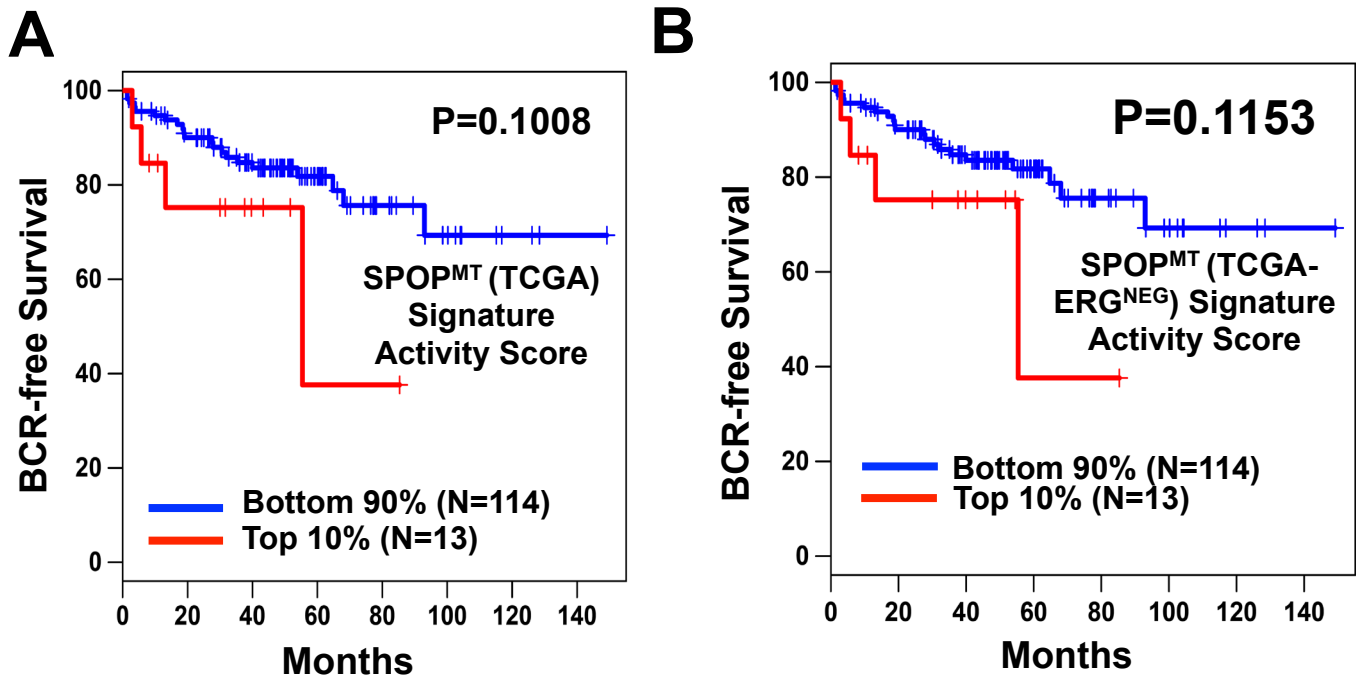
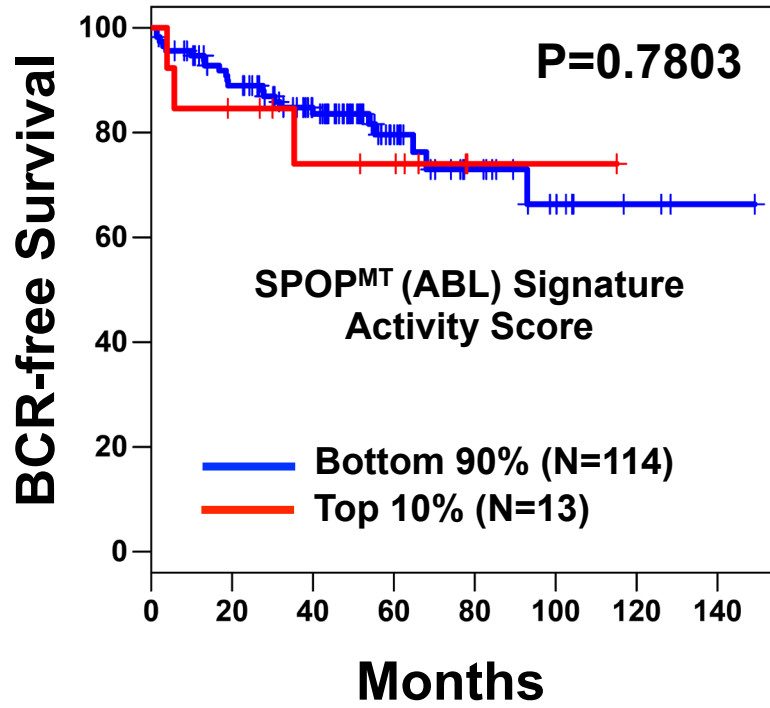


## Supplementary Figure 11

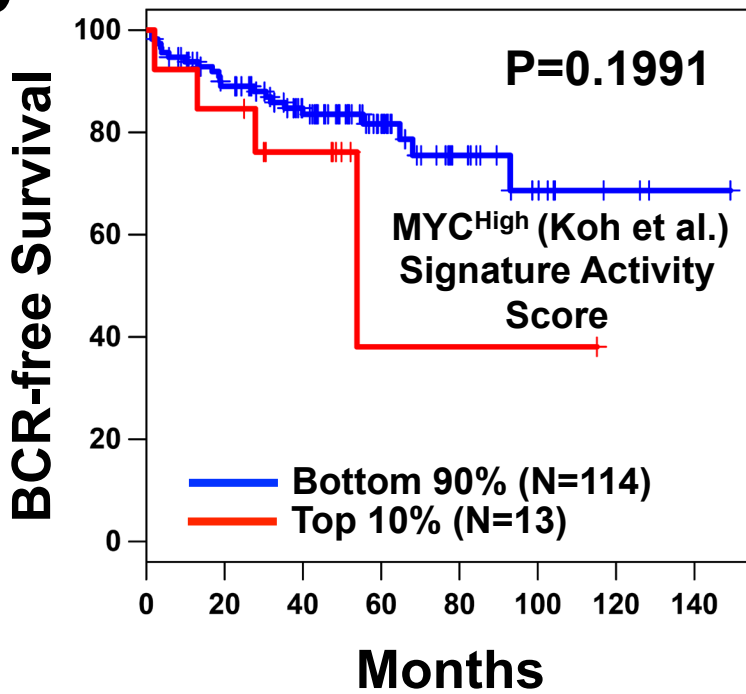
**Supplementary Figure 11: The individual SPOP<sup>MT</sup> or MYC<sup>High</sup> signatures do not achieve prognostic significance in a human PC dataset.** We applied the entire SPOP<sup>MT</sup>(TCGA) signature derived using the TCGA primary PC dataset (**A**), the entire SPOP<sup>MT</sup>(TCGA-ERG<sup>NEG</sup>) SPOP<sup>MT</sup>(TCGA) signature, which is derived only from the ERG<sup>NEG</sup> TCGA specimens (**B**), the entire SPOP<sup>MT</sup>(Abl) signature derived from the transcriptomic footprint of SPOP<sup>MT</sup> in LNCaP-Abl PC cells (**C**), and the entire MYC<sup>High</sup>/MYC<sup>Low</sup> signature from the Koh et al dataset (**D**) to the Taylor et al. 2010 patient cohort. None of these signatures were a statistically significant predictor of BCR-free survival, suggesting that the prognostic significance of the core “SPOP<sup>MT</sup>;MYC<sup>High</sup>” geneset that is observed in Main Fig. 3D-C is not driven by either the c-MYC nor the SPOP component alone. Collectively, these observations highlight the critical functional cooperation of SPOP as a key partner of MYC in transcriptional regulation and clinical outcomes in PC.

