Supplemental data

Impairment of leukemia initiating self-renewal by a novel selective small molecule CBP/p300 bromodomain inhibitor

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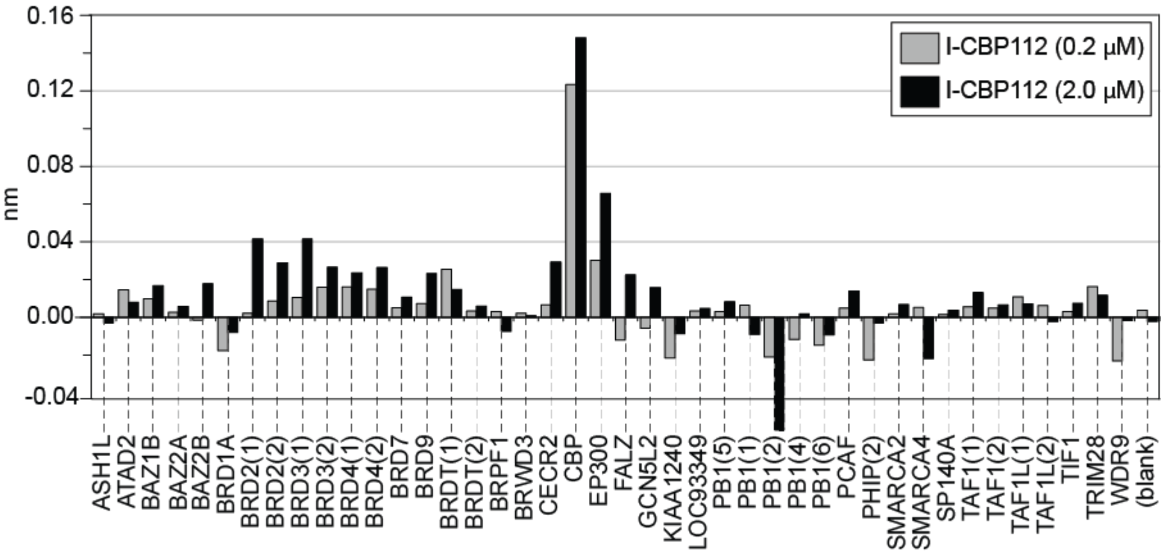
Supplemental Table 1: Temperature shift data of I-CBP112 against a panel of human bromodomains. The values represent the average of three independent measurements.

	Protein	ΔT_m [ºC]		Protein	ΔT_m [ºC]
1	ASH1L	0.24 ± 0.26	23	KIAA1240	0.05 ± 0.14
2	ATAD2	0.14 ± 0.56	24	LOC93349#	0.65 ± 0.61
3	BAZ1A	0.16 ± 1.20	25	PB1(1)	0.77 ± 0.80
4	BAZ2A	0.17 ± 0.41	26	PB1(2)	0.13 ± 0.28
5	BAZ2B	0.12 ± 0.16	27	PB1(3)	-0.24 ± 0.23
6	BRD1	0.43 ± 0.35	28	PB1(4)	0.28 ± 0.62
7	BRD2(1)	1.35 ± 0.48	29	PB1(5)	0.11 ± 0.20
8	BRD2(2)	0.87 ± 0.28	30	PB1(6)	-0.04 ± 0.28
9	BRD3(1)	1.55 ± 0.44	31	PCAF	-0.01 ± 0.29
10	BRD3(2)	0.94 ± 0.25	32	PHIP(2)	0.62 ± 0.49
11	BRD4(1)	2.09 ± 0.41	33	SMARCA2	-0.02 ± 0.15
12	BRD4(2)	0.58 ± 0.20	34	SMARCA4	0.36 ± 0.16
13	BRDT(1)	0.68 ± 0.43	35	SP140	-0.64 ± 0.86
14	BRD9	0.20 ± 0.17	36	TAF1(1)	0.16 ± 0.17
15	BRPF1	0.19 ± 0.60	37	TAF1(2)	-0.13 ± 0.30
16	BRPF3	0.07 ± 0.63	38	TAF1L(1)	0.12 ± 0.40
17	BRWD3(2)	0.64 ± 1.16	39	TAF1L(2)	-0.04 ± 0.45
18	CECR2	0.43 ± 0.19	40	TIF1A#	0.32 ± 0.31
19	CREBBP	7.77 ± 0.53	41	TIF1A(PHD)	0.26 ± 0.68
20	EP300	8.69 ± 0.28	42	TRIM28#	-0.42 ± 0.51
21	FALZ	0.63 ± 0.14	43	TRIM66	0.15 ± 0.41
22	GCN5L2	0.54 ± 0.27	44	WDR9(2)	-0.33 ± 0.56

PDH/BRD dual domain construct

Supplemental Figure 1



Supplemental Figure 1: BLI evaluation of i-CBP112 selectivity using BLI. 42 human bromodomains were biotinylated *in vivo* by fusion with the biotinylation sequence (SSKGGYGLNDIFEAQKIEWHE) inserted at the C-terminus and co-expression of BirA using a pACYC co-expression vector. Bromodomains immobilized on streptavidine tips were screened at two concentrations (0.2 and 2.0 μM). The maximum response reached at this concentration is shown. Strong binding was only observed for CBP/p300. Weaker interactions are also evident for BET bromodomains.

Supplemental Table 2:

Protein	[P] (µM)	[L] (µM)	N	K_d (nM)	ΔH^{obs} (cal/mol)	TΔS (kcal/mol)	ΔG (kcal/mol)
CBP	195	20	0.98	151	-9031 ± 25.8	-0.0380	-8.99
EP300	248	20	0.97	167	-9291 ± 34.5	-0.3456	-8.94
BRD4(1)	450	17	1.01	5587	-5363 ± 129.0	1.5638	-6.92
BRD4(2)	440	17	0.96	20000	-3704 ± 330.4	2.4912	-6.19

Errors shown are errors of the non-linear least square fits. Measurements have been carried out at 15 °C. [P] and [L] show the protein and ligand concentration used in the different experiments.

Supplemental Table 2: Isothermal Titration Calorimetry measurements of the interaction of I-CBP112 with bromodomains.

Supplemental Table 3A (CEREP selectivity data (enzymes))

Enzyme assay	%[Inhibition] at 10 μM (I-CBP112) (S)	%[Inhibition] at 10 μM (I-CBP112) (R)
COX1	-33	-4
COX2	2	14
inducible NOS	-35	-37
PDE2A1	4	2
PDE3B	0	0
PDE4D2	14	15
PDE5 (non-selective)	-2	-1
PDE6 (non-selective)	8	6
ACE	-7	-21
ACE-2	7	6
BACE-1 (beta -secretase)	4	-1
caspase-3	-7	-6
HIV-1 protease	-3	-1
neutral endopeptidase (h)	2	6
MMP-1	-11	-17
MMP-2	16	12
MMP-9	-15	-2
Abl kinase	3	0
CaMK2alpha	0	0
CDK2 (cycA)	-1	2
ERK2 (P42mapk)	7	-1
FLT-1 kinase (VEGFR1)	-3	5
Fyn kinase	-4	-3
IRK (InsR)	20	-1
Lyn A kinase	-1	-7
p38alpha kinase	-1	-1
ZAP70 kinase	-2	11
acetylcholinesterase	21	28
COMT (catechol- O-methyl transferase)	-4	5
xanthine oxidase/ superoxide O2- scavenging	5	-8
ATPase (Na+/K+)	0	0

Supplemental Table 3 B (CEREP selectivity data (GPCRs and ion channels))

GPCR Assay	%[I] at 10 μM (I-CBP112) (S)	%[I] at 10 μM (I-CBP112) (R)
A1 (ago. r.)	4	-5
A2A (ago. r.)	11	1
A2B (anta. r.)	-4	-13
A3 (ago. r.)	-7	-4
alpha 1A (anta. r.)	89	89
alpha 1B (anta. r.)	21	52
alpha 2A (anta. r.)	18	24
alpha 2B (anta. r.)	-9	49
alpha 2C (anta. r.)	39	50
beta 1 (ago. r.)	-4	-9
beta 2 (ago. r.)	0	1
beta 3 (anta. r.)	-3	-15
AT1 (anta. r.)	21	9
AT2 (ago. r.)	-8	-1
APJ (apelin) (ago. r.)	-3	-1
BZD (central) (ago. r.)	-5	-12
BB3 (ago. r.)	-10	-22
B2 (ago. r.)	-5	-7
CB1 (ago. r.)	-5	0
CB2 (ago. r.)	2	5
CCK1 (CCKA) (ago. r.)	6	-6
CCK2 (CCKB) (ago. r.)	-4	-10
CRF1 (ago. r.)	-19	-26
D1 (anta. r.)	11	17
D2S (ago. r.)	12	28
D3 (anta. r.)	-2	18
ETA (ago. r.)	-2	-27
ETB (ago. r.)	-5	-2
GABAA1 (alpha 1,β2,γ2) (ago. r.)	12	-6
GABAB(1b) (anta. r.)	0	4
glucagon (ago. r.)	-8	-16
AMPA (ago. r.)	-14	-14
kainate ago. r.)	-7	-2
NMDA (anta. r.)	-16	0
glycine (strychnine-insensitive)(anta. r.)	0	3
TNF-alpha (ago. r.)	-4	14
CCR2 (ago. r.)	-10	0
H1 (anta. r.)	5	-8
H2 (anta. r.)	3	7
H3 (ago. r.)	3	-5
H4 (ago. r.)	2	-3

BLT1 (LTB4) (ago. r.)	0	-1
CysLT1 (LTD4) (ago. r.)	-12	-21
MCH1 (ago. r.)	7	-9
MC1(ago. r.)	0	0
MC3 (ago. r.)	-6	-21
MC4 (ago. r.)	-10	0
MT1 (ML1A) (ago. r.)	-15	-11
MT3 (ML2) (ago. r.)	45	54
MAO-A (anta. r.)	-6	-5
motilin (ago. r.)	-1	2
M1 (anta. r.)	38	48
M2 (anta. r.)	67	49
M3 (anta. r.)	20	35
M4 (anta. r.)	74	63
NK1 (ago. r.)	4	8
NK2 (ago. r.)	-8	2
Y1 (ago. r.)	-10	-10
N neuronal alpha 4beta 2 (ago. r.)	23	20
N muscle-type (anta. r.)	19	19
delta 2 (DOP) (ago. r.)	8	-7
kappa (KOP) (ago. r.)	-6	-9
mu (MOP) (ago. r.)	3	5
NOP (ORL1) (ago. r.)	6	1
PPARgamma (ago. r.)	-8	-9
PAF (ago. r.)	9	11
PCP (anta. r.)	-4	3
EP2 (ago. r.)	9	8
FP (ago. r.)	-4	-5
IP (PGI2) (ago. r.)	-6	-15
LXRbeta (ago. r.)	15	15
5-HT1A (ago. r.)	16	58
5-HT1B (anta. r.)	9	46
5-HT1D (ago. r.)	18	-1
5-HT2A (ago. r.)	30	62
5-HT2B (ago. r.)	-17	7
5-HT2C (ago. r.)	11	52
5-HT3 (anta. r.)	3	-11
5-HT4e (anta. r.)	32	18
5-HT6 (ago. r.)	-6	-3
5-HT7 (ago. r.)	6	10
sigma (non-selective) (ago. r.)	46	15
sst1 (ago. r.)	15	16
sst4 (ago. r.)	-7	-7
GR (ago. r.)	-5	-1

ERalpha (agonist fluoligand)	5	2
AR (ago. r.)	-3	-24
TR (TH) (ago. r.)	-26	-29
UT (ago. r.)	8	21
VPAC1 (VIP1) (ago. r.)	-2	1
V1a (ago. r.)	4	-2
V2 (ago. r.)	4	-6
Ca^{2+} channel (L, dihydropyridine site) (anta. r.)	4	7
Ca^{2+} channel (L, diltiazem site) (benzothiazepines)(anta. r.)	38	12
Ca^{2+} channel (L, verapamil site) (phenylalkylamine) (anta. r.)	19	23
Ca^{2+} channel (N) (anta. r.)	13	-15
SKCa channel (anta. r.)	6	4
Na^{+} channel (site 2) (anta. r.)	11	8
Cl^{-} channel (GABA-gated) (anta. r.)	-48	-15
norepinephrine transporter (anta. r.)	0	-8
dopamine transporter (anta. r.)	-3	-9
GABA transporter (anta. r.)	0	3
choline transporter (CHT1) (anta. r.)	8	4
5-HT transporter (anta. r.)	-30	-9

Assay data were provided by Cerep. Details on assay conditions and control compounds used can be found on the Cerep home page (http://www.cerep.fr/Cerep/Users/index.asp). Data are shown as [%] inhibition at 10 μM compound concentration, (ago.r.) means (agonist radioligand) and (anta. r.) (antagonist radioligand), respectively.

Supplemental Table 4:

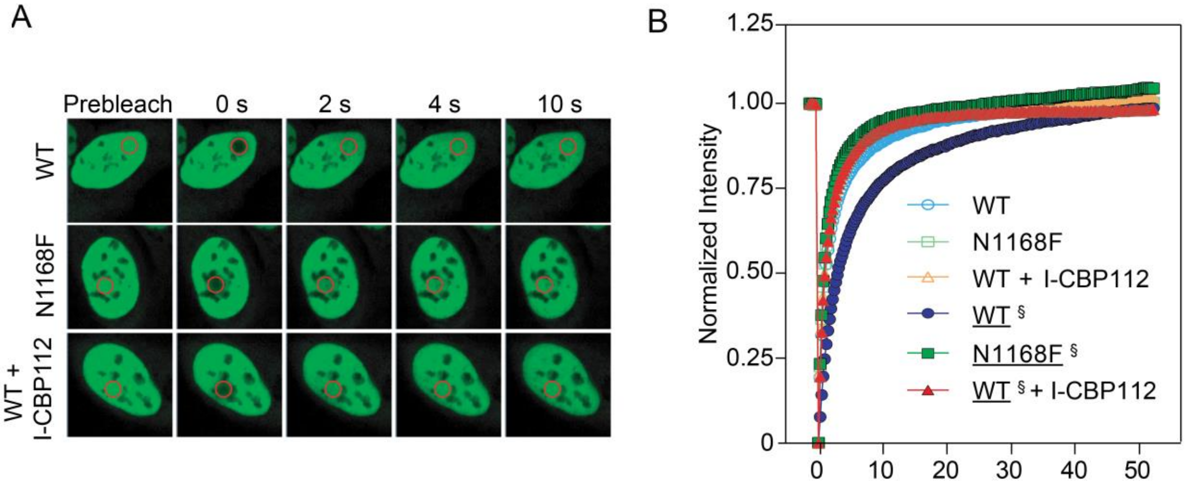
Protein	Peptide	K_D (μM)	ΔH^{obs} (kcal/mol)	N	$T\Delta S$ (kcal/mol)	ΔG (kcal/mol)
CBP	H3K56	13.8 ± 0.4	-7.9 ± 0.1	0.966	-1.6	-6.30
	H4K5/K8	31.0 ± 0.5	-13.7 ± 0.2	0.581	-7.8	-5.85
	H4K5/K8/K12	29.0 ± 0.7	-14.8 ± 0.3	0.508	-8.9	-5.89
P300	H4K5/K8/K12	28.7 ± 0.6	-14.1 ± 0.2	0.602	-8.2	-5.90

Histone peptide sequences used in Isothermal Titration Calorimetry experiments.

