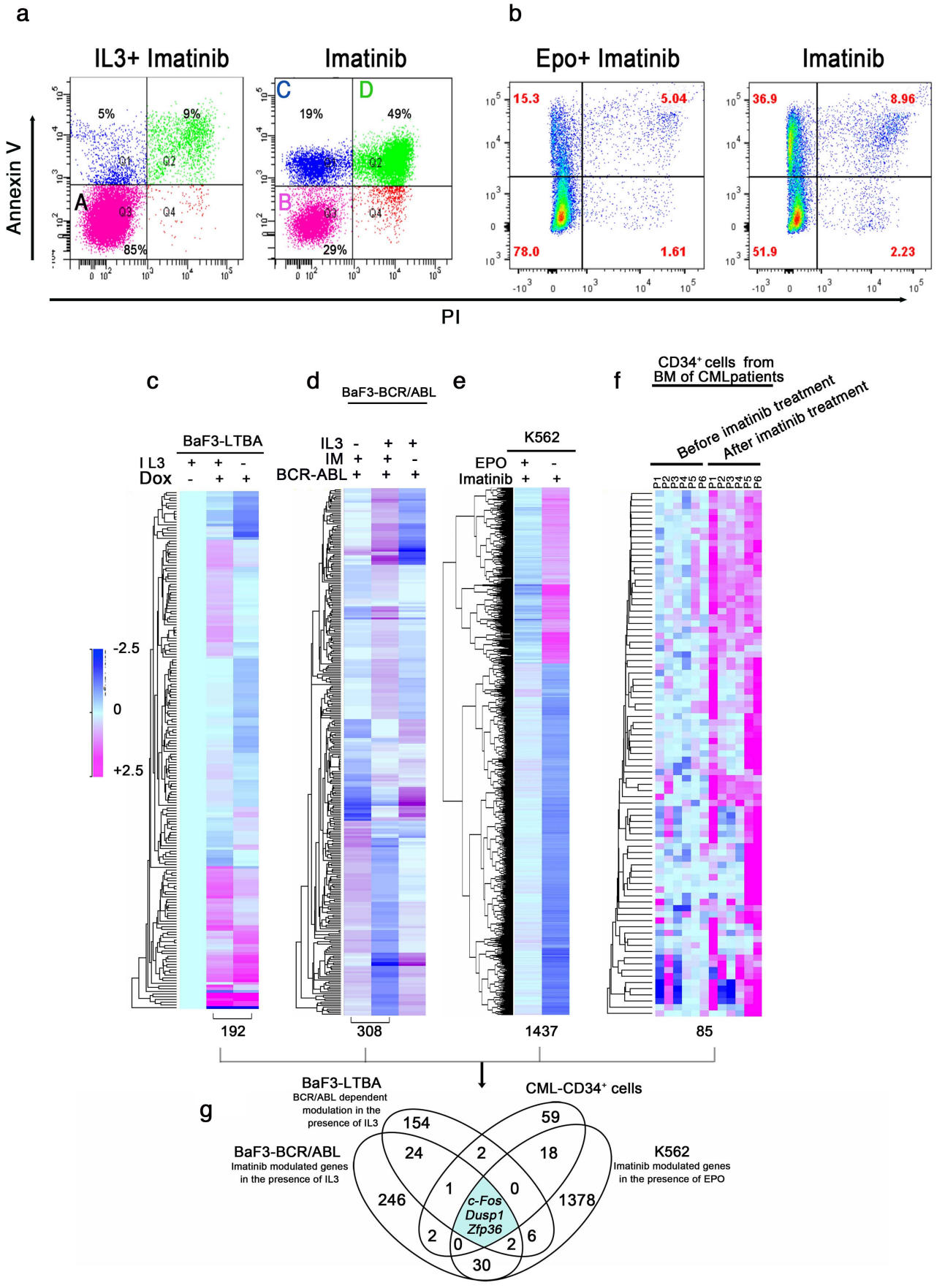
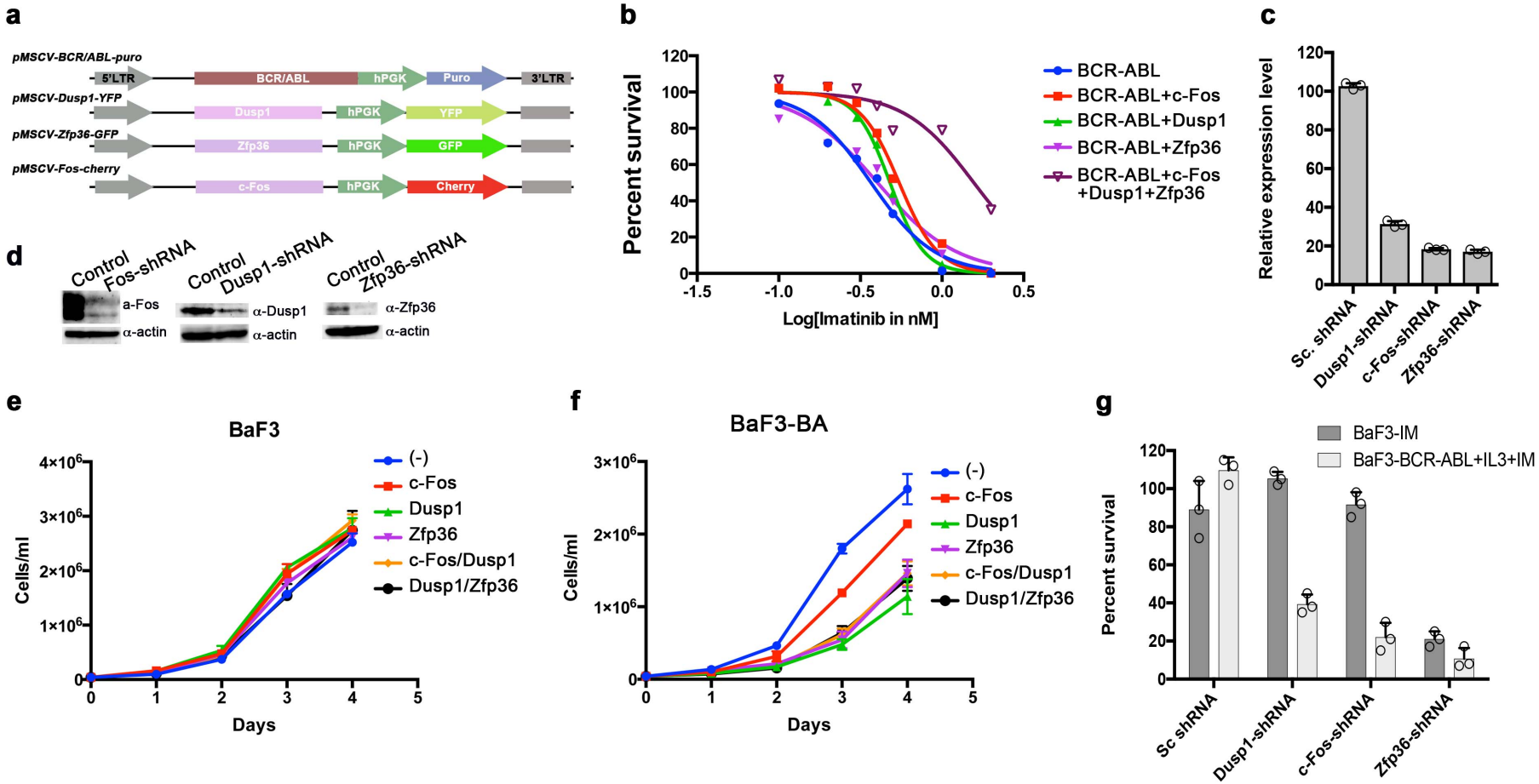


Supplementary Figure 1

Supplementary Figure 1. c-Fos, Dusp1 and Zfp36 constitute a common signature in imatinib resistant cells

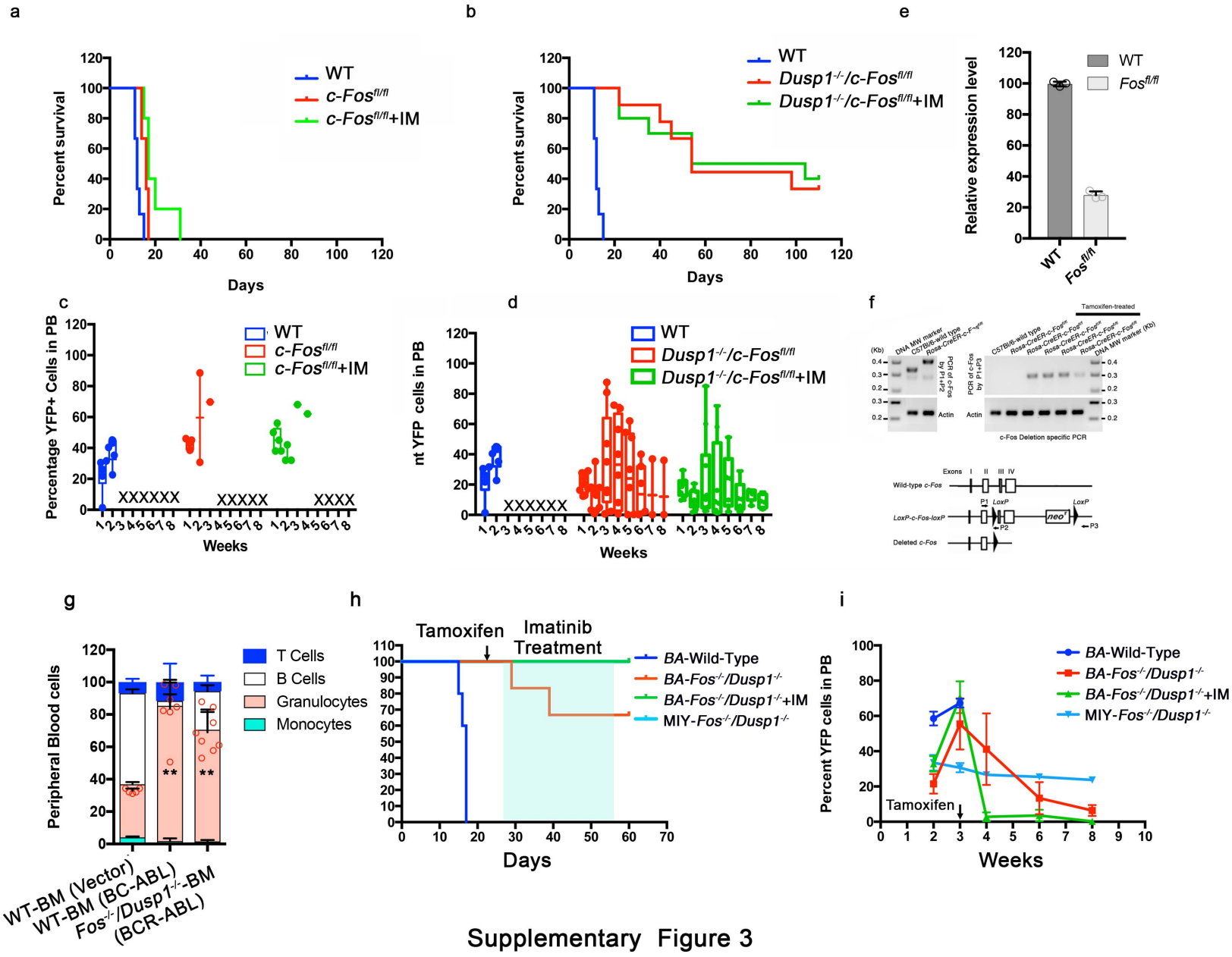
a. Shown are representative scatter plots of BaF3-BCR-ABL cells stained with Annexin V and propidium iodide to quantify and sort the live (pink), early-apoptotic (blue) and dead cells (green), treated with Imatinib with IL3 (left panel) and without IL3 (right panel). Live cells from both groups (labeled as A and B), early apoptotic (labeled as C) and apoptotic or dead cells (labeled as D) from imatinib treated cells without IL3 were sorted by FACS to determine differential expression of genes. **b.** Scatter plots showing the live and dead K562 cells treated with imatinib +/- Epo. Live and early apoptotic cells were sorted for gene expression studies. **c.** Heat map showing differential expression of 192 genes by BCR-ABL in the presence of IL3. To identify the genes that are directly modulated by BCR-ABL and IL3, we used doxycycline inducible BaF3-LTBA cells. As constitutive expression of BCR-ABL destabilizes the genome by modulating several checkpoint and DNA repair enzymes causing irreversible genetic and epigenetic changes. Therefore, it makes difficult to identify genes that are modulated directly by BCR-ABL. To address this we made BaF3-LTBA using a third generation Tet-on promoter that lacks basal expression (shown in Figure 1 A). Total RNA was isolated from the LTBA cells after 12 hrs of doxycycline induction +/-IL3. Likewise, total RNA from the parental BaF3 cells grown with IL3 and doxycycline was used to filter out the background noise. **d.** Heat map showing differential expression of 308 genes between live cells treated with imatinib +/- IL3. **e.** Heat map showing modulation of 1437 genes in K562 cells treated with imatinib +/- erythropoietin. **f.** Heat map of expression profiles from CML $CD34^{+}$ cells showing differential expression of 85 genes in in untreated and after two weeks of imatinib treatment. **g.** A Venn diagram showing induced expression of three genes (*c-Fos, Dusp1 and Zfp36*) by BCR-ABL, IL3 and imatinib.