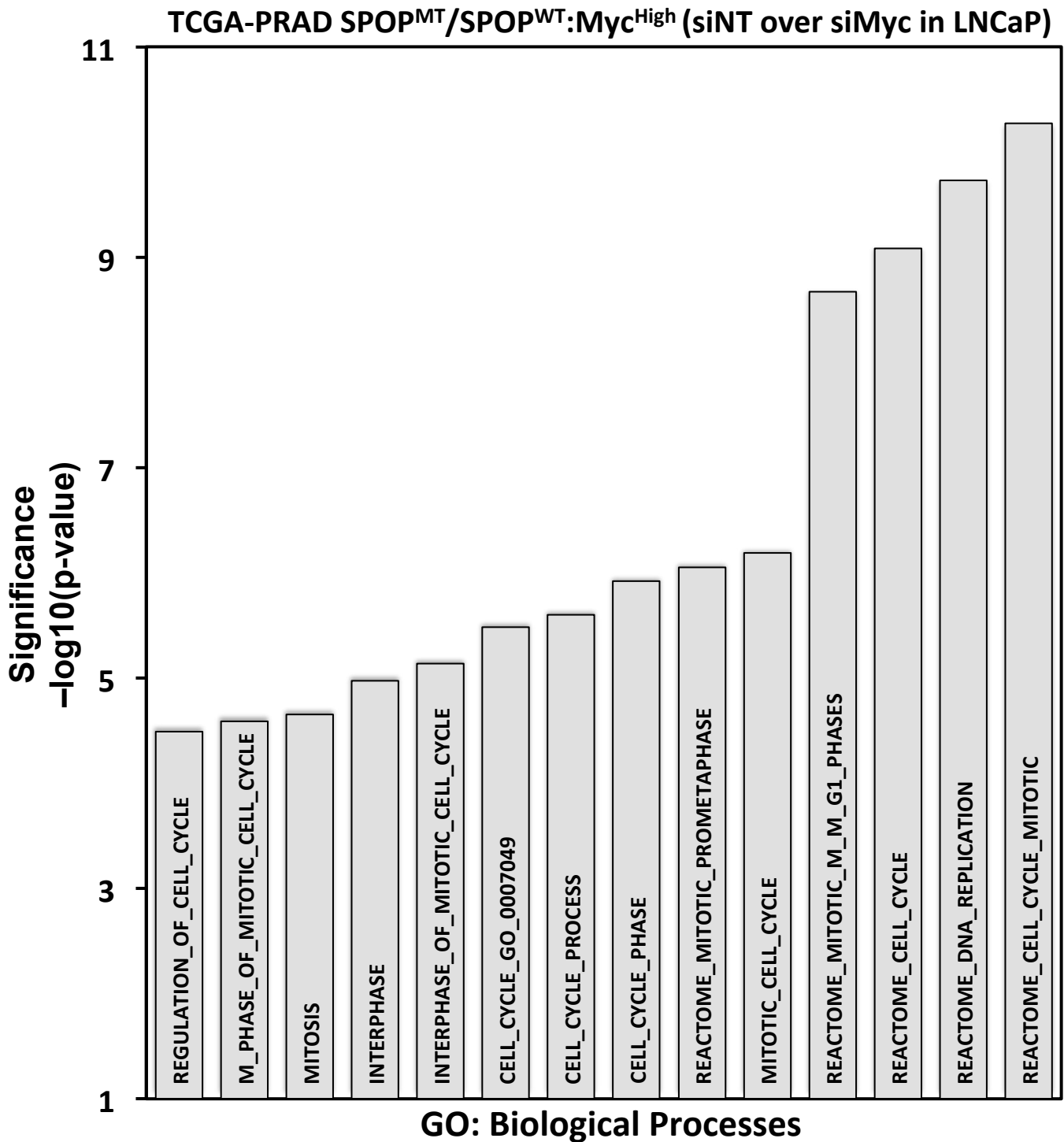


**C**



**D**

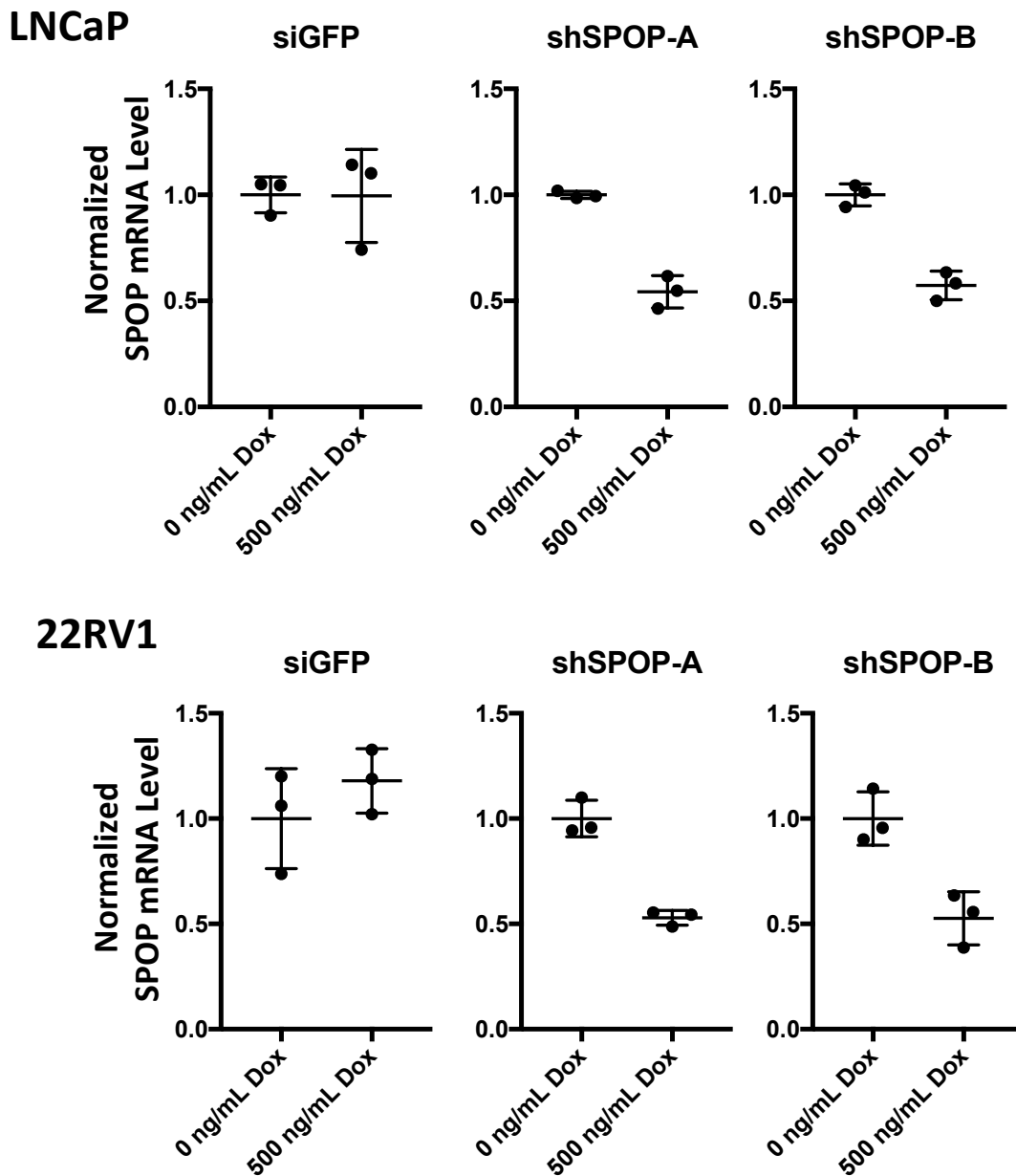




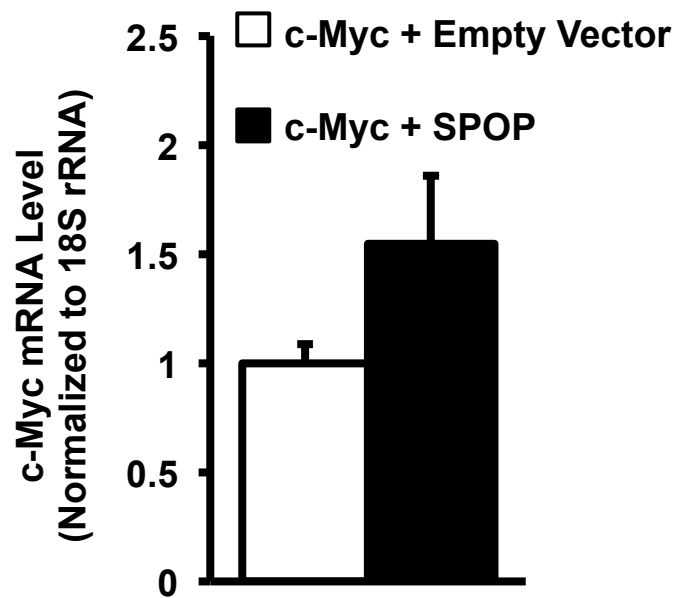
**Supplementary Figure 12: An overlapping, core transcriptomic program between the SPOP<sup>MT</sup> and MYC<sup>High</sup> gene signatures enriches for key cell cycle processes.** We inferred enriched REACTOME pathways and processes represented in the core SPOP<sup>Mut</sup>(TCGA);MYC<sup>High</sup>(Koh et al.) signature genes via the gene set collection as compiled in the Molecular Signature Database (MSigDB). We carried out over-representation analysis (ORA) of pathways and processes to assess significance ( $p < 0.001$ ). The top enriched terms are associated with cell cycle.

## Supplementary Figure 13

**Supplementary Figure 13: Decrease in *SPOP* mRNA upon induction of shSPOP via doxycycline in LNCaP and 22RV1 cells.** Using two distinct *SPOP*-specific short-hairpins, we knocked down *SPOP* in LNCaP and 22RV1. Shown here are the RTqPCR results following induction of shSPOP with 500 ng/ml of doxycycline. Control lines, LNCaP-shGFP and 22RV1-shGFP did not show any significant change in *SPOP* mRNA while lines harboring shSPOPs show decrease in *SPOP* mRNA. In the corresponding westerns, we found that c-MYC protein levels increased following *SPOP* knockdown compared to controls (Main Fig. 5A). Mean with SEM is shown.

