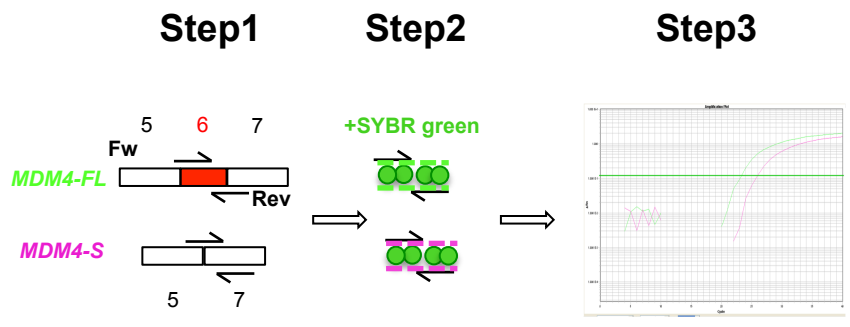
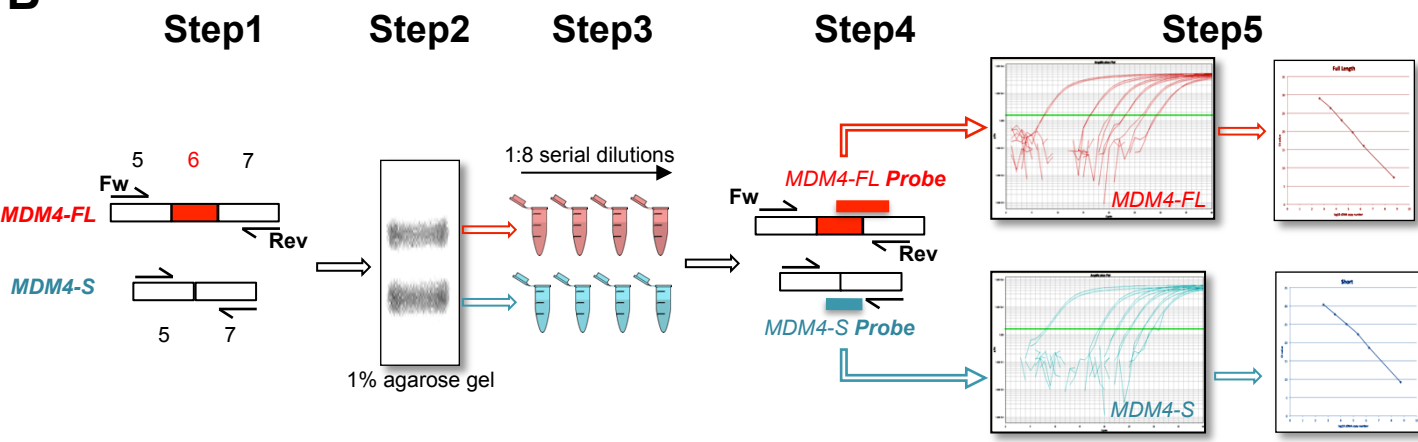


