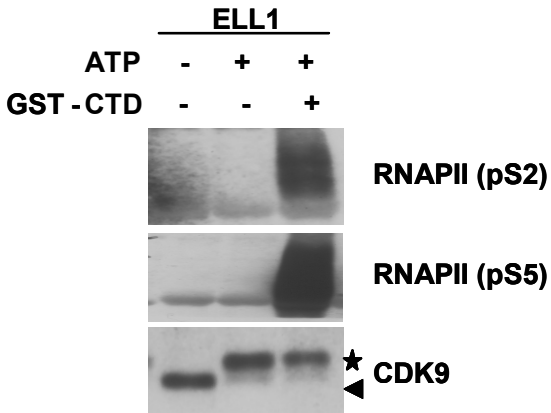
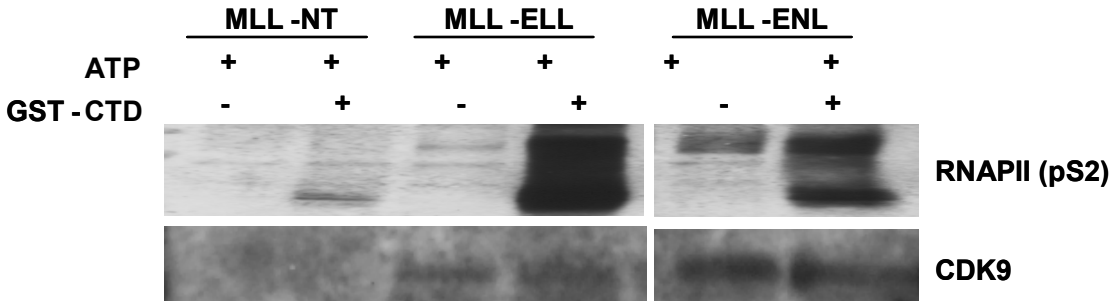