Histone Marks	Peptide Sequence
H3K56	IRRYQ$\mathbf{K}_{ac}$STELL
H4K5/K8	SGRG$\mathbf{K}_{ac}$GG$\mathbf{K}_{ac}$GLG**Y**
H4K5/K8/K12	RG$\mathbf{K}_{ac}$GG$\mathbf{K}_{ac}$GLG$\mathbf{K}_{ac}$GG**Y**

Supplemental Table 4: – Isothermal Titration Calorimetry of human CBP and p300 bromodomains with acetylated histone peptides. Titrations were carried out in 50 mM HEPES pH 7.5 (at 25 °C), 150 mM NaCl and 10 °C while stirring at 1000 rpm. Peptides were titrated into the protein solution.

Supplemental Figure 2



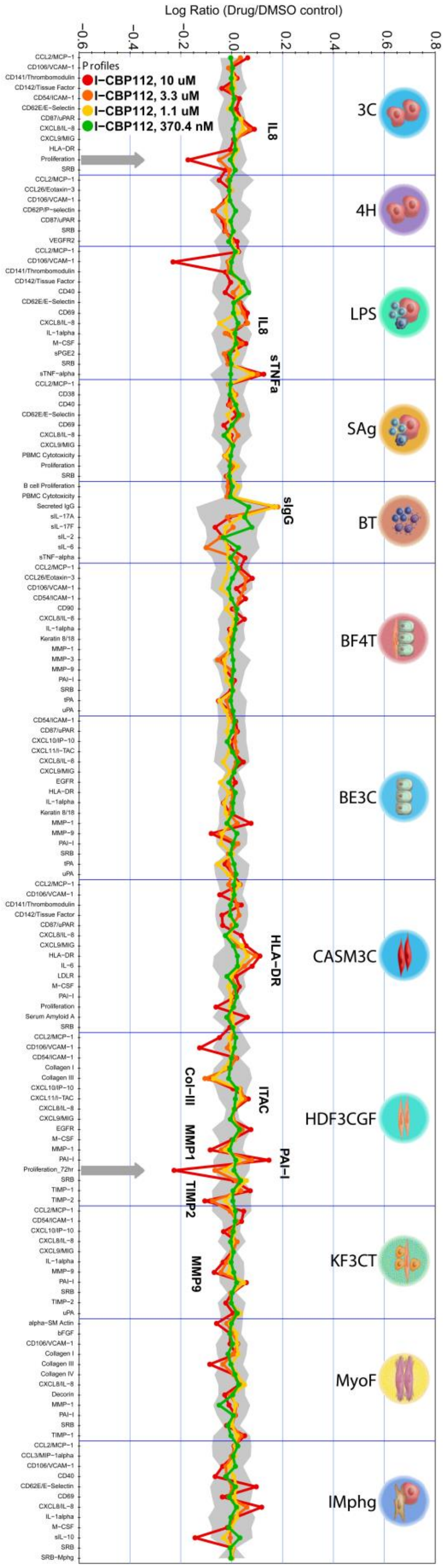
Supplemental Figure 2: FRAP data. A: FRAP experiment showing nuclei of $3xCBP_{BRD}$/GFP transfected cells treated with DMSO (top row), $3x\,BRD_{CBP}^{N1168F}/GFP$ transfected cells treated with DMSO (middle row) as well as $3xCBP_{BRD}$/GFP transfected cells treated with and 1.0 μM I-CBP112. All cells were treated with 2.5 μM SAHA to increase global acetylation levels. The bleached area is indicated by a red circle. **B:** Recovery of the normalized fluorescent signal. Shown are recovery curves averaged from at least 10 different nuclei for the different constructs as indicated in the figure capture. Experiments with SAHA treated cells (2.5 μM) are indicated by & and are underlined.

Supplemental Table 5 – Diffraction data collection and structure refinement statistics

Data Collection	
PDB ID	4NR6
Protein/Ligand	CBP/I-CBP112
Space group	C2
Cell dimensions: a, b, c (Å) α, β, γ (deg)	89.71 34.14 40.40 90.00 93.00 90.00
Resolution* (Å) (last shell)	1.66 (1.75-1.66)
Unique observations*	14891 (2113)
Completeness* (%)	99.0 (97.9)
Redundancy*	3.4 (3.1)
R_{merge}*	0.063 (0.478)
I/ σI*	10.7 (2.1)
Refinement	
Resolution (Å)	1.66
R_{work} / R_{free} (%)	18.1/23.1
Number of atoms (protein/other/water)	971/108/34
B-factors (Å^2) (protein/other/water)21.85	28.75/32.55/29.79
r.m.s.d bonds (Å) r.m.s.d angles (º)	0.015 1.698
Ramachadran Favoured (%) Allowed (%) Disallowed (%)	100.00 0.00 0.00

* Values in parentheses correspond to the highest resolution shell.

Supplemental Figure 3: BioMAP data for I-CBP112.

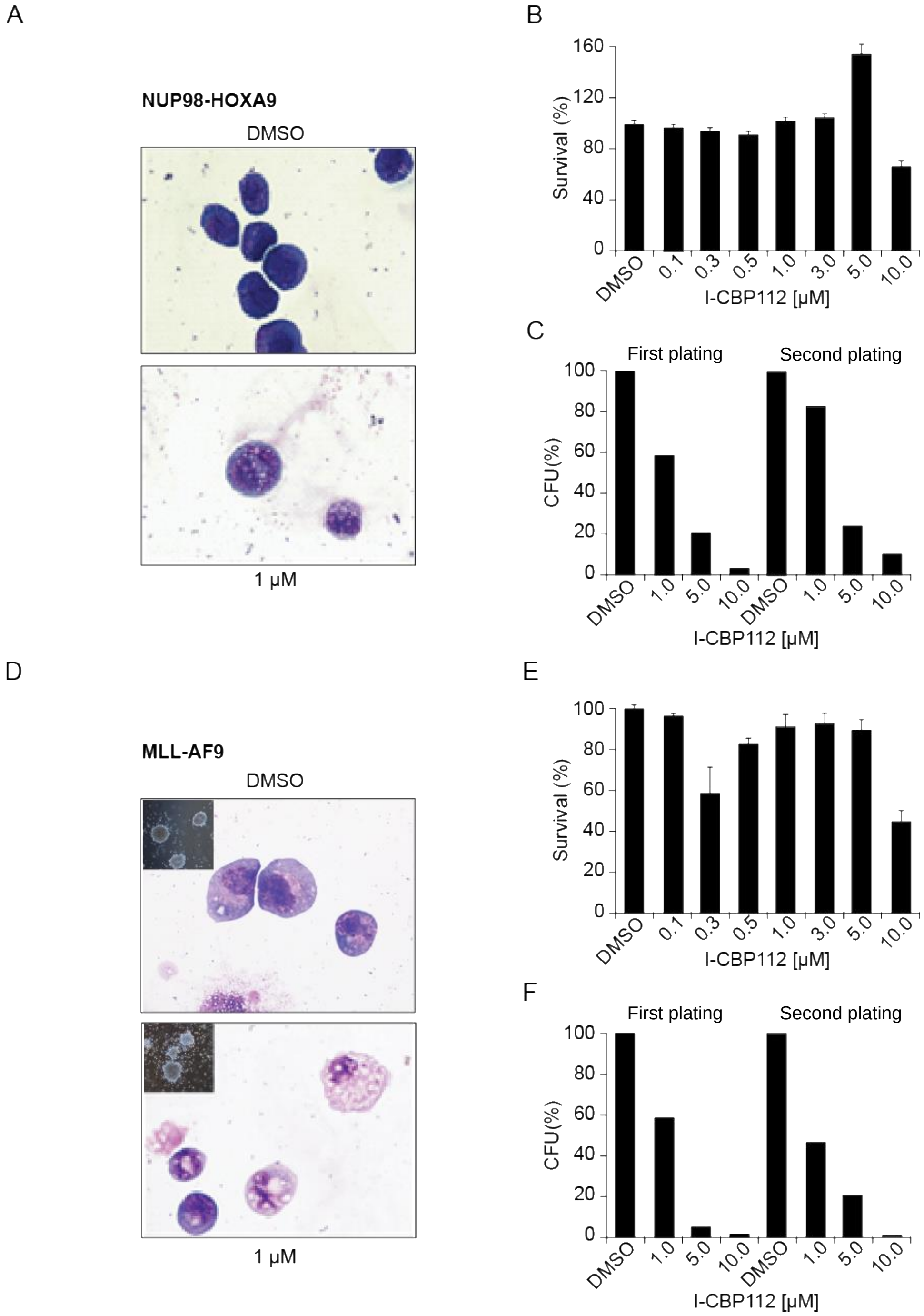


Supplemental Figure 3: Full Biomap profile for I-CBP112. Monitored markers and cellular systems are described in the table below**.**

Relevance	**Cell Type**	**Read Out**	**System**
Allergy, Asthma, Autoimmunity	Venular endothelial cells	CCL2/MCP-1, CCL26/Eotaxin-3, CD106/VCAM-1, CD62P/P-Selectin, CD87/uPAR, SRB, VEGFR2,	**4H**
Allergy, Asthma, Autoimmunity, Oncology	B cells + Peripheral blood mononuclear cells	B cell Proliferation, PBMC Cytotoxicity, Secreted IgG, sIL-17A, sIL-17F, sIL-2, sIL-6, sTNF-α,	**BT**
Allergy, Asthma, Fibrosis, Lung Inflammation	Bronchial epithelial cells + Dermal fibroblasts	CCL2/MCP-1, CCL26/Eotaxin-3, CD106/VCAM-1, CD54/ICAM-1, CD90, CXCL8/IL-8, IL-1 α, Keratin 8/18, MMP-1, MMP-3, MMP-9, PAI-I, SRB, tPA, uPA,	**BF4T**
Autoimmune Disease, Chronic Inflammation	Peripheral blood mononuclear cells + Venular endothelial cells	CCL2/MCP-1, CD38, CD40, CD62E/E-Selectin, CD69, CXCL8/IL-8, CXCL9/MIG, PBMC Cytotoxicity, Proliferation, SRB,	**SAg**
Cardiovascular Disease, Chronic Inflammation	Venular endothelial cells	CCL2/MCP-1, CD106/VCAM-1, CD141/Thrombomodulin, CD142/Tissue Factor, CD54/ICAM-1, CD62E/E-Selectin, CD87/uPAR, CXCL8/IL-8, CXCL9/MIG, HLA-DR, Proliferation, SRB,	**3C**
Cardiovascular Disease, Chronic Inflammation	Peripheral blood mononuclear cells + Venular endothelial cells	CCL2/MCP-1, CD106/VCAM-1, CD141/Thrombomodulin, CD142/Tissue Factor, CD40, CD62E/E-Selectin, CD69, CXCL8/IL-8, IL-1 α, M-CSF, sPGE2, SRB, sTNF-α,	**LPS**
Cardiovascular Disease, Chronic Inflammation, Restenosis	Macrophages + Venular endothelial cells	CCL2/MCP-1, CCL3/MIP-1 α, CD106/VCAM-1, CD40, CD62E/E-Selectin, CD69, CXCL8/IL-8, IL-1 α, M-CSF, sIL-10, SRB, SRB-Mphg,	**lMphg**
Cardiovascular Disease, Restenosis	Coronary artery smooth muscle cells	CCL2/MCP-1, CD106/VCAM-1, CD141/Thrombomodulin, CD142/Tissue Factor, CD87/uPAR, CXCL8/IL-8, CXCL9/MIG, HLA-DR, IL-6, LDLR, M-CSF, PAI-I, Proliferation, Serum Amyloid A, SRB,	**CASM3C**
Chronic Inflammation, Fibrosis	Dermal fibroblasts	CCL2/MCP-1, CD106/VCAM-1, CD54/ICAM-1, Collagen I, Collagen III, CXCL10/IP-10, CXCL11/I-TAC, CXCL8/IL-8, CXCL9/MIG, EGFR, M-CSF, MMP-1, PAI-I, Proliferation_72hr, SRB, TIMP-1, TIMP-2,	**HDF3CGF**
Chronic Inflammation,	Lung fibroblasts	bFGF, CD106/VCAM-1, Collagen I, Collagen III, Collagen IV, CXCL8/IL-8,	**MyoF**