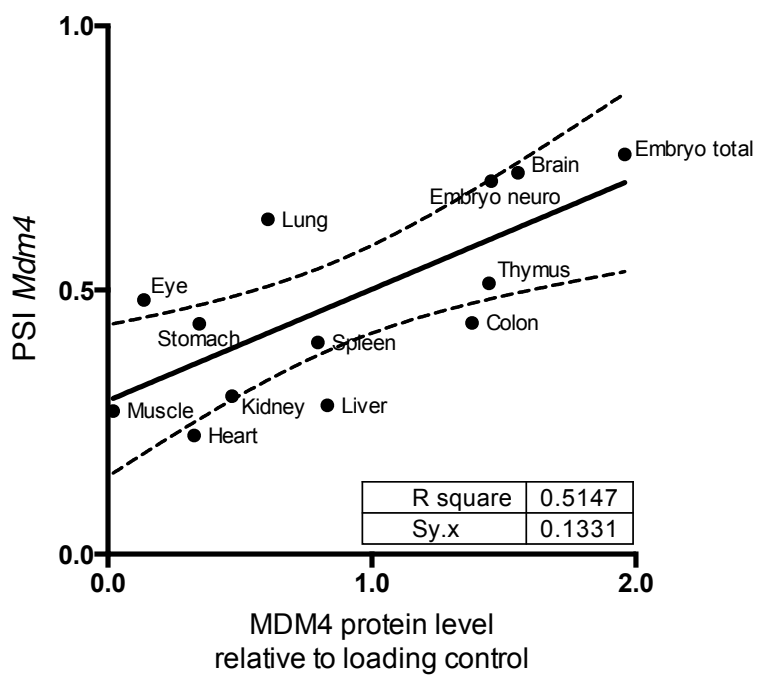
A



B

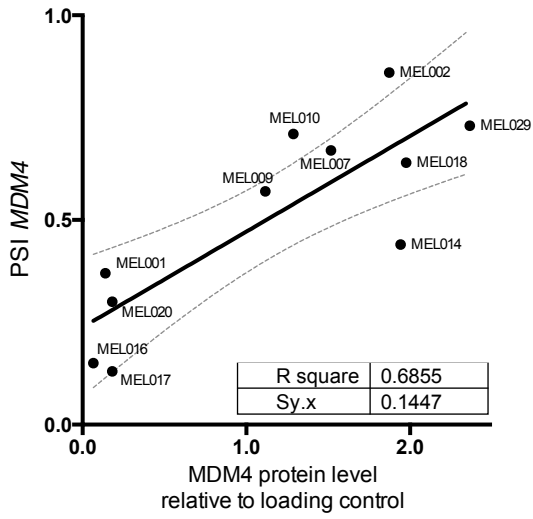


C

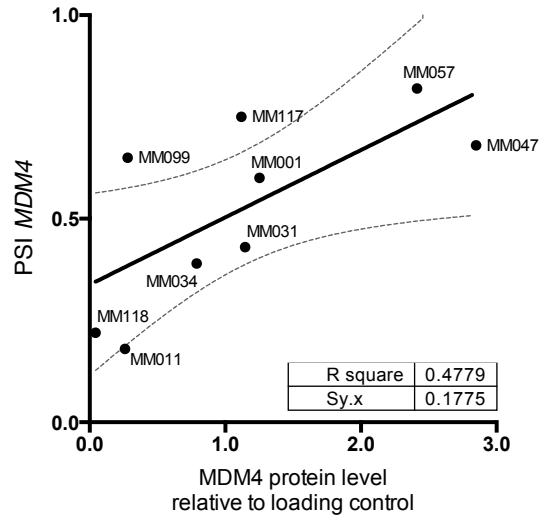


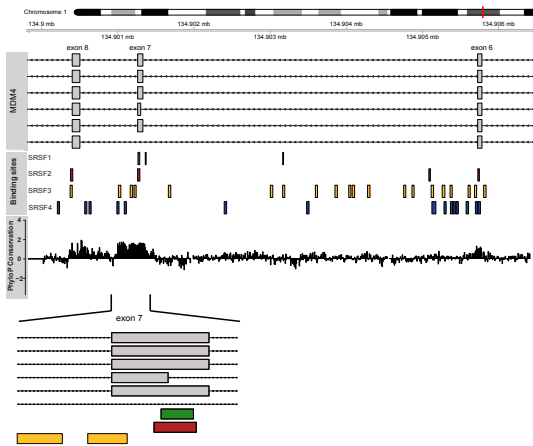
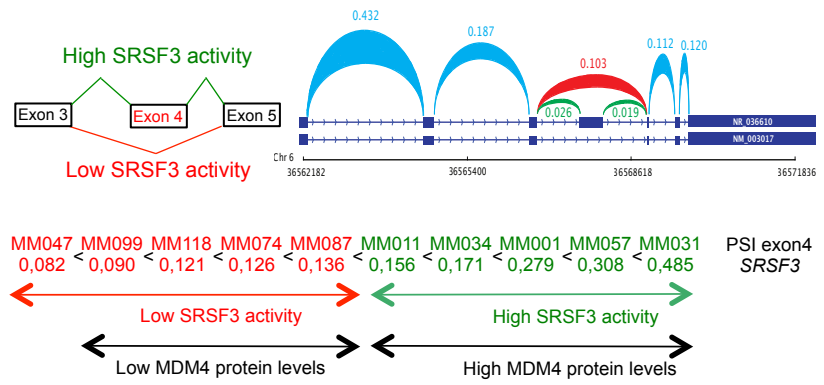
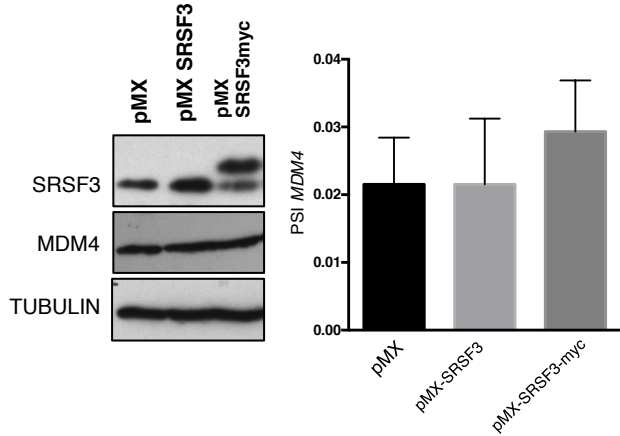
