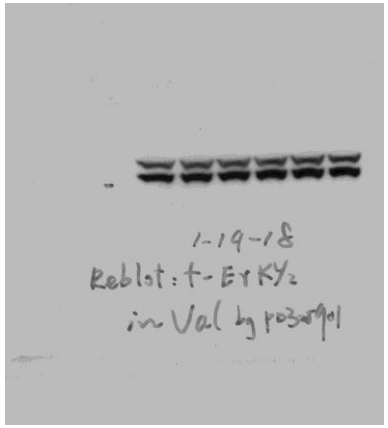


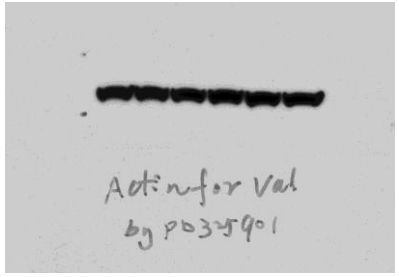
Supplementary Fig.1 E

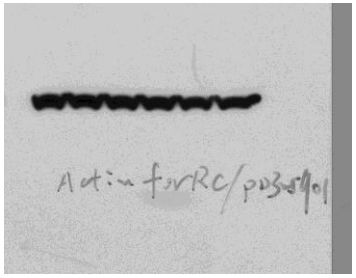




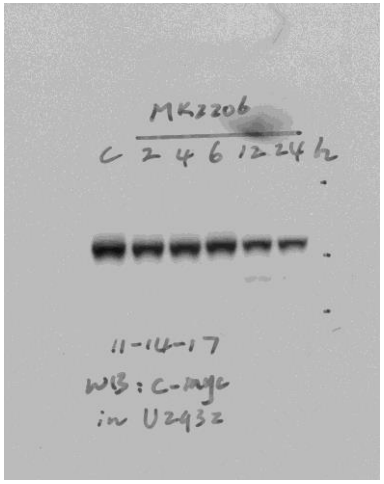


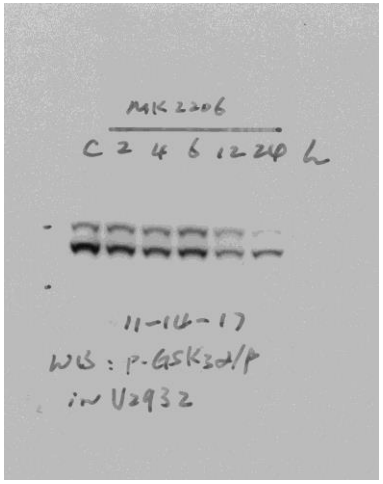