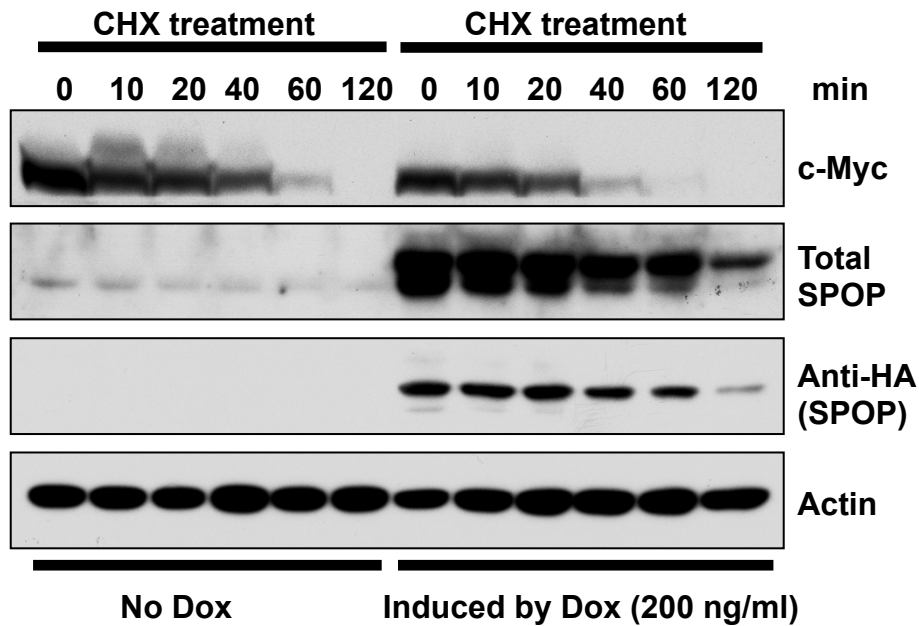


## Supplementary Figure 14



**Supplementary Figure 14: Exogenous SPOP<sup>WT</sup> does not suppress c-Myc mRNA levels in 293T cells.** Cells (293T) were transfected for 24hrs with pcDNA3.1-2xFlag-c-Myc vector along with either pcDNA3.1-HA-SPOPWT or empty vector. RT-qPCR for c-Myc was performed and transcript levels were normalized to 18S rRNA. The results did not demonstrate any evidence of suppression of c-Myc mRNA levels by SPOP<sup>WT</sup>.

## Supplementary Figure 15



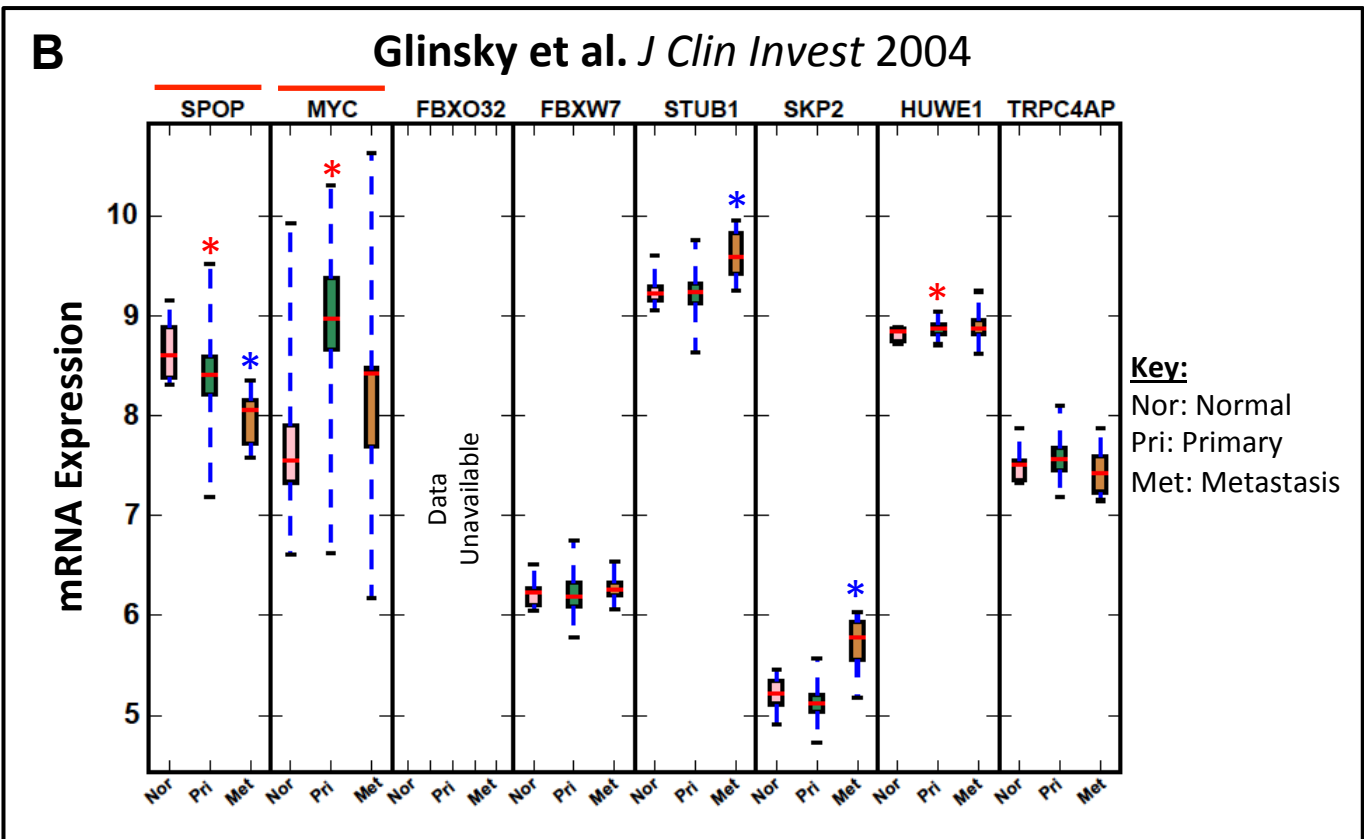
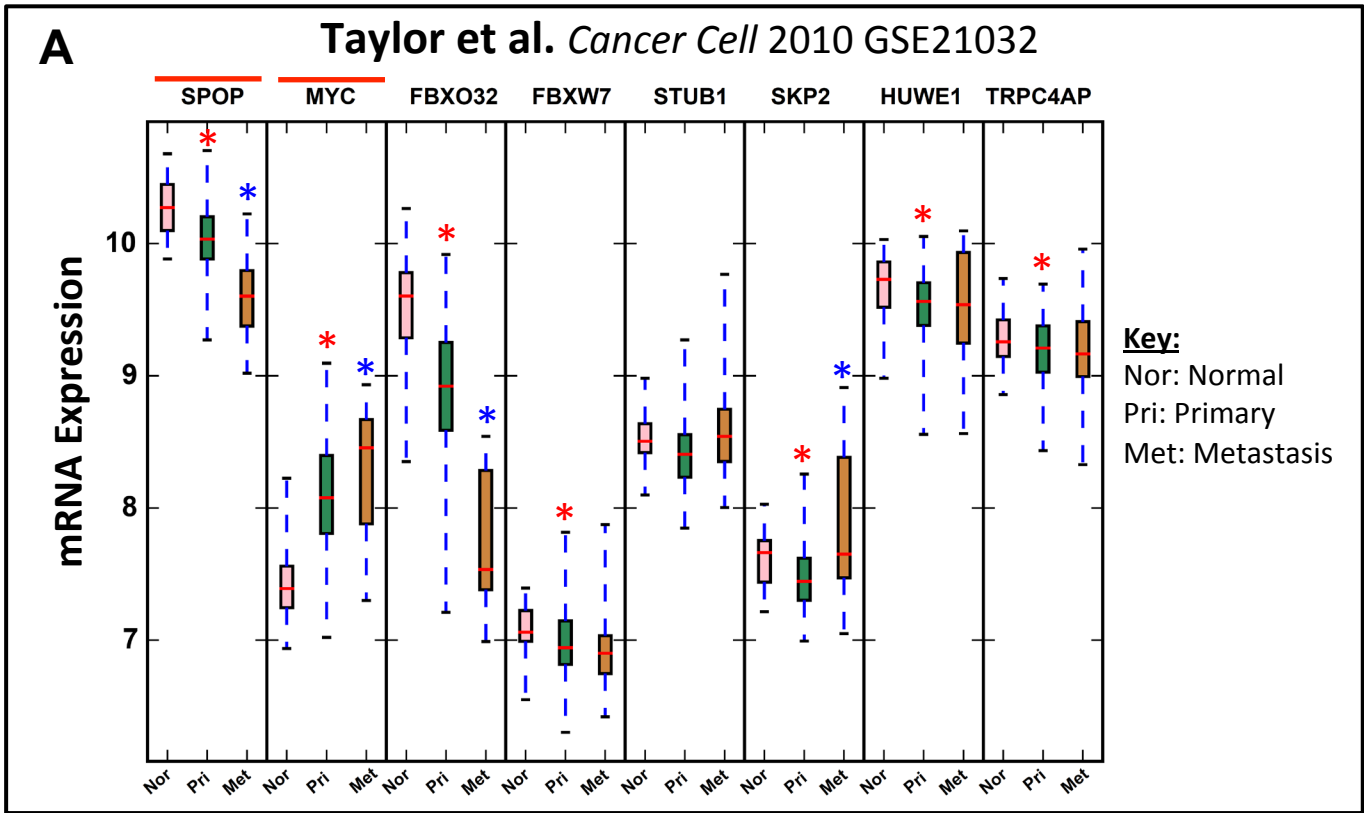
**Supplementary Figure 15: SPOP<sup>WT</sup> decreases the half-life of c-Myc protein in PC cells.** LNCaP cells with Doxycycline-inducible SPOP<sup>WT</sup> were treated with 200 ng/ml Doxycycline or distilled water (control) for 24 hours. Following this, 100  $\mu$ g/ml cycloheximide (CHX, final concentration) was added and the cells were collected 0, 10, 20, 40, 60, and 120 minutes later. The c-Myc protein, HA-tagged (exogenous) SPOP, total SPOP protein and  $\beta$ -actin were detected by immunoblot. Data from densitometric quantification are presented in Main **Fig. 6A**.