Supplementary Figure 2

Supplementary Figure 2. c-Fos, Dusp1 and Zfp36 is required for BCR-ABL dependent survival.

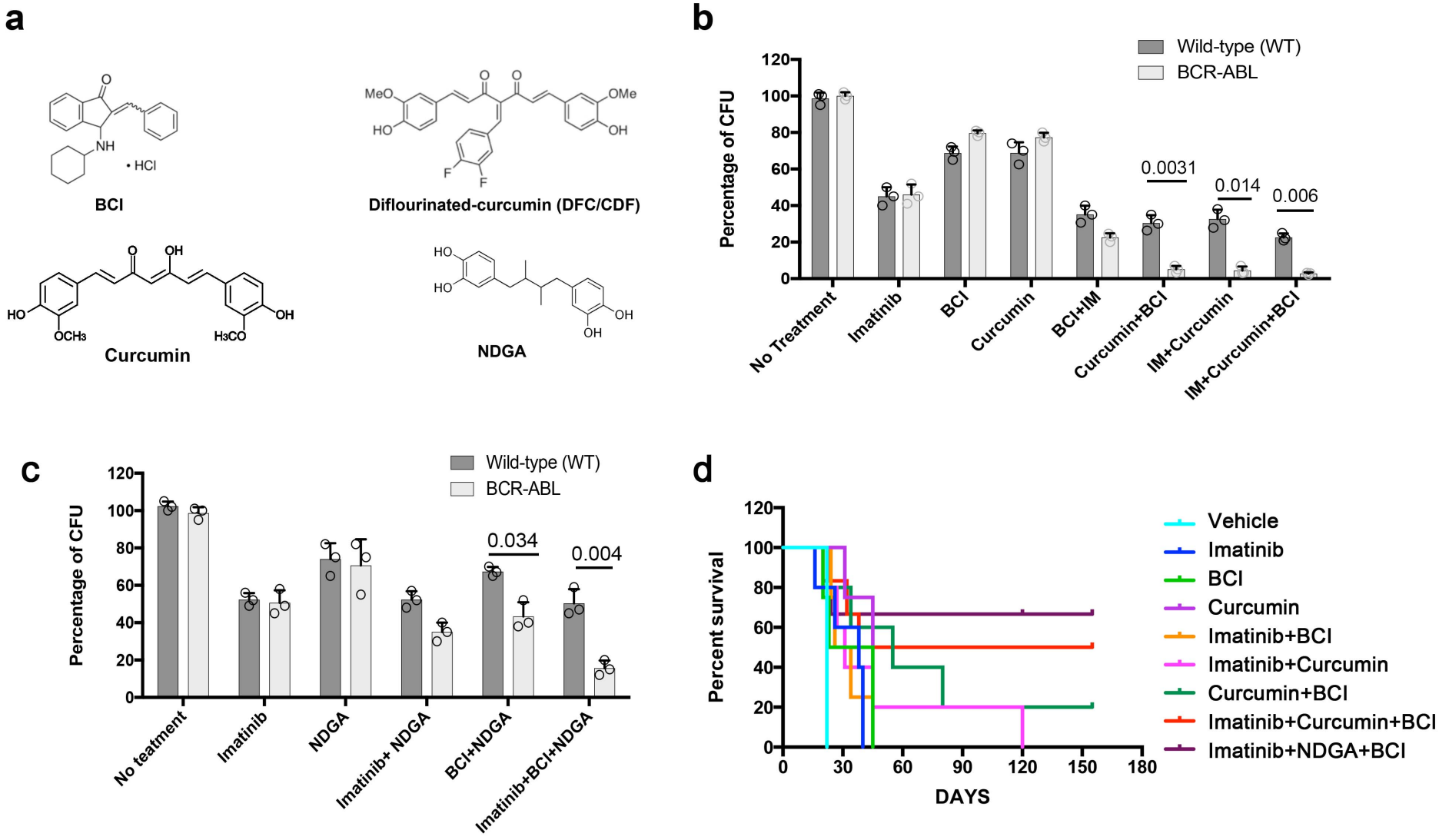
a. A cartoon depiction of retroviral vectors expressing *BCR-ABL, c-Fos, Dusp1*, and *Zfp36* cDNAs with different fluorescent proteins in the BaF3-BCR-ABL cells. **b.** A dose response curve showing overexpression of all three genes, *c-Fos, Dusp1* and *Zfp36,* confers resistance to imatinib in the absence of growth factor, IL3. **c.** A Q-PCR analysis showing the relative expression of *c-Fos , Dusp1* and *Zfp36* in BaF3-BCRABL cells expressing shRNAs for *c-Fos, Dusp1 and Zfp36*, a scrambled SC-shRNA was used as a control. **d.** Immunoblots showing reduced protein expression of Fos, Dusp1 and Zfp36 in BaF3-BA cells expressing gene specific shRNAs in comparison to control (scrambled shRNA). **e.** A cell proliferation curve of parental BaF3 cells expressing shRNAs for *c-Fos, Dusp1* and *Zfp36*. Depletion of *c-Fos, Dusp1* and *Zfp36* did not show any adverse effect on survival and proliferation of BaF3 cells. **f.** Cell proliferation curve of BaF3-BA cells, showing significant reduction in proliferation and survival (>50%) by genetic depletion or *c-Fos, Dusp1* and *Zfp36* alone or a combination of *c-Fos+Dusp1* or *Dusp1+Zfp36*. BaF3 or BaF3-BCRABL cells expressing shRNAs for c-*Fos+ Zfp36* or c-*Fos+Dusp1+Zfp36* did not survive, thus precluded further analysis. **g.** Bar graph showing *c-Fos,* and *Dusp1* knockdown sensitized the BaF3-BA cells to imatinib compared to BaF3 cells in the presence of GF, while Depletion of *Zfp36* equally sensitized both BaF3 and BaF3-BA cells. Individual data points are shown as empty circles in all bar graphs.



Supplementary Figure 3

Supplementary Figure 3. Reduced expression of *c-Fos in c-Fos $^{fl/f}$ /Dusp1$^{-/-}$* mice prolonged the survival of CML mice

a. Survival curve of mice transplanted with BCR-ABL-YFP transduced Kit^{+} cells from *ROSACre^{ERT2}c-Fos$^{fl/fl}$* mice, showing no significant difference with imatinib treatment compared to wild type (WT) donor cells. Data shown are from two independent transplant experiments (n = 12). **b.** Survival curve of mice transplanted with BCR-ABL-YFP transduced cells from *ROSACre^{ERT2}c-Fos$^{fl/fl}$Dusp1$^{-/-}$* mice. Data shown are from two independent transplant experiments (n = 12; p = 0.017). Note the leukemia free survival of 30-40% of mice transplanted with *ROSACre^{ERT2}c-Fos$^{fl/fl}$Dusp1$^{-/-}$* cells. **c and d** Bar graphs illustrating leukemic burden in mice transplanted with *ROSACre^{ERT2}c-Fos$^{fl/fl}$* (c), and *ROSACre^{ERT2}c-Fos$^{fl/fl}$Dusp1$^{-/-}$* (d). Leukemic burden were measured by the level of YFP in peripheral blood as a surrogate for BCR-ABL expression. Cohorts of mice that died are represented as X. **e.** A q-PCR analysis of *c-Fos* in wild type (WT) and *ROSACre^{ERT2}c-Fos$^{fl/fl}$Dusp1$^{-/-}$*bonemarrow cells showing reduced expression of c-Fos (5 fold) in *ROSACre^{ERT2}c-Fos$^{fl/fl}$Dusp1$^{-/-}$* mice, suggesting that the reduced expression *of c-Fos* in the absence *Dusp1* is sufficient to reduce the MRD by imatinib treatment in the absence of full deletion of *c-Fos* (d). **f.** Agarose gel showing a representative PCR analysis of c-Fos gene from the peripheral blood of *ROSACre^{ERT2}c-Fos$^{fl/fl}$* or *ROSACre^{ERT2}c-Fos$^{fl/fl}$Dusp1$^{-/-}$* mice treated with or without tamoxifen. Note amplification of c-Fos deletion specific PCR product (280 bp) by primer P1 and P3 (shown below in a cartoon representation) after tamoxifen treatment, while non-deleted PCR product (0.4 kb) amplified by P1 and P2 are present before or non-tamoxifen treated mice. These mice were monitored for six months after tamoxifen injection and deletion specific PCR were performed periodically that showed persistent presence of Fos deleted cells. Mice were sacrificed after six months, and we did not observe any defect in blood and organs, suggesting that therapeutic targeting of these two genes will not have any adverse effect on normal tissues and organs. **g.** Bar graph showing the levels of granulocytes, monocytes, B, and T cells after two weeks of transplantation from the peripheral blood of mice transplanted with Kit^{+} from wild type and *ROSACre^{ERT2}:c-Fos$^{fl/fl}$/Dusp1$^{-/-}$* mice expressing vector (pMSCV-Ires-YFP) and BCR-ABL. Expression of BCR-ABL induces granulocytosis at the expense of B cells in both wild-type and *Fos$^{fl/fl}$/Dusp1$^{-/-}$* recipient mice. Representative data showing mean values of peripheral blood cells ± S.D. (n=5; ** = p <0.01). **h.** Survival curves of mice transplanted with vector (MIY) and BCR-ABL-YFP transduced Kit^{+} cells from wild type (WT), and *ROSACre^{ERT2}c-Fos$^{fl/fl}$Dusp1$^{-/-}$* . c-Fos was deleted by tamoxifen after establishing the CML (after three weeks of transplantation). **i.** Graph showing the leukemic burden in transplanted mice measured by YFP positive cells in peripheral blood. Note, deletion of both Fos and Dusp1 do not affect the chimerism of vector (MIY) expressing cells, while their deletions in leukemic cells show gradual decrease in chimerism and imatinib treatment completely eradicated the leukemic cells. Individual data points are shown as empty circles in all bar graphs.