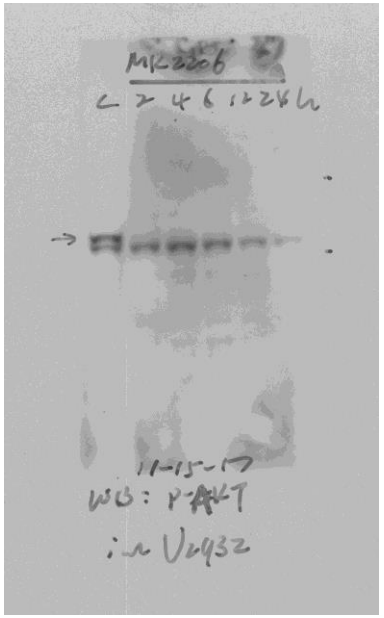


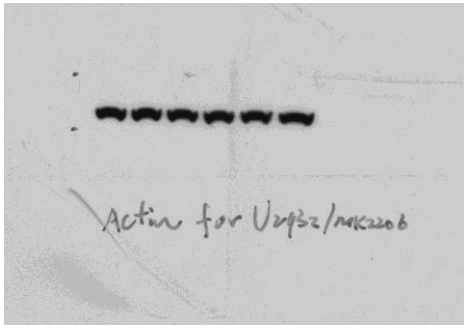


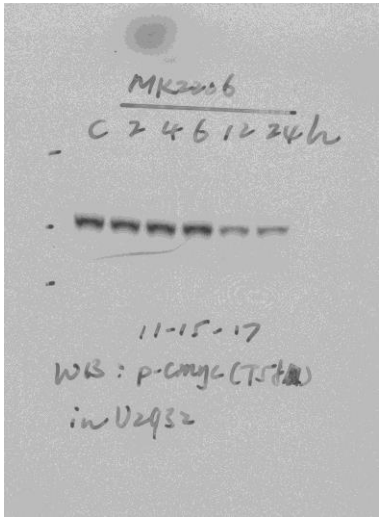
Supplementary Fig.1 F

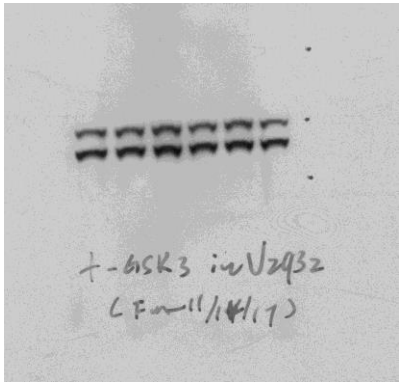


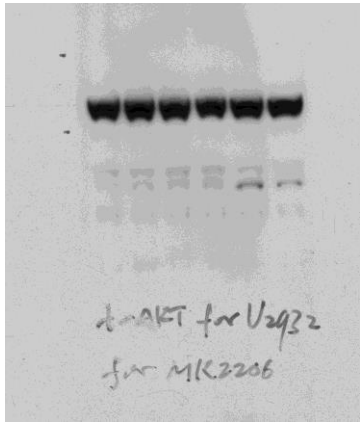




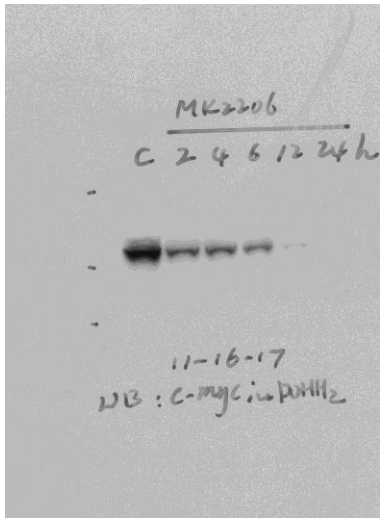