## Supplementary Figure 16

**Supplementary Figure 16: mRNA expression levels of regulators (E3 ligases and adaptors) that affect MYC protein stability.** Box-and-whisker plots of mRNA expression levels of various MYC regulators (E3 ligases and their adaptors) in four different publicly available prostate cancer patient datasets. Two panels for *SPOP* (also presented in **Suppl. Fig. 1**) and *c-MYC* are repeated in panels **A-L** for comparison purposes (red line). \*p-value<0.001. Red asterisks indicate comparison of normal/benign group against primary and blue asterisks indicate comparison of primary group with metastases or CRPC (as applicable). Gene expression levels are shown in log<sub>2</sub> format.

# Supplementary Figure 16

Expression of SPOP and other known regulators of c-Myc protein stability. mRNA levels of Spop and Myc are repeated from Suppl. Fig 1 for comparison purposes (red line).



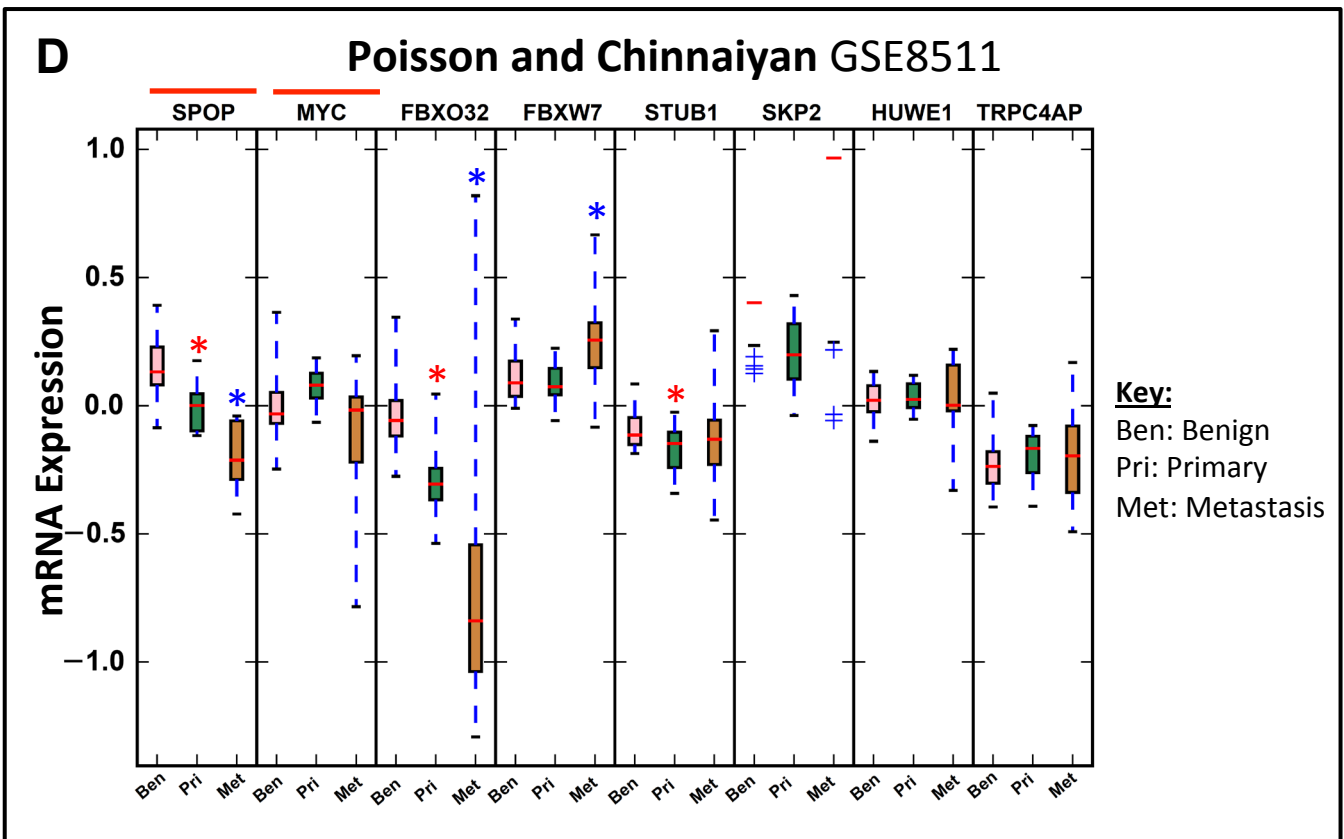
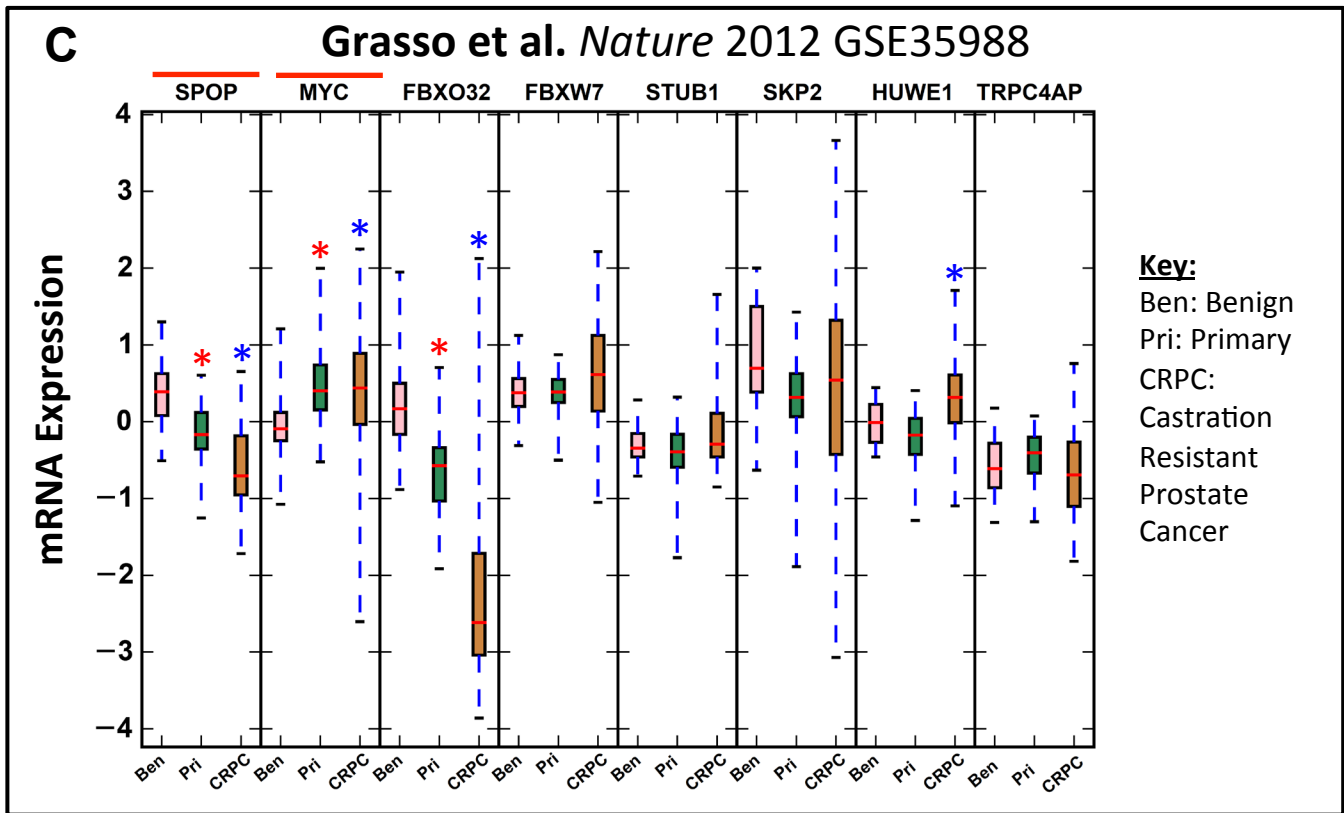
\* p-value <0.05 primary over normal

\* p-value <0.05 metastasis over primary



# Supplementary Figure 16

Expression of SPOP and other known regulators of c-Myc protein stability. mRNA levels of Spop and Myc are repeated from Suppl. Fig 1 for comparison purposes (red line).

