

Supplementary Figure 1. LiPS cells derivation and characterization. (**A-B**) May Grunwald-Giemsa staining show morphology of the human K562 and primary CML cells. (Scale bars:20µm) Immunofluorescence images of the pluripotent transcription factors OCT4 and NANOG and of the pluripotent surface antigen TRA-1-81 and TRA1-60 in LiPS cells (Scale bars:200µm). Representative phase image of embryoid bodies (EBs) derived from LiPS cells cultured in suspension in the absence of FGF (Scale bars:100µm). LiPS clones were differentiated *in vitro* into all three germ layers: mesoderm (Smooth Muscle Actin (SMA) positive cardiomyocytes, red), ectoderm (TuJ1 positive neuronal cells, green), and endoderm (α -fetoprotein positive, green) (Scale bars:100µm). In vivo differentiation through teratoma formation identified derivatives of the three germ layers: muscle cells (mesoderm), neuro-epithelium (ectoderm) and epithelium structures (endoderm) (Scale bars:200µm). C) Western blot analysis for ABL protein shows both the expression of the wild type ABL and of the fusion BCR-ABL onco-protein in LiPS clones derived from primary CML cells. KBM7 expresses low levels of BCR-ABL protein and no ABL protein due to haploidy. β -actin was used as loading control.



Supplementary Figure 2. SNP array analysis of K562 and KBM7 cell lines and their reprogrammed clones. DNA copy number gained (red) or loss (green) of representative genes in parental K562 and KBM/7 cell lines and their LiPS clones. Human CD34⁺ bone marrow cells were used as normal control.



Pluripotent promoters

Supplementary Figure 3. DNA methylation levels at pluripotency genes in leukemic and LiPS cells. Boxplots of % methylation levels in K562, KBM7, primary CML cells and their reprogrammed clones showing a significant reduction of DNA methylation in all pluripotent cells. Human ES, CD34⁺and CD34-iPS cells were used as control. The horizontal bar indicates the median, the box indicates the first and third quartile, the whiskers indicate 1.5 times the interquartile range and points outside of the whiskers represent "outliers".



Supplementary Figure 4. Reprogramming restores myeloid differentiation. A) Schematic outline of *in vitro* differentiation of CML-LiPS derived CD45⁺/CD34⁺ cells and CD45⁺/CD34⁺ bone marrow control; **B)** CML-LiPS derived CD45⁺/CD34⁺ cells retain BCR-ABL expression qRT–PCR, bars indicate mean \pm s.d. (n=2). **C)** Colonies obtained from CML-LiPS derived CD45⁺/CD34⁺ and bone marrow control two weeks in methocult. The bar chart demonstrates average value plus standard deviation of three independent experiments (n=3). **D)** FACS analysis of differentiated CML-LiPS derived CD45⁺/CD34⁺ cells and CD45⁺/CD34⁺ bone marrow control three weeks in methocult. **E)** FACS analysis of differentiated CD45⁺/CD34⁺ cells and CD45⁺/CD34⁺ bone marrow control three weeks in methocult. **E)** FACS analysis of differentiated CD45⁺ LiPS cells and their parental leukemic counterpart K562. **F)** *CEBPA* expression levels in hematopoietic (K562, CD45⁺ LiPS1, CD45⁺ LiPS3, human Cord Blood and U937 leukemia cells) and pluripotent cells (LiPS clone 1, LiPS clone 3 and hES H1 cells). Hematopoietic CD45⁺ LiPS1 and CD45⁺ LiPS3 cells show significant increase in *CEBPA* gene expression as compared to parental leukemia cells. qRT–PCR, bars indicate mean ±s.d.(n=3) (*P<0.05; **P<0.01 and ***P<0.001; Student's t-test **)**. **G)** Effect of reprogramming on DNA methylation of *CEBPA* locus and lollipop representation of bisulfite sequenced clones.



Supplementary Figure 5. Azacitidine treatment in leukemic mice. A) Bone Marrow from BCR-ABL leukemic mice treated for one month with AZA shows restoration of lymphopoiesis and strong reduction of Mac1⁺ and Gr1⁺ myeloid population when compared to the untreated mice, similarly as the Imatinib treated cohort. **B**) Schematic overview of the drug treatment applied for the survival studies (Additional details are described in the Material and Methods).