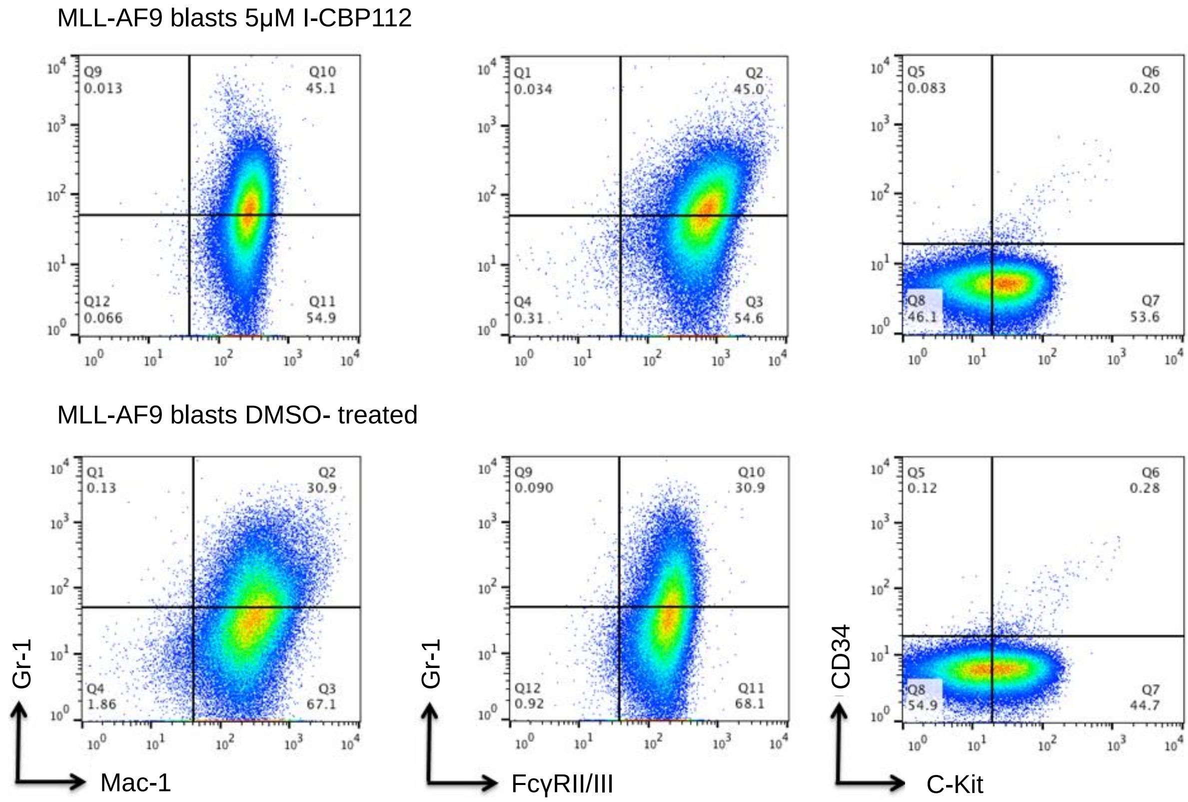
Fibrosis, Matrix Remodeling, Wound Healing		Decorin, MMP-1, PAI-I, SRB, TIMP-1, α-SM Actin,	
COPD, Lung Inflammation	Bronchial epithelial cells	CD54/ICAM-1, CD87/uPAR, CXCL10/IP-10, CXCL11/I-TAC, CXCL8/IL-8, CXCL9/MIG, EGFR, HLA-DR, IL-1 α, Keratin 8/18, MMP-1, MMP-9, PAI-I, SRB, tPA, uPA,	**BE3C**
Dermatitis, Psoriasis	Dermal fibroblasts + Keratinocytes	CCL2/MCP-1, CD54/ICAM-1, CXCL10/IP-10, CXCL8/IL-8, CXCL9/MIG, IL-1 α, MMP-9, PAI-I, SRB, TIMP-2, uPA,	**KF3CT**

Supplemental Figure 4



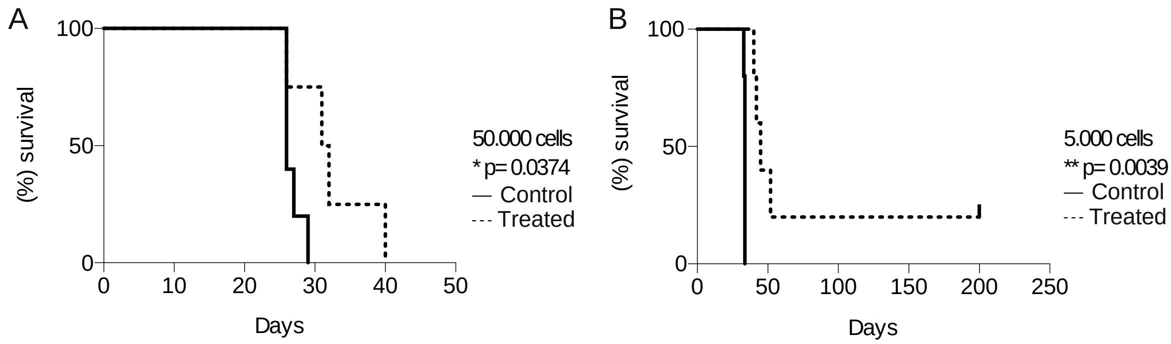
Supplemental Figure 4: Effects of I-CBP112 on NUP98-HOXA9 and MLL-AF9 *in vitro* immortalized cells. Differentiation and clonogenic growth of mouse NUP98-HOXA9 and MLL-AF9. **A**: Cytospot images of NUP98-HOXA9 *in vitro* immortalized cells treated with DMSO (upper panel) and 1 μM I-CBP112 (lower panel). **B**: Cell survival of NUP98-HOXA9 *in vitro* immortalized cells treated with increasing concentration of I-CBP112. **C**: Effect of I-CBP112 on clonogenic growth of NUP98-HOXA9 (first and second plating). **D**: Cytospot images of MLL-AF9 *in vitro* immortalized cells treated with DMSO (upper panel) and 1 μM I-CBP112 (lower panel). **B**: Cell survival of MLL-AF9 *in vitro* immortalized cells treated with increasing concentration of I-CBP112. **C**: Effect of I-CBP112 on clonogenic growth of MLL-AF9 (first and second plating).

Supplemental Figure 5



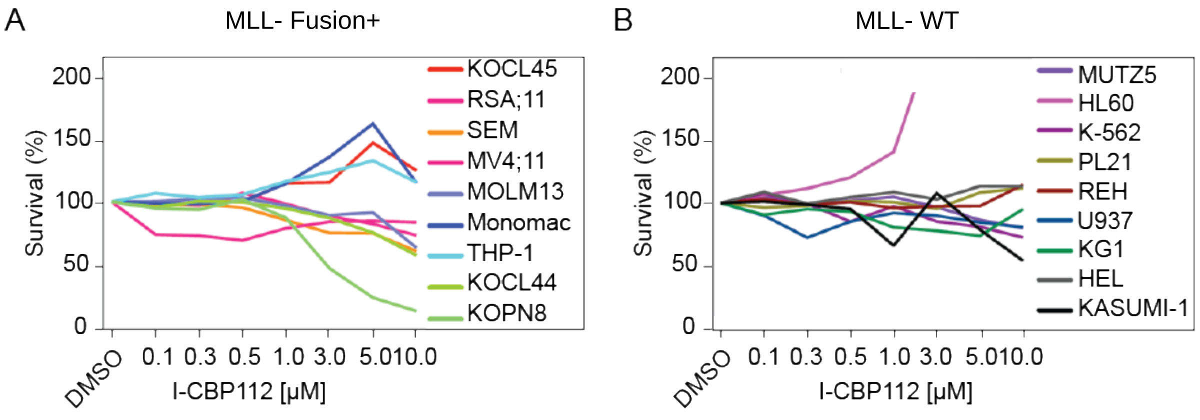
Supplemental Figure 5: Immunephenotype of injected MLL- AF9+ blasts Immunophenotype of injected MLL-AF9 cells prior to transplantation into recipient mice. Marker proteins (Gr-1, Mac-1, FcγRII/III, c-Kit) have been flow cytometrically analysed.

Supplemental Figure 6: Survival data limiting dilution transplantation



Supplemental Figure 6: Kaplan-Meier diagram showing significantly extended survival of mice injected with different number of I-CBP112 (5µM) treated cells (dotted lines) compared to vehicle-treated controls (solid lines). The number of injected cells were **A:** 50 000 cells and **B:** 5 000 cells. P- values were calculated using log- rank (Mantel-Cox) Test, Control group n=5, Treated-group n=4.

Supplemental Figure 7



Supplemental Figure 7: Cell survival of 18 human, leukemic cell lines after 72h in liquid culture. Cell survival data of 18 human leukemic cell lines (**A:** MLL- Fusion+, **B:** MLL-WT) exposed to increasing concentrations of I-CBP112 for 72h in liquid culture. Cell vitality was assessed using WST1 proliferation/survival assays and was plotted as a function of compound (I-CBP112) concentration.

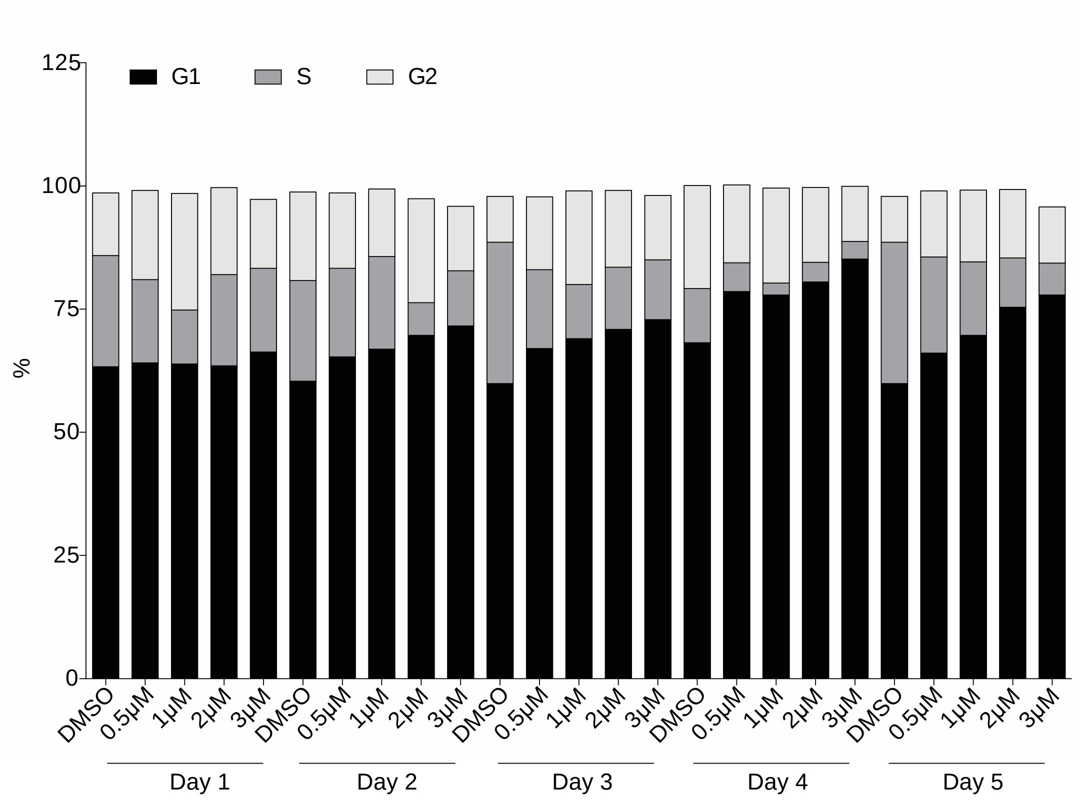
CBP/P300 mutation status of the used cell lines.

Human cell line	Mutation (CCLE)	
	CBP	EP300
K562	-	-
HEL	-	Chr. 22 3'UTR Del
THP1	-	-
RS4;11	-	-
MV4;11	-	-
MOLM13	-	-
SEM	-	-
KOPN8	-	-
PL21	-	-
HL60	-	-
KASUMI-1	-	-
REH	-	-
KG1	-	-
U937	-	-
MONOMAC	-	-
KOCL44	-	-
KOCL45	-	-
SKNO-1	-	-

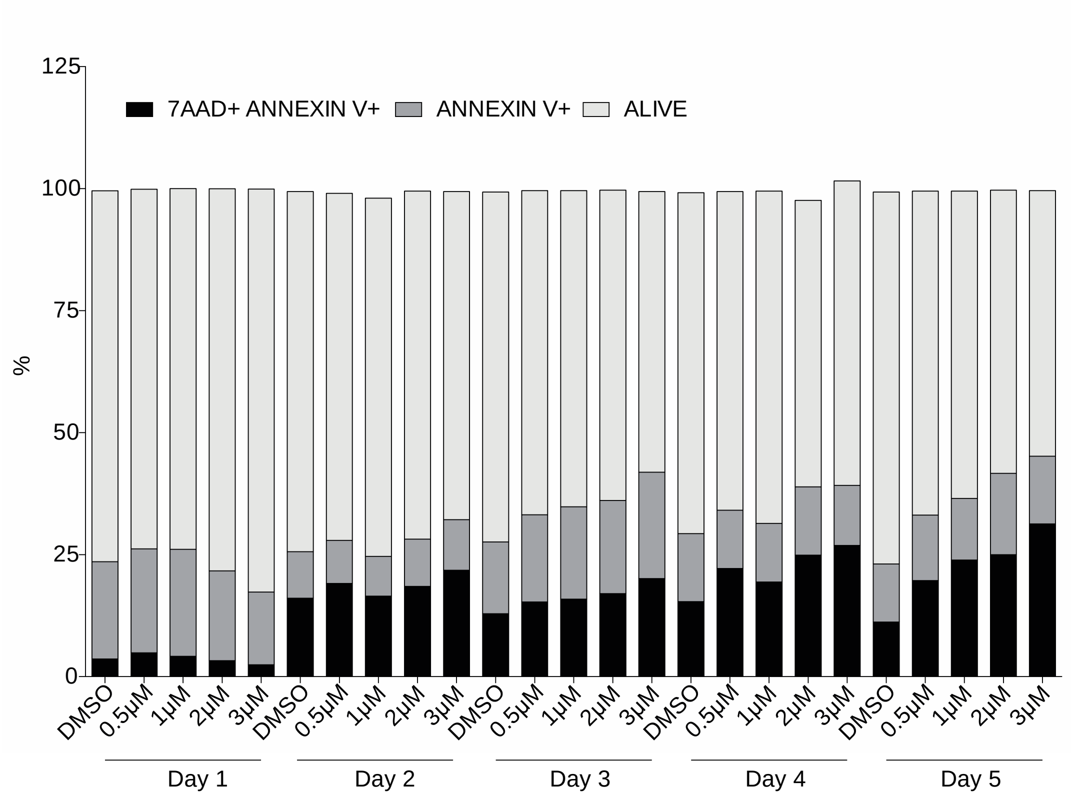
CBP and EP300 mutations in human leukemic cell lines used in this study. Mutations were retrieved from Cancer Cell Encyclopedia Database from Broad Institute. (http://www.broadinstitute.org/ccle)

