Description of Supplementary Files

File name: Supplementary Information Description: Supplementary figures and supplementary tables.

File name: Supplementary Data 1

Description: Differential expression of annotated transcripts in list of transcripts that were differentially expressed in SKMM1 and H929 MM cell lines transduced with FAM46C^{WT}-GFP compared to FAM46C^{mut}-GFP transductions. Following columns with DESeq2 results are assigned to each comparison: 'baseMean' – average of the normalized count values, taken over mutant and wild type samples; 'log2FoldChange' – log2 fold change in the mutant comparing to wild type; 'lfcSE' – the standard error estimate for the log2 fold change estimate; 'stat' – Wald significance test statistics; 'pvalue' - significance test p-value; 'padj'– Benjamini-Hochberg adjusted p-value.

File name: Supplementary Data 2

Description: List of transcripts polyadenylated in SKMM1 and H929 MM cell lines transduced with FAM46C^{WT}-GFP compared to FAM46C^{mut}-GFP transductions. Columns represent "polyadenylation ratios" calculated by dividing the levels of individual mRNA in long poly(A) fractions (#5 and #6) relative to the short poly(A) fraction (#1) in wild-type FAM46C cells using relative levels observed in FAM46C^{mut} cells.

File name: Supplementary Data 3 Description: Mass spectrometry data from FAM46C immunoprecipitations.

File name: Supplementary Data 4 Description: List of oligonucleotides used in this study.