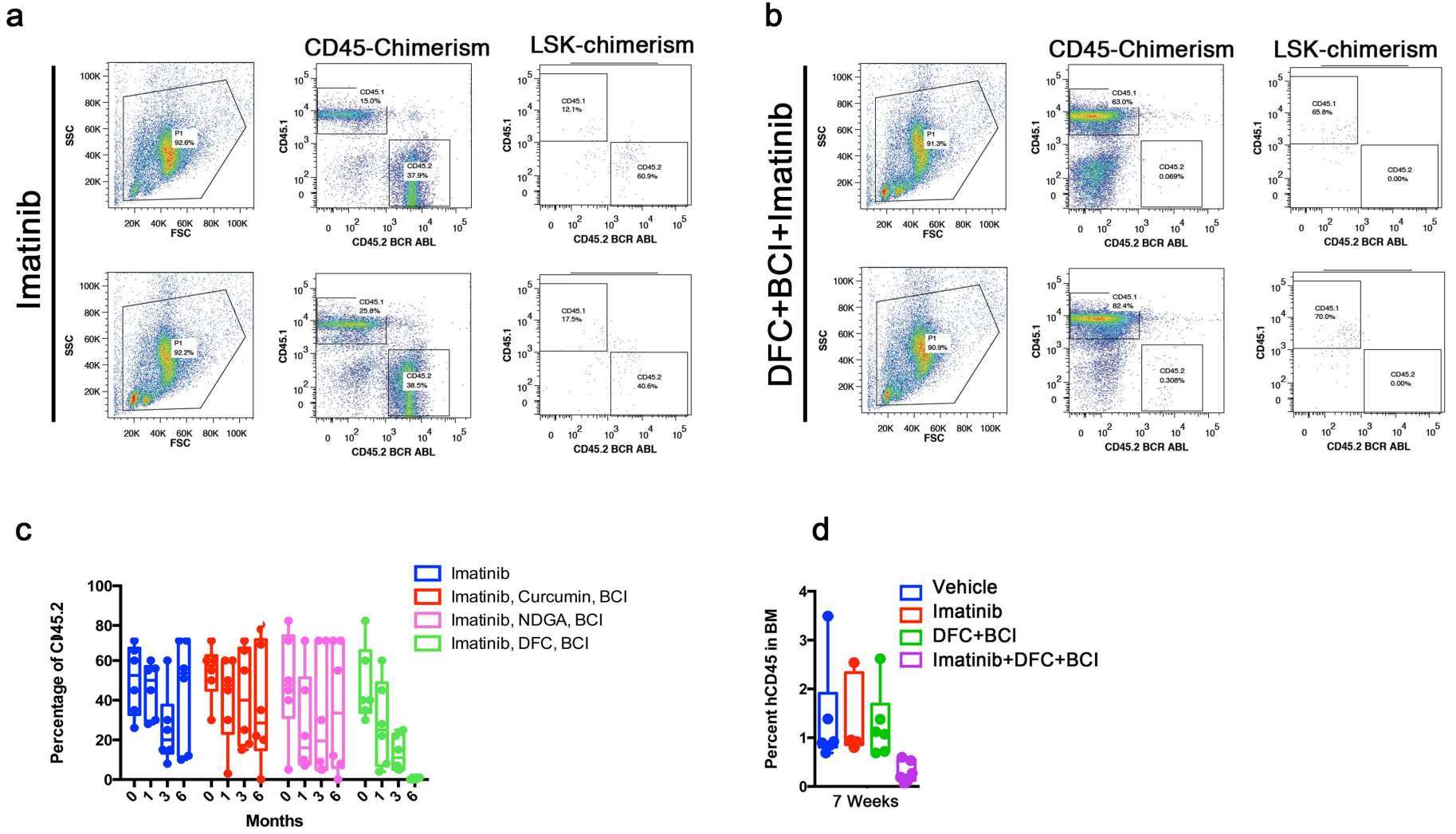


Supplementary Figure 4

Supplementary Figure 4. Chemical inhibition of c-Fos and Dusp1 sensitized leukemic cells to imatinib

a. Shown are chemical structures of small molecule inhibitors targeting Dusp1 ((*E*)-2-Benzylidene-3-(cyclohexylamino)-2,3-dihydro-1H-inden-1-one; BCI) and Fos (Diflourinated curcumin, DFC; Curcumin and NDGA).

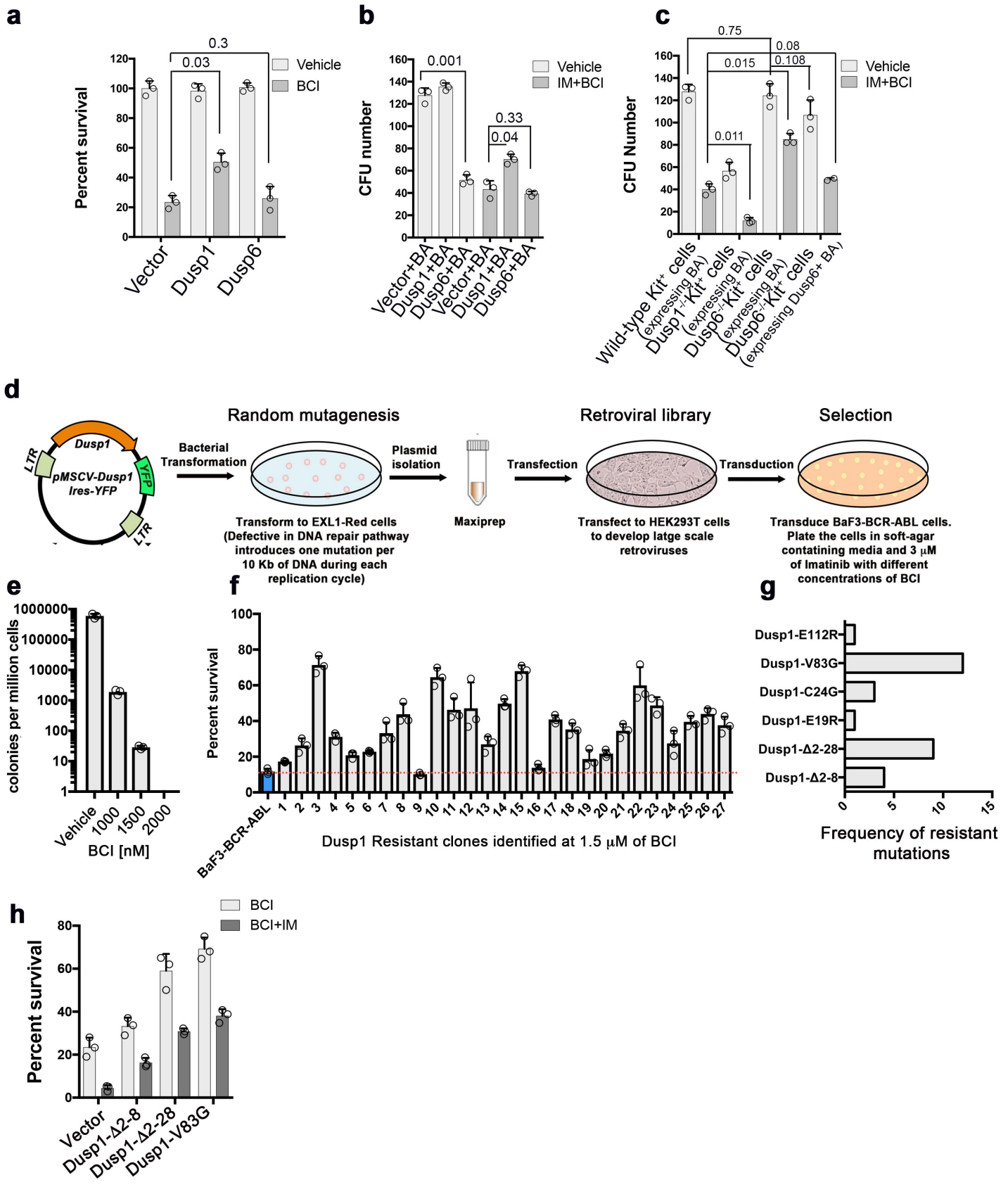
(b and c). Bar graphs showing percent CFU from normal and BCR-ABL LSK cells (Lin^- $Sca1^+Kit^+$), with single and combinations of inhibitors utilizing different c-Fos inhibitors, curcumin (b) and NDGA (c). Representative data shown are the mean colony number from two independent experiments ± S.D. P values are indicated above the compared bars). **d.** Survival curve of mice of two independent experiments transplanted with Kit^+ expressing BCR-ABL-YFP. Treatments with single drugs or combination of two inhibitors are ineffective in treating these mice, most mice showed a marginal 5-7 days prolongation of their survival except BCI+curcumin treated cohort (20 % of CML mice survived). Groups of CML mice treated with triple combinations, imatinib+Curcumin+BCI and imatinib+NDGA+BCI, showed prolonged survival, 50 and 60%, respectively. Individual data points are shown as empty circles in all bar graphs.



Supplementary Figure 5

Supplementary Figure 5. Inhibition of c-Fos, Dusp1 and BCR-ABL eradicated the leukemic stem cells

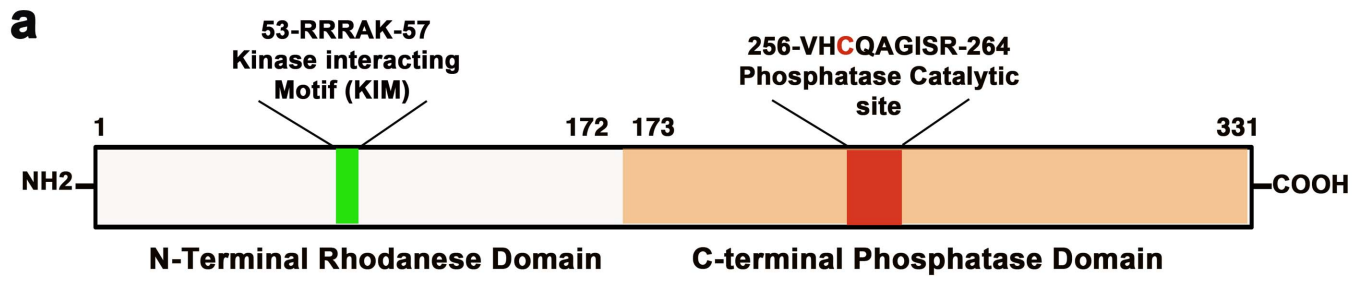
a. Representative scatter plots showing minimal effect by imatinib treatment on BCR-ABL (CD45.2) and (BCR-ABL-Lin$^-$Sca$^+$Kit$^+$) cells. **b**. Representative scatter plots showing eradication of BCR-ABL (CD45.2) and (BCR-ABL-Lin$^-$Sca$^+$Kit$^+$) by imatinib+DFC+BCI treatment. **c** Percentage of leukemic cells (CD45.2) in bone marrow of BoyJ recipients (CD45.1). Imatinib treatment (blue bars) reduces leukemic burden (month 3 = <20%), which after treatment discontinuation rebounds (month 6 = >60%). Treatment with imatinib+curcumin+BCI (red bar) and imatinib+NDGA+BCI (purple) reduces leukemic burden but they relapse after treatment discontinuation. Treatment with imatinib+DFC+BCI (green bar) reduces leukemic burden (month 3 = <10%), without relapse (month 6 = no detection). **d.** Graphs showing the level of human leukemic cells in NSG mice at week seven, chimerism at week 2 and 4 are shown in Fig. 4b.