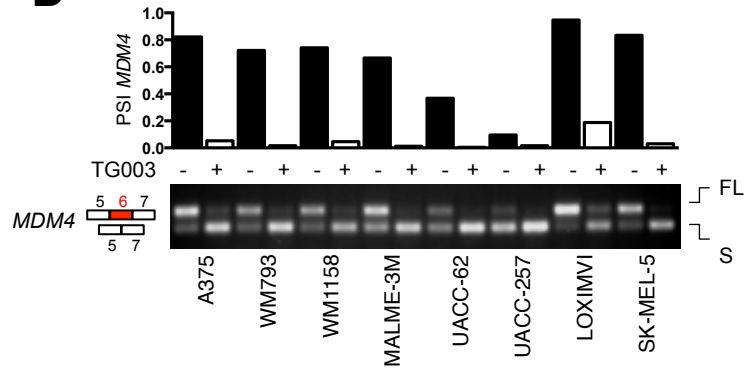
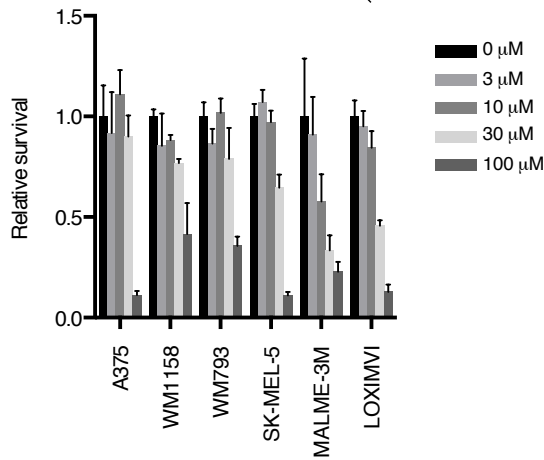
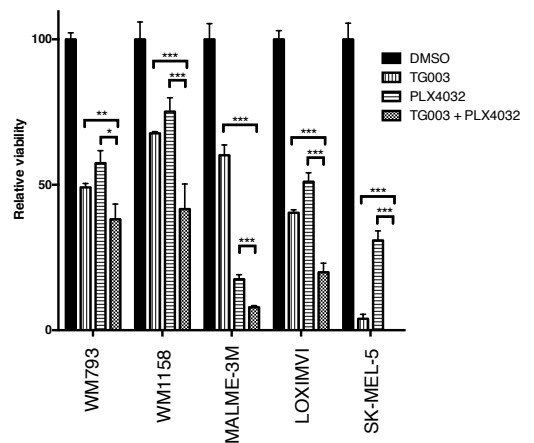
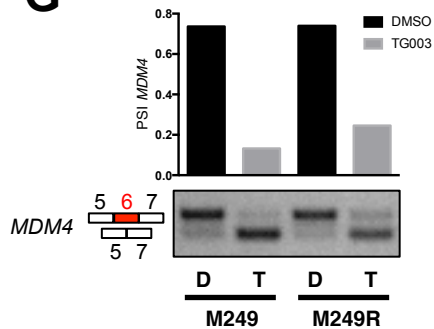
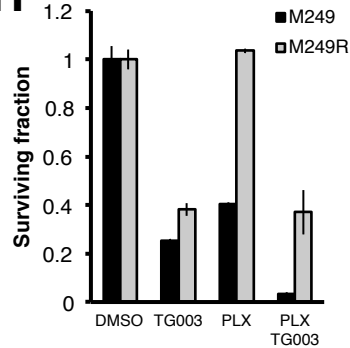
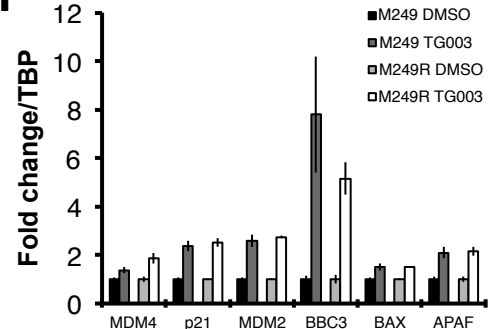
Supplementary Figure 2