File name: Peer review file

	10	20	30	40	50
Fam46C					MAEES
Fam46A	MAEGEGYFAM	SEDELACSPY	IPLGGDFGGG	DFGGGDFGGG	DFGGGGSFGG
Fam46B	M M P S E	SGAERRDRAA	AQVGTAAATA	VATAAPAGGG	PDPEA
Fam46D					
Consistenc	y1000000010	1001000000	0011000000	0000000111	0000002022
	60	70	80	00	100
Fam46C	SCTRDC	MCECULNNDO		WURTHORONE	
Fam46A	HCLDYCESPT	AHCNVLNWEO	VORLDGTLSE	TTPIHGRGNE	PTLELOPSLI
Fam4 6B	LSAFPG	RHLSGLSWPO	VKRLDALLSE	PIPIHGRGNF	PTLSVOPROI
Fam4 6D	MSE	IRFTNLTWDO	VITLDOVLDE	VIPIHGKGNF	PTMEVKPKDI
Consistenc	y1220020000	3 4 4 <mark>6 3 * 6 * 5</mark> *	* <mark>3 6 * 6 3</mark> 7 * 6 *	49***8***	* * 8 6 7 5 5 <mark>6</mark> 3 *
	11	0 120)130) D 90 ¹⁴	D92 150
Fam46C	VQTVRSRLEE	AGIKVHDVRL	NGSAAGHVLV	KDNGLGCKDL	DLIFHVALPT
Fam46A	VKVVRRRLAE	KRIGVRDVRL	NGSAASHVLH	QDSGLGYKDL	DLIFCADLRG
Fam46B	VQVVRSTLEE	QGLHVHSVRL	NCSVASYTTA	PESGLGYKDL	DUVERVOLRS
Consistenc	v957*845*35	5582*577**	7**7*779*3	456*875***	*89*175*45
Consistent					
	16	0	0) 19	0^{\square}
Fam46C	EAEFQLVRDV	VLCSLLNFLP	EGVNKLKISP	VTLKEAYVQK	LVKVCTDTDR
Fam46A	E <mark>G E F Q</mark> T V K D V	VL <mark>DC</mark> LLDFLP	E G V N K E K I T P	LTLKEAYVQK	MVKVCNDSDR
Fam46B	E <mark>a s f q</mark> l t k a v	VL <mark>AC</mark> LLDFLP	AGVSRAKITP	LTLKE AYVQK	LVKVCTDSDR
Fam46D	NEEFQ V VKDA	VLDCLLDFLP	KDVKKEKLSP	DIMKDAYVQK	LVKVCNGHDC
Consistenc	y 7 4 6 * * 5 7 8 6 7	**36**7***	56*584*88*	478*7****	8 * * * * <mark>6 6 5 * </mark> 5
	21	0 220	23(24	250
Fam46C	WSLTSTSNKN		STRROFFESV	DSFOTTLDSL	LEEVDCSNNP
Fam46A	WSLISISNNS	GKNVELKEVD	SLRROFEFSV	DSFOIKLDSL	LLEYECSENP
Fam46B	WSLISLSNKS	GKNVELKFVD	SVRROFEFSI	DSFOILDSL	LLFGOCSSTP
Fam46D	WSLISLSN <mark>NT</mark>	GKNLELKFVS	SLRRQFEFSV	DSFQIVLDPM	LDFYSDKNAK
Consistenc	y * * * * * * * * <mark>66</mark>	* * * 8 * * * * * 7	*7******9	**** <mark>5</mark> ** <mark>6</mark> 8	* 3 * 5 4 5 <mark>7</mark> 5 5 6
		027)280))
Fam46C		0270 GESMYGDFEE	AFDHLQNRLI	ATKNPEEIRG	GGLLKY <mark>SN</mark> LL
Fam46C Fam46A	ISEHFHPTVI MTETFHPTII	0	AFDHLQNRLI AFDHLCNKII	ATKNPEEIRG)
Fam46C Fam46A Fam46B Fam46D	26 ISEHFHPTVI MTETFHPTII MSEAFHPTVT	0	AFDHLQNRLI AFDHLCNKII ALEHLRHRVI	ATKNPEEIRG ATRNPEEIRG ATRNPEEIRG ATRSPEEIRG)
Fam46C Fam46A Fam46B Fam46D Consistenc	26 ISEHFHPTVI MTETFHPTII MSEAFHPTVT LTKESYPVVV v787357*796	GESMYGDFEE GESVYGDFQE GESLYGDFTE AESMYGDFQE 7**6****5*	AFD HLQNRLI AFD HLCNKII ALEHLRHRVI AMTHLQHKLI *55**3677*	ATKNPEEIRG ATRNPEEIRG ATRSPEEIRG CTRKPEEIRG 6*85*****)300 GGLLKYSNLL GGLLKYCNLL GGLLKYCHLL GGLLKYCSLL *****65**
Fam46C Fam46A Fam46B Fam46D Consistenc		GESMYGDFE GESVYGDFQE GESLYGDFTE AESMYGDFQE 7**6****5*	AFDHLQNRLI AFDHLCNKII ALEHLRHRVI AMTHLQHKLI *55**33677*	ATKNPEEIRG ATRNPEEIRG ATRNPEEIRG CTRKPEEIRG 6 * 85 ******)
Fam46C Fam46A Fam46B Fam46D Consistenc		0270 GESMYGDFEE GESVYGDFQE GESLYGDFTE AESMYGDFQE 7**6****5* 0320	0	ATKNPEEIRG ATRNPEEIRG ATRSPEEIRG CTRKPEEIRG 6*85******)
Fam46C Fam46A Fam46B Fam46D Consistenc Fam46C		0270 GESMYGDFEE GESVYGDFQE GESLYGDFTE AESMYGDFQE 7**6****5* 0320 EIKTLERYMC	0	ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG 6*85******)
Fam46C Fam46A Fam46B Fam46D Consistenc Fam46C Fam46A	26 ISEHFHPTVI MTETFHPTVI LTKESYPVVV 787357*796 	0270 GESMYGDFQE GESLYGDFQE AESMYGDFQE 7**6****5* 0320 EIKTLERYMC EIKTLQRYMC	AFDHLQNRLI AFDHLCNKII AFDHLCNKII ALEHLRHVI *55**3677* 0	ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG 6*85***** 0)
Fam46C Fam46B Fam46D Consistenc Fam46C Fam46A Fam46B	26 ISEHFHPTVI MTETFHPTVI LTKESYPVVV 787357*796 31 VRDFRPTDQE VRGFRPA-SD VRGFRPA-SD	0	AFDHLQNRLI AFDHLCNKII AFDHLCNKII ALEHIRHVI AMTHLQHKLI *55**3677* 033 SRFFIDFPDI SRFFIDFPDI SRFFIDFPDI	ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG 6*85******)
Fam46C Fam46A Fam46B Fam46D Consistenc Fam46C Fam46A Fam46B Fam46D		0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII ALEHIRHRVI AMTHLQHKLI *55**3677* SRFFIDFPDI SRFFIDFPDI SRFFIDFPDL SRFFIDFPDL	ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG CTRKPEEIRG G*85****** LEQQRKLESY GEQQRKLESY VEQRRTLERY EEQQKKIESY).