Supplemental Figure 8

A



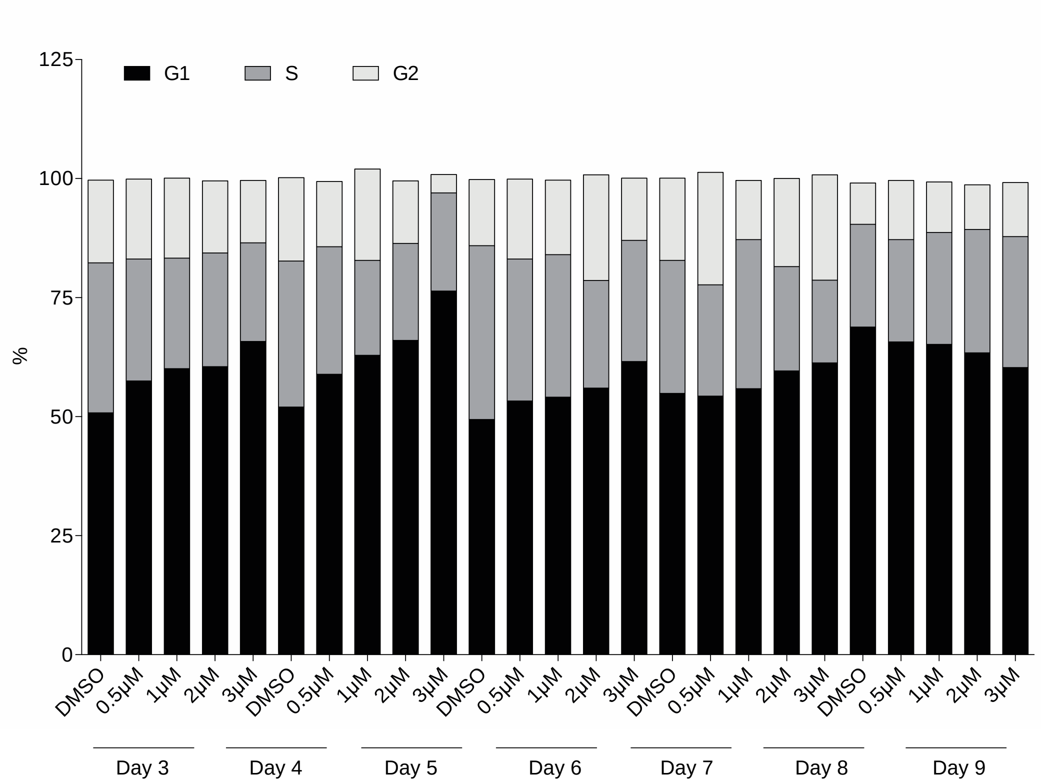
B



Supplemental Figure 8: Prolonged exposure of KASUMI-1 to I-CBP112 A: Cell Cycle phase distribution and **B:** Apoptosis of KASUMI-1 cells analysed by flow cytometry upon treatment with increasing doses of I-CBP112 at different time points. Medium and compound were renewed after 3 days.

Supplemental Figure 9

A



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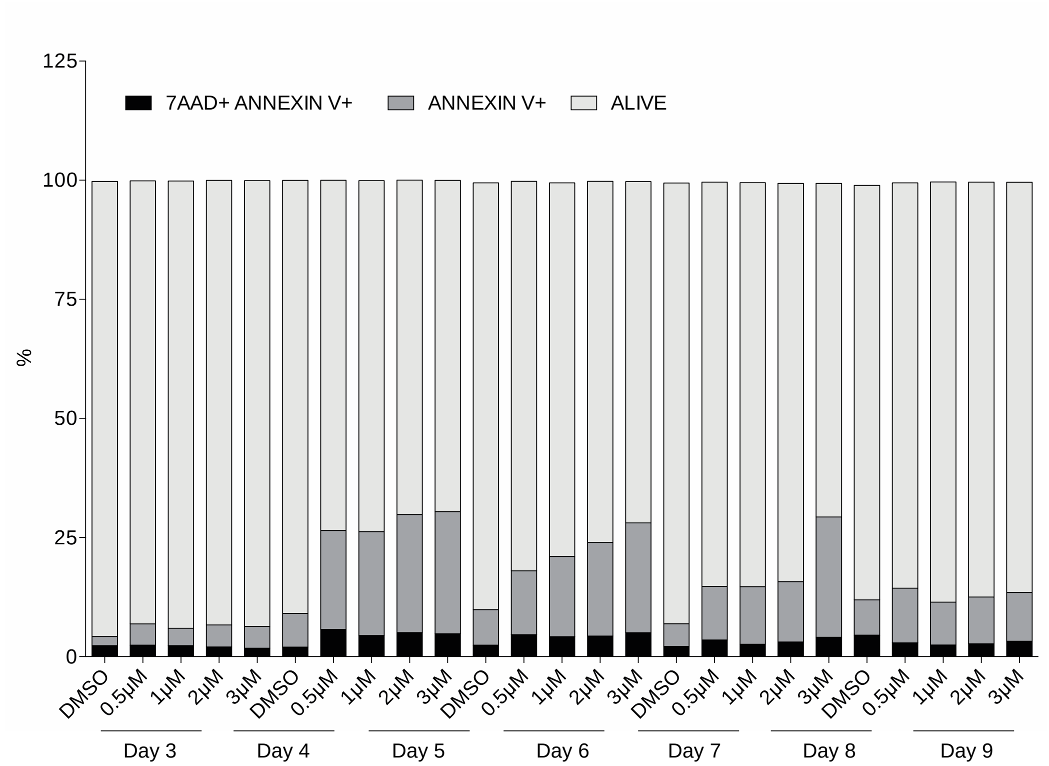
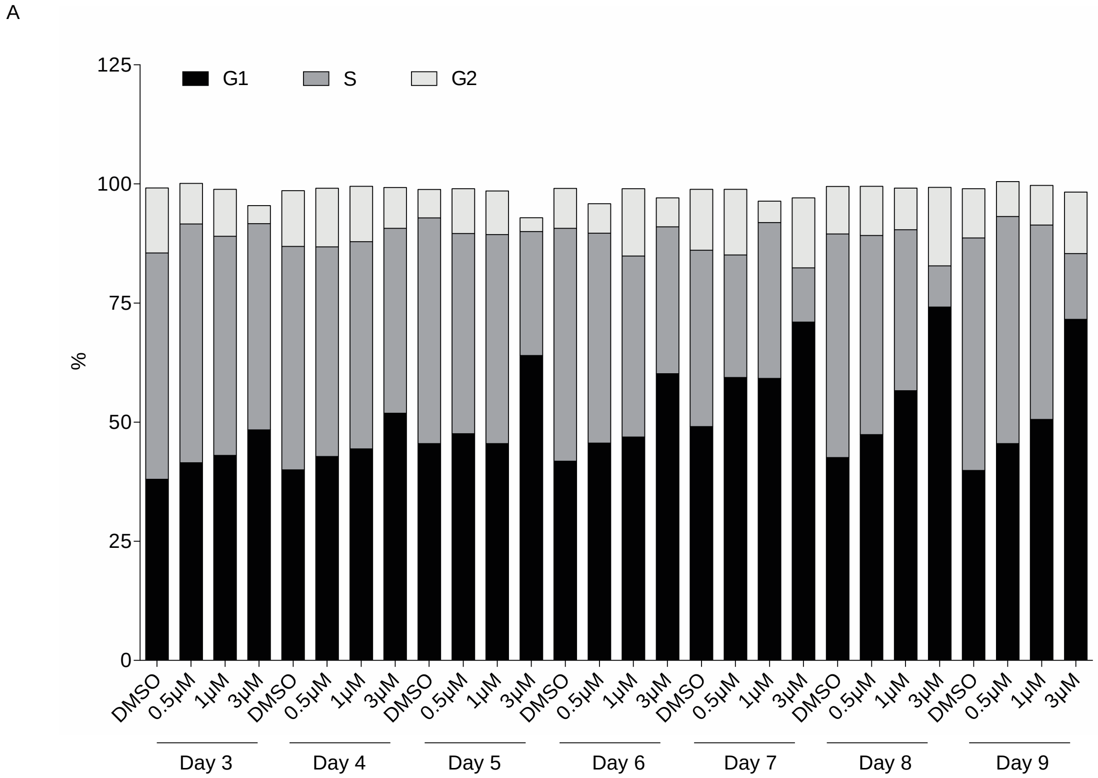
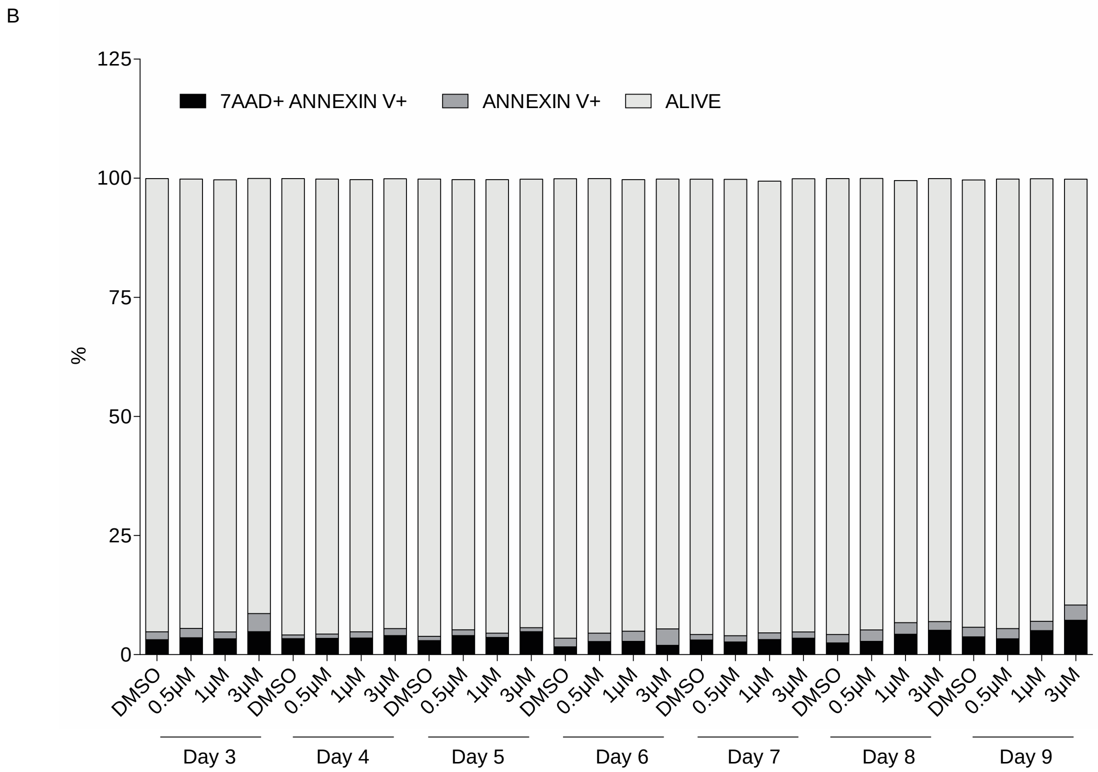


Supplemental Figure 9: Prolonged exposure of MOLM13 to I-CBP112. A: Cell Cycle phase distribution and **B:** Apoptosis of MOLM13 cells analysed by flow cytometry upon treatment with increasing doses of I-CBP112 at different time points. Medium and compound were renewed after 3 days.