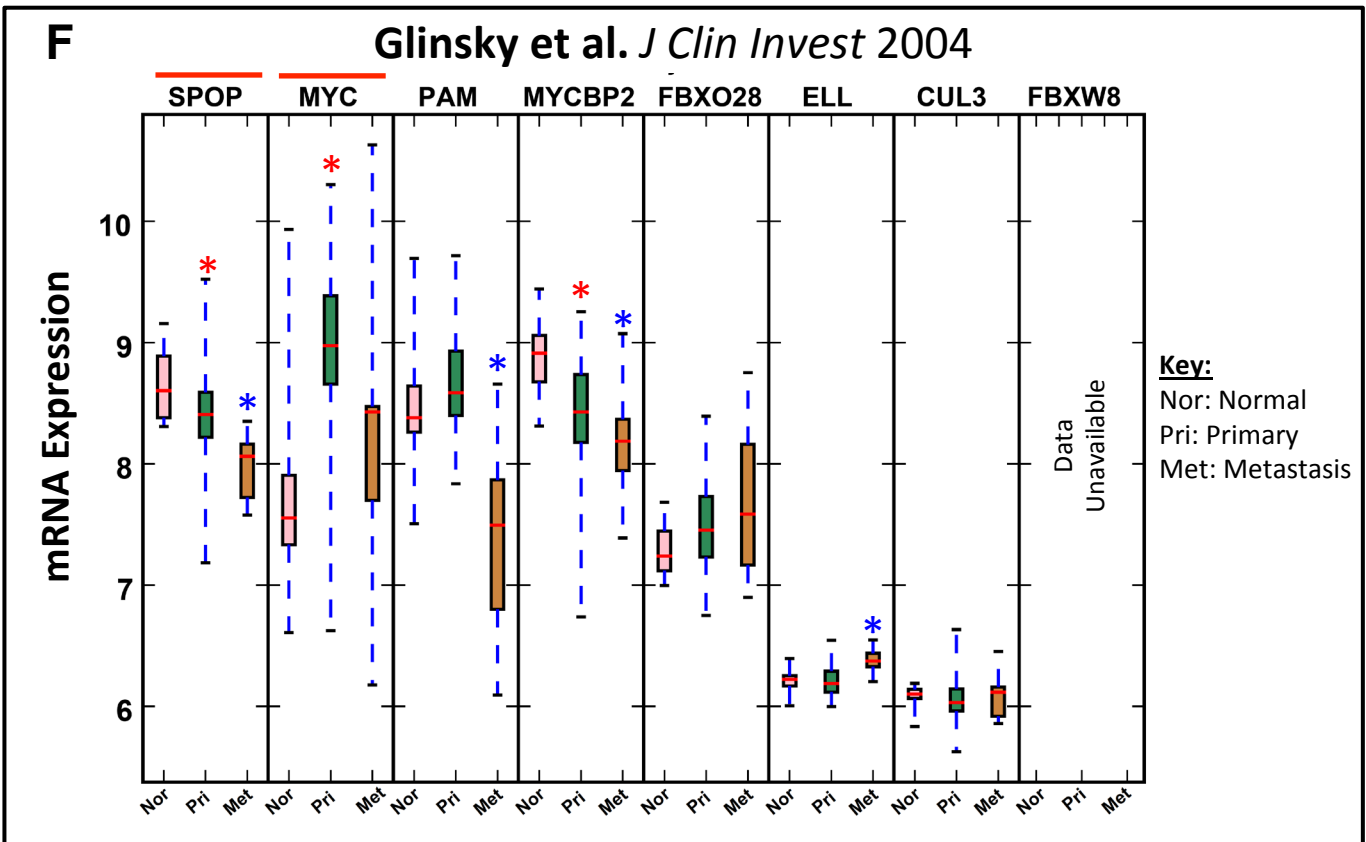
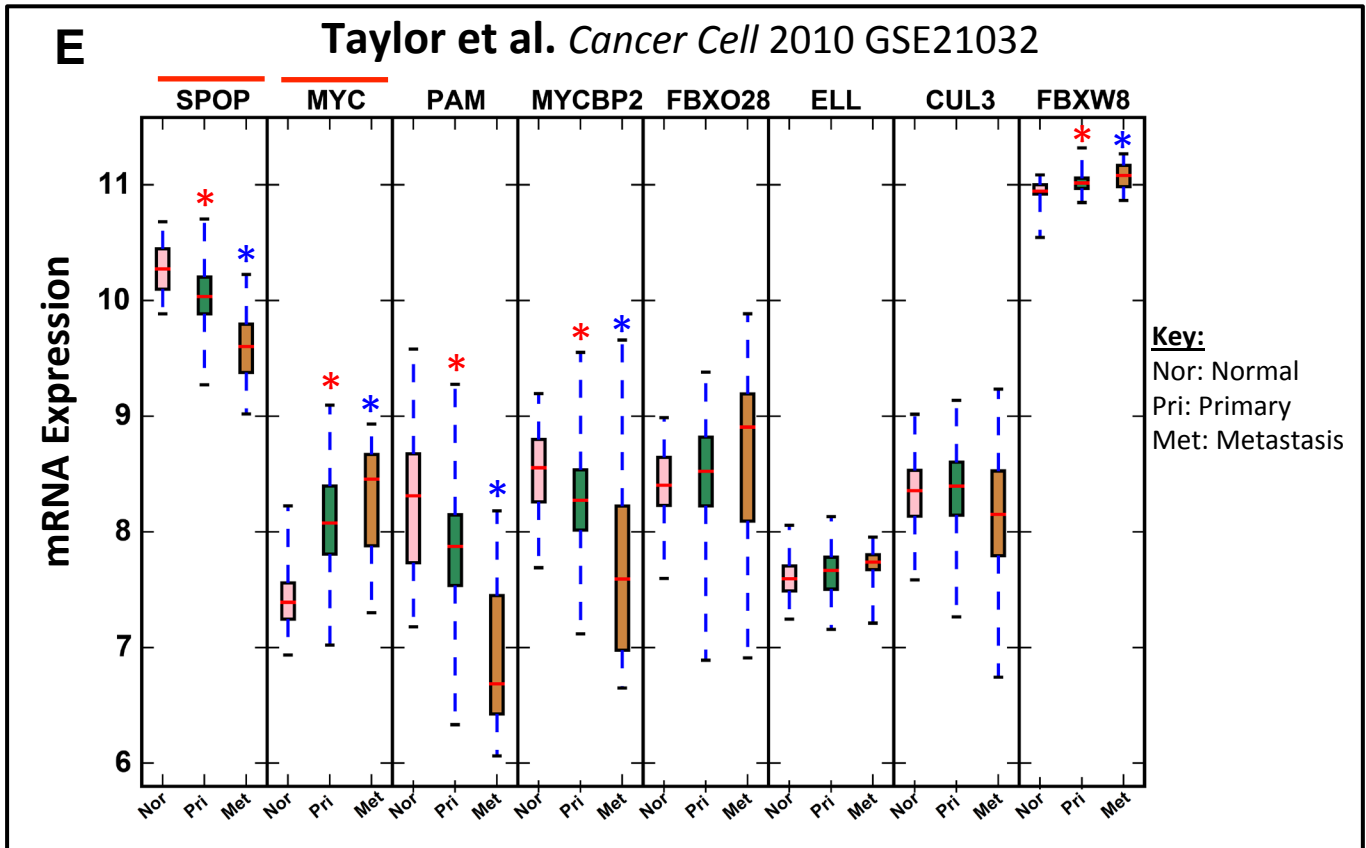


\* p-value < 0.05 primary over benign

\* p-value < 0.05 metastasis over primary

# Supplementary Figure 16

Expression of SPOP and other known regulators of c-Myc protein stability. mRNA levels of Spop and Myc are repeated from Suppl. Fig 1 for comparison purposes (red line).