Gated on CD45.2



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Supplementary Figure 6. Methylation and Expression analysis of Azacytidine treated mice. A) Outline of the experiment; B) FACS analysis of donor (CD45.2) LSK population shows expansion of the HSCs compartment in the untreated group and drastic reduction in the AZA-treated as compared to control; C), Expression levels of murine Gdf3 in both total Bone Marrow (left) and CD45.2⁺/LSK cells (right) qRT–PCR, bars indicate mean ±s.d.(n=2); D) DNA methylation analysis of murine Gdf3 promoter in control, untreated and AZA-treated mice by Methylation Specific PCR (MSP).





Supplementary Figure 7. Full blot and gel. A Full BCR-ABL western blot (with and without the membrane). The areas outlined by dotted white lines indicate the parts presented in Supplementary Figure 1C. **B** Full gel of murine Gdf 3 methylation analysis. The areas outlined by dotted white lines indicate the parts presented in Supplementary Figure 6D. (M: methylated; U: unmethylated).

Supplementary Table_1

LiPSC_vs_cancer_GO_BP_hyper_promoters_top500						
GOMFID	Pvalue	OddsRatio	ExpCount	Count	Size	Term
GO:0007159	0.0001	14.736	0.4278	5	25	leukocyte cell-cell adhesion
GO:0050900	0.0002	4.0605	2.9773	11	174	leukocyte migration
GO:0048872	0.0003	4.2516	2.5837	10	151	homeostasis of number of cells
GO:0045580	0.0005	6.6895	1.0095	6	59	regulation of T cell differentiation
GO:0042110	0.0005	3.345	3.9013	12	228	T cell activation
GO:0060986	0.0008	11.1636	0.4278	4	25	endocrine hormone secretion
GO:0009812	0.0009	116.1436	0.0513	2	3	flavonoid metabolic process
GO:0071593	0.0009	116.1436	0.0513	2	3	lymphocyte aggregation
GO:0006952	0.0009	2.113	13.5175	26	790	defense response
GO:1990266	0.0016	9.0125	0.5133	4	30	neutrophil migration
GO:0045409	0.0017	58.0663	0.0684	2	4	negative regulation of interleukin-6 biosynthetic
						process
GO:0045588	0.0017	58.0663	0.0684	2	4	positive regulation of gamma-delta T cell
						differentiation
GO:0022610	0.0025	2.0732	11.4985	22	672	biological adhesion
GO:0042060	0.0026	2.3666	7.2721	16	425	wound healing
GO:0002227	0.0028	38.7072	0.0856	2	5	innate immune response in mucosa
GO:0019731	0.0028	38.7072	0.0856	2	5	antibacterial humoral response
GO:0045656	0.0028	38.7072	0.0856	2	5	negative regulation of monocyte differentiation
GO:0051459	0.0028	38.7072	0.0856	2	5	regulation of corticotropin secretion
GO:0042089	0.0033	5.4401	1.0095	5	59	cytokine biosynthetic process
GO:0042102	0.0039	6.8866	0.6502	4	38	positive regulation of T cell proliferation
GO:0050798	0.0039	10.9333	0.3251	3	19	activated T cell proliferation
GO:0045086	0.0042	29.0276	0.1027	2	6	positive regulation of interleukin-2 biosynthetic
						process
GO:0045579	0.0042	29.0276	0.1027	2	6	positive regulation of B cell differentiation