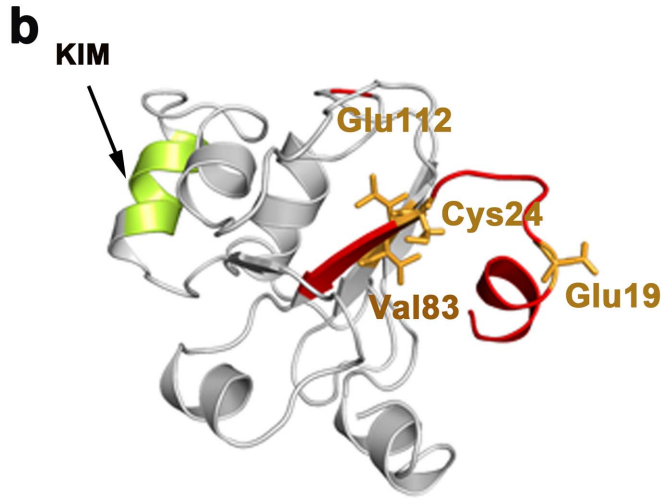


Supplementary Figure 6

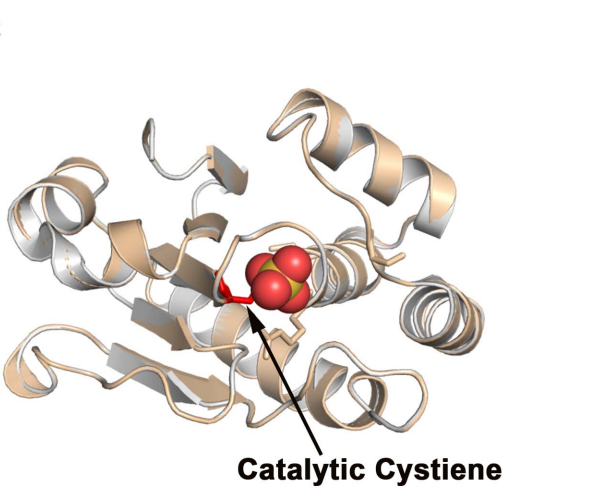
Supplementary Figure 6. BCI resistant screening identified drug resistant mutations in the Dusp1

a. Bar graph showing overexpression of Dusp1, not the Dusp6, confers resistance to BCI in BaF3-BA cells. Data shown are from two independent experiments ± S.D (n = 3; P values are indicated above the compared bars). **b.** Bar graphs showing CFU numbers derived from Kit^+ cells from WT mouse coexpressing BCR-ABL with either Dusp1 or Dusp6. Expression of Dusp1 show normal CFU numbers but confers modest resistance to IM [3μM]+BCI [0.5μM] treatment. Surprisingly, expression of Dusp6 show significantly reduced CFU number and treatment with IM+BCI did not show any significant change. Data shown are from two independent experiments ± S.D (n = 3; P values are indicated above the compared bars). **c.** Bar graphs showing CFU numbers derived from Kit^+ cells from wild-type, *Dusp1*$^{-/-}$ and *Dusp6*$^{-/-}$ mice expressing BCR-ABL and BCR-ABL+Dusp6. Unlike *Dusp1*$^{-/-}$ cells, *Dusp6*$^{-/-}$ cells expressing BCR-ABL show normal CFU numbers compared to WT, but conferred drug resistance to IM+BCI treatment. Expression of Dusp6 in *Dusp*$^{-/-}$ cells with BCR-ABL partially reduced the CFU numbers and abrogated the drug resistance. Data shown are from two independent experiments ± S.D (n = 3; coexpressing BCR-ABL with either Dusp1 or Dusp6). **d**. A schematic of random mutagenesis of Dusp1 for in vitro screening of BCI resistant clones. **e.** Bar graph showing frequency of resistant clones per million of BaF3-BA cells expressing randomly mutagenized Dusp1. **f.** Bar graph showing BCI resistance conferred by 25 out of 27 clones (except # 9 and #16), isolated from the resistant screen selected at 1.5 μM of BCI. **g.** Bar graph showing the frequency of mutations in 25 sequenced resistant clones. **h.** Expression of Dusp1 mutants in BaF3-BA cells conferred resistance to BCI and imatinib+BCI. Note, Dusp1-V83G as a single mutation conferred significant resistance to both BCI alone and in combination of imatinib. Individual data points are shown as empty circles in all bar graphs.

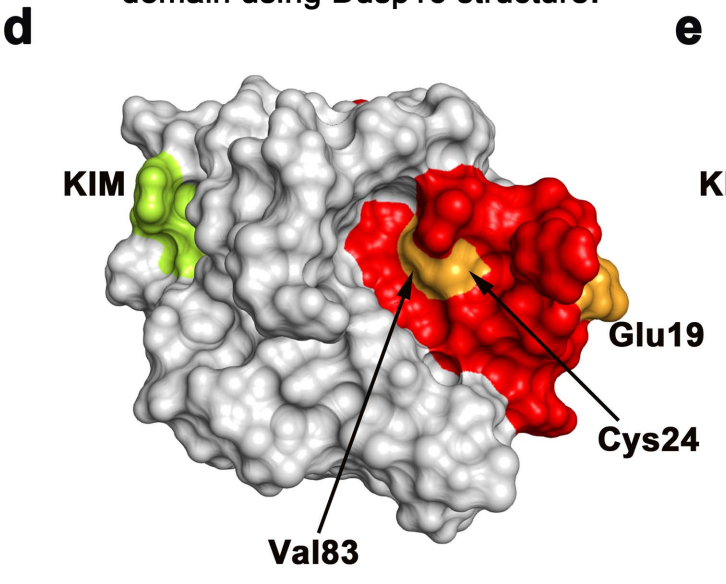


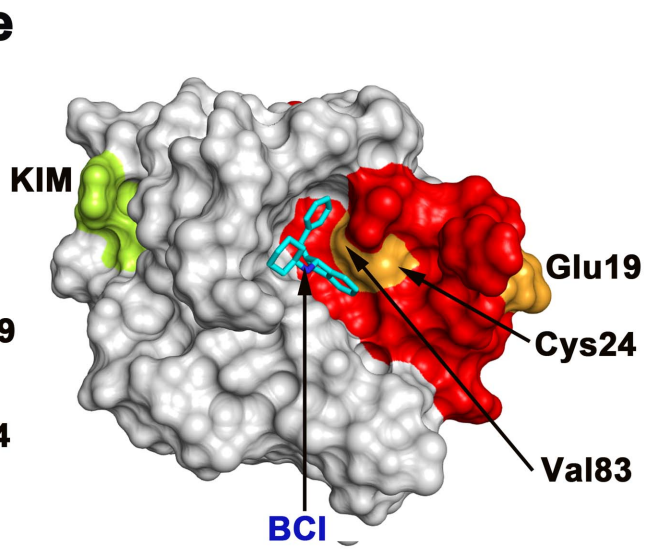


A homology model of Dusp1 rhodanese domain using Dusp16 structure.



A homology model of Dusp1 catalytic domain using Dusp6 structure.

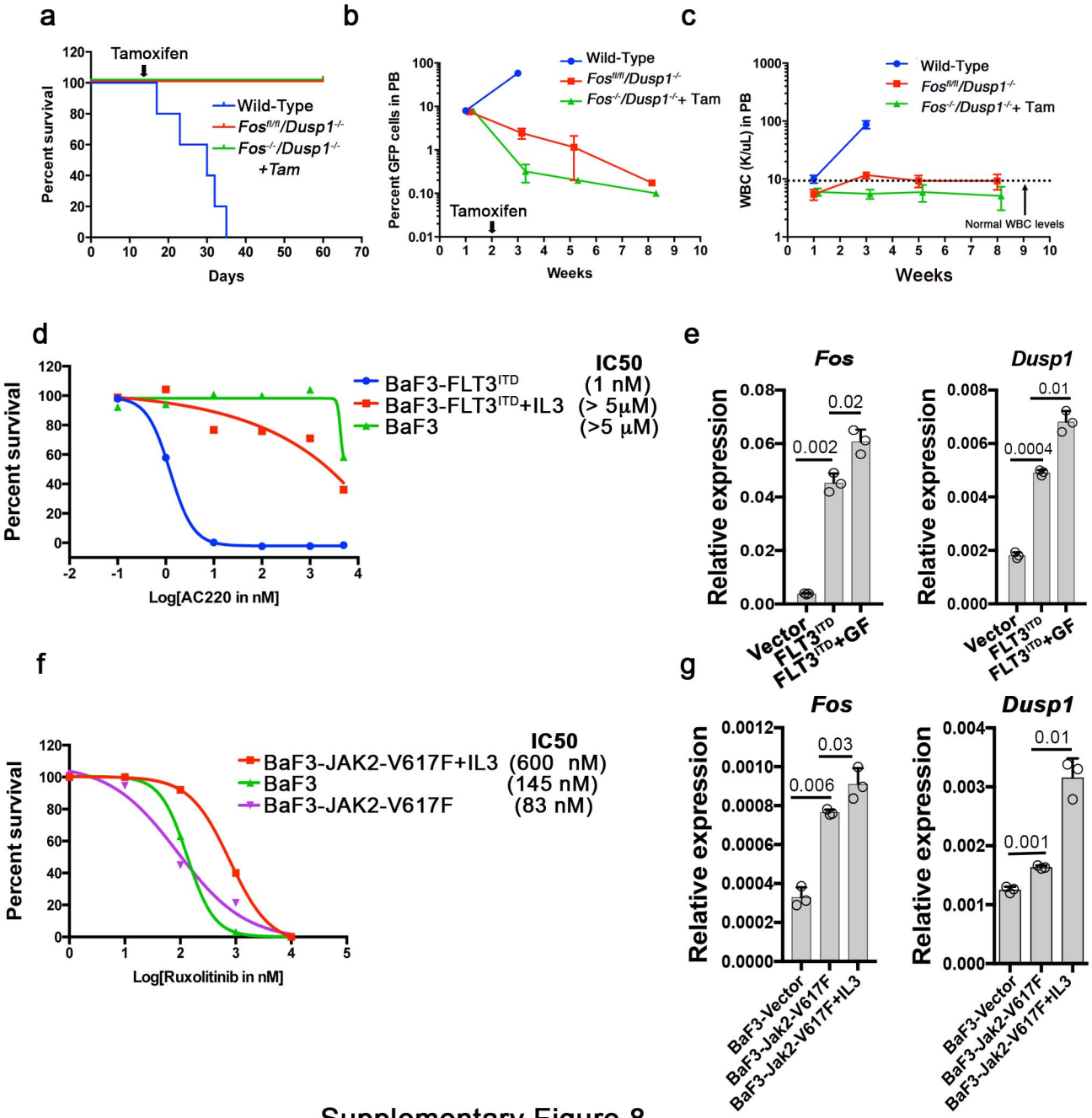




Supplementary Figure 7

Supplementary Figure 7. BCI resistant mutations are clustered in allosteric domain