Fam46C Fam46A Fam46B Fam46D Consistenc Fam46C Fam46A Fam46B Fam46D Consistenc	ISEHFHPTVI MTETFHPTII MSEAFHPTVT LTKESYPVVV V787357*796	0	AFDHLQNRLI AFDHLCNKII AFDHLCNKII AEHIRHRVI AMTHLQHKLI *55**3677* 033 SRFFIDFPDI SRFFIDFPDI SRFFIDFPDI SRFFIDFPDL SRFFIDFPDL *******668	ATKNPEEIRG ATRNPEEIRG ATRSPEEIRG CTRKPEEIRG CTRKPEEIRG GEQQRKLBTY GEQQRKLESY VEQRRTLERY EEQQKKIESY 2*7868*5)
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Fam46C Fam46B Fam46D Consistenc Fam46C Fam46A Fam46D Consistenc Fam46D	ISEHFHPTVI MTETFHPTII MSEAFHPTVT LTKESYPVVV y7357*796	0	AFDHLQNRLI AFDHLCNKII AFDHLCNKII ALEHIRHVI AMTHLQHKLI * 55 * * 3 677* O	ATKNPEEIRG ATRNPEEIRG ATRNPEEIRG CTRKPEEIRG GEQQRKLETS VEQRKLESY VEQRKLESY 2*7868*5* NLISLLALRY)
Fam46C Fam46B Fam46D Consistenc Fam46C Fam46A Fam46D Consistenc Fam46C Fam46C Fam46C	1 SEHFHPTVI MTETFHPTVI MSEAFHPTVT LTKESYPVVV 787357*796	0270 GE SMYGDF EE GE SLYGDF E GE SLYGDF E AE SMYGDF QE 7 * 6 * * * 5 * 0	0280 AFDHLQNRLI AFDHLCNKII ALEHIRHRVI AMTHLQHKLI *55**3677* 0330 SRFFIDFPDI SRFFIDFPDI SRFFIDFPDI SRFFIDFPDL SRFFIDFPL ******668 0380 IMGHERRQTL IMGHERRQTL	ATKNPEEIRG ATRNPEEIRG ATRNPEEIRG CTRKPEEIRG CTRKPEEIRG GEQQRKLETY GEQQRKLETY VEQRRTLEY 2*7868*5* NLISLALRV NLITALARV)
Fam46C Fam46B Fam46B Fam46D Consistenc Fam46C Fam46B Fam46D Consistenc Fam46C Fam46C Fam46C	ISEHFHPTVI MTETFHPTVI MSEAFHPTVT LTKESYPVVV Y87357*796 VRGFRPTDQE VRGFRPA-SD VRGFRPACMS JEXYZYTAND ARRYACLVTL	0	0	ATKNPEEIRG ATRNPEEIRG ATRNPEEIRG CTRKPEEIRG CTRKPEIRG 6*85****** J)
Fam46C Fam46A Fam46B Fam46D Consistenc Fam46C Fam46D Consistenc Fam46C Fam46C Fam46C Fam46A Fam46B	1 26 I SEHFHPTVI MTETFHPTVI MSEAFHPTVT LTKESYPVVV 787357*796 VRGFRPDST VRGFRPA SD SE SD SD <td>0</td> <td>AFDHLQNRLI AFDHLQNRLI AFDHLCNKII AEDHLRHVI AMTHLQHKLI *55**3677* </td> <td>ATKNPEEIRG ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG CTRKPEEIRG GEQCKLESY VEQRRTLERY EEQQKKIESY 2**7868*5* NLISLLALRV NLISLLALQA HLITMMALKV</td> <td>)</td>	0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII AEDHLRHVI AMTHLQHKLI *55**3677*	ATKNPEEIRG ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG CTRKPEEIRG GEQCKLESY VEQRRTLERY EEQQKKIESY 2**7868*5* NLISLLALRV NLISLLALQA HLITMMALKV)
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Fam46C Fam46B Fam46D Consistenc Fam46C Fam46B Fam46D Consistenc Fam46C Fam46C Fam46C Fam46C Fam46C Fam46C	1 26 I SEHFHPTVI MTETFHPTII MSEAFHPTVT LTKESTYPVVV 787357*796	0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII AEHIRRYI ALEHIRRYI AMTHQHKI * 55 * 3 677*	ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG 6*85***** 	300 GGLLKYSNLL GGLLKYCNLL GGLLKYCHL GGLLKYCLL GGLLKYCLL
Fam46C Fam46B Fam46D Consistenc Fam46C Fam46C Fam46D Consistenc Fam46D Consistenc	1 26 ISEHFHPTVI MTETFHPTII MSEAFHPTVT LTKESYPVVV 787357*796	0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII AEDHLCNKII ALEHIRHVI AMTHLQHKLI * 55**3677*	ATKNPEEIRG ATRNPEEIRG ATRNPEEIRG CTRKPEEIRG 6*85***** ATRSPEEIRG GEQQRKLESY VEQRKLESY 2*7868*5* ALLING NLISLLALRV NLISLLALRV NLITMLAIRV DLIAALALQA HLITMMALKV 5*658*867	0
Fam46C Fam46B Fam46D Consistenc Fam46C Fam46A Fam46B Fam46D Consistenc Fam46D Consistenc Fam46C Fam46C Fam46C	1 SEHFHPTVI MTETFHPTVI MSEAFHPTVT LTKESYPVVV 787357*796	0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII ALEHIRHVI AMTHLQHKI * 55 * 3 677*	ATKNPEEIRG ATRNPEEIRG ATRNPEEIRG CTRKPEEIRG 6*85***** ATRNPEEIRG GEQQRKLETY VEQRKLETY VEQRKLETY EEQQKKIDSY 2*7868*5* NLISLLALRV NLITMLAIRV DLIAALALQA HLITMMALKV 5*65*****)