GO:0007229	0.0044	5.063	1.078	5	63	integrin-mediated signaling pathway
GO:0045321	0.0046	2.3564	6.3481	14	371	leukocyte activation
GO:0098602	0.0047	2.6689	4.3975	11	257	single organism cell adhesion
GO:0006334	0.0053	4.8126	1.1293	5	66	nucleosome assembly
GO:0050852	0.0053	4.8126	1.1293	5	66	T cell receptor signaling pathway
GO:0009312	0.0058	23.2199	0.1198	2	7	oligosaccharide biosynthetic process
GO:0046643	0.0058	23.2199	0.1198	2	7	regulation of gamma-delta T cell activation
GO:0050896	0.0071	1.4585	82.0805	99	479	response to stimulus
					7	
GO:0002260	0.0072	5.707	0.77	4	45	lymphocyte homeostasis
GO:0051251	0.0075	3.305	2.2586	7	132	positive regulation of lymphocyte activation
GO:0001553	0.0076	19.3481	0.1369	2	8	luteinization
GO:0002251	0.0076	19.3481	0.1369	2	8	organ or tissue specific immune response
GO:0042534	0.0076	19.3481	0.1369	2	8	regulation of tumor necrosis factor biosynthetic
						process
GO:0050911	0.0076	19.3481	0.1369	2	8	detection of chemical stimulus involved in sensory
						perception of smell
GO:0002429	0.0081	3.2523	2.2928	7	134	immune response-activating cell surface receptor
			1.2.10.1	_		signaling pathway
GO:1902107	0.0082	4.3143	1.2491	5	73	positive regulation of leukocyte differentiation
GO:0030098	0.0088	2.9206	2.9088	8	170	lymphocyte differentiation
GO:0045638	0.009	5.3164	0.8213	4	48	negative regulation of myeloid cell differentiation
GO:0001894	0.0092	3.5655	1.7966	6	105	tissue homeostasis
GO:0050776	0.0096	2.0884	7.6314	15	446	regulation of immune response
GO:0008272	0.0097	16.5825	0.154	2	9	sulfate transport
GO:0014067	0.0097	16.5825	0.154	2	9	negative regulation of phosphatidylinositol 3-
						kinase signaling
GO:0045136	0.0097	16.5825	0.154	2	9	development of secondary sexual characteristics
GO:2000833	0.0097	16.5825	0.154	2	9	positive regulation of steroid hormone secretion

LiPSC_vs_cancer_GO_BP_hypo_promoters_top500						
GOMFID	Pvalue	OddsRatio	ExpCount	Count	Size	Term
GO:0032501	0	1.6932	103.5794	138	4043	multicellular organismal process
GO:0035295	0.0002	2.3731	11.4775	25	448	tube development
GO:0032502	0.0002	1.6018	76.585	103	3097	developmental process
GO:0007275	0.0003	1.6337	60.7919	85	2537	multicellular organismal development
GO:0010830	0.0005	6.8396	1.0248	6	40	regulation of myotube differentiation
GO:0009888	0.0005	2.3599	10.131	22	414	tissue development
GO:0048513	0.0006	1.8539	24.521	41	1062	organ development
GO:0070294	0.0007	Inf	0.0512	2	2	renal sodium ion absorption
GO:0045661	0.0008	11.861	0.4355	4	17	regulation of myoblast differentiation
GO:0003014	0.0011	5.8103	1.1785	6	46	renal system process
GO:0009887	0.0011	1.9812	15.798	29	621	organ morphogenesis
GO:0030182	0.0013	1.8087	22.1608	37	865	neuron differentiation
GO:0060562	0.0017	2.5435	6.328	15	247	epithelial tube morphogenesis
GO:0014028	0.0019	76.6176	0.0769	2	3	notochord formation
GO:0021530	0.0019	76.6176	0.0769	2	3	spinal cord oligodendrocyte cell fate
						specification
GO:0061364	0.0019	76.6176	0.0769	2	3	apoptotic process involved in luteolysis
GO:0072197	0.0019	76.6176	0.0769	2	3	ureter morphogenesis
GO:0048869	0.002	1.4974	62.1784	83	2427	cellular developmental process
GO:0042219	0.0024	14.4091	0.2818	3	11	cellular modified amino acid catabolic process
GO:0048741	0.0024	6.0345	0.9479	5	37	skeletal muscle fiber development
GO:0007411	0.0024	2.3767	7.1991	16	281	axon guidance
GO:0045597	0.0025	2.0584	11.4263	22	446	positive regulation of cell differentiation
GO:0046579	0.0025	8.1107	0.5892	4	23	positive regulation of Ras protein signal
						transduction
GO:0046717	0.0027	4.739	1.4091	6	55	acid secretion