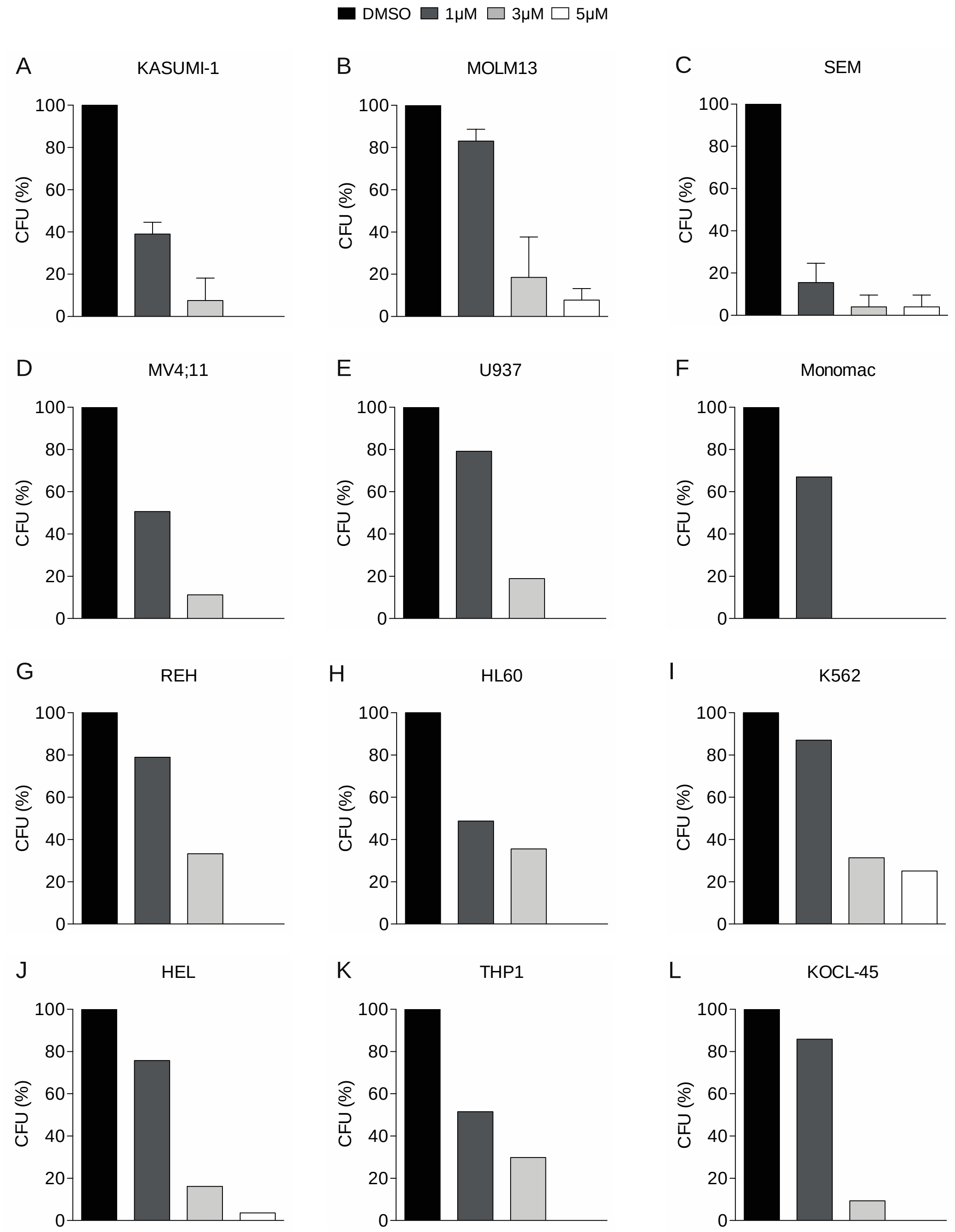
Supplemental Figure 10





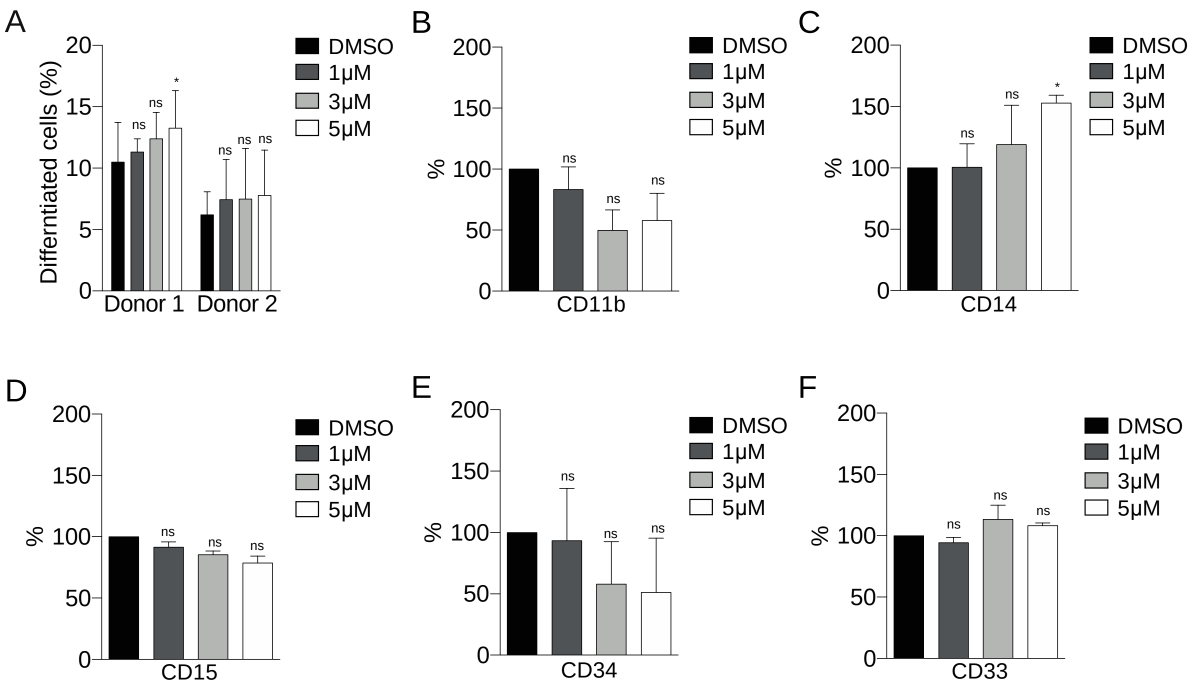
Supplemental Figure 10: Prolonged exposure of SEM to I-CBP112. A: Cell Cycle phase distribution and **B:** Apoptosis of SEM cells analysed by flow cytometry upon treatment with increasing doses of I-CBP112 at different time points. Medium and compound were renewed after 3 days.

Supplemental Figure 11



Supplemental Figure 11: Colony formation of 12 human leukemic cell lines upon exposure to I-CBP112. Colony formation of 12 human leukemic cell lines in methylcellulose, exposed to increasing concentrations of I-CBP112.

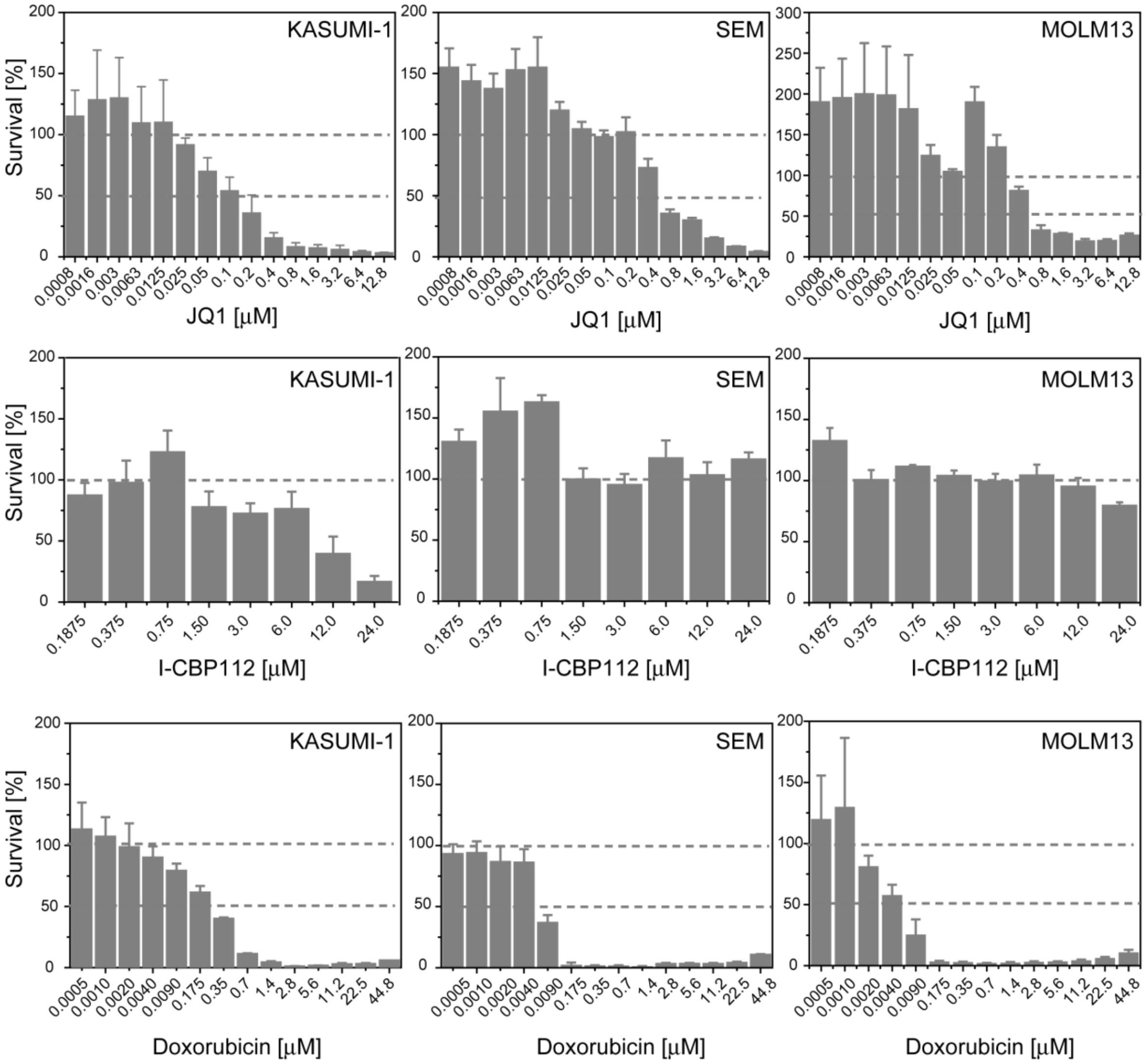
***S*upplemental Figure 12**



Supplemental Figure 12: Differentiation of CD34+ HSCs derived from healthy donors upon exposure to I-CBP112. A: CD34+ HSCs derived from healthy donors were plated into methylcellulose with increasing concentrations of I-CBP112. Cells were resuspended, spotted on glass slides, Wright- Giemsa stained and morphological changes microscopically analysed. The percentage of differentiated cells was normalized to the total amount counted cells. In total, 20 fields (n) were scored. Shown is the average of differentiation per condition (±SD). P- values were calculated using ANOVA and Dunnett multiple comparison, * $p<0.05$. **B- F:** CD34+ derived from healthy donors were plated into methylcellulose with increasing concentrations of I-CBP112. Cells were resuspended and stained with antibodies against CD11b, CD14, CD15, CD34 and CD33 and measured by flow cytometry. Percentages of differentiation were normalized to vehicle- treated cells. Shown is the average of differentiation per condition (±SD). P- values were calculated using ANOVA and Dunnett multiple comparison, * $p<0.05$, n=2.

Supplemental Figure 13

A



B

		JQ-1 1x=0.1uM		or DOXORUBICINE 1x=350nM					
		8:1	**4:1**	**2:1**	**1:1**	**1:2**	**1:4**	**1:8**	**1:16**
	8x	1x	2x	4x	8x	16x	32x	64x	128x
	4x	0.5x	1x	2x	4x	8x	16x	32x	64x
I-CBP	**2x**	0.25x	0.5x	1x	2x	4x	8x	16x	32x
1x=3uM	**1x**	0.125x	0.25x	0.5x	1x	2x	4x	8x	16x
	0.5x	0.0625x	0.125x	0.25x	0.5x	1x	2x	4x	8x
	0.25x	0.03x	0.0625x	0.125x	0.25x	0.5x	1x	2x	4x
	0.125x	0.016x	0.03x	0.0625x	0.125x	0.25x	0.5x	1x	2x
	0.0625x	0.008x	0.016x	0.03x	0.0625x	0.125x	0.25x	0.5x	1x

C

KASUMI

Dose JQ1 (µM)	Dose iCBP112 (µM)	CI
0.0125	0.1875	0.07151
0.0125	0.375	0.08530
0.0125	0.75	0.11946
0.0125	1.5	0.07852
0.0125	3.0	0.05995
0.025	0.187	0.10927
0.025	0.375	0.13419
0.025	0.75	0.13744
0.025	1.5	0.14688
0.025	3.0	0.12384
0.05	0.185	0.13160
0.05	0.375	0.27133
0.05	0.75	0.29643
0.05	1.5	0.22394
0.05	3.0	0.20312

SEM

Dose JQ1 (µM)	Dose iCBP112 (µM)	CI
0.025	0.1875	0.03736
0.025	0.375	0.04123
0.025	0.75	0.04741
0.025	1.5	0.04710
0.025	3.0	0.06295
0.05	0.1875	0.07162
0.05	0.375	0.08459
0.05	0.75	0.07302
0.05	1.5	0.07726
0.05	3.0	0.11681
0.1	0.1875	0.12969
0.1	0.375	0.16130
0.1	0.75	0.13019
0.1	1.5	0.10142
0.1	3.0	0.17312
0.2	0.75	0.24473
0.2	1.5	0.16754
0.2	3.0	0.18006
0.4	0.75	0.41170
0.4	1.5	0.41068
0.4	3.0	0.26769

MOLM13

Dose JQ1 (µM)	Dose iCBP112 (µM)	CI
0.025	0.75	138229.
0.025	1.5	0.59428
0.025	3.0	0.16364
0.05	0.75	138234.
0.05	1.5	276458.
0.05	3.0	552906.
0.1	0.75	0.24331
0.1	1.5	0.13580
0.1	3.0	0.06637
0.2	0.75	0.09736
0.2	1.5	0.21797
0.2	3.0	0.07806
0.4	0.75	0.07310
0.4	1.5	0.12545
0.4	3.0	0.13012

D

KASUMI

Dose Doxorubicine(nM)	Dose iCBP112 (µM)	CI
5.6	0.375	0.09798
10.5	0.375	0.18102
10.5	0.75	0.12549
21.0	0.375	0.28315
21.0	0.75	0.32060
21.0	1.5	0.23050
44.0	0.375	0.73736
44.0	0.75	0.58487
44.0	1.5	0.61536
44.0	3.0	0.52256

SEM

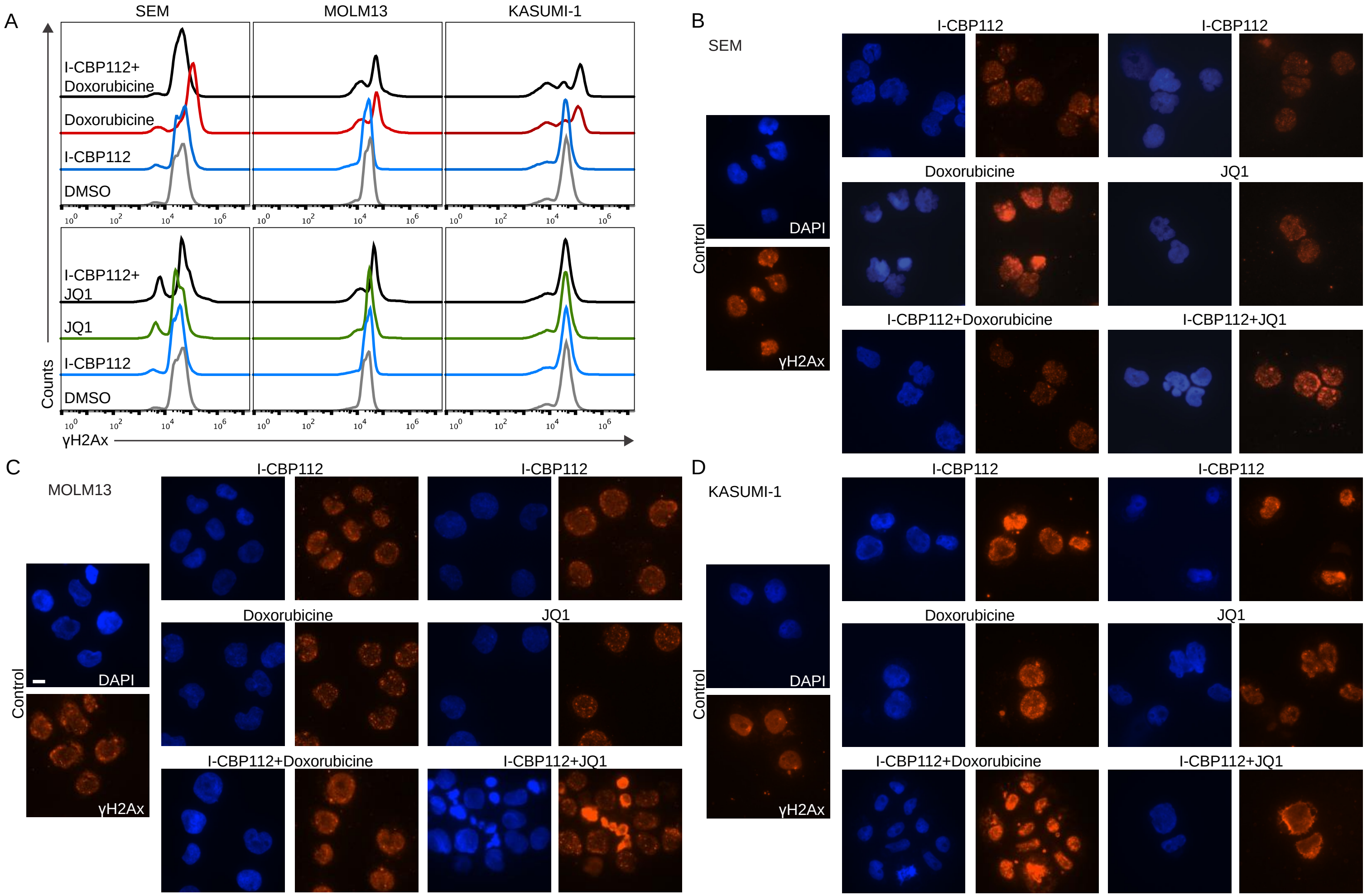
Dose Doxorubicine (nM)	Dose iCBP112(µM)	CI
10.5	0.75	0.27611
10.5	3.0	0.55575
21.0	0.75	0.96205
21.0	1.5	1.59866
21.0	3.0	1.41032
44.0	0.75	1.30639
44.0	1.5	2.87646
44.0	3.0	0.57656