A

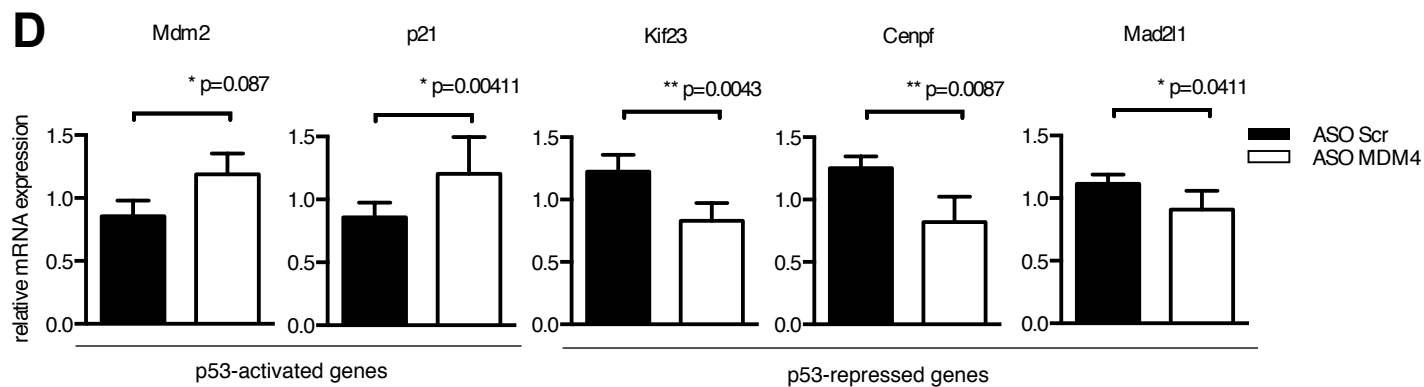
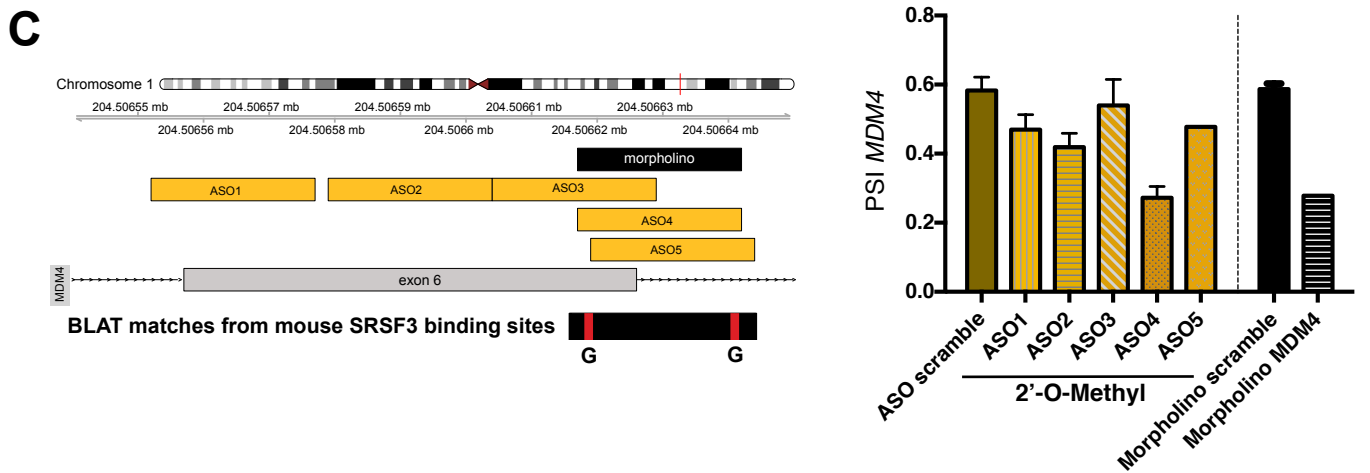