GO:0048839	0.0029	3.046	3.5355	10	138	inner ear development	
GO:0010665	0.0031	12.8069	0.3074	3	12	regulation of cardiac muscle cell apoptotic	
						process	
GO:0043524	0.0032	3.5314	2.4595	8	96	negative regulation of neuron apoptotic	
						process	
GO:0044699	0.0036	1.5866	217.3554	235	8484	single-organism process	
GO:0052652	0.0038	3.8218	1.9983	7	78	cyclic purine nucleotide metabolic process	
GO:0021779	0.0038	38.3051	0.1025	2	4	oligodendrocyte cell fate commitment	
GO:0021780	0.0038	38.3051	0.1025	2	4	glial cell fate specification	
GO:0033058	0.0038	38.3051	0.1025	2	4	directional locomotion	
GO:0072289	0.0038	38.3051	0.1025	2	4	metanephric nephron tubule formation	
GO:0060284	0.0045	1.9187	12.7585	23	498	regulation of cell development	
GO:0008584	0.0046	3.6658	2.0752	7	81	male gonad development	
GO:0009968	0.0049	1.7901	16.6783	28	651	negative regulation of signal transduction	
GO:0009187	0.0049	3.269	2.6388	8	103	cyclic nucleotide metabolic process	
GO:0030903	0.0049	10.4764	0.3587	3	14	notochord development	
GO:0060579	0.0049	10.4764	0.3587	3	14	ventral spinal cord interneuron fate	
						commitment	
GO:0006935	0.005	1.9986	10.6321	20	415	chemotaxis	
GO:0022008	0.005	1.6355	25.5938	39	999	neurogenesis	
GO:0007268	0.0051	1.8978	12.8866	23	503	synaptic transmission	
GO:0000904	0.0056	1.8085	15.2948	26	597	cell morphogenesis involved in differentiation	
GO:0071300	0.0056	4.8239	1.1529	5	45	cellular response to retinoic acid	
GO:0007423	0.0059	2.0474	9.3255	18	364	sensory organ development	
GO:0010658	0.006	9.6024	0.3843	3	15	striated muscle cell apoptotic process	
GO:0060429	0.0061	1.7233	18.5485	30	724	epithelium development	
GO:0030802	0.0062	3.932	1.6653	6	65	regulation of cyclic nucleotide biosynthetic	
						process	
GO:0045137	0.0062	2.7033	3.9454	10	154	development of primary sexual characteristics	
GO:0007154	0.0066	1.376	93.0755	113	3633	cell communication	

GO:0030814	0.0072	3.8023	1.7165	6	67	regulation of cAMP metabolic process	
GO:1900371	0.0072	3.8023	1.7165	6	67	regulation of purine nucleotide biosynthetic	
						process	
GO:0072078	0.0073	8.8629	0.4099	3	16	nephron tubule morphogenesis	
GO:0090103	0.0073	8.8629	0.4099	3	16	cochlea morphogenesis	
GO:0031960	0.0073	3.3467	2.2545	7	88	response to corticosteroid	
GO:0007186	0.0073	1.9996	9.5336	18	378	G-protein coupled receptor signaling pathway	
GO:0002444	0.0077	5.7032	0.7942	4	31	myeloid leukocyte mediated immunity	
GO:0051148	0.0077	5.7032	0.7942	4	31	negative regulation of muscle cell	
						differentiation	
GO:0097305	0.0078	2.4776	4.714	11	184	response to alcohol	
GO:0002064	0.0079	2.7749	3.4586	9	135	epithelial cell development	
GO:0051093	0.0082	1.8696	11.8874	21	464	negative regulation of developmental process	
GO:0030324	0.0082	2.7528	3.4842	9	136	lung development	
GO:0007218	0.0083	3.6809	1.7677	6	69	neuropeptide signaling pathway	
GO:0016486	0.0087	8.229	0.4355	3	17	peptide hormone processing	
GO:0007168	0.0092	19.1489	0.1537	2	6	receptor guanylyl cyclase signaling pathway	
GO:0051823	0.0092	19.1489	0.1537	2	6	regulation of synapse structural plasticity	
GO:2000252	0.0092	19.1489	0.1537	2	6	negative regulation of feeding behavior	
GO:0007517	0.0092	2.2267	6.1743	13	241	muscle organ development	
GO:0055002	0.0092	3.188	2.357	7	92	striated muscle cell development	

Supplementary Table 1. Gene Ontology categories associated with hyper- or hypomethylated promoters in LiPs ver sus CML.