MOLM13

Dose Doxorubicine (nM)	Dose iCBP112 (µM)	CI
10.5	3.0	0.40183
21.0	0.75	0.46833
21.0	1.5	0.71276
21.0	3.0	0.52810
44.0	0.75	0.71040
44.0	1.5	0.85015
44.0	3.0	0.64417

Supplemental Figure 13: Validation of the synergistic effect in drug combinantion studies. A: Assessment of cytotoxicity of JQ-1, I-CBP112 and Doxorubicin in KASUMI-1, SEM and MOLM13 cells. Cytotoxicity of panBET inhibitor JQ-1, I-CBP112 and Doxorubicin was assessed using WST1 proliferation/survival assays and was plotted as a function of increasing compound concentration. **B:** Schematic showing the set up of the different combinations of I-CBP112 and Doxorubicine or JQ1 used for the treatment of MOLM13, KASUMI-1 and SEM. Tables showing the combination index (CI) upon combination of I-CBP112 and JQ1 (**C:**) or Doxorubicine (**D:**) calculated by the CompuSyn software for KASUMI-1, SEM and MOLM13. Concentrations that gave either no or extreme effect for the single treatment were excluded. CI<1 indicates synergism.

Supplemental Figure 14: Effect of I-CBP112 drug combinations on γH2Ax



A: SEM, MOLM13 and KASUMI-1 cells were treated with I-CBP112, JQ1, doxorubicine or combination and γH2Ax (pSer^{139}) was assessed by flow cytometry.

B-D: Immunofluorescent staining of γH2Ax. Representative images for SEM (**B**) MOLM13 (**C**) and KASUMI-1 cells (**D**). Concentrations used for SEM and MOLM13 cells were 1.5µM I-CBP112 and 0.4µM JQ1 or both and 3µM I-CBP112 and 44nM doxorubicine or both. For KASUMI-1, concentrations used were 0.187µM I-CBP112 and 12.5nM JQ1 or both and 3µM I-CBP and 44nM doxorubicine or both. Bar: 10µm

Supplemental Table 7: Significantly regulated genes by exposure to I-CBP112 in KASUMI-1 cells after a 4 day exposure.

SYMBOL	ACCESSION	logFC
RNASE2	NM_002934.2	-1.877835933
FCGR1B	NM_001017986.1	-1.702248652
TNFSF13B	NM_006573.3	-1.67989315
SLC2A5	NM_003039.1	-1.672716922
ANKRD22	NM_144590.2	-1.627742908
TNFSF13B	NM_006573.3	-1.602234026
TRH	NM_007117.1	-1.427931544
DHRS9	NM_005771.3	-1.417342182
RN7SK	NR_001445.1	1.401097459
FCGR1A	NM_000566.2	-1.400344501
ANKRD22	NM_144590.1	-1.36621096
HIST1H2BD	NM_138720.1	1.329553007
CTSG	NM_001911.2	-1.30647185
TP53INP1	NM_033285.2	1.292337987
TP53INP1	NM_033285.2	1.284178791
PDE4B	NM_002600.3	-1.275221813
	BU521176	1.266766603
SLC18A2	NM_003054.2	-1.226578349
GAL	NM_015973.3	-1.193818971
P2RY13	NM_023914.2	-1.187211052
LILRA2	NM_006866.1	-1.177311285
CLEC5A	NM_013252.2	-1.164826148
TGM5	NM_004245.2	-1.150686072
PRIC285	NM_033405.2	1.147669149
RNASE3	NM_002935.2	-1.13822367
CA2	NM_000067.1	-1.116445878
RNU1G2	NR_004426.1	1.111258156
IRF8	NM_002163.2	-1.108626173
LOC100008588	NR_003286.1	1.102030627
CFC1B	NM_001079530.1	-1.098726204
FCGR1B	NM_001004340.1	-1.079403736
SLC22A4	NM_003059.2	-1.078694844
IL8	NM_000584.2	-1.07207046
LOC643332	XR_016287.1	-1.065588146
TCTEX1D1	NM_152665.1	-1.063047603
ARHGAP5	NM_001173.2	-1.057545115
RNU1A3	NR_004430.1	1.045536953
LCP1	NM_002298.2	-1.039447122
CLECL1	NM_172004.2	-1.033544741
LOC100008589	NR_003287.1	1.03060784
TCEA3	NM_003196.1	-1.025015506

SLC44A2	NM_020428.2	1.023368002
KIAA1666	XM_942124.2	1.022623989
RNU1-3	NR_004408.1	1.02212079
GATS	NM_178831.4	1.01158528
RN7SK	NR_001445.1	1.010060857
IGFBP7	NM_001553.1	-1.007405198
ITM2A	NM_004867.3	1.003967171
LMNA	NM_005572.3	0.996687984
ABTB1	NM_032548.2	0.986131497
MXD4	NM_006454.2	0.980475523
RNU1-5	NR_004400.1	0.977493995
SERPINA1	NM_001002236.1	-0.976151167
IL11RA	NM_004512.3	0.975740714
VSIG4	NM_007268.2	-0.965293232
DNAH10	NM_001083900.1	-0.956736082
ID2	NM_002166.4	0.945885703
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ALOX5	XM_001127464.1	0.927333724
ID2	NM_002166.4	0.926328665
NPTX1	NM_002522.2	-0.9251063
CUGBP2	NM_001025076.2	0.923891112
LOC100132394	XM_001713809.1	0.92349068
KLHL24	NM_017644.3	0.923149838
CCL5	NM_002985.2	-0.920773455
NCRNA00085	NR_024330.1	0.91845852
FCGR1C	NM_001128589.1	-0.916015504
LPP	NM_005578.2	0.913557764
TGM5	NM_201631.2	-0.911908708
CCDC92	NM_025140.1	0.911353818
SIGLEC12	NM_053003.2	-0.910665443
PLAC8	NM_016619.1	-0.909829172
ADCY6	NM_020983.2	0.909384648
P2RY13	NM_176894.1	-0.909315511
PLAC8	NM_016619.1	-0.908090985
LOC100133565	XM_001724542.1	0.905216492
KIF1A	NM_004321.4	-0.900979672
LOC100132564	XM_001713808.1	0.893565916
PTRF	NM_012232.3	0.892204925
SERPINA1	NM_001002235.1	-0.888617683
YPEL5	NM_016061.1	0.886604293
MLKL	XM_001126647.1	-0.885082105
LOC727877	XM_001126181.1	0.883305271
CCL5	NM_002985.2	-0.879878746
PRSSL1	NM_214710.2	-0.875868217
RNU4-2	NR_003137.2	0.874835085

SMPDL3B	NM_014474.2	-0.872676098
TM7SF2	NM_003273.2	0.86554732
KIAA1370	NM_019600.2	0.862331804
NINJ2	NM_016533.4	-0.855603147
TMEM71	NM_144649.1	0.855409203
RGL4	NM_153615.1	-0.854372522
TESK2	NM_007170.2	0.853568261
RASSF2	NM_170773.1	0.8534815
NCOA3	NM_181659.1	0.849884433
LOC100008589	NR_003287.1	0.848939478
INSIG1	NM_198336.1	-0.848246145
DLK1	NM_003836.4	-0.846431063
HIST1H2AC	NM_003512.3	0.843040423
CA2	NM_000067.1	-0.841206782
SECISBP2L	NM_014701.2	0.837905551
	CA841942	0.834963108
RPS6KA2	NM_001006932.1	0.833074165
LGALS12	NM_033101.2	-0.831446232
SRGN	NM_002727.2	-0.830685962
RNU6-1	NR_004394.1	0.829563839
STMN3	NM_015894.2	0.829339729
C1orf63	NM_020317.3	0.828028355
FTHL12	NR_002205.1	0.825968874
CCNG2	NM_004354.1	0.824977259
CYTH2	NM_017457.4	0.824749723
SMPDL3B	NM_014474.2	-0.823444679
SAT2	NM_133491.2	0.822114216
ZFP36L1	NM_004926.2	0.820692762
LOC441763	XM_930284.1	0.819514952
KRCC1	NM_016618.1	0.818167224
CHST4	NM_005769.1	-0.81320542
ABCB1	NM_000927.3	0.812903278
STOM	NM_004099.4	-0.811988893
SH3GLB2	NM_020145.2	0.81025036
OCIAD2	NM_001014446.1	0.809796052
MT2A	NM_005953.2	-0.808054071
FTHL16	XR_041433.1	0.805749392
NCOA7	NM_181782.2	-0.805381486
ALOX5AP	NM_001629.2	-0.80425683
ITM2C	NM_001012516.1	0.800105429
LBR	NM_002296.2	-0.798207513
FTHL8	NR_002203.1	0.794555377
RNU6-15	NR_028372.1	0.794393014
DHRS9	NM_005771.3	-0.793265337
NCF2	NM_000433.2	-0.791115019

ITM2C	NM_001012516.1	0.790243251
VSTM1	NM_198481.3	-0.788502886
NFE2	NM_006163.1	-0.78583396
KIAA1370	NM_019600.1	0.783799882
CD247	NM_000734.2	-0.783573864
DRAM1	NM_018370.2	-0.780332899
TRPT1	NM_031472.2	0.780034716
LAMA5	NM_005560.3	0.77978001
SLC22A4	NM_003059.2	-0.778123798
	U62823	0.777208339
CEACAM6	NM_002483.3	-0.776121412
LAX1	NM_017773.2	-0.77448784
CAPN5	NM_004055.4	0.77336783
GAPT	NM_152687.2	-0.772746224
	AK092638	0.772226064
EMR2	NM_152916.1	0.770953593
CCM2	NM_001029835.1	0.76700636
LOC338758	XM_931359.2	0.766703959
LOC100134364	XM_001713810.1	0.766591561
BMF	NM_033503.3	0.764226844
	BC035116	0.762094469
TP53I3	NM_147184.1	0.760896032
SLC22A18	NM_002555.3	0.76042985
CSF3R	NM_172313.1	-0.759201113
SESN1	NM_014454.1	0.756629772
ITGA3	NM_002204.1	0.755436013
FTHL11	NR_002204.1	0.755052893
ST3GAL6	NM_006100.2	-0.753690727
RET	NM_020975.4	-0.752906428
GPR84	NM_020370.1	-0.752814282
KIAA0913	NM_015037.2	0.750458835
EAF2	NM_018456.4	-0.74608937
AGTRAP	NM_001040196.1	-0.745490903
PIK3IP1	NM_052880.3	0.744644082
HBP1	NM_012257.3	0.744163883
FAM116B	NM_001001794.2	0.740225594
KIAA1683	NM_025249.1	0.738507873
ID3	NM_002167.2	0.737841726
ECHDC2	NM_018281.2	0.73715926
POLR3G	NM_006467.2	-0.735486629
LOC730517	XM_001715215.1	-0.732031558
HLA-DMA	NM_006120.2	0.731783475
SHISA2	NM_001007538.1	-0.731193571
CCM2	NM_001029835.1	0.730566218
IRF7	NM_004029.2	0.73052072

MERTK	NM_006343.2	0.730178672
CCNG1	NM_199246.1	0.730060899
	AK055652	0.7274365
AIF1	NM_032955.1	-0.726402363
NDRG1	NM_006096.2	0.724979086
C1orf63	NM_207035.1	0.724226792
S100P	NM_005980.2	-0.721819575
CUGBP2	NM_006561.2	0.720962508
SSBP2	NM_012446.2	0.7209271
RGL1	NM_015149.3	0.720319412
	AF131784	0.717526357
NMI	NM_004688.1	-0.716831381
CTSB	NM_001908.3	0.716777886
ECE2	NM_014693.2	-0.715872055
BTG1	NM_001731.1	0.715026787
CD247	NM_198053.1	-0.712791412
LMNA	NM_005572.3	0.712283107
RNU1F1	NR_004402.1	0.709590265
LOC100133999	XM_001716785.1	0.709133489
AMT	NM_000481.2	0.708810348
FTHL7	NR_002202.2	0.705767355
XPOT	NM_007235.3	-0.705013519
IL1RAP	NM_002182.2	-0.704628555
IL1RAP	NM_134470.2	-0.703317255
MGST1	NM_020300.3	-0.701071913
RPS7	NM_001011.3	-0.698490687
RNU6ATAC	NR_023344.1	0.697287569
GSN	NM_198252.2	-0.695932003
PCBP4	NM_020418.2	0.694727061
KLF12	NM_007249.4	0.694174037
CDR2L	NM_014603.1	0.691743337
TIPIN	NM_017858.1	-0.691653487
CFD	NM_001928.2	0.690555215
RFC2	NM_181471.1	-0.689877528
FTHL12	NR_002205.1	0.689573183
MOAP1	NM_022151.4	0.686746952
KIFC2	NM_145754.2	0.685649227
FAM89A	NM_198552.1	0.685606807
XYLT1	NM_022166.3	0.685480593
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FTHL2	NR_002200.1	0.682539387
C5orf41	NM_153607.1	0.682279717
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KIAA0355	NM_014686.3	0.680904277