Fam46C Fam46B Fam46B Fam46D Consistenc Fam46A Fam46D Consistenc Fam46C Fam46C Fam46D Consistenc Fam46C Fam46C Fam46C	1 SEHFHPTVI MTETFHPTVI MSEAFHPTVT LTKESYPVVV 787357*796 31 VRGFRPA-SD INTMTS INVTCYQFA TAALWARPA	0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII ALEHIRHVI AMTHLQHKLI *55**3677* 0330 SRFFIDFPDI SRFFIDFPDI SRFFIDFPDI SRFFIDFPII ************************************	ATKNPEEIRG ATKNPEEIRG ATRSPEEIRG CTRKPEEIRG CTRKPEEIRG G*85*****)
Fam46C Fam46A Fam46B Fam46D Consistenc Fam46A Fam46B Fam46D Consistenc Fam46C Fam46A Fam46C Fam46C Fam46C Fam46C Fam46C Fam46B Fam46B	1 SEHFHPTVI MTETFHPTVI MSEAFHPTVT LTKESYPVVV 787357*796 VRGFRPA VRGFRPA SURGFRPA	0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHCNKI SFFIDFDI SRFFIDFDI SRFFIDFDI SRFFIDFPHI ************************************	ATKNPEEIRG ATKNPEEIRG ATRSPEEIRG CTRKPEEIRG CTRKPEEIRG G*85****** LEQQKLESY VEQRTLERY EEQQKLESY 2*7868*5* NLITMLAIRV NLITMLAIRV DIAALAQA HLITMNALKV 5*658*867 444 SQPYPTW TCQQQTYSTW AHAYPTW	GGLLKYSNLL GGLLKYSNLL GGLLKYCNLL GGLLKYCNLL GGLLKYCLL GGLLKYCLL GGLLKYCLL GGLLKYCLL GGLLKYCLL GGLLKYCLL GGLLKYCLL GGLLKYCLL GGLLKYCLL GGLLYCL GGLYCL
Fam46C Fam46A Fam46B Fam46D Consistenc Fam46A Fam46A Fam46D Consistenc Fam46A Fam46A Fam46A Fam46C Fam46A Fam46B Fam46B Fam46B Fam46B	1 SEHFHPTVI MTETFHPTVI MSEAFHPTVT LTKESYPVVV 787357*796 VRGFRPTDQE VRGFRPA SD VRGFRPA SS ST SS SS SS VTGFYQPA ANVTCYQPA AALAWRPFQ QXVTCFYQPA Y54776667	0	0	ATKNPEEIRG ATRNPEEIRG ATRNPEEIRG CTRKPEEIRG CTRKPEEIRG G*85****** LEQQRKLEY VEQRRTLERY EEQQKKIESY 2*7868*5* NLISLLALRY NLISLLALRV NLISLLALRV NLISLLALQA HLITMMALKV 5*658*867)
Fam46C Fam46A Fam46D Consistenc Fam46C Fam46A Fam46D Consistenc Fam46A Fam46B Fam46B Fam46B Fam46B Fam46B Fam46B Fam46B Fam46B Fam46B	1 SEHFHPTVI MTETFHPTVI MSEAFHPTVT LTKESYPVVV 787357*796 31 VRGFRPTDQE VRGFRPAST VRGFRPAST VRGFRPAST VRGFRVACMS Y*66*8*4044 36 RSKYDYIMIL DRKYEYLMIL DRKYEYLMIL ARYACLVTL Y258*55*77*	Q 270 GE SMYGDF E 270 GE SLYGDFTE 320 GE SLYGDFTE 320 GE SLYGDFTE 320 AESMYGDF QE 7**6***5* 0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII ALEHIRHVI AMTHLQHKI *55**3677*	ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG CTRKPEEIRG G*85*****)
Fam46C Fam46B Fam46D Consistenc Fam46C Fam46A Fam46D Consistenc Fam46D Consistenc Fam46D Consistenc Fam46D Fam46D Fam46C Fam46B Fam46C	1 26 I S E H F H P T V I M TE T F H P T I I M SE A F H P T V T L T KE S Y P V V 78 7 3 5 7 * 7 9 6	0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII ALEHIRHVI AMTHLQHKI * 55 * 3 677*	ATKNPEEIRG ATRNPEEIRG CTRKPEEIRG CTRKPEEIRG G*85***** GEQQRKLEY VEQRKLEY Z*7868*5* N)
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Fam46C Fam46A Fam46D Consistenc Fam46C Fam46A Fam46D Consistenc Fam46D Consistenc Fam46C Fam46C Fam46C Fam46C Fam46C Fam46C Fam46A Fam46D Consistenc Fam46C Fam46B Fam46B Fam46B Fam46B		0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHLCNKII AFDHLSK SFFIDFDI SRFFIDFDI SRFFIDFDI SRFFIDFDI SRFFIDFDI SRFFIDFU SYVAHPVY SYVAHPVY SYVAHPVY SYVAHPVY SYVAHPY SYVAHPY SYVAHPY SYVAHPY </td <td>ATKNPEEIRG ATKNPEEIRG ATRSPEEIRG CTRKPEEIRG CTRKPEEIRG GCRKLEST VEQRKLEST VEQRKLEST VEQRKLEST 2 * 78 68 5 * * * * * * NIISLLALRY NIITMLAIRV DIAALALQA HLITMNALKV 5 * 6 58 * 8 67 </td> <td>0</td>	ATKNPEEIRG ATKNPEEIRG ATRSPEEIRG CTRKPEEIRG CTRKPEEIRG GCRKLEST VEQRKLEST VEQRKLEST VEQRKLEST 2 * 78 68 5 * * * * * * NIISLLALRY NIITMLAIRV DIAALALQA HLITMNALKV 5 * 6 58 * 8 67 	0
Fam46C Fam46A Fam46B Fam46D Consistenc Fam46A Fam46B Fam46D Consistenc Fam46C Fam46A Fam46C Fam46C Fam46C Fam46C Fam46C Fam46B Fam46B Fam46B Fam46C Fam46C Fam46C Fam46C	1 S E H F H P T V I M TE T F H P T V I M S E A F H P T V T L T K E S Y P V V 78 7 3 5 7 * 7 9 6	0	AFDHLQNRLI AFDHLQNRLI AFDHLCNKII ALEHIRHVI AMTHQHKI *55**3677*	ATKNPEEIRG ATRNPEEIRG ATRSPEEIRG CTRKPEEIRG CTRKPEEIRG G*85****** LEQQKKLESY VEQRTLERY EEQQKKLESY 2*7868*5* NLISLLALRV NLISLLALRV NLISLLALRV NLISLLALRV NLISLLALRV S*658*867 	0