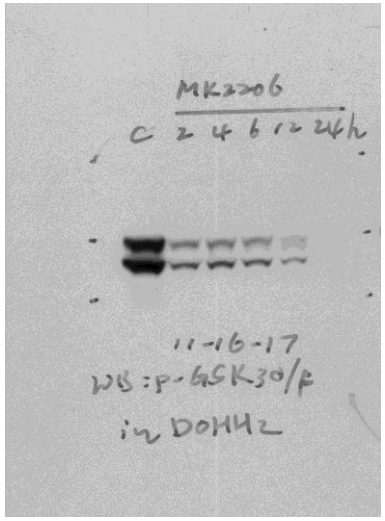


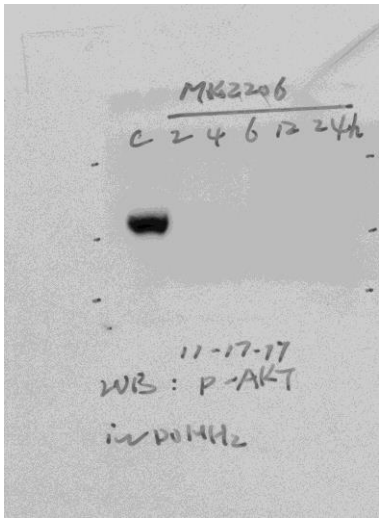


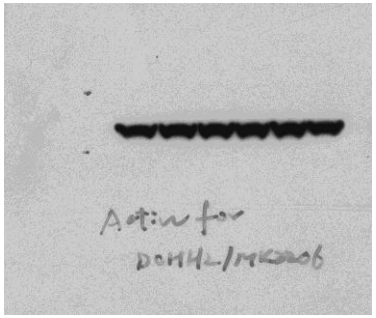


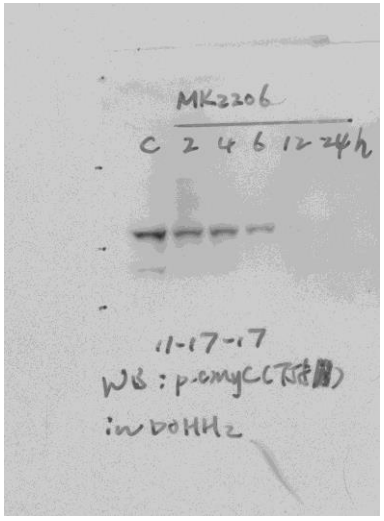
Supplementary Fig.1 F

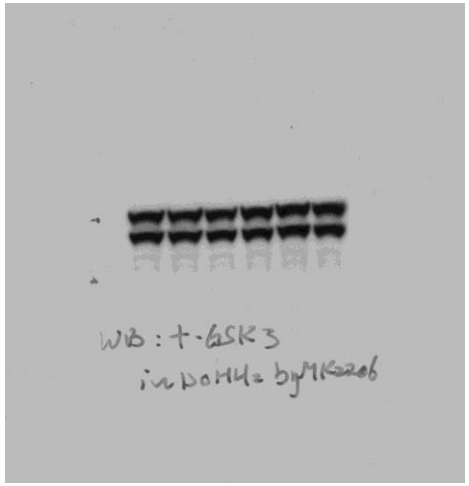