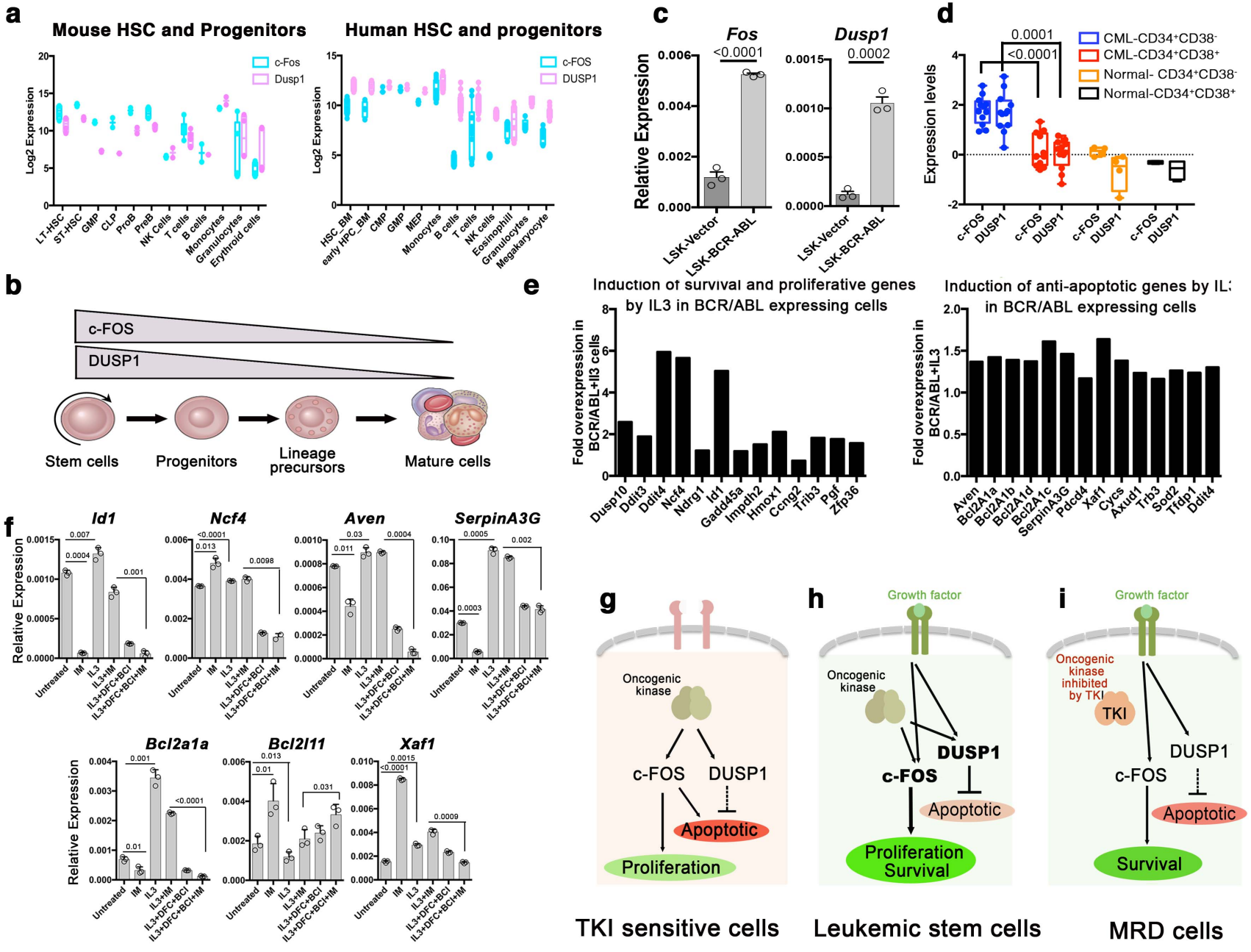
a. Showing primary structure of Dusp1where catalytic domain lies at the C-terminus of protein. Catalytic cysteine in catalytic-site is shown in red. The N-terminal rhodanese domain harboring kinase interaction motif (KIM) required for binding with MAPKs shown in green. **b.** A ribbon depiction of homology based model of Dusp1 rhodanese domain. Mapping of BCI resistant mutations identified a single clusture in the rhodanese domain. Deletion mutations are shown in red while point mutations are shown in golden. **c.** A cartoon depiction homology based model of Dusp1 catalytic domain. Catalytic lysine and an inorganic phosphate are shown in red. **d**. Surface depiction of Dusp1 rhodanese domain showing the BCI resistant mutations clustered at the N-terminus of allosteric domain. Deletion mutations are shown in red while point mutations are shown in golden. **e.** Unbiased in silico docking of BCI revealed a binding pocket to which BCI seemingly binds (ΔG= -7.6).



Supplementary Figure 8

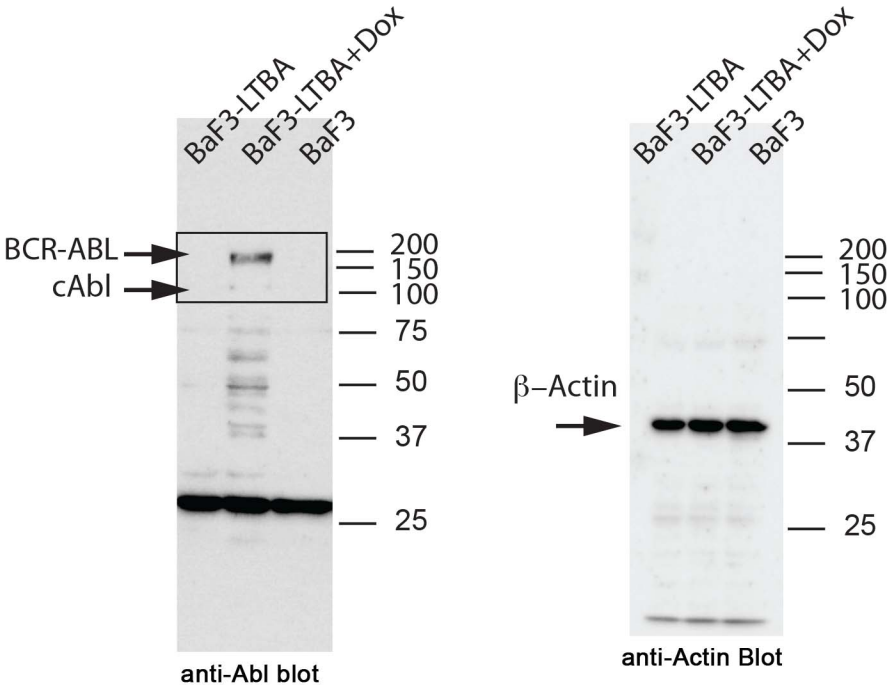
Supplementary Figure 8. Deletion of Fos and Dusp1 is synthetic lethal to B-ALL development.

a. Survival curves of mice transplanted with vector and BCR-ABL-YFP (p190) transduced Kit^{+} cells from wild type (WT), and *ROSACre^{ERT2}c-Fos$^{fl/fl}$Dusp1$^{-/-}$* mice. c-Fos was deleted by tamoxifen injection (three doses of 2mg/kg) after two weeks of transplantation. Mice transplanted with wild-type cells expressing p190 BCR-ABL developed lethal B-ALL and died within 4-5 weeks, while mice transplanted with *Fos$^{fl/fl}$Dusp1$^{-/-}$* cells show gradual depletion of BCR-ABL expressing cells **(b),** and do not develop leukemia determined by WBC count **(c).** Deletion of Fos accelerates the depletion of BCR-ABL positive cells compared to Fos non-deleted cells. **d.** Dose response analysis of BaF3 cells expressing FLT3-ITD showing complete resistance to AC220 under growth factor signaling (IL3). **e.** Bar graph showing induced expression of *c-Fos* and *Dusp1* by FLT3-ITD with additional induction by IL3. Data for qPCR analysis are shown ± S.D. (P values are indicated between the compared bars). **d.** Dose response analysis of BaF3 cells expressing Jak2-V617F showing 7-8-fold résistance to ruxolitinib in the presence of IL3. **e.** Bar graph showing induced expression of *c-Fos* and *Dusp1* by JAK2-V617F under growth factor signaling. Data for qPCR analysis are shown ± S.D. (P values are indicated between the compared bars). Individual data points are shown as empty circles in all bar graphs.