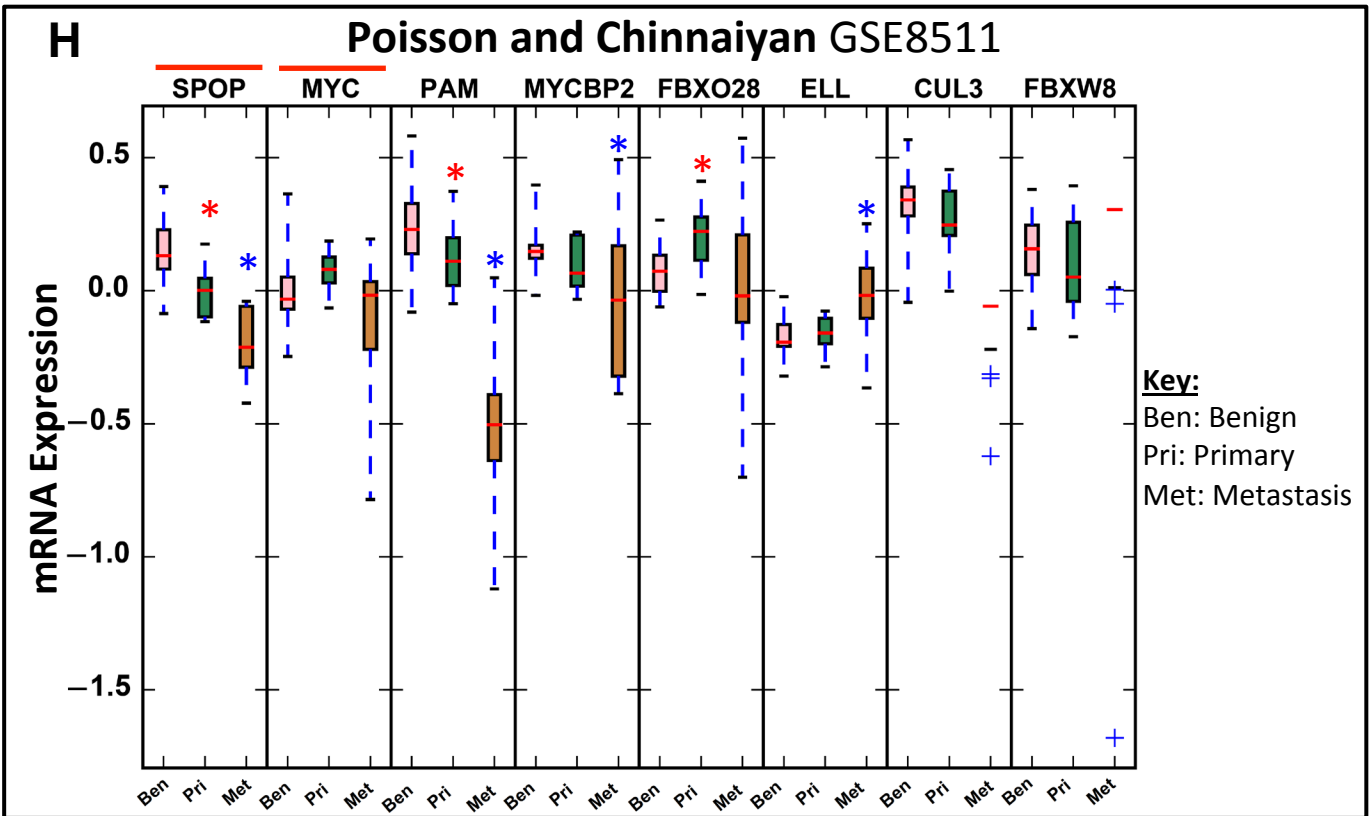
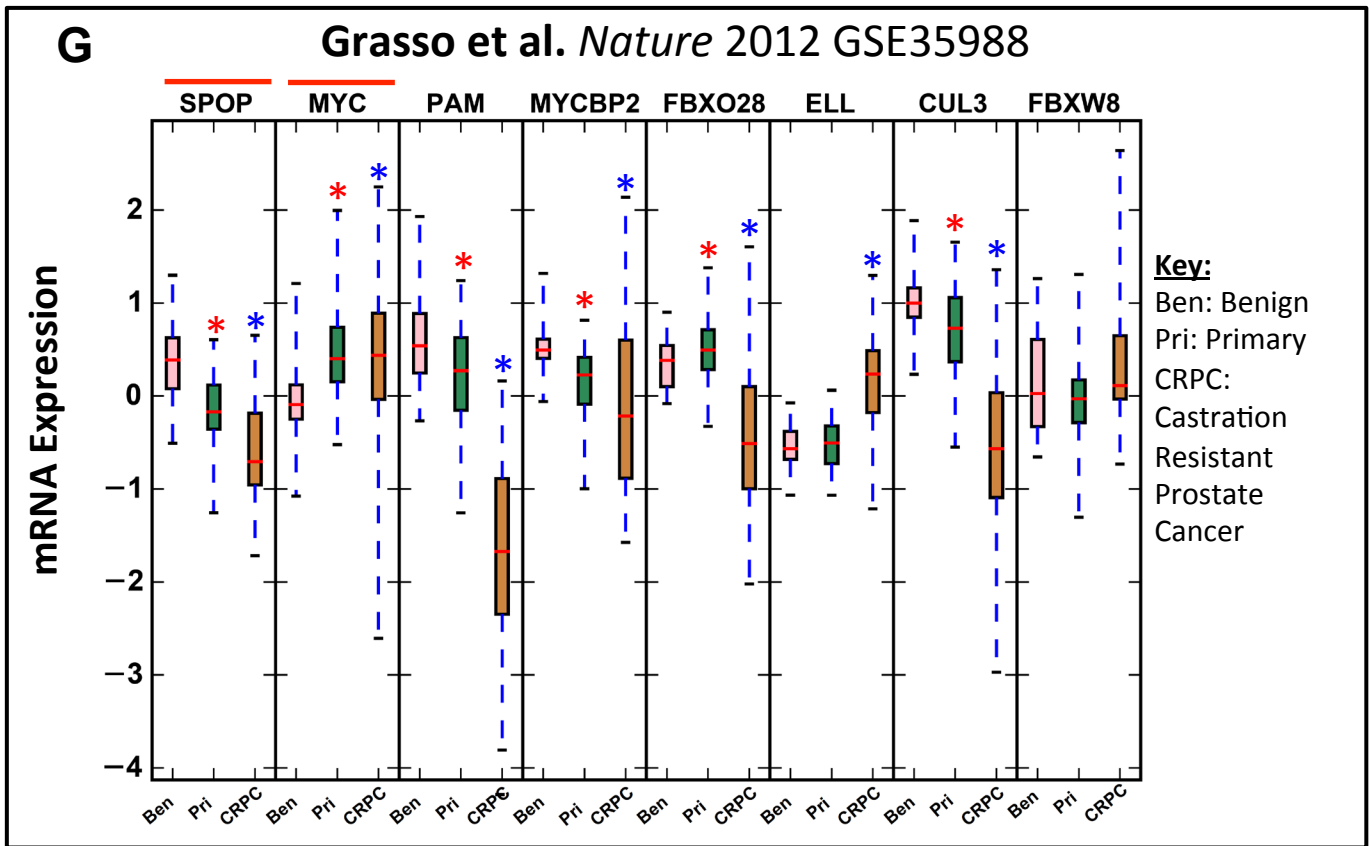


\* p-value <0.05 primary over normal

\* p-value <0.05 metastasis over primary

# Supplementary Figure 16

Expression of SPOP and other known regulators of c-Myc protein stability. mRNA levels of Spop and Myc are repeated from Suppl. Fig 1 for comparison purposes (red line).

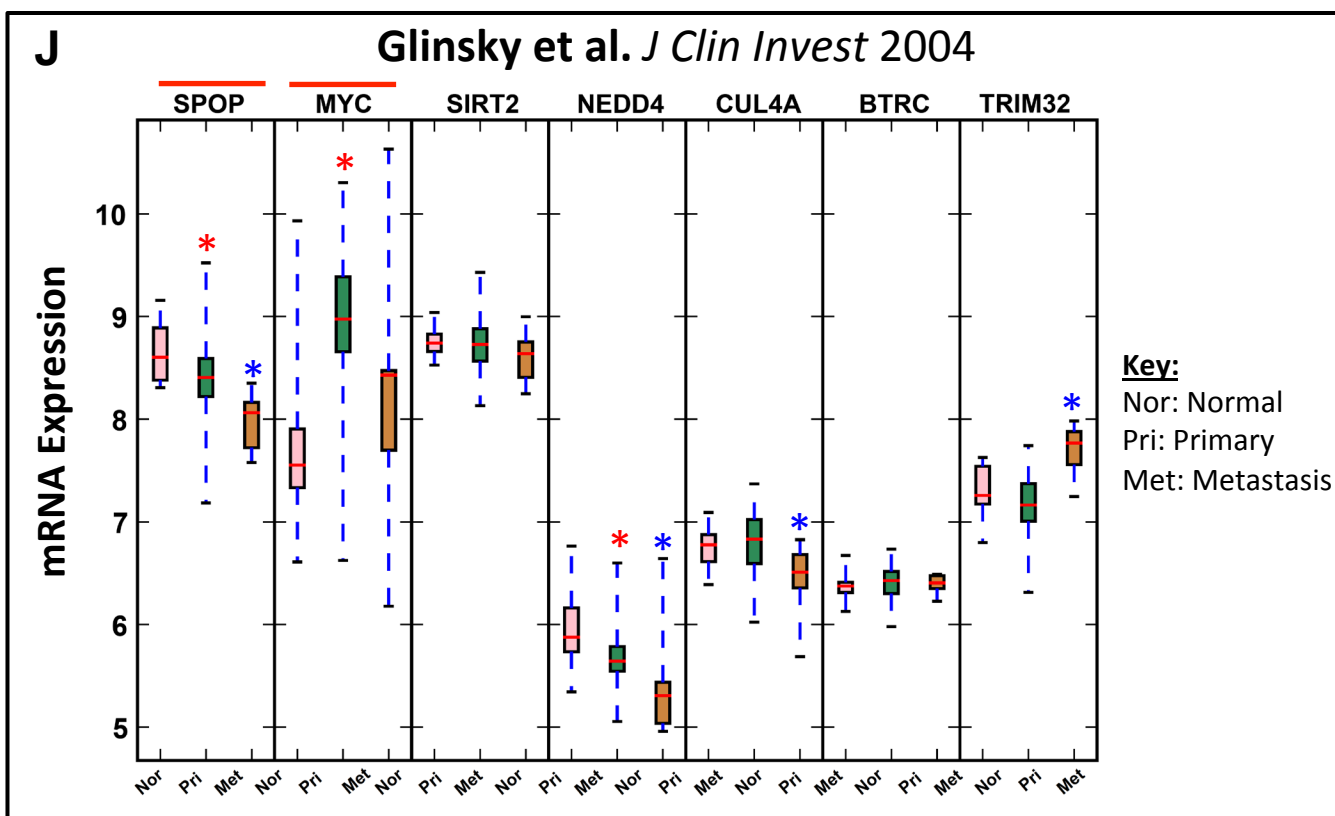
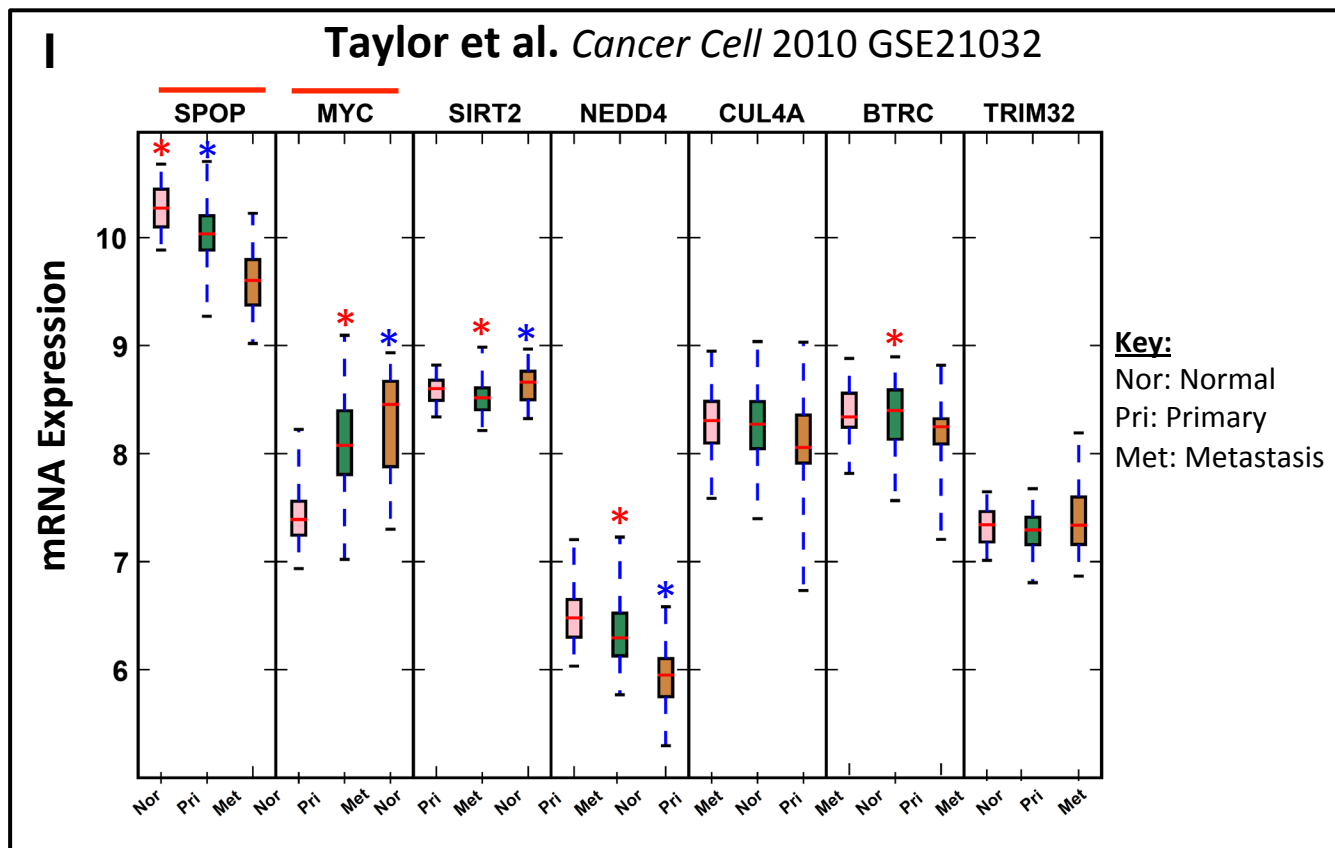