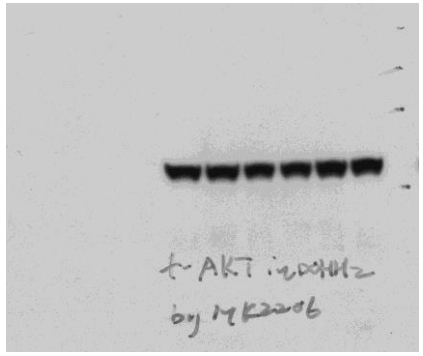




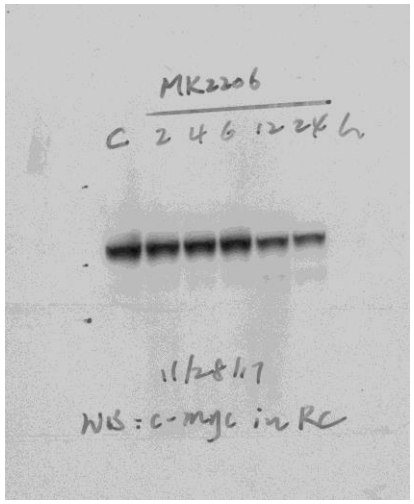


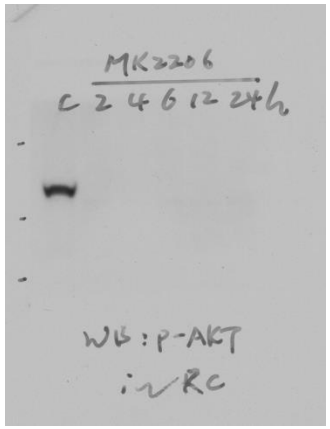


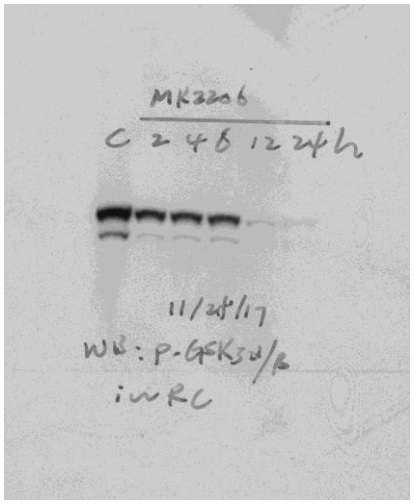


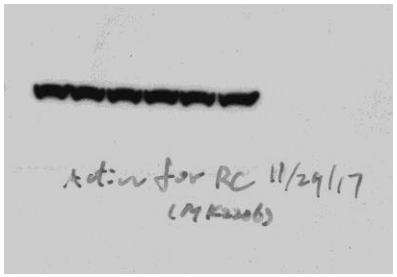


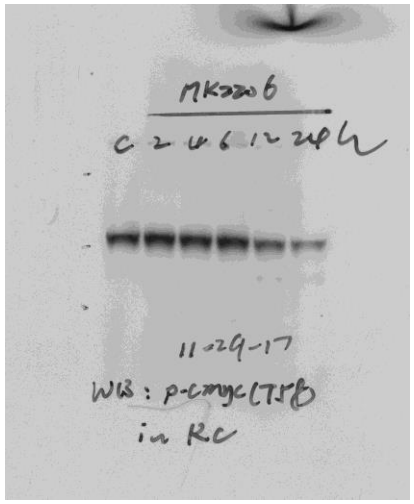