Supplementary Table_2

promoter name	mean methylation	mean methylation in	difference between
	in control mice	sick (leukemic) mice	control and sick
			mice
Traip	0.1463916666666667	0.7941	-0.7013166666666667
C130050O18Rik	0.358637234042553	0.754273076923077	-0.395635842880524
Ntn1	0.0251576923076923	0.36527777777778	-0.340112393162393
NA	0.50395	0.9	-0.39605
Gnas	0.440853936298077	0.737755110062893	-0.296901173764816
BC046401	0.475271036877395	0.679853574611663	-0.204582537734268
Mir1905	0.56596969981697	0.756290095039888	-0.216809513421375
Nap115	0.54281	0.74886	-0.20605
Gm4252	0.645440461060612	0.810739743589744	-0.207317698617393
Gm20546	0.645440461060612	0.810739743589744	-0.207317698617393
Ptafr	0.65875	0.9	-0.2079166666666667
Gm17033	0.713840911973617	0.928211170212766	-0.214370258239149
Gm7271	0.55995	0.911775	-0.351825
Mecom	0.84405	1	-0.24015
NA	0.059433333333333333	0.451283333333333	-0.39185
Vgll4	0.185076923076923	0.416217443249701	-0.231140520172778
Нрса	0.3082	0.4405	-0.2202
Tmc8	0.00859411764705882	0.366666666666666	-0.3630416666666667
3830406C13Rik	0.2239626666666667	0.285714285714286	-0.22004666666666667
Bdnf	0.096538474025974	0.3541666666666667	-0.257628192640693
9130019O22Rik	0.04275	0.301275	-0.258525
Gm14303	0.72315	0.9605875	-0.2374375
Gm16152	0.5280833333333333	1	-0.3196
Kenj13	0.772	1	-0.206
Gm13217	0.3884	0.5302166666666667	-0.3973
H13	0.147725	0.35715	-0.209425
Gm14494	0.45486	0.616608333333333	-0.23182
Wfdc15a	0.554266666666666	1	-0.385125
Gm9857	0.5422125	0.779375	-0.2371625
4921515J06Rik	0.5422125	0.779375	-0.2371625
Gm12384	0.0721	0.35665	-0.28455
Gm11222	0.5833	0.94445	-0.36115
Ube2u	0.42889387755102	0.676043879781421	-0.2471500022304
NA	0.78215	1	-0.21785
Csn3	0.4345	1	-0.4643
Gm7932	0.4286	0.277783333333333	-0.40475
Gdf3	0.2967	0.6316	-0.3349
Gm17263	0.45318970464135	0.8	-0.316365443037975
Hapln3	0.116125	0.8333	-0.6822
Ctf1	0.2217	0.5385	-0.3168

Gm17387	0.6667	1	-0.3333
Gm15303	0.29005	0.5	-0.20995
Ap1m2	0.5556	0.7857	-0.2301
Rps6-ps3	0.5917	0.8621	-0.2704
NA	0.635708750208098	0.902559487179487	-0.262920525391307
1700048O20Rik	0.5201166666666667	0.737533333333333	-0.2174166666666667
Gm10275	0.2564	0.6226	-0.3662
Prdm1	0.09354166666666667	0.4893	-0.3489875
Ano4	0.002316666666666667	0.313710752688172	-0.445566129032258
4933414I15Rik	0.57827	0.99255	-0.37755
Gm12246	0.796525	1	-0.203475
Hoxb1	0.045125	0.30505	-0.259925
Tomm201	0.1041666666666667	0.4545666666666667	-0.3504
Mir539	0.04375	0.266675	-0.222925
Mir544	0.04375	0.266675	-0.222925
4930563I02Rik	0.0733906788710908	0.318195454545455	-0.210403078496637
gene body name	mean methylation	mean methylation in	difference between
	in control mice	sick (leukemic) mice	control and sick
			mice
Gm14204	0.022925	0.9128833333333333	-0.8878833333333333
Rdh8	0.37625	0.7457	-0.21705
NA	0.319069596153846	0.597629047619048	-0.278559451465201
Impact	0.356808333333333	0.669325	-0.3125166666666667
NA	0.50395	0.9	-0.39605
C130050O18Rik	0.542908814589666	0.632323846153846	-0.229951505728314
Gm4252	0.743934584699454	0.961538461538462	-0.312294292139554
Ctf1	0.20855043983615	0.415647489564007	-0.207097049727858
Mex3a	0.567144674831049	0.749702153376111	-0.206741255642474
AI747448	0.556675	0.85835	-0.301675
Nap115	0.54281	0.74886	-0.20605
2410137F16Rik	0.657622739541161	0.859663461538462	-0.202040721997301
Gm17033	0.696654549298157	0.904281560283688	-0.207627010985531
Gm11052	0.7167	0.93405	-0.21735
Gm14228	0.7780125	1	-0.2219875
Vmn2r109	0.747725	0.959175	-0.21145
Clrl	0.57287380952381	0.9655	-0.201428571428572
Zfp174	0.062270125	0.3095666666666666	-0.209666458333333
Skint4	0.4574333333333333	0.683133333333333	-0.2257
3830406C13Rik			
	0.223962666666666	0.285714285714286	-0.220046666666666
Neil2	0.2239626666666667 0.703525	0.285714285714286	-0.2200466666666667 -0.296475