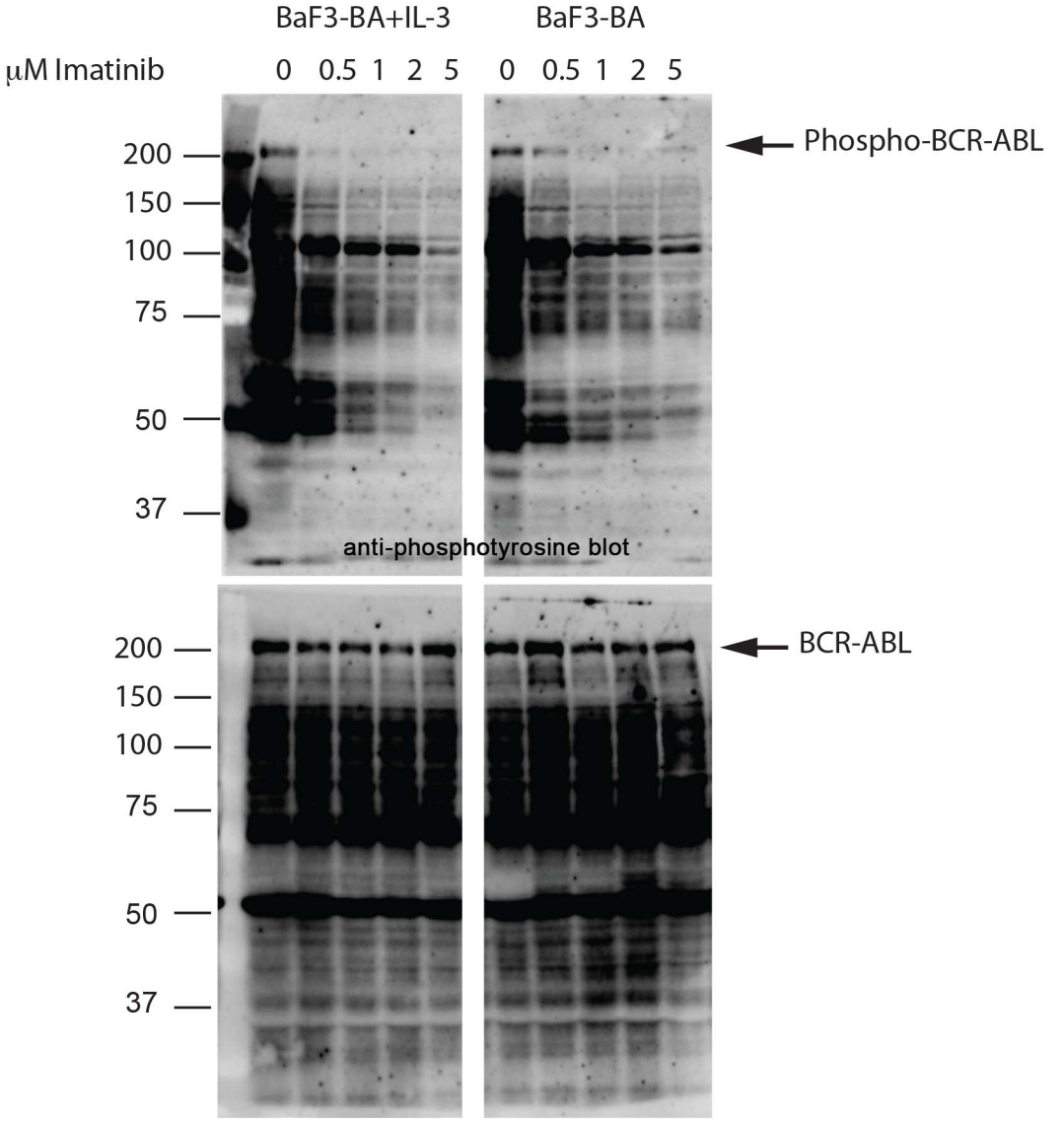
Supplementary Figure 9

Supplementary Figure 9. A model for therapeutic mechanism of TKI efficacy
a. Graph showing the expressions of c-Fos (cyan) and Dusp1 (pink) in hematopoietic cells in mouse (left) and human (right). Each dot in the plot corresponds the expression of FOS and DUSP1 in a microarray. **b.** A cartoon depiction showing downregulation of c-Fos and Dusp1 with differentiation during normal hematopoiesis. **c.** Bar graph showing the overexpression of c-Fos and Dusp1 in leukemic stem cells of mice (BCR-ABL^+ LSK-$Lin^-Sca1^+Kit^+$ cells). Representative data shown are from two independent experiments ± S.D. (P values are indicated above the compared bars). **d.** Bar graph showing the overexpression of c-FOS and DUSP1 in human leukemic stem cells ($CD34^+$ $CD38^-$) from CML patients. Each dot in the plot corresponds the expression of c-FOS and DUSP1 in a microarray (GSE40721). P values are indicated above the compared samples. **e.** Histograms showing the overexpression of cell proliferation genes (left panel) and anti-apoptotic genes (right panel) in BaF3-LTBA cells grown with IL-3. **f**. Bar graph showing q-PCR analysis of expression of proliferative or survival genes (Id1 and Ncf4) and anti-apoptotic genes (Aven, SerpinA3G, Bcl2a1a, Bcl2l11 and Xaf1) in BaF3-BCR-ABL cells+IL3 with and without drug treatments (imatinib, DFC+BCI and DFC+BCI+Imatinib). Note, treatment with Fos and Dusp1 inhibitor (DFC+BCI) and in combination with imatinib suppressed their expression suggesting their regulation by Fos and Dusp1. Representative data shown are the mean values of qPCR analysis ± S.D. (P values are indicated above the compared bars). **g-i.** A model of TKI response in drug sensitive and leukemic stem cells. Our model suggests that during normal hematopoiesis c-Fos and Dusp1 are downregualted with differentiation. In differentiated bulk of leukemia cells which is sensitive to TKI, expression of an activated kinase induces the expression of c-Fos and Dusp1, which induces both proliferative and pro-apoptotic signal. Therefore, an acute inhibition of activated oncogene induces oncogenic shock resulting to apoptosis in cells expressing suboptimal level of c-Fos and Dusp1 (g). In leukemic stem cells, convergence of oncogenic and growth factor signaling induces high levels of c-Fos and Dusp1 expression, which seemingly reprograms transcriptional network to induce pro-survival and anti-apoptotic genes. Thus, levels of c-Fos and Dusp1 determines the net transcriptional out-put for proliferative/pro-apoptotic genes or pro-survival/anti-apoptotic genes in oncogenic condition. Thus, inhibition of oncogene by TKI is ineffective against leukemic stem/progenitor cells (h), failure to induce apoptosis under TKI treatment results into MRD (i). Individual data points in each bar graphs are shown as empty circles.



Supplemntray Figure 10

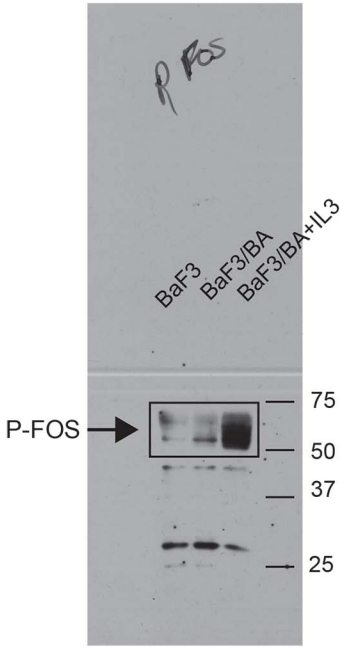
Supplementary Figure 10. Original images of representative western blots in Fig. 1a



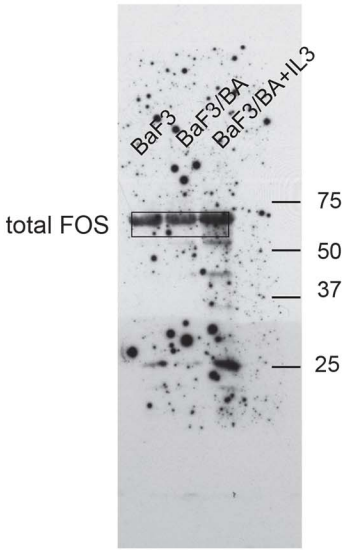
Supplementary Figure 11

Supplementary Figure 11. Original images of representative western blots in Fig. 1d

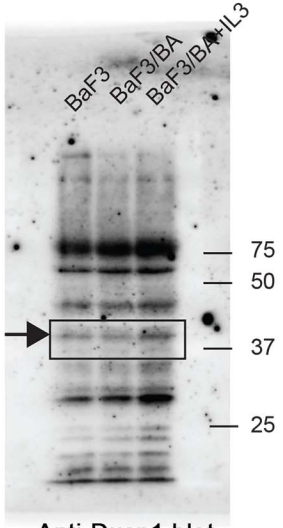
Figure 1h



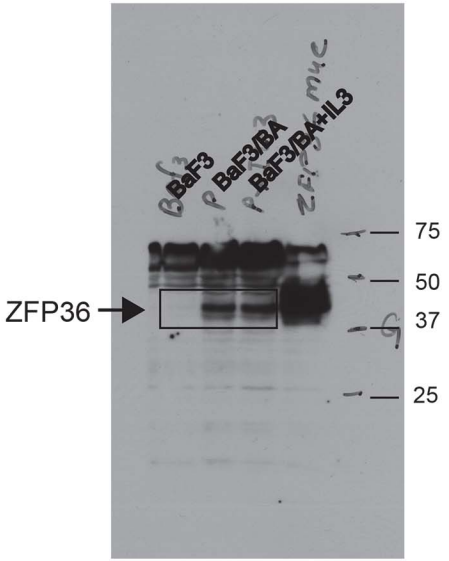
anti-Phpspho Fos blot



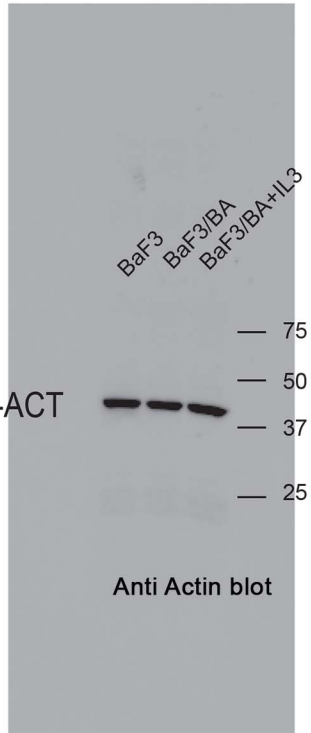
anti- Fos-blot



Anti-Dusp1 blot



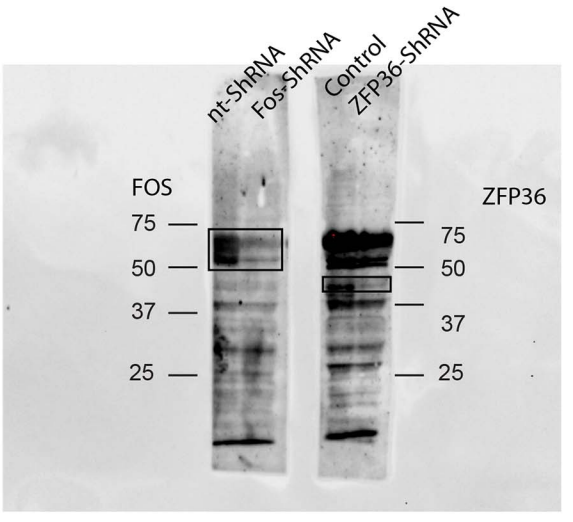
Anti Zfp36 blot

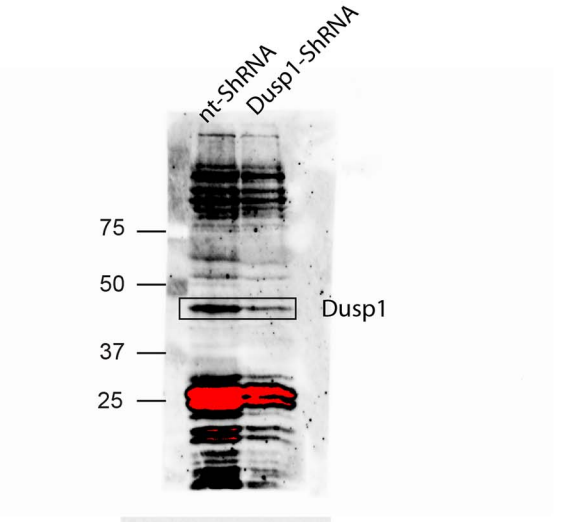


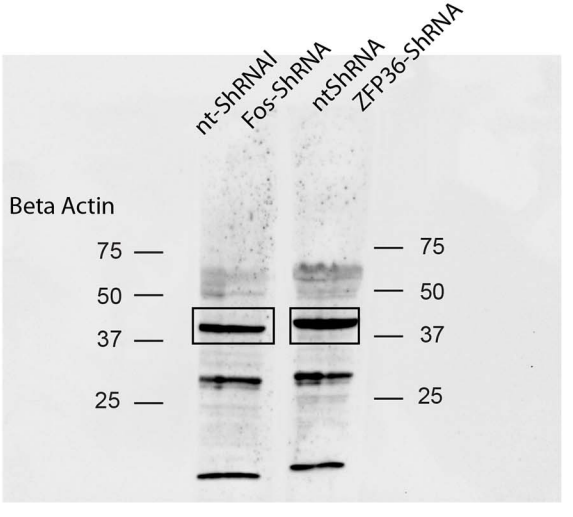
Anti Actin blot

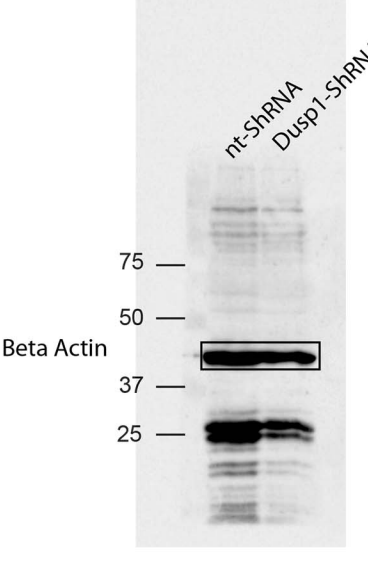
Supplementary Figure12

Supplementary Figure 12. Original images of representative western blots in Fig. 1h