Supplementary Fig.1 F

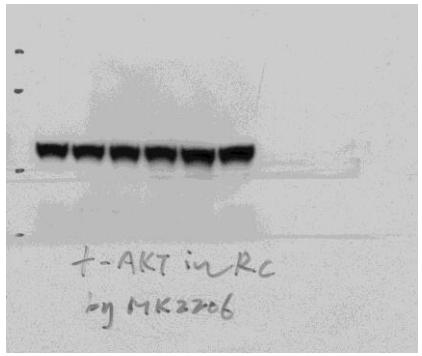


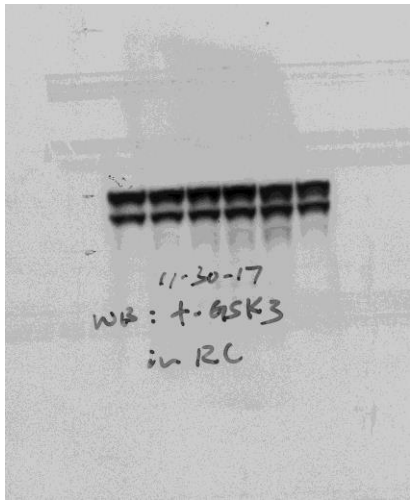




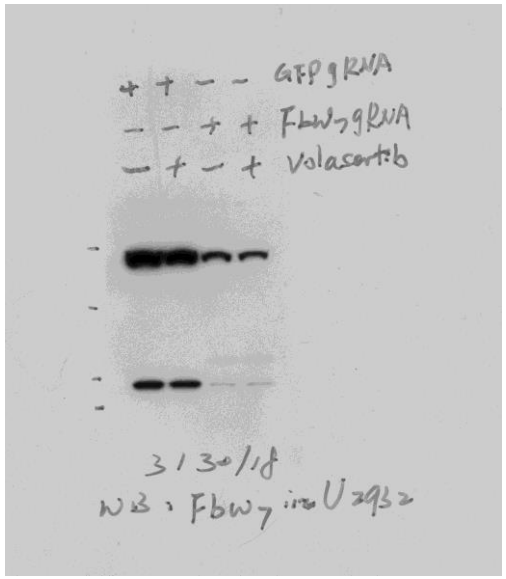


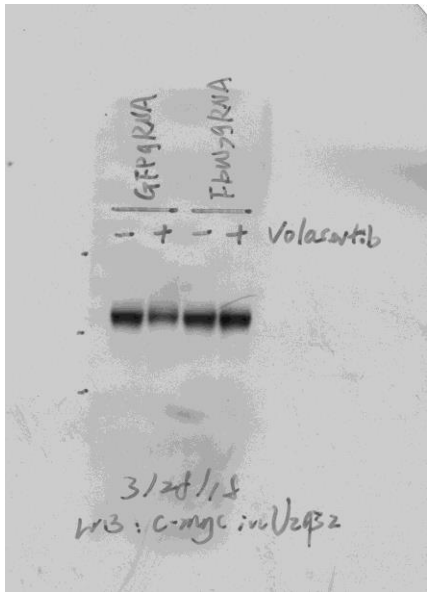


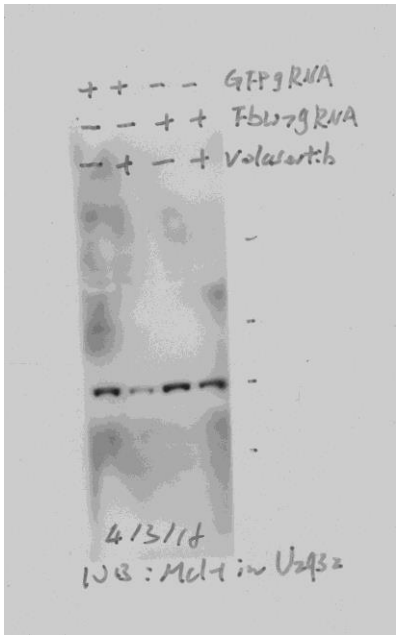