Supplementary Figure 1. Multiple sequence alignments color-coded for amino acid conservation of FAM46 protein family representatives in humans performed by PRALINE. The scoring color scheme starts at 0 for the least conserved alignment position up to 10 for the most conserved alignment position. Invariant catalytic residues from highly conserved NTase domain ([DE]h[DE]h are shown in boxes (D90 and D92 in case of FAM46C).



Supplementary Figure 2. (a) Northern blot analysis of RL mRNA from control HEK293 cells (lanes 4-9) after tethering of NHA-FAM46C^{WT} (lanes 10-15) or NHA-FAM46C^{mut} (lanes 16-21) which were fractionated based on the length of the poly(A) tails. Input RNAs are shown in lanes 1-3 (b) Northern blot analysis of RL mRNA from control HEK293 cells (lanes 4-9) after tethering of NHA-FAM46D^{WT} (lanes 10-15) or NHA-FAM46D^{mut} (lanes 16-21) which were fractionated based on the length of the poly(A) tails. Input RNAs are shown in lanes 1-3. (c) Time course of actinomycin-D treatment. Northern blot detection of RL transcript from: control HEK293 cells (lanes 1-4), after tethering of NHA-FAM46C^{WT} (lanes 5-8) and NHA-FAM46C^{mut} (lanes 9-12). GAPDH mRNA was used as loading controls for all northern blots. (d) RL mRNA half-life quantifications shown as a plot with SD error bars (n=3).