\* p-value < 0.05 primary over normal

\* p-value < 0.05 metastasis over primary

# Supplementary Figure 16

Expression of SPOP and other known regulators of c-Myc protein stability. mRNA levels of Spop and Myc are repeated from Suppl. Fig 1 for comparison purposes (red line).

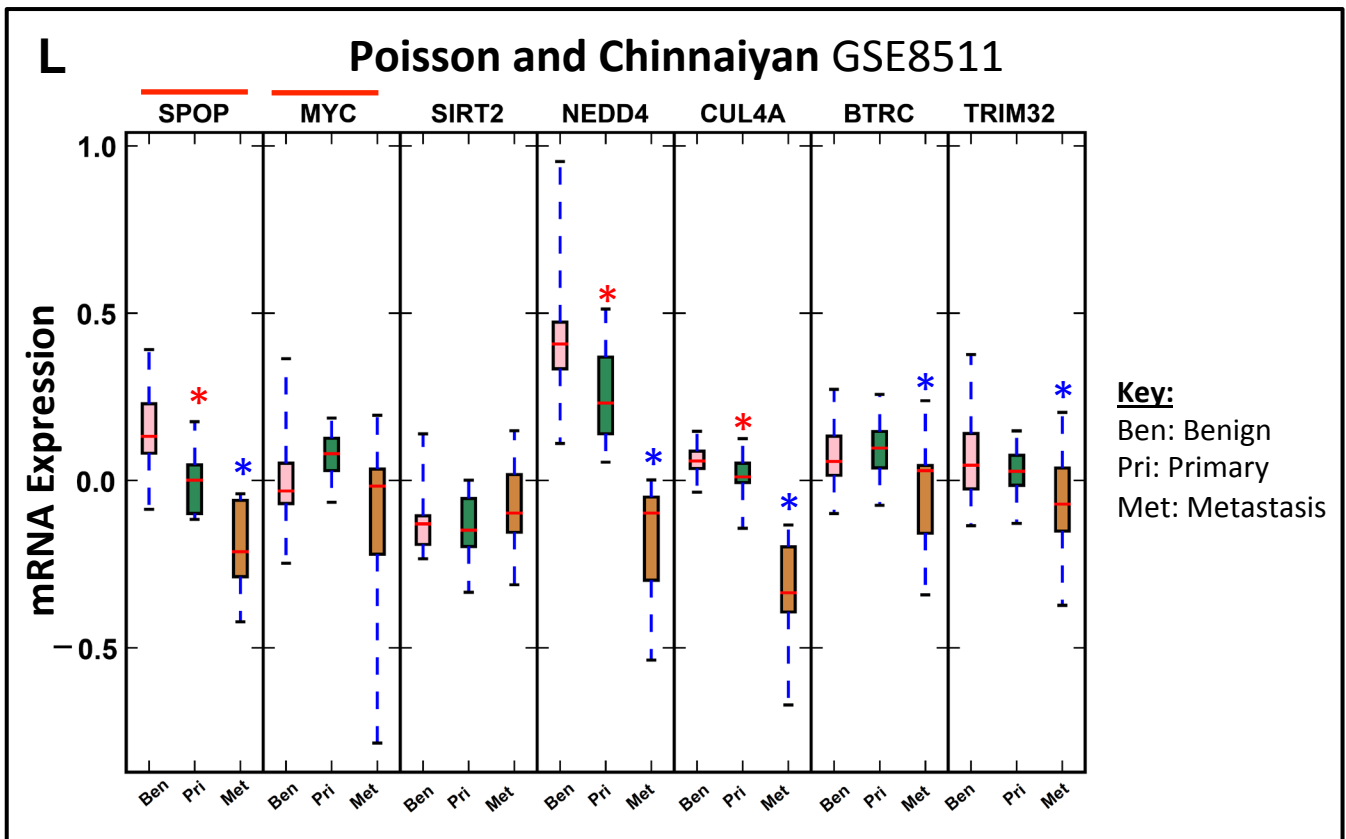
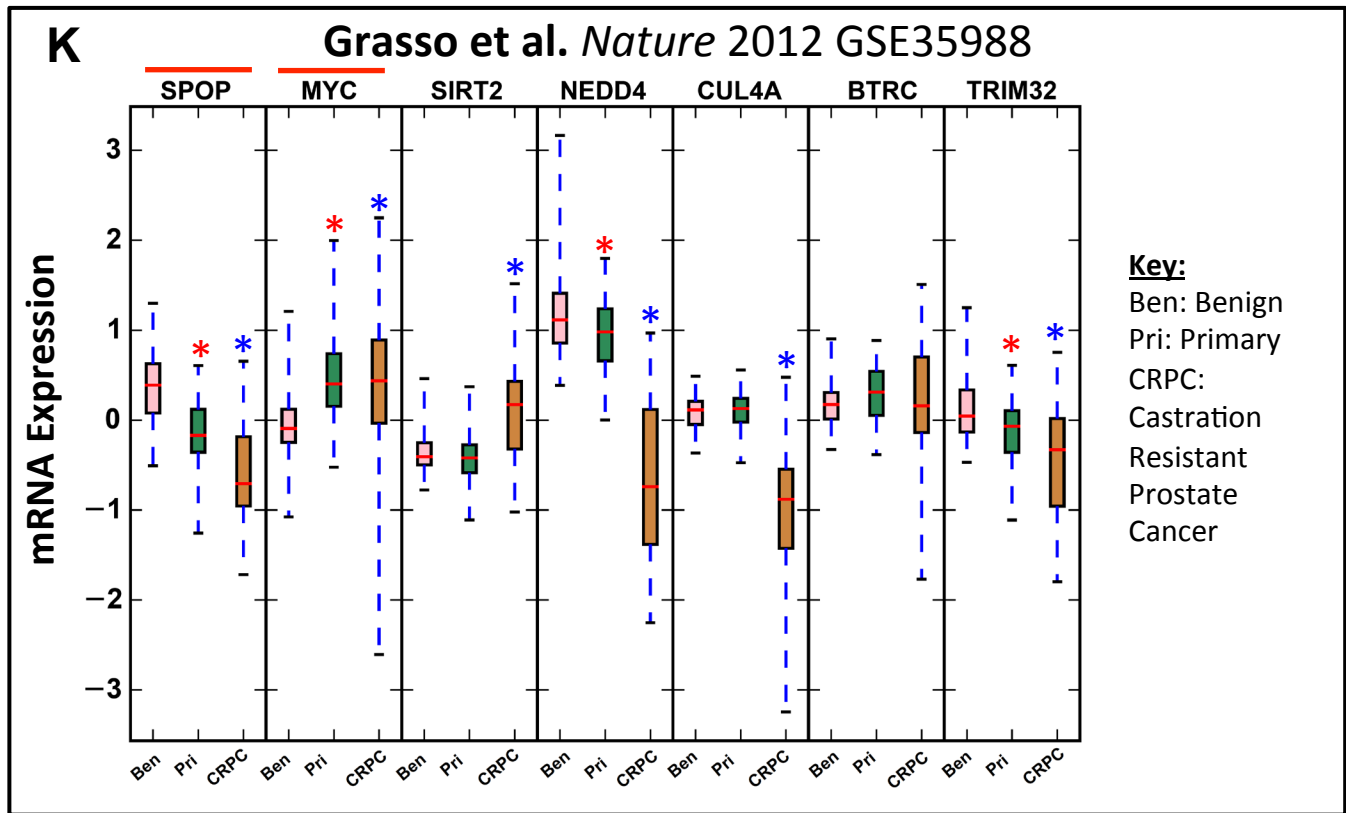