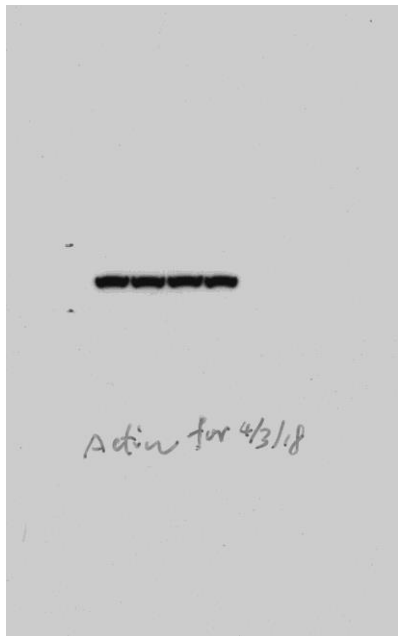


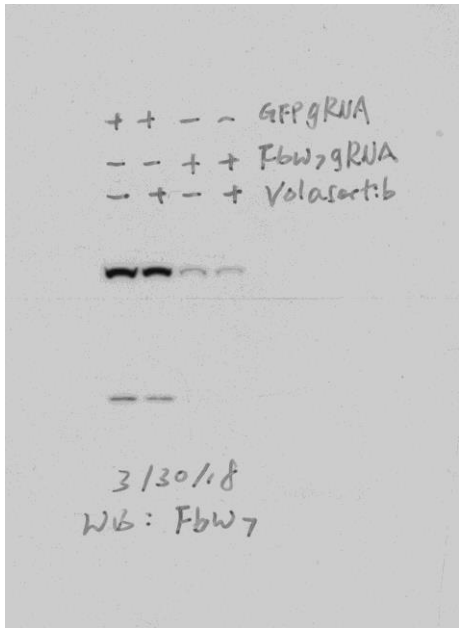
Supplementary Fig.2B



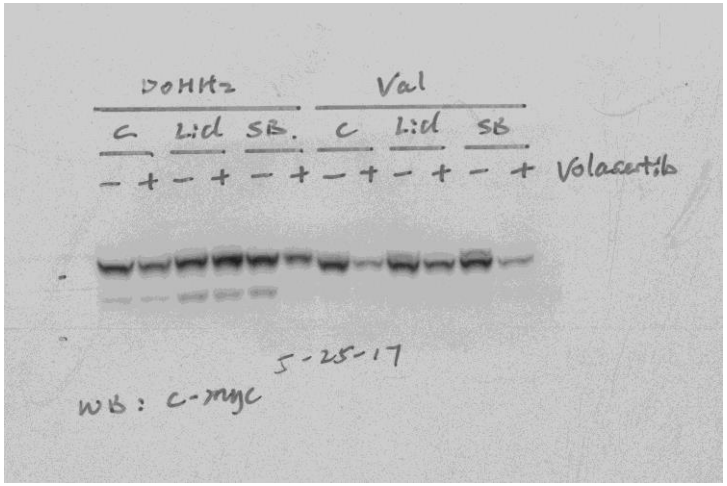


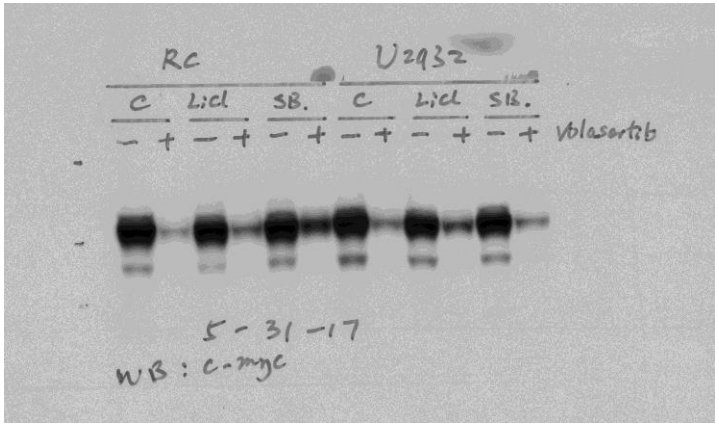


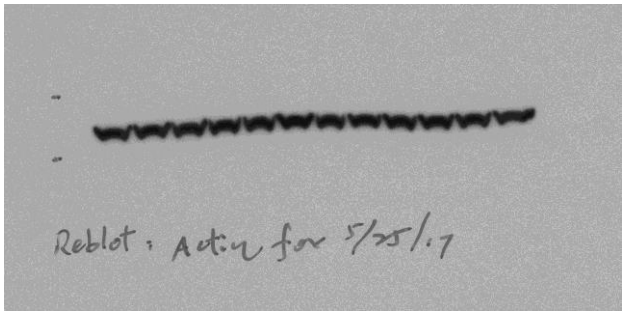


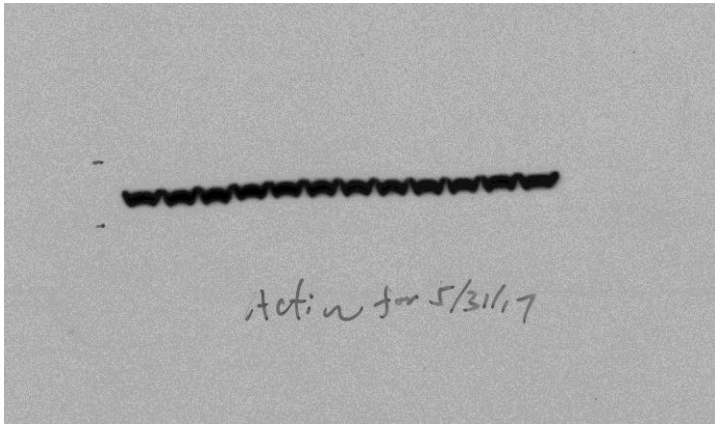