Supplementary Figure 3. Expression of FAM46C^{WT} induces multiple myeloma cell death. (**a**, **b**) Summary of flow cytometry analyses presented as bar graphs showing GFP expression levels and reduced viability of HEK293T (**a**) and RPMI8226 multiple myeloma cell line (**b**) depending on the amount of virus used for transduction and the time of expression analysis. Data are presented as percentage of cells \pm SD (n=3). *P* values were calculated using 2-way ANOVA tests (**P*<0.05, ***P*<0.01, ****P*<0.001, ****P*<0.0001).

H929 sells 80cells s sells FLAG-FAM46C^{WT} NHA-FAM46C^W NHA-FAM46C^{mL} 80 FAM46C^{WT}FLAG % of PI negative % of PI negative 60 40 % of PI negative 40 -20 -40-20 b √ days post transduction days post transduction days post transduction 80 -80 -% of GFP positive cells GFP-FAM46C^{WT} GFP-FAM46C^{WT}
GFP-FAM46C^{mull} 80 60 -40 -% of PI negative 40 20-SKMM1 cells 80 NHA-FAM46C^{WT} NHA-FAM46C^{mull} Sells 80. cells 80 FAM46C^{WT}FLAG FAM46C^{mul}FLAG FLAG-FAM46C^{WT} FLAG-FAM46C^{mut} 6 of PI negative 60-40-20-% of PI negative % of PI negative 60 40 20 ♦ 1 days post transduction 100 -80 -*** cells % of GFP positive cells GFP-FAM46C^{WT} GFP-FAM46C^{mut} GFP-FAM46C^{WT} GFP-FAM46C^{mut} 80 6 of PI negative 60 -40 -20 days post trai A days post transduction **RPMI8226** sells 80of PI negative cells 08 Cells 80-FLAG-FAM46C^{WT} FLAG-FAM46C^{mul} FAM46C^{WT}FLAG NHA-FAM46C^{WT} NHA-FAM46C^{mut} % of PI negative 60-40-% of PI negative 60-40-20-20-► 1 days post transduction days post transduction days post transduction % of PI negative cells 80-GFP-FAM46C^{WT} GFP-FAM46C^{WT} 60-40-20days post transduction days post transduction

Supplementary Figure 4. Different tags at the N and C termini of FAM46C protein do not affect the function of the protein. Summary of flow cytometry analyses presented as bar graphs showing reduced viability of multiple myeloma cell lines (H929, SKMM1, and RPMI8226) throughout the time course of FLAG-FAM46C, FAM46C-FLAG, GFP-FAM46C and NHA-FAM46C expression. Data are presented as percentage of cells \pm SD (n=3). *P* values were calculated using 2-way ANOVA tests (**P*<0.05, ***P*<0.01, ****P*<0.001, *****P*<0.0001).



Supplementary Figure 5. Expression of PAPOLA-GFP, POLS-GFP, and GLD2-GFP constructs had no major effect on multiple myeloma cell death. Summary of FACS analyses presented as bar graphs showing GFP expression level and reduced viability of SKMM1 multiple myeloma cell lines transduced with a lentivirus carrying PAPOLA, POLS, or GLD2. Data are represented as percentage of cells \pm SD (n=3).



Supplementary Figure 6. FAM46C tethering enhanced expression of *Renilla* luciferase (RL) reporter in MM cells. SKMM1 (a) and H929 cells (b) expressing reporter genes of *Renilla* luciferase (RL) and Firefly luciferase (FL) or RL containing five boxB sites in its 3'-UTR (RL5Box) and FL were transduced with lentiviruses carrying *FAM46C*^{WT} or *FAM46C*^{mut} harboring the N-terminal λ N boxB binding domain and HA-tag. Western blot detection of RL and FL proteins in non-transduced (**a**, **b**; lanes 1 and 4) and after NHA-FAM46C^{WT} (**a**, **b**; lane 2 and 5) or NHA-FAM46C^{mut} (**a**, **b**; lane 3 and 6) tethering. Expression of NHA-tagged FAM46C proteins were confirmed using an α -HA antibody. DBC1 and RPS5 served as a loading control. Asterisk indicates non-specific signals for HA and FLuc antibodies.



Supplementary Figure 7. Analysis of FAM46C substrates in MM cells. (**a**, **b**) Functional GO terms annotation clustering of significantly upregulated transcripts in FAM46C^{WT} overexpressing SKMM1 (**a**) and H929 (**b**) cell lines. (**c**, **d**) Histogram representing the distribution of FAM46C-dependent polyadenylation rations monitored in fraction #5 (**c**) and #6 (**d**) in H929 cell lines. Modeled normal distribution is fitted as a red line to emphasize the outlying population of FAM46C polyadenylated transcripts. (**e**) The sequence composition of significantly overrepresented motifs (P value <10⁻¹²) in 3'UTRs of FAM46C substrates. The distance was calculated based on the Pearson Correlation Coefficient and an unweighted pair group method with arithmetic mean (UPGMA) tree-construction algorithms was used.