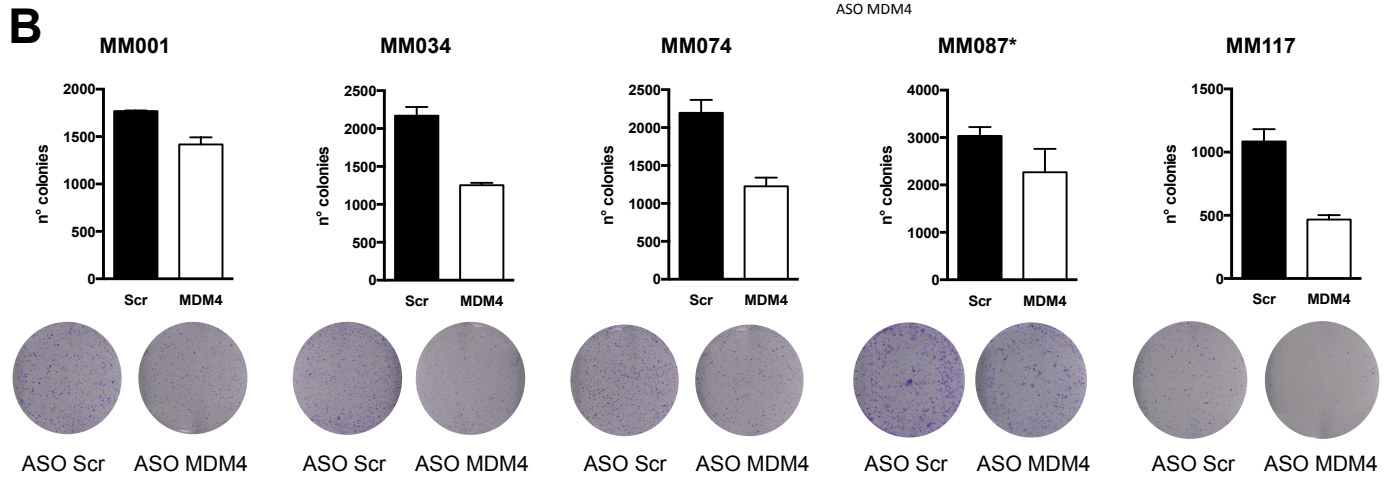
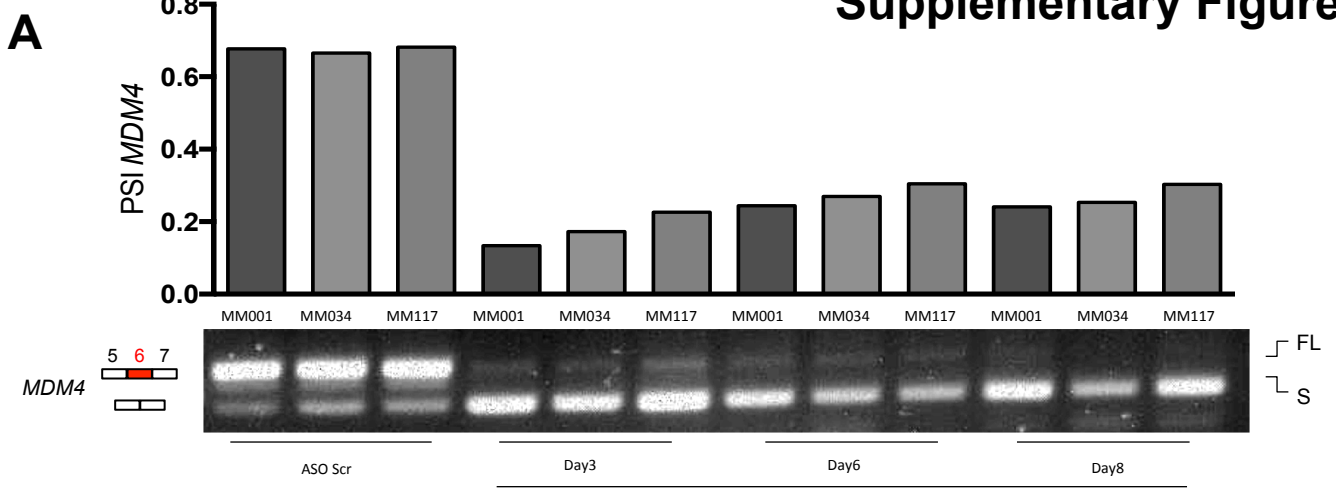