Supplemental Figure S1

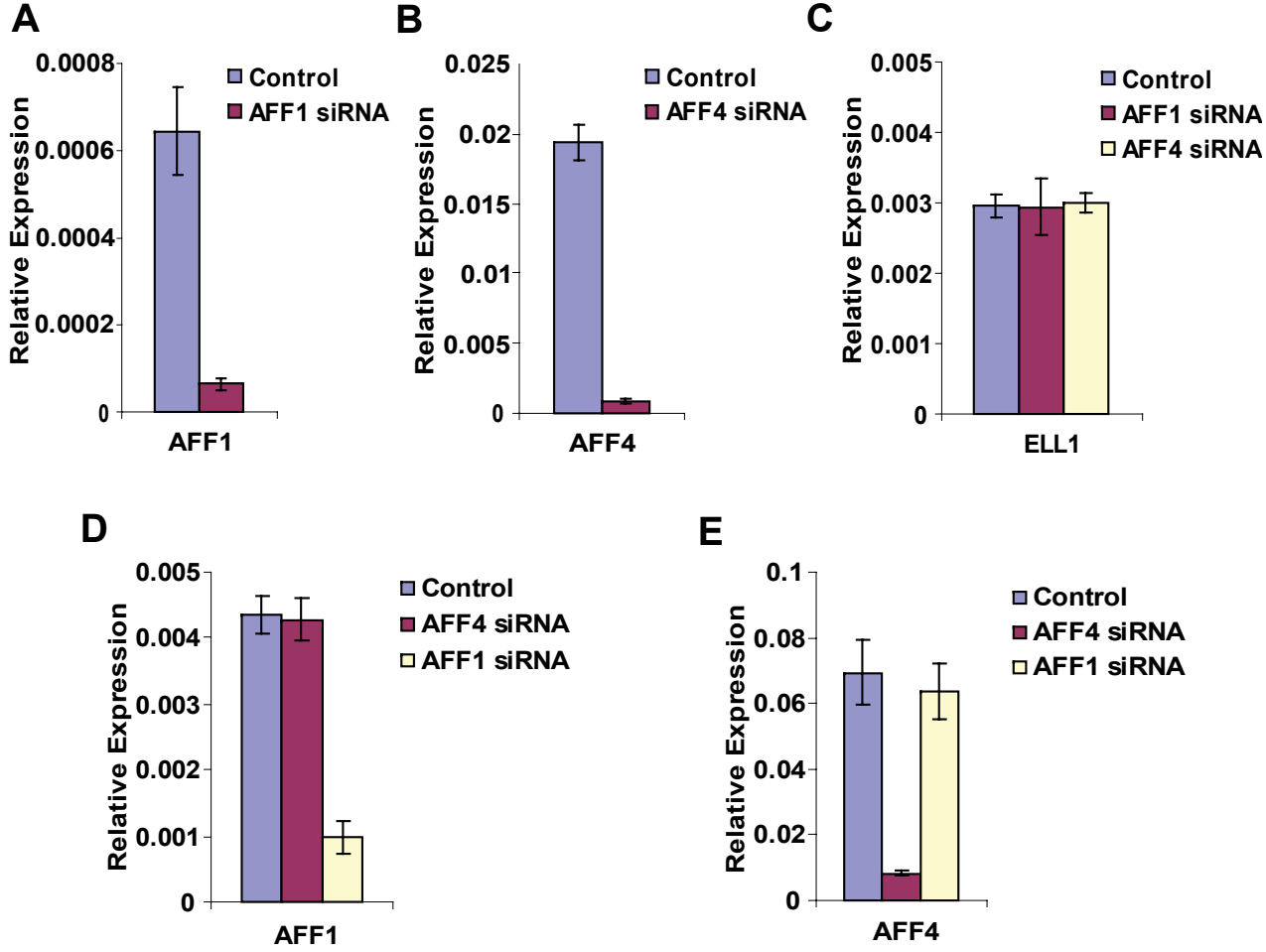
A



B



Supplemental Figure S2



Supplemental Figure S3

A

AFF9/ENL Binding Region

dAFF4_D. melanogaster	EAR T	TTPH L T S	VCK L	D	LSK E	SR ER
XP_698757_D. rerio	PTI	PHRGLK L	VVR L	D	LCL L	GR VP
AFF1_H. sapiens	PLR	DTPPPQ S	VVK L	T	LDL L	SR IP
AFF1_M. musculus	PLR	DS PPPTS	VVK L	T	LDL L	TR IP
AFF1_G. gallus	FVR	DV PGNPS L	VVR L	D	LPL L	SR VP
AFF4_H. sapiens	PLS	EP DDR Y P L	VK L	D	LN L L	TR IP
AFF4_M. musculus	PLS	EP DDR Y P L	VK L	D	LN L L	TR IP
AFF4_G. gallus	PLS	DP DERY P L	VK L	D	DLS XXX L	SR IP
AFF4_M. domestica	PLS	DP DDR Y P L XXX	VK L	D	LS L L	SR IP
AFF4_D. novemcinctus	PLS	EP DDR Y P L	VK L	D	LN L L	TR IP
AFF4_R. ferrumequinum	PLS	EP DDR Y P L	VK L	D	XXX LN L L	TR IP

B

AFF1 C-terminal Homology Domain

dAFF4_D. melanogaster	-----DDPRKNNQFLQFAI-----NRKHAADLE-----RISFNQVTLTYL	DAVY Y L T L T A D A M E R	-----CSS-----E D A I N T M Y K D T I S L I L	K F I S T K E R P Y Q Q	-----O S
XP_698757_D. rerio	-----TVPLSIVSHHAEYYMHFAK-----RIKHRADAMVGOV	DKL G K A V N Y V	DAAL S F M E C G K A M E E	G-----P L E	S K S P Y T M Y A E T V E L L
AFF1_H. sapiens	-----OVKE-DKQO-ADLHMRFAK-----KMKOKALM-----DNRVGA	K F K Y L	DAVLS F E C G I L E S	E-----S Q S	S K S A Y S Y S E T V D L L
AFF1_M. musculus	-----S-DRQO-ADFHMKFAK-----KIKCKAATM-----VAKAG	A F K Y L	DAVLS F E C G M S E S	-----E S S	A K S A V A Y S E T V D L L
AFF1_G. gallus	-----QIKF-ERCHLSSEYYLFAK-----KMKHEADAMXXXXM	D K T G A P Q Y L	DAAL S F V E Y G M A L E S	N-----A V A	P K P A Y S T A D T I D L L
AFF4_H. sapiens	-----KLVFEDDRNYSADHYLQFAK-----KIKHNAADAL	S R R F E K A V Y Y L	DAVVS F E C G N A L E K	N-----A Q E	S K S P E P M Y S E T V D L L
AFF4_M. musculus	-----KLVFEDDRNYSADHYLQFAK-----KIKHNAADAL	S R R F E K A V Y Y L	DAVVS F E C G N A L E K	N-----A Q E	S K S P E P M Y S E T V D L L
AFF4_G. gallus	-----KLVFEDDRNYSADHYLQFAK-----KIKHNAADAL	S R R F E K A V Y Y L	DAVVS F E C G N A L E K	N-----A Q E	S K S P E P M Y S E T V D L L
AFF4_M. domestica	-----KLVFEDDRNYSADHYLQFAK-----KIKHNAADAL	S R R F E K A V Y Y L	DAVVS F E C G N A L E K	N-----A Q E	S K S P E P M Y S E T V D L L
AFF4_D. novemcinctus	-----KLVFEDDRNYSADHYLQFAK-----KIKHNAADAL	S R R F E K A V Y Y L	DAVVS F E C G N A L E K	N-----A Q E	S K S P E P M Y S E T V D L L
AFF4_R. ferrumequinum	-----KLVFEDDRNYSADHYLQFAK-----KIKHNAADAL	S R R F E K A V Y Y L	DAVVS F E C G N A L E K	N-----A Q E	S K S P E P M Y S E T V D L L