Gm14319	0.569	0.6684	-0.209
2410152P15Rik	0.693875	0.6578125	-0.2131166666666667
Pla2g4d	0.5314916666666667	0.700878571428571	-0.236346428571429
1700007G11Rik	0.808748182773109	0.932746	-0.210118907563025
Gm7137	0.7112	0.7777	-0.206925
Nostrin	0.137917307692308	0.3636	-0.225682692307692
6030422M02Rik	0.11015	0.5714	-0.46125
Gm11608	0.14140303030303	0.3889	-0.24749696969697
Kcnj13	0.772	1	-0.206
Serpinb5	0.805175	1	-0.22925
Ptpn7	0.681425	0.485887096774194	-0.282212096774194
Gm13217	0.3884	0.7857	-0.3973
Gm13767	0.402285714285714	0.640471428571429	-0.238185714285714
1810024B03Rik	0	0.25	-0.25
Gm14494	0.45486	0.616608333333333	-0.23182
Gm16098	0.10365	0.4615	-0.35785
1700013F07Rik	0.796533333333333	1	-0.31415
Gm9857	0.5422125	0.779375	-0.2371625
4921515J06Rik	0.5422125	0.6235	-0.2371625
Gm12384	0.0721	0.594975	-0.28455
Gm11222	0.776025	0.94445	-0.36115
Gm12746	0.5445333333333333	0.91665	-0.409425
Tnfrsf1b	0.7149125	0.8889	-0.28785
2310043J07Rik	0.0625	0.3158	-0.2533
4930448H16Rik	0.67345	0.8	-0.4293
Ocm	0.715	1	-0.285
1110019D14Rik	0.67645	1	-0.32355
Lrguk	0.5	0.8788	-0.3182
Abp1	0.0294	0.8	-0.7706
Zfp551	0.38475	0.8333	-0.2681
Gm16282	0.790475	1	-0.25
Gm6226	0.0820166666666666	0.314633333333333	-0.2326166666666667
Gm16159	0.6993	0.9593	-0.26
Chrna6	0.642975	0.9348	-0.291825
Purg	0.376152196969697	0.704761904761905	-0.203225642135642
9330133O14Rik	0.2645	0.519275	-0.254775
Gm15606	0.6655	0.9	-0.2345
Rps6-ps3	0.5917	0.8621	-0.2704
Gcm1	0.6667	0.86	-0.2333
ll20rb	0.75	1	-0.25
4930535L15Rik	0.08665	0.625	-0.4517
Gm10275	0.2564	0.6226	-0.3662
8430429K09Rik	0.225561333333333	0.70835	-0.35275

D130052B06Rik	0.8296	0.8333	-0.27175
4933414I15Rik	0.657371428571429	0.935675	-0.2006125
Gm12246	0.796525	1	-0.203475
Gm12278	0.760469608636977	0.730775	-0.302995587044534
Aloxe3	0.890759856630824	1	-0.221620430107527
Vps53	0.77215	1	-0.22785
Slfn2	0	0.388397413793103	-0.388397413793103
C330019F10Rik	0.8498	1	-0.24745

Supplementary Table 2. The table shows methylation values of gene promoters (upper part) and gene bodies (lower part) which gain significant aberrant methylation after BCR-ABL activation (sick mice) in HSCs population.