B

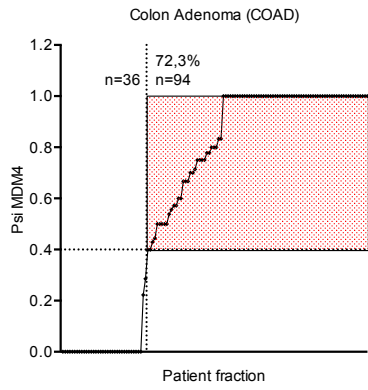
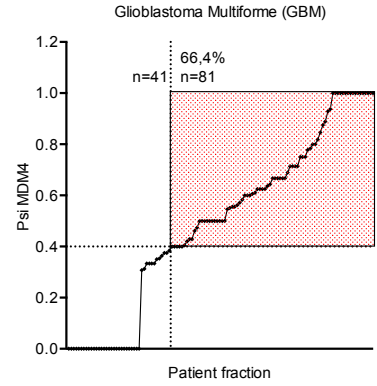
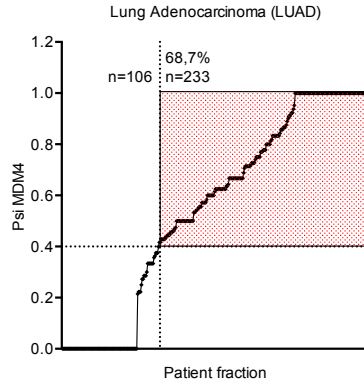
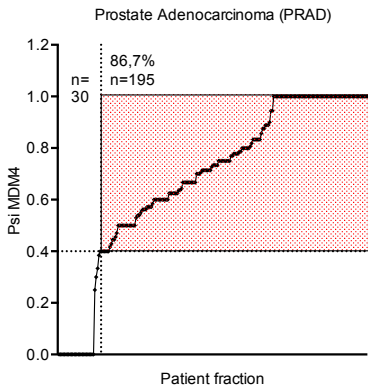
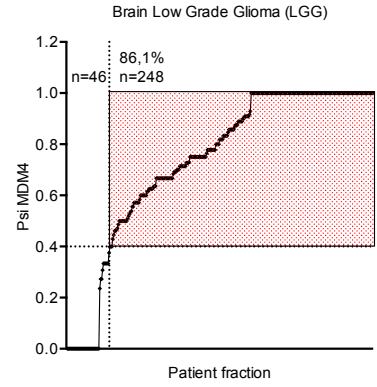
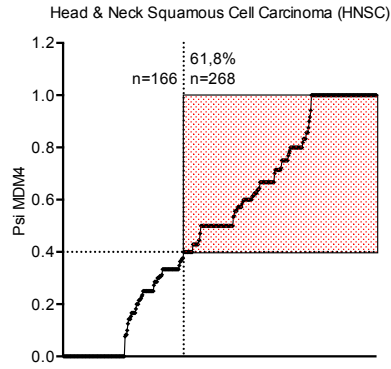
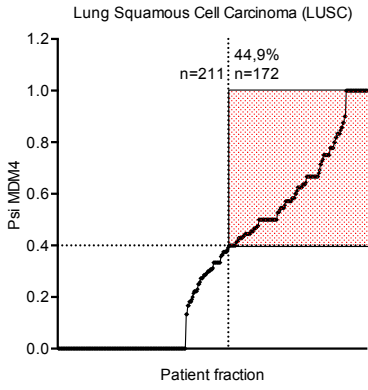


A**B****Supplementary Figure 3****C****D****E****F****G****H****I**

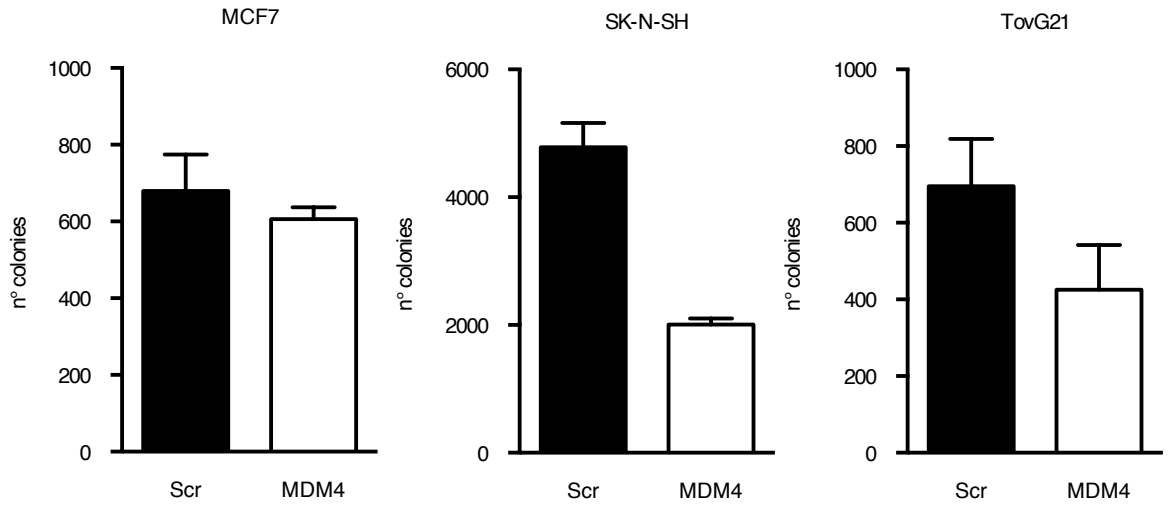
Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure 6