Supplementary Figure 8. *SSR2* mRNA, similarly to *SSR4*, is polyadenylated by FAM46C. (a) High resolution northern blot analysis of *SSR2* transcript from MM cell lines H929 (lanes 1-3), SKMM1 (lanes 4-6) transduced with GFP (lanes 1, 4), FAM46C^{WT}-GFP (lanes 2, 5), and FAM46C^{mut}-GFP (lanes 3, 6). High-resolution northern blot analyses were performed using 4% denaturing PAGE gel. (b) High-resolution northern blot analysis of *SSR2* transcripts from H929 (lanes 1-6) and SKMM1 cells (lanes 7-12) transduced with GFP (lanes 1, 2, 7, 8), FAM46C^{WT}-GFP (lanes 3, 4, 9, 10), and FAM46C^{mut}-GFP (lanes 5, 6, 11, 12) after RNase H treatment (lanes 2, 4, 6, 8, 10, 12) to remove the poly(A) tail in the presence of oligo(dT)₂₅. Control reactions were carried out in the presence of oligo(dT)₂₅ without RNase H (lanes 1, 3, 5, 7, 9, 11). (c) *SSR4* is not the substrate for PAPOLA, POLS, and GLD2. High-resolution northern blot analysis of *SSR4* transcripts from SKMM1 cells transduced with lentiviruses carrying *PAPOLA* (lane 2), *POLS* (lane 3), *GLD2* (lane 4), and control cells (lane 1). RN7 RNA served as a loading control.



Supplementary Figure 9. (a-c) Tethering of PABPC1 to reporter RL mRNA leads to increase of its steady state level. (a) Northern blot analysis of total RNA from HEK293 cells transfected with pRL-5BoxB and plasmids encoding NHA-BCCIPB (lane 2) and NHA-PABPC1 (lane 3) using a probe against Renilla luciferase. Cells transfected with pRL-5BoxB only were used as controls (lane 1). Membrane methylene blue staining shown as a loading control. (b) Quantification of northern blots shown in panel a using Multigauge software. Bars represent mean values \pm SD (n=3). (c) Western blot detection of NHA-BCCIP β (lane 2) and NHA-PABPC1 (lane 3) with α-HA antibodies and reporter-encoded Renilla luciferase proteins using α-RL antibodies in control cells (lane 1). (d-f) Silencing of FAM46C interactors has no effect on its activity in tethering assays. (d) Western blot detection of BCCIP or PABPC1 proteins in control cells (lanes 1-3) and after siRNA-mediated knockdowns (lanes 4-6). FAM46C tethering cells were transfected with pRL-5BoxB only (lanes 1, 4) or co-transfected additionally with plasmids encoding NHA-FAM46C^{WT} (lanes 2, 5), and NHA-FAM46C^{mut} (lanes 3, 6). (e) Western blot detection of NHA-FAM46C^{WT} and NHA-FAM46C^{mut} proteins using α-HA antibodies, Renilla luciferase proteins with an α-RL antibody in control HEK293 cells (lanes 1-3), or reduced levels of BCCIP (lanes 4-6) or PABPC1 (lanes 7-9). (f) Northern blot analysis of total RNA from control HEK293 cells (lanes 1-3) or with reduced levels of BCCIP (lanes 4-6) or PABPC1 (lanes 7-9) transfected with pRL-5BoxB only (lanes 1, 4, 7) or co-transfected additionally with plasmids encoding NHA-FAM46C^{WT} (lanes 2, 5, 8) or NHA-FAM46C^{mut} (lanes 3, 6, 9) using probes against *Renilla* luciferase. Membrane methylene blue staining is shown as a loading control.

a Figure 1b

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b Figure 1d



Ponceau S Staining







____15

Ponceau S Staining

15

e











Supplementary Figure 10. Unprocessed scans of selected blots and gels. (a) Scan of gel corresponding to Fig. 1b. (b) Blots corresponding to Fig. 1d. (c) Western blots corresponding to Fig. 3a, Fig. 3b, Fig. 3c. (d) Northern blots corresponding to Fig. 3e, 3h, 3i. (e) Western blots and membrane Ponceau S staining corresponding to Fig. 5a and Fig. 5b. (f) Northern blots corresponding to Fig. 8. (g) Western blots corresponding to Fig. 9b and Fig. 9c.