POLR3G	NM_006467.2	-0.680346596
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SPSB3	NM_080861.3	0.6772486
PDE4B	NM_002600.3	-0.676925141
ATP9A	NM_006045.1	-0.676837733
SYNGR1	NM_004711.3	-0.676686047
OSTalpha	NM_152672.4	-0.675509103
KIAA1602	NM_020941.1	0.675010441
DDAH2	NM_013974.1	0.674953842
TNFAIP8	NM_001077654.1	-0.674662204
IGLL1	NM_020070.2	-0.674187524
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PSCD1	NM_017456.1	0.672916405
BCL6	NM_001706.2	0.670887872
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TRIM8	NM_030912.2	0.669794276
HSPD1	NM_002156.4	-0.669694607
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SLC7A5	NM_003486.5	-0.666822405
ECM1	NM_022664.1	-0.666818915
CEBPE	NM_001805.2	-0.665448617
LOC730167	XM_001726158.1	-0.664750249
MT1G	NM_005950.1	-0.664688101
P2RX1	NM_002558.2	0.663092985
BNIP3L	NM_004331.2	0.66282058
HIST1H2BD	NM_138720.1	0.661919954
AKNA	NM_030767.3	0.659628157
CDO1	NM_001801.2	0.656206461
PRKDC	NM_006904.6	-0.65620356
CDKN2C	NM_078626.2	0.655944952
RRAS	NM_006270.3	0.655916007
CYTH1	NM_017456.2	0.655539202
	BX097705	-0.655389778
MRPL35	NM_145644.1	-0.653997665
TXNIP	NM_006472.2	0.653424334
GHDC	NM_032484.3	0.653006313
CORO1B	NM_001018070.1	0.652516334
PPP1R15A	NM_014330.2	0.652091186
CTSB	NM_147780.2	0.651905251
UBE1	NM_153280.1	-0.651303867
NTSR1	NM_002531.2	-0.65071254
MLKL	NM_152649.1	-0.650248547
RANBP1	NM_002882.2	-0.649999647
STX5	NM_003164.3	0.649182523

LYAR	NM_017816.1	-0.648106132
CCND3	NM_001760.2	0.647916175
CCDC58	NM_001017928.2	-0.64726471
TTLL3	NM_015644.3	0.644822356
SNORD3D	NR_006882.1	0.644508922
MFSD6	NM_017694.3	0.642543707
LOC100134144	XM_001717999.1	0.642472057
GAPT	NM_152687.2	-0.641792835
LMO2	NM_005574.2	-0.641576633
ADCY6	NM_020983.2	0.641492433
C9orf103	NM_001001551.1	0.639404177
RN5S9	NR_023371.1	0.638596481
HOMER2	NM_199332.2	-0.638269318
SLC25A19	NM_021734.3	-0.6381119
ECM1	NM_004425.2	-0.638015907
DNAJB2	NM_006736.5	0.63765721
AXUD1	NM_033027.2	0.636833989
DBN1	NM_004395.2	0.636620656
TNFRSF6B	NM_032945.2	0.636470315
LOC643870	XM_927140.1	0.63623206
SRGN	NM_002727.2	-0.635497918
LTA4H	NM_000895.1	0.635176309
LAIR2	NM_021270.2	-0.634719989
BIK	NM_001197.3	-0.63449453
RASGRP2	NM_005825.2	-0.633425058
SYT11	NM_152280.2	0.633056298
FAM43A	NM_153690.4	0.632231485
CTDSP2	NM_005730.3	0.631752015
ZNF581	NM_016535.3	0.631005189
CACNB3	NM_000725.2	0.629865677
P2RY5	NM_005767.4	0.629641289
	BX641108	0.628565042
LRRC17	NM_005824.1	-0.628457473
LOC85390	NR_001454.1	-0.628300935
CD68	NM_001251.1	-0.627528383
ZNF211	NM_006385.2	0.627481848
S100A4	NM_019554.2	0.627175686
PPM1G	NM_177983.1	-0.62456829
SC4MOL	NM_006745.3	-0.624455616
MS4A7	NM_206938.1	-0.623637243
PTGER2	NM_000956.2	-0.622068997
TUG1	NR_002323.1	0.621592305
TSPAN9	NM_006675.3	0.620161447
C2orf65	NM_138804.3	-0.619464591
ICAM3	NM_002162.2	0.61939787

PTMS	NM_002824.4	0.619301501
ZMIZ1	NM_020338.2	0.618878221
MLKL	XM_001126647.1	-0.61866213
MYO1G	NM_033054.1	0.617504858
FAM89A	XM_939093.1	0.617246513
GART	NM_175085.1	-0.61661938
HOMER2	NM_199331.2	-0.616447403
MNDA	NM_002432.1	-0.616388269
MGEA5	NM_012215.2	0.615816839
LRMP	NM_006152.2	-0.615757849
ASMTL	XM_942506.1	0.614244868
MTSS1	NM_014751.4	0.613367328
PHF17	NM_024900.3	-0.613235638
TUFT1	NM_020127.1	0.612393134
NFKBIE	NM_004556.2	-0.61212368
RHOC	NM_175744.4	0.611937489
RCOR3	NM_018254.2	0.610821781
ASS1	NM_000050.4	-0.609848981
TGFBR2	NM_001024847.2	0.609692395
BRI3BP	NM_080626.5	-0.609568246
PDE4D	NM_006203.3	-0.609471243
ANKDD1A	NM_182703.3	0.608932951
LRCH4	NM_002319.2	0.608665413
INSIG1	NM_198336.1	-0.608446056
CNFN	NM_032488.2	0.607397975
BRI3BP	NM_080626.5	-0.606384615
ATP5G1	NM_005175.2	-0.606358576
LOC728047	XM_001126912.1	-0.606015376
ARSD	NM_001669.2	0.605826016
MFSD6	NM_017694.3	0.604045483
RPL37	NM_000997.3	0.604005073
CDC25A	NM_001789.2	-0.603948054
SHANK3	NM_001080420.1	0.603667952
LOC727761	XM_001126211.1	-0.603332553
MMP28	NM_001032278.1	0.603221248
GATA2	NM_032638.3	0.60315307
ELOVL6	NM_024090.1	-0.601851932
CROP	NM_016424.3	0.601134848
LOC791120	NR_015357.1	0.601015752
SLC38A5	NM_033518.1	-0.600923909
BAZ2B	NM_013450.2	0.600864634
LYAR	NM_017816.1	-0.600640929
PHACTR1	NM_030948.1	-0.599881581
NMB	NM_021077.3	-0.599807393
PKD2	NM_000297.2	0.599096317

TOR3A	NM_022371.3	-0.598939175
RNU4-1	NR_003925.1	0.598803729
LOC100130892	XM_001720172.1	0.598800657
LRRC17	NM_001031692.1	-0.598235129
LOC653344	XM_933085.1	0.598008851
ABCB1	NM_000927.3	0.597637727
TSPYL3	XR_001421.1	0.597611318
FAM89B	NM_001098784.1	0.597217488
	AK092074	0.597188448
CEBPD	NM_005195.3	-0.596688203
TPRG1L	NM_182752.3	0.596467979
NPC2	NM_006432.3	0.59639002
LGSN	NM_016571.1	0.596251234
LOC644914	XM_930111.2	0.59622382
ERO1L	NM_014584.1	-0.595578478
CCDC24	NM_152499.1	0.595513371
PRIM2A	XM_001134299.1	-0.594758774
NCRNA00219	NR_015370.1	0.594001793
HCST	NM_001007469.1	0.593612238
LPIN1	NM_145693.1	0.593567028
BHLHB2	NM_003670.1	0.59334335
ZWILCH	NM_017975.3	-0.592021701
RRS1	NM_015169.3	-0.591416436
ZNF326	NM_182976.1	-0.591339579
C5orf41	NM_153607.1	0.590530783
LOC644162	XM_933956.1	-0.590046944
LSM12	NM_152344.2	-0.58963917
GTF2H3	NM_001516.3	-0.588718397
C14orf179	NM_052873.1	0.587394635
COL4A5	NM_000495.3	0.587210266
OSBPL2	NM_144498.1	0.586381288
CAST	NM_001042442.1	0.586223935
B3GNTL1	NM_001009905.1	-0.586183713
SLC38A10	NM_138570.2	-0.586011882

Supplemental Table 8: Significantly regulated genes by exposure to I-CBP112 in MOLM13 cells after a 4 day exposure.

SYMBOL	ACCESSION	logFC
PRG2	NM_002728.4	-1.639232194
MS4A3	NM_006138.4	-1.47321975
IL8	NM_000584.2	-1.396195453
CACNA2D3	NM_018398.2	-1.344117221
MPO	NM_000250.1	-1.327633118
MS4A3	NM_006138.4	-1.297766477
AIF1	NM_032955.1	-1.295411069
CST7	NM_003650.2	-1.285628397
RNASE3	NM_002935.2	-1.262303279
CTSG	NM_001911.2	-1.261036568
CHI3L1	NM_001276.2	-1.217610872
SERPINB10	NM_005024.1	-1.131353157
CUX2	NM_015267.2	-1.118701772
NFE2	NM_006163.1	-1.109079544
LOC643332	XR_016287.1	-1.09412978
FCGR1A	NM_000566.2	-1.089914598
RNASE2	NM_002934.2	-1.074627798
C5orf20	NM_130848.2	-1.032472915
EGR1	NM_001964.2	1.011502202
MS4A6A	NM_152851.1	-1.002900864
RGS18	NM_130782.2	-1.002391126
S100A8	NM_002964.3	-1.001889746
AIF1	NM_001623.3	-0.993513043
S100A9	NM_002965.2	-0.972289041
CFC1B	NM_001079530.1	-0.957997689
FGR	NM_001042729.1	-0.955300402
IL8	NM_000584.2	-0.949369292
C19orf59	NM_174918.2	-0.946978511
SPNS3	NM_182538.3	-0.944210941
CCR2	NM_000647.3	-0.941974527
LOC730517	XM_001126166.1	-0.938078431
CORO2A	NM_003389.2	-0.927753323
SNORA12	NR_002954.1	0.923431985
PRSSL1	NM_214710.2	-0.90604267
ARHGAP5	NM_001173.2	-0.885604357
MS4A6A	NM_022349.2	-0.866908432
CD36	NM_000072.2	-0.853740183
ORM1	NM_000607.1	-0.853486456
LILRA2	NM_006866.1	-0.849052167
RAB7B	NM_177403.3	-0.848573119
CCR2	NM_000647.4	-0.84591215

CSF3R	NM_172313.1	-0.84467196
SERPINB2	NM_002575.1	-0.833119858
PECAM1	NM_000442.3	-0.831750476
SERPINB2	NM_002575.1	-0.830261994
MLC1	NM_015166.3	-0.829717972
FCGR1B	NM_001017986.1	-0.824932499
BPI	NM_001725.1	-0.824047912
CCL3L1	NM_021006.4	-0.82157174
CD52	NM_001803.2	-0.813481394
TNFSF13B	NM_006573.3	-0.812783834
THBS4	NM_003248.3	-0.810154773
HLA-DRA	NM_019111.3	-0.792283023
SCARNA14	NR_004388.1	0.778835793
MNDA	NM_002432.1	-0.778103696
TIFAB	NM_001099221.1	-0.769664747
CCR2	NM_000648.2	-0.769503313
TSPAN32	NM_005705.4	-0.768712406
SERPINB8	NM_002640.3	-0.767695904
FCGR1B	NM_001004340.1	-0.753559572
MS4A4A	NM_148975.1	-0.752748701
ASMTL	XM_942506.1	0.747425804
SCARNA13	NR_003002.1	0.746507053
RN5S9	NR_023371.1	0.742090357
CXCR4	NM_001008540.1	-0.740410413
FCER2	NM_002002.3	-0.724726185
IFI6	NM_022873.2	0.721309592
ARHGEF10	NM_014629.2	-0.719462384
LST1	NM_007161.2	-0.717548735
CPVL	NM_019029.2	0.714203485
TBC1D10C	NM_198517.2	-0.711969457
C13orf18	NM_025113.1	-0.707352932
SNORD31	NR_002560.1	0.705285853
TMEM45A	NM_018004.1	-0.704596247
TRAPPC6A	NM_024108.1	0.703279731
CSPG4	NM_001897.4	-0.701991311
PRDM8	NM_020226.3	-0.699029818
TGM5	NM_004245.2	-0.696730621
CD36	NM_001001548.1	-0.694044215
S1PR3	NM_005226.2	-0.685589366
FCGR1C	NM_001128589.1	-0.675616436
CYFIP2	NM_014376.2	0.671141626
ATP6V1C2	NM_144583.3	-0.669259049
TMEM14A	NM_014051.3	0.667309603
MS4A6A	NM_152851.1	-0.663502021
PNOC	NM_006228.3	-0.663144916

SNORA57	NR_004390.1	0.660109179
GPR18	NM_001098200.1	-0.659289432
LY96	NM_015364.2	0.658397331
RARRES3	NM_004585.3	0.656919611
IDI1	NM_004508.2	-0.656310383
	AY129027	-0.6537868
37134	NM_002688.4	-0.650478319
DHRS9	NM_005771.3	-0.645904872
FTHL7	NR_002202.2	0.645039294
	BX093329	-0.638482928
PTPN22	NM_015967.3	-0.638457746
NANOS1	NM_001009553.1	-0.636033874
SNX10	NM_013322.2	-0.635840359
DYSF	NM_003494.2	-0.635214108
SCARNA8	NR_003009.1	0.635192062
SYTL1	NM_032872.1	-0.628275589
PSAP	NM_001042465.1	0.626516856
BASP1	NM_006317.3	-0.624755931
LOC100134379	XM_001720508.1	-0.623016327
TGM5	NM_201631.2	-0.621688195
SERPINB8	NM_198833.1	-0.621530316
CLCF1	NM_013246.2	-0.616351318
TNFSF13B	NM_006573.3	-0.615822026
FCER1G	NM_004106.1	-0.613515389
RASGRP2	NM_005825.2	-0.612685259
PLAC8	NM_016619.1	-0.612598797
C13orf18	NM_025113.1	-0.611826776
GPR84	NM_020370.1	-0.610399762
LOC100134648	XM_001724681.1	0.608430501
SQRDL	NM_021199.2	-0.606590774
SLC22A4	NM_003059.2	-0.606522551
IGLL1	NM_020070.2	-0.606142732
MLKL	NM_152649.1	-0.605608678
WNT7B	NM_058238.1	-0.605008071
PSTPIP1	NM_003978.2	-0.604192959
CCL3L3	NM_001001437.3	-0.595676743
SHISA2	NM_001007538.1	-0.59528192
METTL7B	NM_152637.1	-0.594434951
C3orf54	NM_203370.1	-0.591699864
CAT	NM_001752.2	-0.589083482
INSIG1	NM_198336.1	-0.586611857
CHST13	NM_152889.1	-0.586012155
PLD3	NM_001031696.1	0.585269752

Supplemental Table 9: Significantly regulated genes by exposure to I-CBP112 in SEM cells after a 4 day exposure.