SP-Rich Region

dAFF4_D. melanogaster	T I N I Q H E T H N K V A L T S L R C O S L Y L R F K L K K	-----K-----DCR-----A I I N S T D F	FRVGRGD	-----I A N G N T P	-----S S T S P S N S V G S Q
XP_698757_D. rerio	AS-----QEDKQLAVTCFRCLALTYAOMFRLKK-----D-----HAI	K Y S K V T L D Y	FK-SSPK	-----G P H N P P T	-----R N D S G R G T I
AFF1_H. sapiens	AP-----TQEKIFAVLCMRCOSLHMAFERCKK-----D-----IAL	K Y S R T L N K H	FK-SSSK	-----V A O A P S P	-----C I A
AFF1_M. musculus	-----N-TMFAQEKIFAVLCMRCOSLHMAFERCKK-----D-----TVM	K Y S R T L S E H	FK-STSK	-----V A O A P S P	-----C T A R S T G V P
AFF1_G. gallus	ASXXXXSHHEHVFAVLCMRCOSLHMAFERVYKR-----D-----TAI	K Y S R L N D H	FK-SSSR	-----V T O A P S P	-----C V A
AFF4_H. sapiens	AT-----AADKRLTVLCMRCOSLYLRFK L K K	-----E-----NAT	K Y S K T L T E H	L K-N S Y N	-----N S O A P S P
AFF4_M. musculus	AT-----AADKRLTVLCMRCOSLYLRFK L K K	-----E-----NAT	K Y S K T L T E H	L K-N S Y N	-----N S O A P S P
AFF4_G. gallus	AT-----AADKRLAVLCMRCOSLYLRFK L K K	ESXXXXAL	K Y S K T L T E H	L K-N S Y N	-----N S O A P S P
AFF4_M. domestica	AT-----SADKRLAVLCMRCOSLYLRFK L K K	-----E-----NAT	K Y S K T L T E H	L K-N S Y N	-----N S O A P S P
AFF4_D. novemcinctus	AT-----VADKRLTVLCMRCOSLYLRFK L K K	-----E-----NAT	K Y S K T L T E H	L K-N S Y N	-----N S O A P S P
AFF4_R. ferrumequinum	AT-----AADKRLTVLCMRCOSLYLRFK L K K	ESXXXXAT	K Y S K T L T E H	L K-N S Y N	-----N S O A P S P