Supplementary Table ST1. PDX xenopatient information

Xenopatient	MEL002	MEL006	MEL010	BCL13
Gender	Female	Female	Female	Male
Year of birth	1931	1947	1955	1962
Melanoma Stage	In transit metastasis	In transit metastasis	Lymph node	n.a.
Biopt location	Upper leg	Arm	Chest	Pleural effusion
Treatment prior to biopt	Dacarbazine	Surgery, ipilimumab, dabrafenib-trametinib	Surgery, dabrafenib-trametinib	CHOP, RICE, intrathecal methotrexate/cytarabine, DHAP
BRAF V600 status	WT	V600E	V600E	-
NRAS Q61 status	WT	WT	WT	-
p53 status	WT (SNP c.215C>G; p.P72R)	WT (SNP c.215C>G; p.P72R)	WT (SNP c.215C>G;p.P72R)	HET (c.907G>G/C (WT/missense))

Supplementary Table ST2. Antibodies

Protein	Reactive species	Company	Clone/Catalog number	Working concentration
MDM4	Human	Millipore	8C6	1:1000
MDM4	Mouse	Sigma-Aldrich	MDMX-82	1:1000
MDM2	Human	Homemade mAb + Santa Cruz Biotechnology	4B2 (Homemade) and SMP14, sc-965	1:1000
p53	Human	Santa Cruz Biotechnology	DO-1, sc-126	1:5000
p21	Human	Santa Cruz Biotechnology	F-5, sc-6246	1/500
SRSF3	Human	Abcam	Ab125124	1/500
Actin	Human/Mouse	Sigma-Aldrich/Santa Cruz Biotechnology	A2066/C4	1:10000/1:1000
b-Tubulin	Human	Sigma-Aldrich	T5168	1:10000
GAPDH	Human/Mouse	Abcam	Ab9485	1:1000

Supplementary Table ST3. Primers

SybrGreen-based RT-qPCR			
Gene	Forward	Reverse	
Human	<i>Total MDM4</i>	AGGTGCGCAAGGTGAAATGT	CCATATGCTGCTCCTGCTGAT
	<i>MDM4-FL</i>	GATGCTGCTCAGACTCTCGC	TGCACTTTGCTTCAGTTGGTC
	<i>MDM4-S</i>	GCCACTGCTACTACAGCAAAG	TCTGAGGTAGGCAGTGTGGG
	<i>MDM2</i>	AGGAGATTTGTTTGGCGTGC	TGAGTCCGATGATTCCTGCTG
	<i>p21</i>	GGCCTGGACTGTTTTCTCTCG	GAGAAACGGGAACCAGGACAC
	<i>BBC3</i>	GACCTCAACGCACAGTA	CTAATTGGGCTCCATCT
	<i>SRSF1</i>	TGGTTGTCTCTGGACTGCCT	ACACCAGTGCCATCTCGGTA
	<i>SRSF2</i>	CGGAGCCGCAGCCCTA	AGATCGAGAACGAGTGCCGG
	<i>SRSF3</i>	AGCTGATGCAGTCCGAGAG	GGTGGGCCACGATTTCTAC
	<i>SRSF4</i>	TCTGAAGAACGGATATGGTTTTGTG	CTCGCTCACCACAAAGGTCT
	<i>CENPF</i>	CTCTCCCGTCAACAGCGTTC	GTTGTGCATATTCTTGGCTTGC
	<i>KIF23</i>	TGCTGCCATGAAGTCAGCGAGAG	CCAGTGGGCGCACCCTACAG
	<i>MAD2L1</i>	AAGTGGTGAGGTCCTGGAAA	TTCCAACAGTGGCAGAAATG
	<i>TBP</i> (RefGen)	AATCTGTGCATGCTGGTCTGCC	AGGAGATTTGTTTGGCGTGC
	<i>UBC</i> (RefGen)	ATTTGGGTCGCGGTTCTTG	TGCCTTGACATTCTCGATGGT
<i>YWHAZ</i> (RefGen)	ACTTTTGGTACATTGTGGCTTCAA	CCGCCAGGACAAACCAGTAT	
Mouse	<i>total Mdm4</i>	GACCGACTGAAGCACGGTGCAA	ACCAAGGCAGGCCAGCAACG
	<i>Mdm4-FL</i>	TTCTGTGAAAGATCCAAGCCCT	AGTCTGAGCAGCATCTGTGTTA
	<i>Mdm4-S</i>	TGTGAAAGATCCAAGCCCTCT	TGTTGCACCGTGCTGTGTTA
	<i>Eif3f</i> (RefGen)	GAACCCATTACCTCACGG	GAGGTCAACTCCAATGCGTTC
	<i>Heatr3</i> (RefGen)	ACTCTTGCTCAGCACCTGTC	TCAGGGGTCATACACTGTGG
	<i>Psm4</i> (RefGen)	GGAGGCAAGATGGTGTGGA	ACAGTCATTGGCCAGTGTGA