\* p-value < 0.05 primary over normal

\* p-value < 0.05 metastasis over primary

## Supplementary Figure 16

Expression of SPOP and other known regulators of c-Myc protein stability. mRNA levels of Spop and Myc are repeated from Suppl. Fig 1 for comparison purposes (red line).



\* p-value <0.05 primary over normal

\* p-value <0.05 metastasis over primary

**Table 1:** Correlation between Myc activity (calculated based on Myc overexpression signature from murine (GSE37428)) versus mRNA levels of Myc protein stability regulators (E3 ligases and their adaptors) applied to Taylor et al. 2010 dataset.

<b>mRNA Levels of Regulators of Myc Protein Stability</b>	<b>Pearson's Correlation Coefficient</b>	<b>P-value</b>
<b>SPOP</b>	-0.64	6.88E-16
<b>FBXO32</b>	-0.50	2.38E-09
FBXW7	-0.26	0.002957242
STUB1	0.42	7.95E-07
SKP2	-0.01	0.928320715
<b>HUWE1</b>	-0.22	0.011035811
TRPC4AP	-0.04	0.657784598
<b>PAM</b>	-0.54	8.63E-11
<b>MYCBP2</b>	-0.35	4.42E-05
<b>FBXO28</b>	-0.27	0.001894881
ELL	0.35	4.87E-05
<b>CUL3</b>	-0.39	5.02E-06
FBXW8	0.17	0.050718045
SIRT2	0.25	0.004919893
<b>NEDD4</b>	-0.37	2.06E-05
<b>CUL4A</b>	-0.22	0.011614155
BTRC	-0.17	0.053290011
TRIM32	-0.09	0.30420196

**Table 2:** Correlation between Myc activity (calculated based on Myc overexpression signature from LNCaP (GSE51384)) versus mRNA levels of Myc protein stability regulators (E3 ligases and their adaptors) applied to Taylor et al. 2010 dataset.

<b>mRNA Levels of Regulators of Myc Protein Stability</b>	<b>Pearson's Correlation Coefficient</b>	<b>P-value</b>
<b>SPOP</b>	-0.55	2.16E-11
<b>FBXO32</b>	-0.36	2.66E-05
FBXW7	-0.41	1.59E-06
STUB1	0.54	8.21E-11
SKP2	-0.18	0.044128544
<b>HUWE1</b>	-0.24	0.007449648
TRPC4AP	-0.09	0.315804394
<b>PAM</b>	-0.45	1.37E-07
<b>MYCBP2</b>	-0.63	3.94E-15
<b>FBXO28</b>	-0.48	7.57E-09
ELL	0.75	3.43E-24
<b>CUL3</b>	-0.63	1.68E-15
FBXW8	-0.10	0.245070343
SIRT2	0.47	2.28E-08
<b>NEDD4</b>	-0.48	8.40E-09
<b>CUL4A</b>	-0.50	3.13E-09
BTRC	-0.40	2.55E-06
TRIM32	-0.09	0.31245268

**Table 3:** Correlation between Myc activity (calculated based on siNT over siMyc signature from LNCaP (Koh et al. 2011 )) versus mRNA levels of Myc protein stability regulators (E3 ligases and their adaptors) applied to Taylor et al. 2010 dataset.

<b>mRNA Levels of Regulators of Myc Protein Stability</b>	<b>Pearson's Correlation Coefficient</b>	<b>P-value</b>
<b>SPOP</b>	-0.52	2.54E-10
<b>FBXO32</b>	-0.28	0.001541723
FBXW7	0.01	0.902838627
STUB1	-0.15	0.082081341
SKP2	-0.01	0.884682309
<b>HUWE1</b>	-0.41	1.56E-06
TRPC4AP	-0.46	6.15E-08
<b>PAM</b>	-0.35	5.45E-05
<b>MYCBP2</b>	-0.45	1.40E-07
<b>FBXO28</b>	-0.47	3.03E-08
ELL	0.29	0.001149674
<b>CUL3</b>	-0.45	1.00E-07
FBXW8	0.06	0.506142492
SIRT2	0.07	0.456292481
<b>NEDD4</b>	-0.19	0.036683614
<b>CUL4A</b>	-0.53	9.60E-11
BTRC	-0.57	3.84E-12
TRIM32	-0.03	0.723728607



**Table 4:** Correlation between Myc activity (calculated based on Myc overexpression signature from murine (GSE37428)) versus mRNA levels of Myc protein stability regulators (E3 ligases and their adaptors) applied to TCGA-PRAD 2015 dataset.

<b>mRNA Levels of Regulators of Myc Protein Stability</b>	<b>Pearson's Correlation Coefficient</b>	<b>P-value</b>
<b>SPOP</b>	-0.42	4.38E-23
<b>FBXO32</b>	-0.41	1.26E-21
FBXW7	0.08	0.067467323
STUB1	0.48	2.31E-30
SKP2	0.09	0.055250399
<b>HUWE1</b>	-0.39	1.83E-19
TRPC4AP	0.08	0.060535485
<b>PAM</b>	-0.65	7.91E-61
<b>MYCBP2</b>	-0.50	7.17E-33
FBXO28	0.02	0.670132404
ELL	0.27	1.25E-09
CUL3	-0.04	0.346576706
FBXW8	0.15	0.000584216
SIRT2	0.23	2.99E-07
<b>NEDD4</b>	-0.46	7.47E-28
<b>CUL4A</b>	-0.15	0.000809463
<b>BTRC</b>	-0.16	0.000519766
TRIM32	-0.15	0.001123754

**Table 5:** Correlation between Myc activity (calculated based on Myc overexpression signature from LNCaP (GSE51384)) versus mRNA levels of Myc protein stability regulators (E3 ligases and their adaptors) applied to TCGA-PRAD 2015 dataset.

<b>mRNA Levels of Regulators of Myc Protein Stability</b>	<b>Pearson's Correlation Coefficient</b>	<b>P-value</b>
<b>SPOP</b>	-0.32	3.06E-13
<b>FBXO32</b>	-0.21	3.28E-06
FBXW7	0.06	0.195537536
STUB1	0.43	3.00E-23
SKP2	-0.01	0.908511693
<b>HUWE1</b>	-0.27	1.31E-09
TRPC4AP	0.07	0.099223185
<b>PAM</b>	-0.44	2.14E-24
<b>MYCBP2</b>	-0.41	4.71E-22
FBXO28	-0.13	0.002836123
ELL	0.38	4.16E-18
CUL3	-0.20	6.16E-06
FBXW8	0.13	0.003092748
SIRT2	0.16	0.000300755
<b>NEDD4</b>	-0.36	2.01E-16
<b>CUL4A</b>	-0.16	0.000420676
<b>BTRC</b>	-0.13	0.002760294
TRIM32	-0.12	0.005766786

**Table 6:** Correlation between Myc activity (calculated based on siNT over siMyc signature from LNCaP (Koh et al. 2011 )) versus mRNA levels of Myc protein stability regulators (E3 ligases and their adaptors) applied to TCGA-PRAD 2015 dataset.

<b>mRNA Levels of Regulators of Myc Protein Stability</b>	<b>Pearson's Correlation Coefficient</b>	<b>P-value</b>
<b>SPOP</b>	-0.31	1.46E-12
<b>FBXO32</b>	-0.26	2.13E-09
FBXW7	0.23	1.47E-07
STUB1	0.21	2.26E-06
SKP2	0.31	1.46E-12
<b>HUWE1</b>	-0.12	0.005615569
TRPC4AP	-0.06	0.219292071
<b>PAM</b>	-0.27	1.44E-09
<b>MYCBP2</b>	-0.33	1.69E-14
FBXO28	0.05	0.233621701
ELL	0.23	1.22E-07
CUL3	-0.04	0.32792196
FBXW8	0.06	0.189161173
SIRT2	0.11	0.013286303
<b>NEDD4</b>	-0.38	2.23E-18
<b>CUL4A</b>	-0.17	0.000101077
<b>BTRC</b>	-0.28	1.23E-10
TRIM32	0.14	0.001205518