SYMBOL	ACCESSION	logFC
LOC100008589	NR_003287.1	2.444459698
LOC100132394	XM_001713809.1	2.318606627
LOC100008589	NR_003287.1	2.310711627
LOC100134364	XM_001713810.1	2.063037994
LOC100133565	XM_001724542.1	1.990136006
CSF1R	NM_005211.2	-1.985680186
ADAMTSL2	NM_014694.2	1.902519787
LOC441763	XM_930284.1	1.887924452
SLC7A7	NM_003982.2	-1.842173109
ID2	NM_002166.4	1.730565243
ID2	NM_002166.4	1.637947926
MGC33556	NM_001004307.1	-1.63673205
SMAD7	NM_005904.2	1.63331177
VENTX	NM_014468.2	-1.566521159
HSPB7	NM_014424.3	-1.525703903
SNORA12	NR_002954.1	1.519383144
CST7	NM_003650.2	-1.512389163
CSPG4	NM_001897.4	-1.505235008
NFE2	NM_006163.1	-1.471124194
BMF	NM_033503.3	1.432866046
PDGFRB	NM_002609.3	-1.401235528
PRSSL1	NM_214710.2	-1.331933325
TMEM119	NM_181724.1	1.305513996
IL21R	NM_181078.1	-1.299587543
SCD	NM_005063.4	-1.297479005
ADA	NM_000022.2	-1.28400768
ANXA2	NM_001002857.1	-1.279952046
CD72	NM_001782.1	-1.278144098
NELL2	NM_006159.1	1.27783016
MIR1978	NR_031742.1	-1.270179683
SMAD7	NM_005904.2	1.260744223
SCARNA13	NR_003002.1	1.259635487
CD52	NM_001803.2	-1.252455896
ISG20	NM_002201.4	-1.247740807
CYSLTR1	NM_006639.2	-1.245432152
IFITM1	NM_003641.3	-1.232095307
LCN6	NM_198946.2	-1.231159153
SLC43A2	NM_152346.1	1.228705384
C17orf87	NM_207103.1	-1.226024261
LRIG1	NM_015541.2	1.207224498

RGS2	NM_002923.1	-1.206134551
BMF	NM_001003943.1	1.203282656
ECM1	NM_022664.1	-1.192197833
NQO1	NM_000903.2	1.18281644
FOS	NM_005252.2	-1.17586733
BAMBI	NM_012342.2	1.164360057
MXD4	NM_006454.2	1.160080602
ACAD11	NM_032169.4	-1.14365653
HLA-DRB4	NM_021983.4	-1.139998934
EGR1	NM_001964.2	-1.137059502
AK3L1	NM_013410.2	-1.120208128
TLE4	NM_007005.3	1.119221832
LILRA2	NM_006866.1	-1.115064082
CA2	NM_000067.1	-1.108890281
PLEK	NM_002664.1	-1.107076323
CYP1A1	NM_000499.2	1.107044348
PGAM1	NM_002629.2	-1.097093724
LRIG1	NM_015541.2	1.09512074
DAAM1	NM_014992.1	1.093623976
SREBF1	NM_001005291.1	-1.093074921
	AK026966	-1.088680791
GP9	NM_000174.2	-1.087262843
NLGN4X	NM_020742.2	-1.085104953
REEP1	NM_022912.1	1.066683035
C17orf87	NM_207103.2	-1.065368685
CCL5	NM_002985.2	-1.053819584
NPW	NM_001099456.2	-1.052619524
SLC15A3	NM_016582.1	-1.051897951
EVL	NM_016337.2	-1.05121774
NKG7	NM_005601.3	-1.047671857
CTNNBL1	NM_030877.3	-1.033308027
FAM69B	XM_001130258.1	-1.033251279
VWA5A	NM_014622.4	1.026270141
SORBS2	NM_003603.4	1.024122526
HSH2D	NM_032855.2	-1.007776123
CHN2	NM_004067.2	1.007047038
LOC728188	XM_001126103.2	-1.004808883
DDN	NM_015086.1	-1.004787523
SNORD13	NR_003041.1	0.99059668
APOBEC3G	NM_021822.1	-0.988783363
CACNA2D4	NM_172364.4	-0.981774933
RFTN1	NM_015150.1	0.981498214
TLE4	NM_007005.3	0.971960662
ARSD	NM_001669.2	0.971143967
ADARB1	NM_001112.2	0.970185563

HOPX	NM_139212.2	0.969015484
LIMS2	NM_017980.3	-0.968395228
RGL1	NM_015149.3	0.965748132
S100A13	NM_001024211.1	-0.96570075
KAZALD1	NM_030929.3	-0.959295913
SLC16A3	NM_004207.2	-0.958353187
CARD9	NM_052813.3	-0.950676565
RUNX2	NM_001024630.2	0.949879104
AK3L1	NM_203464.1	-0.948593208
CTSO	NM_001334.2	0.944958519
LOC387841	XM_932678.1	-0.941383181
ANPEP	NM_001150.1	0.940240348
SLA	NM_006748.1	-0.933212782
MCOLN2	NM_153259.2	-0.92582889
SH3BP4	NM_014521.2	0.922806371
ACACA	NM_198839.1	-0.915553918
CLEC11A	NM_002975.2	-0.912467558
TBC1D10C	NM_198517.2	-0.911651062
ANGPT1	NM_001146.3	-0.908733882
LOC643384	XR_016363.2	-0.906382262
CCDC81	NM_021827.3	-0.905115396
SPIRE1	NM_020148.2	0.900306925
CYTH1	NM_017456.2	0.899583409
SORBS2	NM_003603.4	0.898761626
CTNNA1	NM_001903.2	0.898648128
HNRPLL	NM_138394.2	0.898274719
UNC93B1	NM_030930.2	-0.898201169
CA2	NM_000067.1	-0.89534568
SORD	XM_001132175.1	-0.893251578
ABLIM1	NM_006720.3	0.890419807
MYO10	NM_012334.1	0.889352737
SLC22A16	NM_033125.2	-0.886518474
GPM6B	NM_001001995.1	-0.885789177
CRMP1	NM_001014809.1	0.884390825
EFNB2	NM_004093.2	0.884331445
IRAK2	NM_001570.3	-0.882557916
FADS1	NM_013402.3	-0.881501449
MPPE1	NM_023075.4	0.880816171
CD86	NM_006889.3	-0.880811133
CCL5	NM_002985.2	-0.879251206
C19orf59	NM_174918.2	-0.87427298
ITPRIPL2	NM_001034841.2	-0.870008173
TCF7	NM_213648.1	0.866048729
DHCR7	NM_001360.1	-0.865962211
FAM65B	NM_015864.2	-0.862169363

TCF7	NM_201632.1	0.861658995
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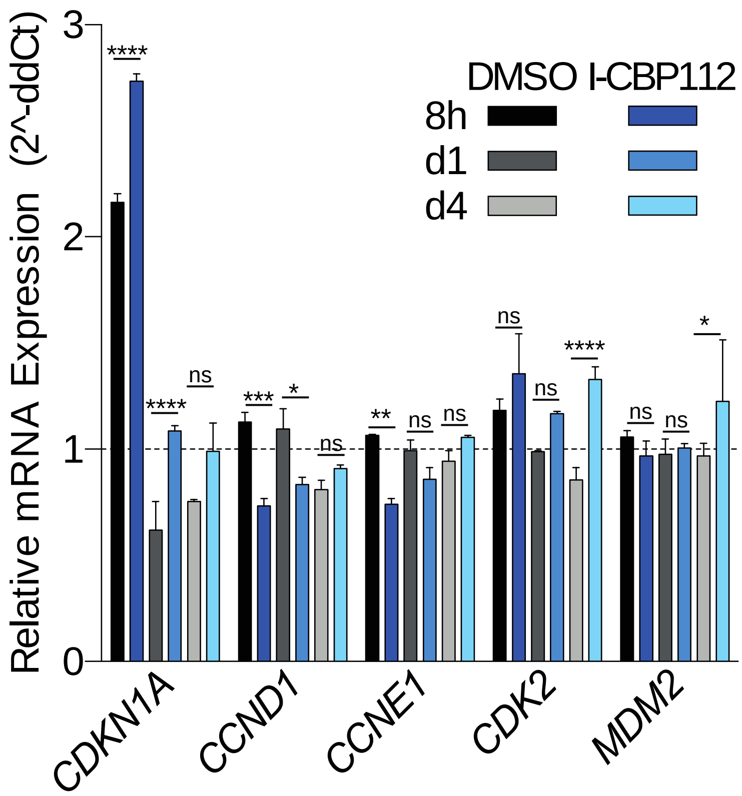
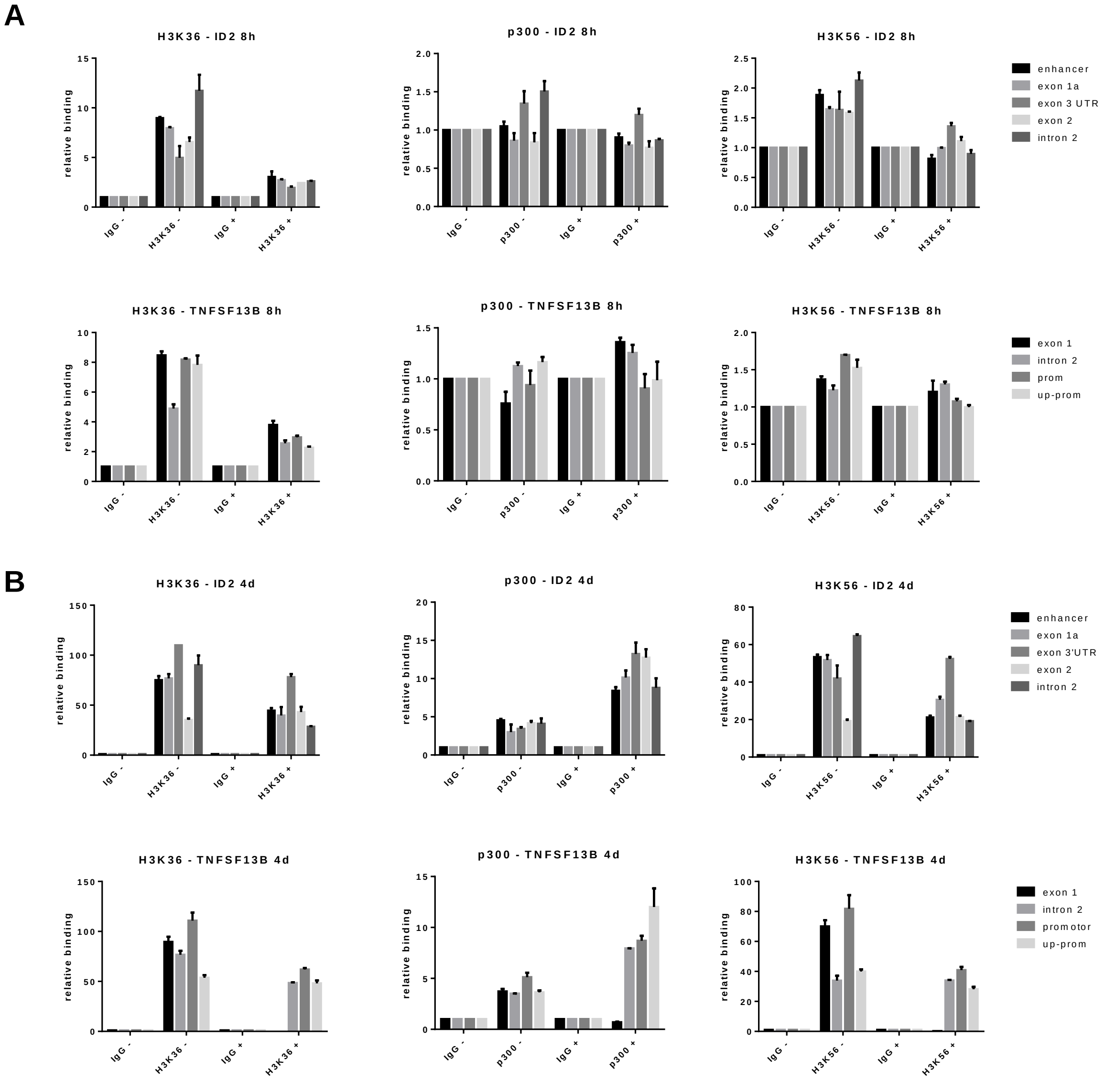
Supplemental Figure 15:

A



Supplemental Figure 15. Expression changes of selected cell cycle regulator target genes on mRNA level in KASUMI-1 cells upon exposure of I-CBP112: Expression changes of selected cell cycle target genes on mRNA level, measured by q-RTPCR, in KASUMI-1 cells upon exposure of I-CBP112 (3µM) for 8 hours, 1 and 4 days. Ct were first normalized to GAPDH housekeeping gene and then to the average of vehicle- treated (DMSO) cells (Relative expression=1). P- values were calculated using a two- way ANOVA test and Turkey multiple comparison: ns= not significant, * p<0.05 ** p<0.01 *** p<0.001 **** p<0.0001, n=2.

Supplemental Figure 16:



Supplemental Figure 16. ChIP qPCR data on two regulated genes. I-CBP112-induced reduction of P300-binding to gene loci of ID2 and TNFSF13B. ChIP qPCR from different gene regions of the ID2 and the TNFSF13B locus after treatment with DMSO or 3 µM I-CBP112 for 8 h (**A**) or 4 days (**B**). The relative enrichment is expressed as mean and error bars represent the standard deviation. DMSO treated cells are indicated by a “-“ and I-CBP112 treated cells by “+”.