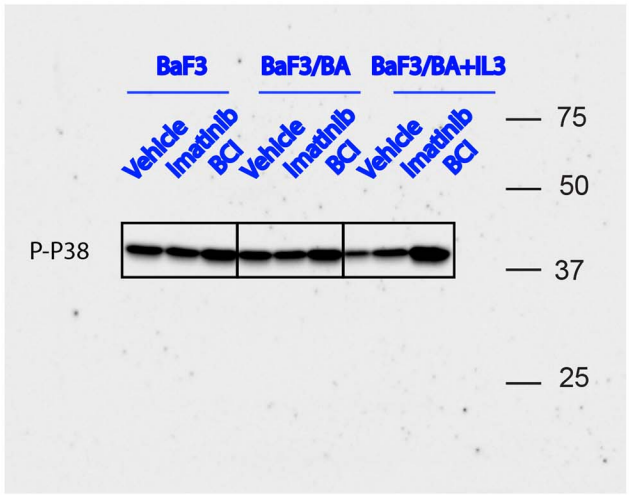


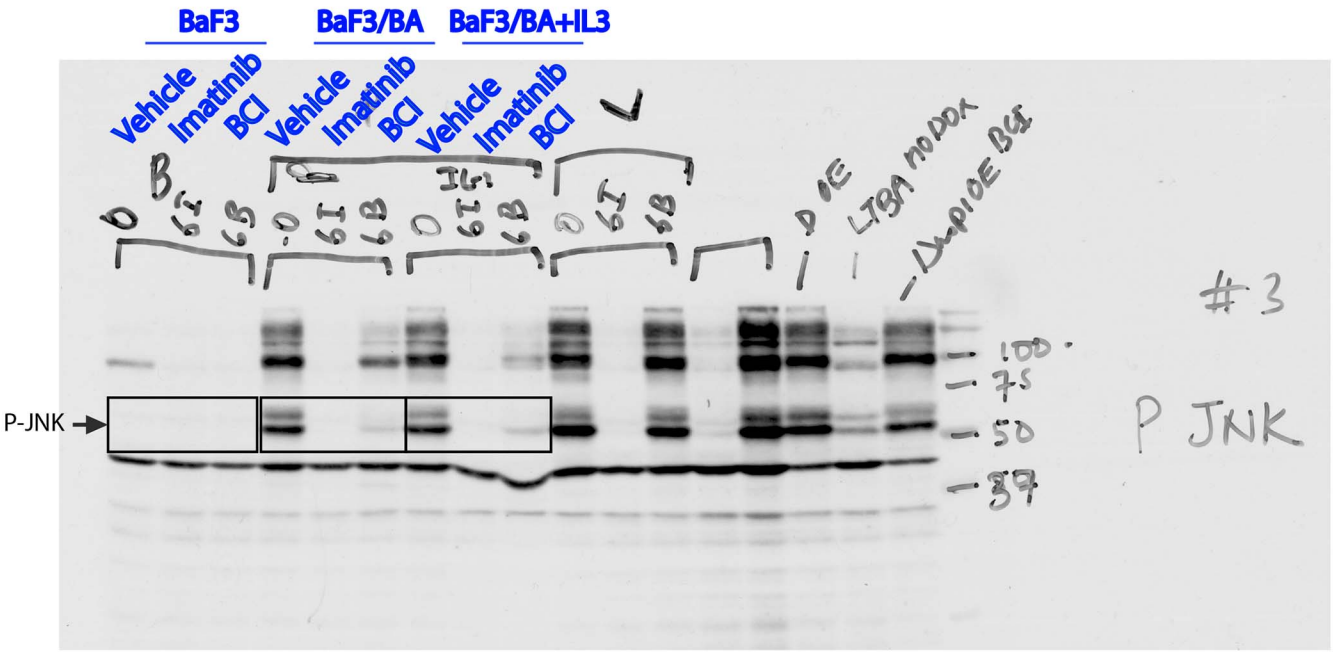


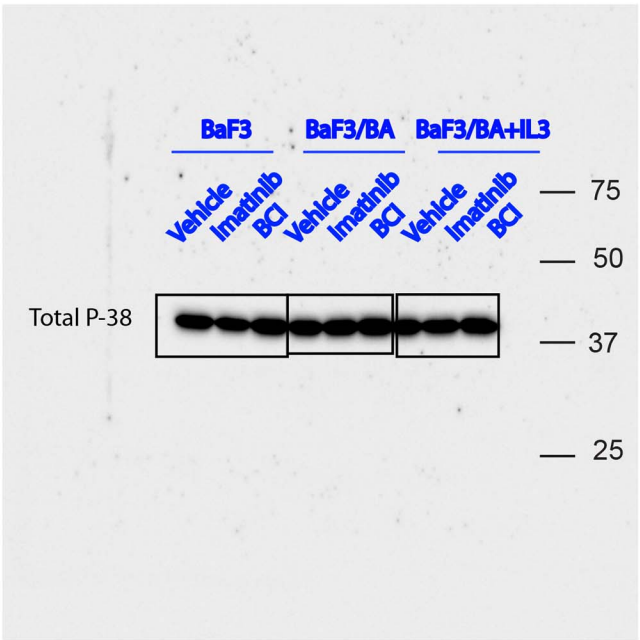


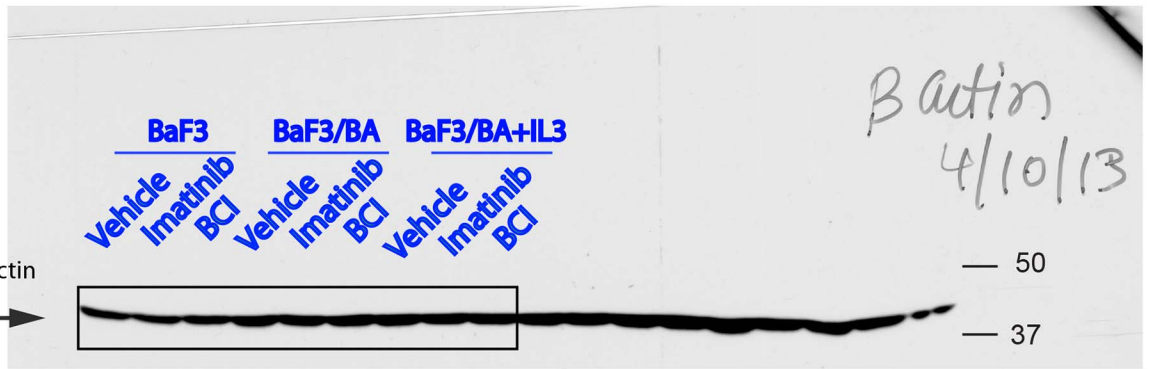
Supplementary Figure 13

Supplementary Figure 13. Original images of representative western blots in supplementary figure 2d



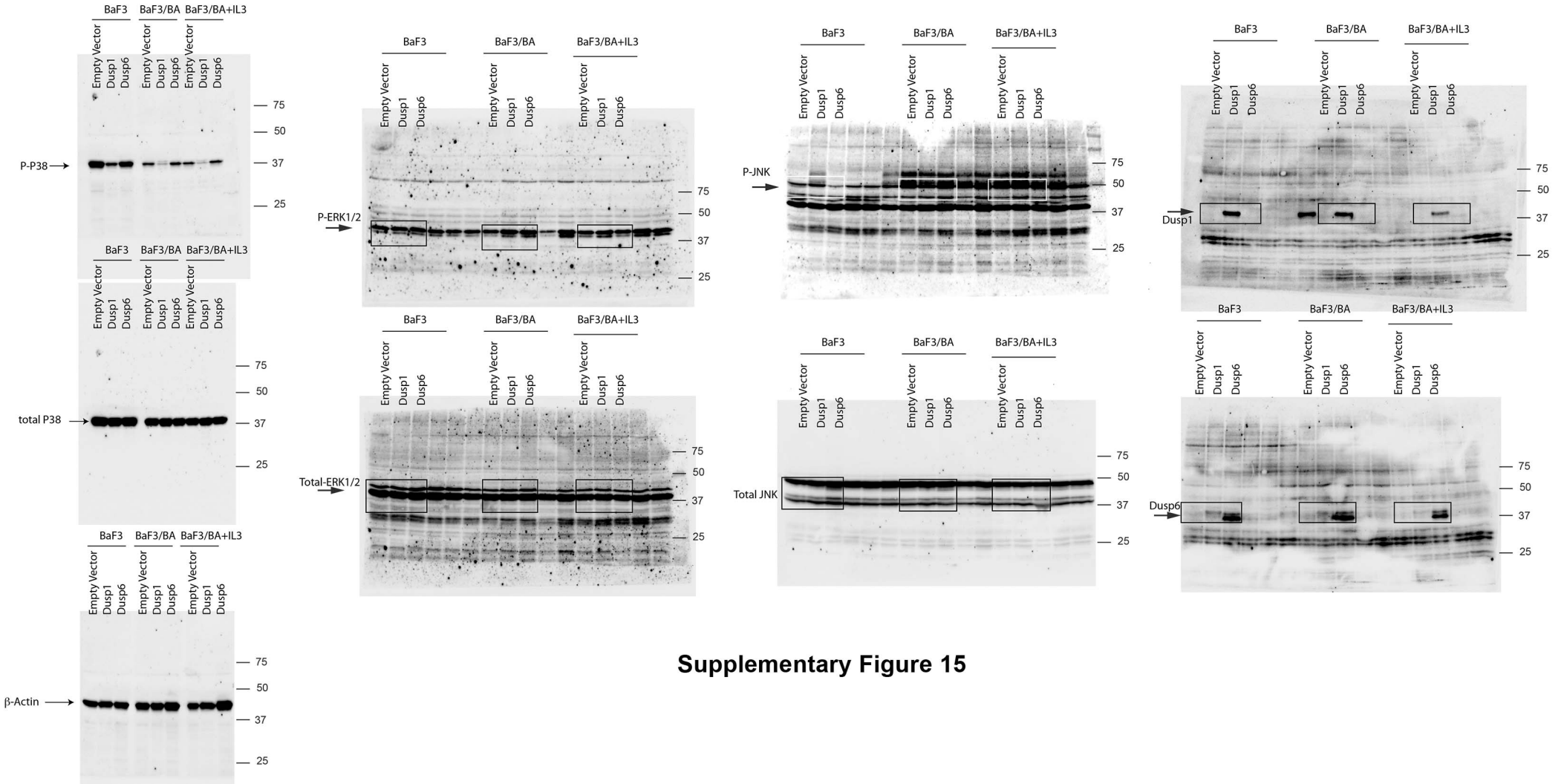






Supplementary Figure 14

Supplementary Figure 14. Original images of representative western blots in Fig. 6a