Multiple myeloma cell lineMutations in FAM46C geneSKMM1Homozygotic deletion c.519delT (p.I173fsX36)H929Hemizygotic insertion c.278-279insC (p.L93fsX15)MM1.SHemizygotic substitution c.808A>G (p.M270V)RPMI8226None

Supplementary Table 1. Cell lines used in this study.

Supplementary Table 2. Antibodies used in this study.

Antibodies and Cell Isolation Kits	Manufacturer and catalog number
Anti- <i>Renilla</i> Luciferase	Millipore; Anti-Renilla Luciferase clone 5B11.2; MAB4400
Anti- <i>Firefly</i> Luciferase	Abcam; Anti-Firefly Luciferase antibody; ab21176
Anti-BCCIP	Abcam; Anti-BCCIP antibody; ab97577
Anti-HA	Abcam; Anti-HA tag antibody [HA.C5]; ab18181
Anti-PABPC1	Abcam; Anti-PABP antibody; ab21060
Anti-DBC1	Bethyl Lab; DBC1/p30 DBC Antibody; A300-434A
Anti-FLAG	Invitrogen; DYKDDDDK Tag Polyclonal Antibody; PA1-984B
Anti-GFP	Santa Cruz; GFP Antibody (B-2); sc-9996
Anti-RPS5	Santa Cruz; Ribosomal Protein S5 (464-J); sc-100832
Anti-GAPDH	Novus Biologicals; anti-GAPDH antibody; NB300-327
Anti-SSR4	Abcam; Anti-Signal sequence receptor delta; ab58009
Anti-Histone H4	Anti-Histone H4, pan, clone 62-141-13; 05-858
Anti-FAM46C 1	Abcam; Anti-FAM46C antibody; ab74754
Anti-FAM46C 2	Abcam; Anti-FAM46C antibody; ab169699
Anti-FAM46C 3	Santa Cruz; FAM46C (D-14); sc-164330
Anti-FAM46C 4	Santa Cruz; FAM46C (P-12); sc-164332
Anti-GRP94	Santa Cruz; GRP 94 (9G10); sc-32249

anti-CD20-Alexa	Novus Biologicals; MS4A1/CD20 Antibody (AISB12); NBP1-
Fluor 700	43435AF700
Anti-CD138-PE	DB; BD 553714
anti-CD45.2 Horizon V500	DB; anti-Mouse CD45.2 (Clone 104); BD 562129
Anti-PSPC1	Abcam; Anti-PSPC1 antibody (ab104238)
B Cell Isolation Kit, mouse	Miltenyi Biotec; 130-090-862
CD138+ Plasma Cell Isolation Kit, mouse	Miltenyi Biotec; 130-092-530

Supplementary Table 3. siRNAs used in this study.

Targeted gene	Stealth Select RNAi [™] siRNA reference number	Name used in this study
BCCIP	HSS125584	siBCCIP_1
BCCIP	HSS125585	siBCCIP_2
BCCIP	HSS125586	siBCCIP_3
PABPC1	HSS167099	siPABPC1_1
PABPC1	HSS167100	siPABPC1_2
PABPC1	HSS167101	siPABPC1_3

Supplementary Table 4. shRNAs used in this study.

construct	Catalog or TRC	Sequence of insert
	Number	
pLKO.1-Empty	SHC001 (pLKO.1-puro	No shRNA Insert
	Empty Vector)	
sh2 (hFAM46C	TRCN0000168752	CCGGGCAGAATTTCAGCTGGTTAGACTCGAGTCTAACCA
-sh2)		GCTGAAATTCTGCTTTTTTG
sh3 (hFAM46C	TRCN0000166958	CCGGGCCTAAATCTTGTTTACCTATCTCGAGATAGGTAAA
-sh3)		CAAGATTTAGGCTTTTTTG
sh5 (hFAM46C	TRCN0000172684	CCGGGCTGAAGTTTGTCGACTCCATCTCGAGATGGAGTCG
-sh5)		ACAAACTTCAGCTTTTTTG

Supplementary Table 5. Genotypes of mice used in this study.

Mouse lines	Mutations in FAM46C gene
FAM46C-/- mouse line	Homozygotic indel c.261_271delins301nt ¹ (p.G85fsX26)
FAM46C-FLAG mouse line	Homozygotic insertion c.1176ins24bp ² (p.N391insDYKDDDDK)

¹ – apparently this indel consists of c.261_271delTTGCAAAGATCTGGATC (g.16015_16061del) and insertion of translocated intronic duplication g.15373_15670 fragment:

 $^2-$ full sequence of the c.1176ins24bp: insGACTACAAAGACGATGACGACAAG