Supplementary Fig.2A

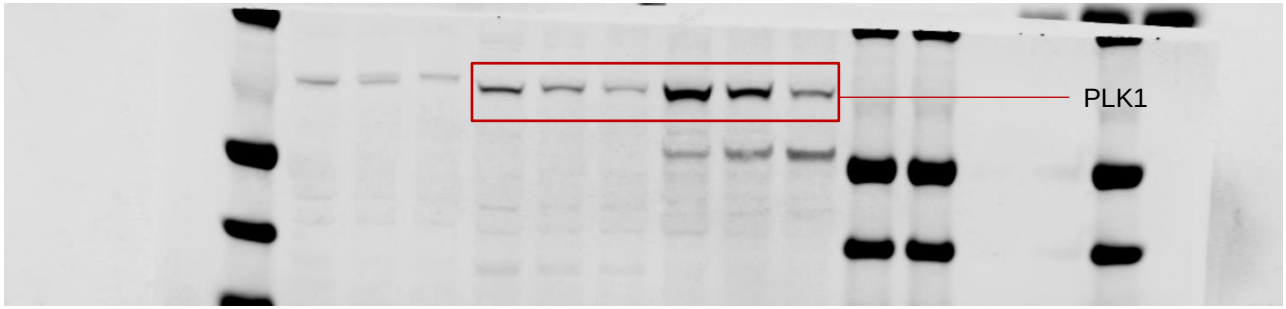


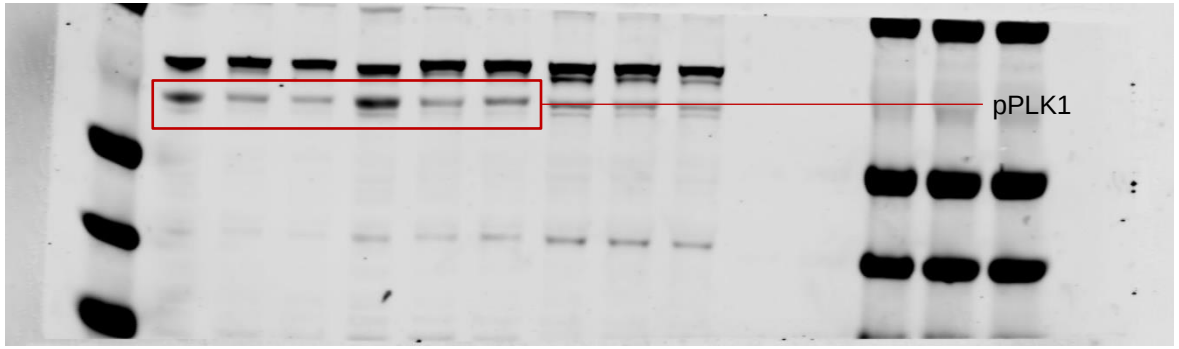


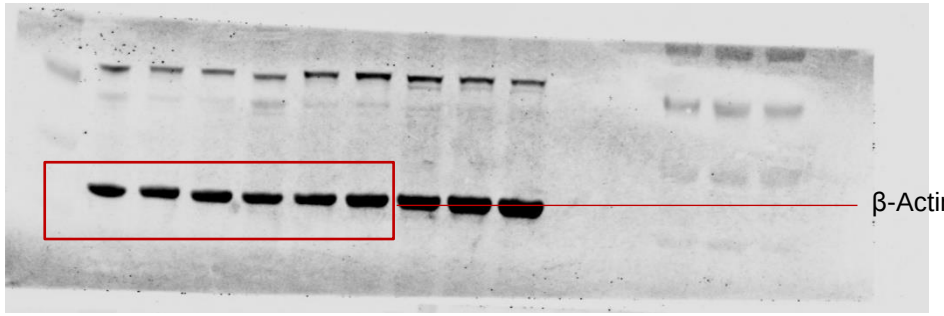


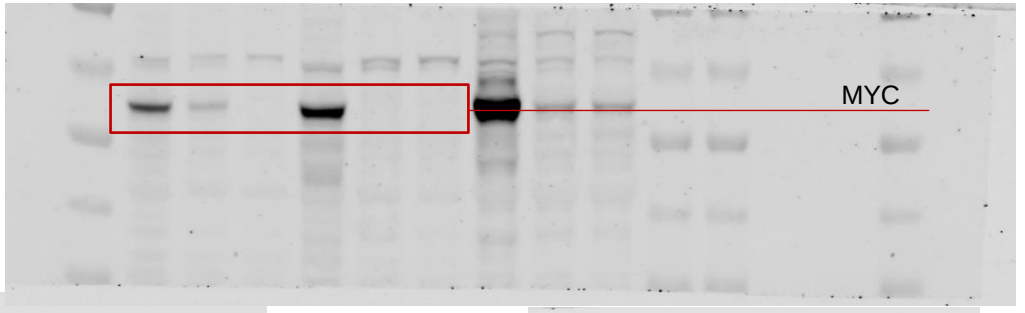


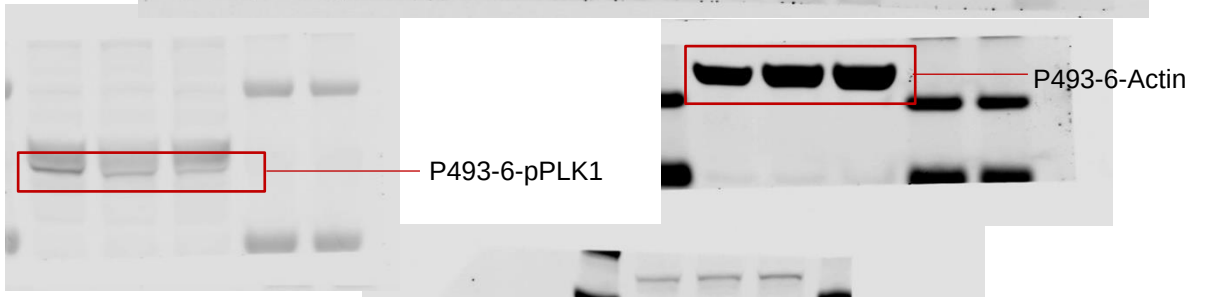