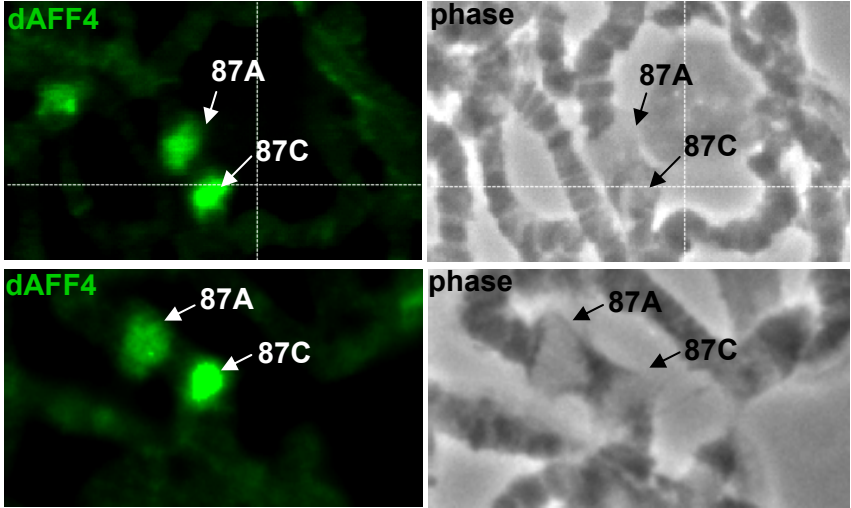
SP-Rich Region

dAFF4_D. melanogaster	G G S N T P	-----P G R I V P E I H N Y L C K Q N E F L S	-----Y L N S A H E I L	W D A E R L V
XP_698757_D. rerio	I G K S P S	-----T V I S I P R I H Q M A A N H L N I T N	-----S V L Y S Y E Y	W E V A D
AFF1_H. sapiens	Q S S A G -S V	-----A T I S T P V T I Q N T S S Y V T I T S	-----H V L T A F D I	W E O A E
AFF1_M. musculus	S S A G S S M G S V G V T	-----A T V S T P V S T Q N T S S Y V T I T S	-----H V L T A F S L	W E O A E
AFF1_G. gallus	Q G S N G S N C	-----N S I G S V T I P S I T S S Y V N I T S	-----Y V L Y A Y N I L	W E I A L X X X X A
AFF4_H. sapiens	S G A S S A S A	S-----G-----S S V T I P O K I H Q M A A S Y V Q V T S	N-----F L Y A T E I L	W D O A E
AFF4_M. musculus	S G S S A S A	S-----G-----S S V T I P O K I H Q M A A S Y V Q V T S	N-----F L Y A T E I L	W D O A E
AFF4_G. gallus	S G T A N P S G	S G X X X X	S S V T I P O R I H Q M A A S Y V Q V T S	N-----F L Y A T E I L
AFF4_M. domestica	S G A S S T X X	X X S G S S	S S V T I P O K I H Q M A A N Y V Q V T S	N-----F L Y A T E I L
AFF4_D. novemcinctus	S G A S S A S A	S-----G-----S S V T I P O K I H Q M A A S Y V Q V T S	N-----F L Y A T E I L	W D O A E
AFF4_R. ferrumequinum	S G A S S A S A	S X X X X G	S S V T I P R I H H M A A S Y V Q V T S	N-----F L Y A T E I L

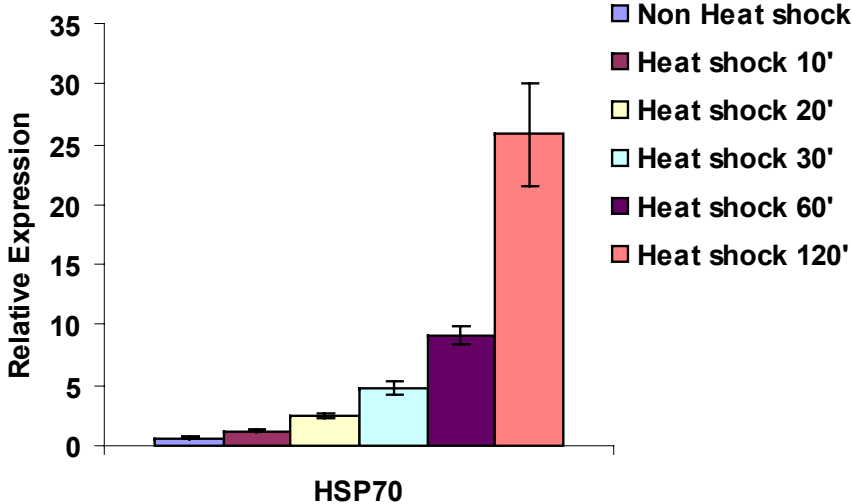
SP-Rich Region

dAFF4_D. melanogaster	-----R I G N H I D H I R E I D H E N G P T L H S T	-----M-----H E V F R Y V A C L K T R D A V S H P	-----H H O S G
XP_698757_D. rerio	-----L A K E N K L E N Y I N P L T G P T L H S S	-----M-----A H V O M T R O G L W R I S A N L S	-----
AFF1_H. sapiens	-----L T R K N K E F F A R S T N V C T A L N S S	-----I-----V D I V H Y T R O G F Q Q G E L T K T P	-----
AFF1_M. musculus	-----L T R K N K E F F A O S T K V R V A L N S S	-----I-----V D I V H Y T R O G L O R E K Q S P K G P	-----
AFF1_G. gallus	-----L S K N N K E F F A E S T A V C P A L T S S	-----M-----A E M V H Y T R O G L H W R L N T S T P	-----
AFF4_H. sapiens	-----L S K E O K E F F A E D K V M G P I F N A S	-----I M-----T D I L V R Y T R O G L H W R L Q D A K L I S	-----
AFF4_M. musculus	-----L S K E O K E F F A E D K V M G P I F N A S	-----I M-----T D I L A R Y T R O G L H W R L Q D A K L I S	-----
AFF4_G. gallus	-----L S K E O K E F F A E D K A M G P V F N S S I X X X X	-----I M-----T D I L V R Y T R O G L H W R L D A K I S	-----
AFF4_M. domestica	-----L I K E O K E F F A E D K V M G P I F X X X X N S S I M	-----I M-----T D I L V R Y T R O G L H W R L D A K I S	-----
AFF4_D. novemcinctus	-----L S K E O K E F F A E D K V M G P I F N A S	-----I M-----T D I L V R Y T R O G L H W R L Q D A K L I S	-----
AFF4_R. ferrumequinum	-----L S K E O K E F F A E D K V M G P I F N A S X X X X I M	-----I M-----T D I L V R Y T R O G L H W R L Q D A K I S	-----