Supplementary Figure 15

Supplementary Figure 15. Original images of representative western blots in Fig. 6b

Supplementary Table1. Description of CML patient samples

Sample ID	Diagnosis	Treatment	Age	Sex	Date of sample	FISH (%Ph+)	Karyotype comments	Origin	BCR-ABL1 sequencing
CP1	CML -Chronic Phase	Treated with Hydrea (1000 mg)	40	Male	3/17/15	98	46,XY,t(9;22)	Peripheral Blood	WT
CP2	CML -Chronic Phase	Untreated	30	Female	6/15/05	13	46,XX,t(9;22)	Bone Marrow	WT
CP3	CML -Chronic Phase	Untreated	30	Female	4/18/07	64	46,XX,t(9;22)	Bone Marrow	WT
CP4	CML -Chronic Phase	Untreated	35	Male	5/18/05	99.2	46,XY,t(9;22)	Peripheral Blood	WT
BC1	CML-Blast Crisis	Untreated	38	Male	12/1/04	72.5	46,XY,t(9;22)	Peripheral Blood	WT
BC2	CML-Blast Crisis	Untreated	59	Female	1/1/13	13.5	46,XX,t(9;22)	Peripheral Blood	WT
BC3	CML-Blast Crisis	Untreated	34	Male	9/1/13	64	46,XY,t(9;22).Mutation in ASXL1.	Peripheral Blood	WT

Supplementary Table 2. Primers for cloning

Genes	Primers	Primers for cloning
GFPBAMFP	Forward Primer	AGGGGATCCATGGTGAGCAAGGGCGAGG
GFPSEXRP	Reverse Primer	ACACCACCTGGTTTACTTGTACAGCTCGTCC
c-FOS-FP	Forward Primer	CACCATGATGTTCTCGGGCTTCAACG
c-FOS-HA-RP	Reverse Primer	CAAGCGTAATCTGGAACATCGTATGGGTACATGGTCAGGGCCAGCAGCGTGGGTGAG
Dusp1-FP	Forward Primer	ATGGTGATGGAGGTGGGCATC
Dsup1-MycRP	Reverse Primer	TCACAGATCTTCTTCAGAAATAAGTTTTTGTTCCATGCAGCTTGGAGAGGTGGTGATG
Zfp36-FP	Forward Primer	CACCATGGATCTCTCTGCCATCTAC
Zfp36-myc-RP	Reverse Primer	TCACAGATCTTCTTCAGAAATAAGTTTTTGTTCCATCTCAGAGACAGAGATACGA
c-FOS-DRK-FP	Forward Primer	GAGGGGCAAGGTGGAACAGTTAGAGCTGACTGATACACTCCAAG
c-FOS-DRK-RP	Reverse Primer	CTTGGAGTGTATCAGTCAGCTCTAACTGTTCCACCTTGCCCCTC

Supplementary Table 3: ShRNA clones

Genes	Ref seq no	TRCN
c-Fos	NM_010234	42679
Zfp3636	NM_011756	102302
Dusp1	NM_013642	54678
Dusp10	NM_022019	81110

Supplementary Table 4: Antibodies used for immunoblotting and FACS

Antibody	Catalog no	Manufacturer	Clone no	Dilution
A. Western Blotting				
Anti-phospho-Tyr-HRP	SC-7020	Santa Cruz Biotechnology	PY99	1:1000
Anti-ABL	SC-23	Santa Cruz Biotechnology	K12	1:1000
Anti-phospho-Fos-ser32	5384S	Cell Signaling Technology	D82C12	1:1000
Anti-c-Fos	4384S	Cell Signaling Technology	9F6	1:1000
Anti-DUSP1	07-535	EMD Millipore	-	1:1000
Anti-DUSP6	3058S	Cell signaling technology	-	1:1000
Anti-Zfp36	ABE285	EMD Millipore	-	1:1000
Anti-β-Actin	5125S	Cell Signaling Technology	13E5	1:1000
Anti-P38	9212	Cell Signaling Technology	-	1:1000
Anti-phospho-P38	9211	Cell Signaling Technology	-	1:1000
Anti-JNK	9259	Cell Signaling Technology	-	1:1000
Anti-phospho-JNK	9258	Cell Signaling Technology	-	1:1000
Anti-ERK 1/2	9102	Cell Signaling Technology	-	1:1000
Anti-phosho-ERK 1/2	9101	Cell Signaling Technology	-	1:1000
Anti-phospho-Dusp1	2857S	Cell Signaling Technology	S359	1:0000
B. FACS				
Antibody	**Catalog no**	**Manufacturer**	**Clone no**	**Dilution**
Anti mouseLy-6A/E (Sca1)-PECY7	25-5981	eBioscience	D7	1:100
Anti mouseCD117 (c-kit)-APC	17-1171	eBioscience	2B8	1:100
Anti mouse CD45.1-FITC	11-0453-85	eBioscience	A20	1:100
Anti mouse CD45.2-PE	12-0454-83	eBioscience	104	1:100
Anti mouse CD45-APC Cy7	560694	BD Biosciences	104	1:100
Anti human CD45-FITC	555482	BD Biosciences	H130	1:20
Anti-mouse CD11b-BV510	562950	BD biosciences	M1/70	1:100
Anti-mouse B220-APC	553092	BD biosciences	RA36B2	1:100
Anti-mouse CD3-PerCP	561089	BD biosciences	145-2C11	1:100
Anti-mouse GR1-BUv395	563849	BD biosciences	RB6-8C5	1:100

Supplementary Table 5: Primer sequence for q-PCR analysis

Genes	Forward Primer	Reverse Primer
c-Fos	CGGGTTTCAACGCCGACTA	TTGGCACTAGAGACGGACAGA
Dusp1	GTTGTTGGATTGTCGCTCCTT	TTGGGCACGATATGCTCCAG
Zfp36	TCTCTGCCATCTACGAGAGCC	CCAGTCAGGCGAGAGGTGA
Dusp10	CCATCTCCTTTAGACGACAGGG	GCTACCACTACCTGGGCTG
Actb	GGCTGTATTCCCCTCCATCG	CCAGTTGGTA ACAATGCCATGT
FOS	AGAATCCGAAGGGAAAGGAA	CTTCTCCTTCAGCAGGTTGG
Gapdh	AGGTCGGTGTGAACGGATTTG	TGTAGACCATGTAGTTGAGGTCA
DUSP1	CTGCCTTGATCAACGTCTCA	ACCCTTCCTCCAGCATTCTT
ZFP36	CTGTCACCCTCTGCCTTCTC	TCCCAGGGACTGTACAGAGG
ACTB	CATGTACGTTGCTATCCAGGC	CTCCTTAATGTCACGCACGAT
BCR-ABL	CACTCAGCCACTGGATTTAAGC	TTCCTTGGAGTTCCAACGAG
Id1	CCTAGCTGTTCGCTGAAGGC	CTCCGACAGACCAAGTACCAC
Ncf4	GTCATCGAGGTCAAAACAAAAGG	GCCCATGTAGACTTTGGCTG
Ddit4	CAAGGCAAGAGCTGCCATAG	CCGGTACTTAGCGTCAGGG
Impdh2	ATTAGCGGAGGCACCTCTTAC	CAGTGAAGTCGATATACCCAGGA
Hmox1	AAGCCGAGAATGCTGAGTTCA	GCCGTGTAGATATGGTACAAGGA
pgf	TCTGCTGGGAACAACTCAACA	GTGAGACACCTCATCAGGGTAT
Bcl21a1	GGCTGAGCACTACCTTCAGTA	TGGCGGTATCTATGGATTCCAC
Aven	ACTCGGGTGGAAGAAGACAG	CTCCTCAGCAAATCGGAACTG
SerpinA3G	CTTCCCAACGGCTGGAATCTA	ACTGTCCAATCAGGCATAGCG
Xaf1	AGCCATGTGTCTGAGTGCAAA	GCAAAGATCACAACGGGTTTTTC
Bcl2l11	CCCGGAGATACGGATTGCAC	GCCTCGCGGTAATCATTTGC
Il6	TAGTCCTTCCTACCCCAATTTCC	TTGGTCCTTAGCCACTCCTTC
Lif	ATTGTGCCCTTACTGCTGCTG	GCCAGTTGATTCTTGATCTGGT

Supplementary Methods.

Plasmids.
For overexpression studies, of c-Fos, Dusp1 and Zfp36, cDNA clones of these genes were purchased from the PlasmID repository of the DNA resource core at Harvard Medical School. Protein epitope tags were attached at the C-terminus of each gene by PCR using forward and reverse primers (Supplementary Table 2); c-Fos was tagged with a HA epitope, whereas Dusp1 and Zfp36 were cloned with Myc Tag. The PCR products with the tagged sequences were cloned into pENTR (Invitrogen), which generated pENTR-FOS/HA, pENTER-Dusp1/Myc, pENTER-Zfp36/Myc, using the pENTR/SD/D-TOPO cloning kit (Life Technologies) per the manufacturer's protocol. Retroviral expression clones of these genes were created by recombination using destination vectors, pMSCV-Ires-GFP.GW, pMSCV-Ires-YFP.GW, and pMSCV-Ires-cherry.GW as described earlier[1,2]. These destination vectors were subjected to recombination using pENTR-FOS/HA, pENTER-Dusp1/Myc, pENTER-Zfp36/Myc and LR clonase to generate pMSCV-Fos-Ires-YFP.GW, pMSCV-Fos-Ires-cherry.GW, pMSCV-Dusp1-Ires-YFP.GW, pMSCV-Dusp1-Ires-cherry.GW, and pMSCV-Zfp36-Ires-GFP.

ShRNAs targeting c-Fos, Dusp1 and Zfp36 cloned in pLKO-puro vector were purchased from Cincinnati Children's robotic lentiviral library core. The RNA consortium numbers for the individual shRNA constructs are presented in Supplementary Table 3. To express c-Fos, Dusp1 and Zfp36 shRNA together, the selection marker puromycin was replaced with YFP, mCherry and GFP respectively in the original pLKO1. To clone the fluorescent proteins the coding sequences of GFP, YFP and Cherry were amplified using the primers GFPBAMFP and GFPSEXRP (supplementary Table 2). The PCR products were double digested with BamHI and SexI followed with ligation to BamHI and SexI digested (that removes the puromycin) pLKO-ShRNA vectors shown in Supplementary Table 3.

Generation of Stable Cell Lines
For gene-specific overexpression or knockdown studies, BaF3 and BaF3-BA cells were transduced with retroviruses (expressing c-Fos, Dusp1, Zfp36 cDNAs) or lentiviruses (expressing gene specific shRNAs, such as shFos, ShDusp1 and shZfp36). Retroviral preparation and transduction were performed as described earlier[3,4]. Cells expressing cDNA constructs (c-Fos-Cherry, Dusp1-Venus and Zfp36-GFP) were selected by FACS assisted cell sorting. Cells expressing shRNAs were selected for puromycin resistance (1μg/ml) for single shRNA expression, while for expression of multiple hairpins targeting all three genes were selected by FACS assisted cell soring.

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