semi-qPCR			
Gene	Forward	Reverse	
Human	<i>MDM4</i> splice status	TGTGGTGGAGATCTTTTGGG	GCAGTGTGGGGATATCGT
	<i>GAPDH</i>	TGCCATGTAGACCCCTGAAG	ATGGTACATGACAAGGTGCGG
Mouse	<i>Mdm4</i> splice status	TGTGGTGGAGATCTTTTGGG	TCAGTTCTTTTTCTGGGATTGG
	<i>Gapdh</i>	AGGTTGTCTCCTGCGACTTCA	GGTGGTCCAGGGTTTCTTACTC

Supplementary Table ST4. shRNA from MISSION pLKO1 shRNA library

TRC code	SHORT CODE	Target gene
TRCN0000001227	227	SRSF3
TRCN0000273171	171	SRSF3
TRCN0000273170	170	SRSF3
TRCN0000001224	224	SRSF3
TRCN0000273174	174	SRSF3
TRCN0000231449	449	SRSF4
TRCN0000231448	448	SRSF4
TRCN0000001095	95	SRSF1
TRCN0000001096	96	SRSF1
TRCN0000000109	109	SRSF2
TRCN0000000084	84	SRSF2
TRCN0000000140	140	SRSF5
TRCN0000000141	141	SRSF5
TRCN0000231443	443	SRSF6
TRCN0000006620	620	SRSF6
TRCN0000001142	142	SRSF7
TRCN0000273401	401	SRSF7
TRCN0000320890	890	SRSF9
TRCN0000320892	892	SRSF9
TRCN0000074835	835	SRSF10
TRCN0000074836	836	SRSF10
TRCN0000284895	895	SRSF11
TRCN0000314691	691	SRSF11
TRCN0000001309	309	SRSF12
TRCN0000001307	307	SRSF12

Supplementary Table ST5. Morpholino and ASO sequences

Morpholino Scramble	CGGTGTGTGTATCATTCTCTAGTGT
Morpholino MDM4	CGTGTGGTGATTTACCTTCAGTTG
Scramble ASO	TTGCACGAGTGCAAAGGTCTTCAT
ASO1	GCGAGAGTCTGAGCAGCATCTGGAT
ASO2	ATATCCATACTGTGATCCTGTGCGA
ASO3	TACCTTCAGTTGGTCTTGACTTGGA
ASO5	ACCGTGTGGTGATTTACCTTCAGT
ASO4	CGTGTGGTGATTTACCTTCAGTTG

Supplementary Table ST6. TaqMan qPCR and probes

Forward primer	AAGAAAGAATCTTGTCACCTTAGCC
Reverse primer	GGGATATCGTCTTCTGTAGTTCTT
Exon 5-7 (MDM4-S) - 5' 6-FAM™ - ZEN - 3' Iowa Black® FQ	ACTGCTACTACAGCAAAGTGCAGAGG
Exon 6-7 (MDM4-FL)- 5' TET™ - ZEN - 3' Iowa Black® FQ	CACTTTGCTTCAGTTGGTCTTGACTTGG

Supplementary Table ST7. RIP primers

Upstream MDM4 exon 6	GATATGGCCTGTCTTGGTCTT	GCCAGGTTTAGTCCCTAGAAAT
Predicted SRSF3 binding site on 5'SS of MDM4 exon 6	AGTCAAGACCAACTGAAGGTAAA	TCCAAGATCCATAGGTACAGAGA
SRSF3 exon 4 (positive control)	CGCCAACCAACTAAATCCAAC	AAGCTAGAAATGGTGAGGTGAG