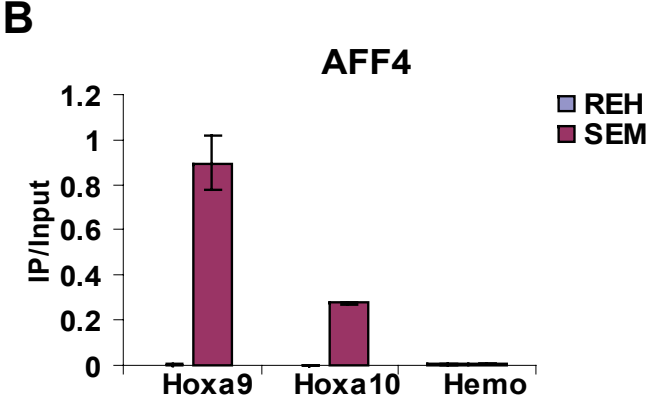
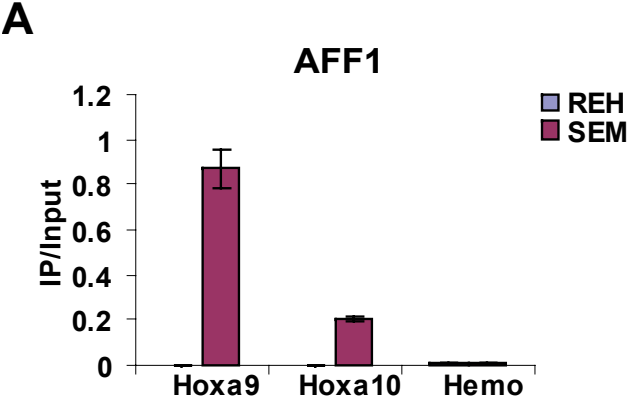
Supplemental Figure S4



Supplemental Figure S5



Supplemental Figure S6



Supplemental Table 1

Protein	MLL-NT dNSAF AVG	MLL- ELL1 dNSAF AVG	MLL- AFF1 dNSAF AVG	MLL-AF9 dNSAF AVG	MLL-ENL dNSAF AVG
MLL-NT	0.050949	0	0	0	0
MLL- ELL1	0	0.084755	0	0	0
MLL- AFF1	0	0	0.012444	0	0
MLL- AF9	0	0	0	0.051766	0
MLL- ENL	0	0	0	0	0.06576
Menin	0.21546	0.088819	0.04613	0.053286	0.151354
LEDGF	0.000885	0.000533	0.000192	0.001115	0.001327
AFF4	0	0.001971	0.000831	0.000593	0.000127
Dot1L	0	0	0	0.001484	0.000048

Supplemental Table 2

Protein	ELL1 dNSAF AVG	ELL2 dNSAF AVG	ELL3 dNSAF AVG	AFF4 dNSAF AVG
ELL1	0.185148	0.000385	0.003368	0.006379
ELL2	0.000542	0.054255	0	0.004369
ELL3	0	0	0.111228	0.006603
AFF4	0.004663	0.006674	0.015106	0.03917
AFF1	0.001422	0.001296	0.003659	0.00077
AF9	0.001334	0.00052	0.002346	0.005846
ENL	0.001637	0.000988	0.003198	0.011151
CDK9	0.005979	0.002635	0.007835	0.029597
CCNT1	0.00124	0.000513	0.001316	0.021903
Cyclin T 2a	0.000261	0.000071	0.001236	0.003648
Cyclin T 2b	0.000237	0.000065	0.001122	0.003313
EAF1	0	0.072906	0.02451	0.000652
EAF2	0	0.002226	0.002792	0