Supplementary Figure 3B

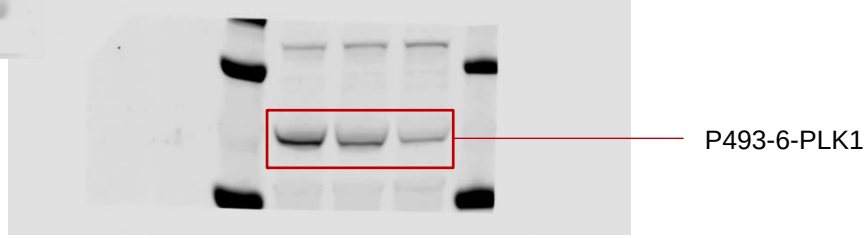


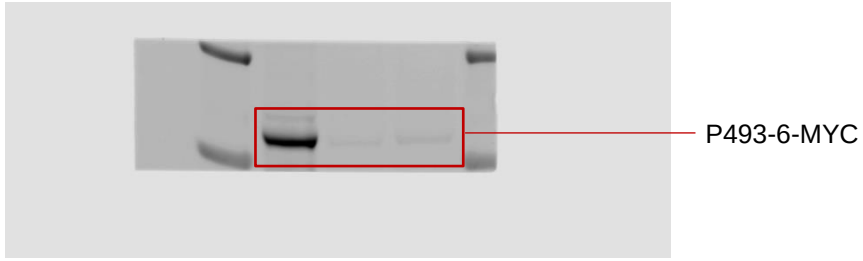


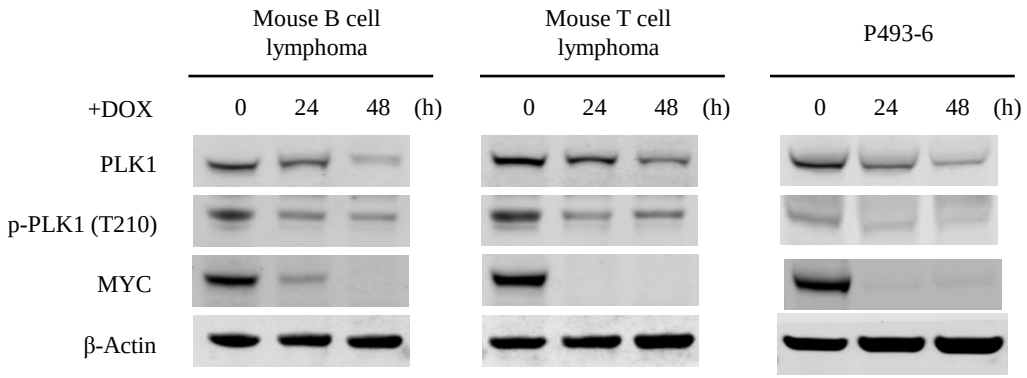




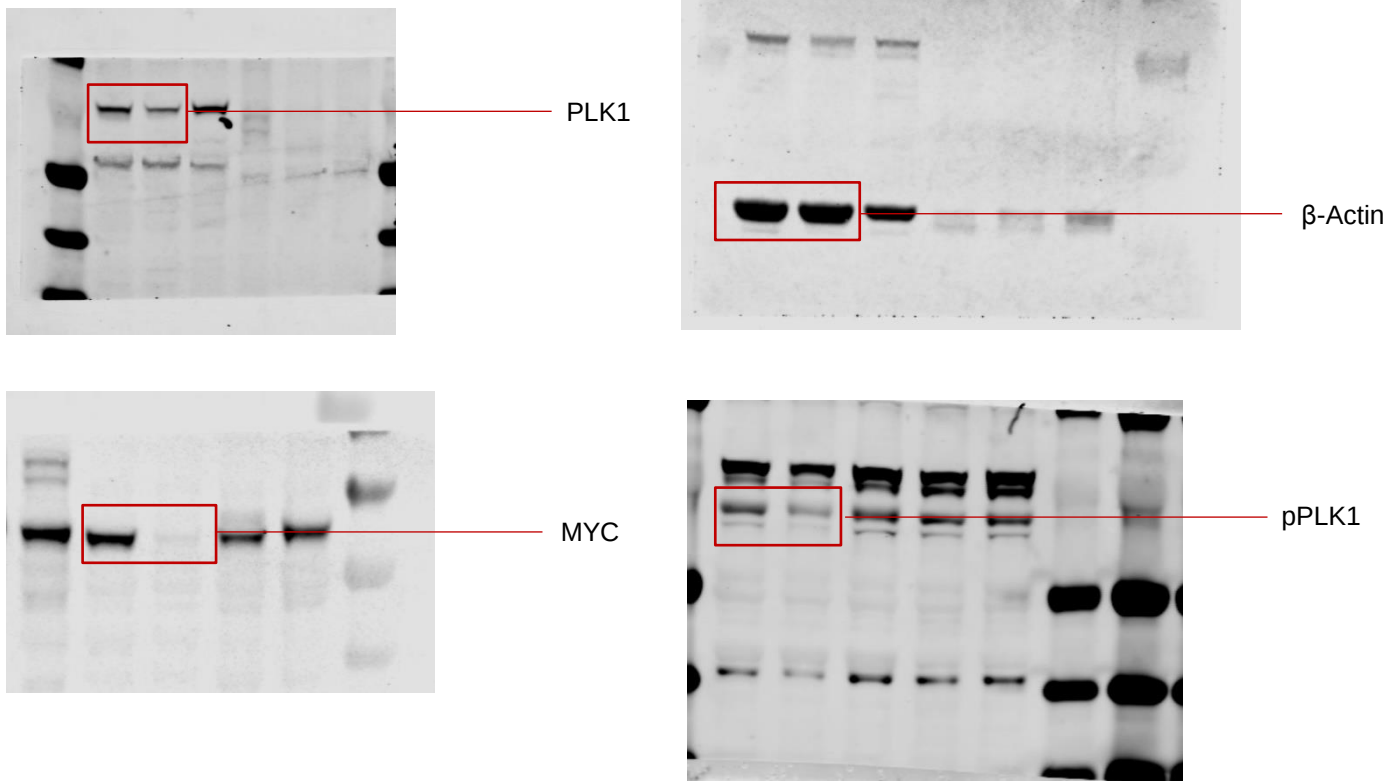








Supplementary Figure 3C



Supplementary Fig.3 E