

Supplementary Table 1 | Adverse Events during Mobilization Protocol

Patient ID	Patient 1	Patient 2	Patient 3	Patient 4 1st mobilization	Patient 4 2 nd mobilization
D+1	None	None	None	None	None
D+2	None	Anemia (1) Myalgia (1)	None	Chill (1)	None
D+3	Bone pain (1) Myalgia (1)	Anemia (2) Bone pain (1)	Bone pain (1)	Myalgia (1)	Bone pain (1) Headache (1)
D+4	None	None	Anemia (1) Bone pain (1)	Myalgia (1)	Bone pain (1)
D+5	Anemia (1)	Anemia (1)	Fatigue (1) Bone pain (1)	Myalgia (1)	Bone pain (1) Myalgia (1)
D+6	Anemia (2)	Anemia (1)	Headache (1) Anemia (2)	Anemia (1) Myalgia (1)	Anemia (1) Bone pain (1) Myalgia (1)
D+7	None	None	None	Anemia (1) Myalgia (1)	None

D, day past G-CSF injection; grading (in parenthesis) as per the National Institute of Health Common Terminology Criteria for adverse events (CTCAE) version 4.03;

Supplementary Table 2 | Cyto-reduction and Engraftment Data

Patient ID	Patient 1	Patient 2	Patient 3	Patient 4	Median
Cumulative Busulfan Exposure (AUC in mg* μ l/h)	53.4	47.8	39.8	59.7	47.8
Neutropenia duration (d)	5	6	11	10	8
Neutrophil engraftment (d)	16	18	24	20	19
Platelet engraftment (d)	20	19	25	14	20
Discharge post HSCT (d)	20	23	25	21	22
Follow-up (months)	96	94	75	60	84

AUC, area under the curve; Neutropenia, absolute neutrophil count (ANC) <500/ μ L; Neutrophil engraftment, ANC exceeding 500/ μ L for 3 consecutive days. The first of these 3 consecutive days was considered the day of engraftment; Platelet engraftment, a platelet count exceeding 20,000/ μ L without transfusion support for 7 consecutive days. The first of these 7 consecutive days was considered the day of engraftment; d, day; HSCT, Hematopoietic stem-cell transplantation; Follow up to last qPCR data.

Supplementary Table 3 | Non-hematologic Toxicity of Busulfan

Patient ID	Patient 1	Patient 2	Patient 3	Patient 4
Oral mucositis	1	2	2	2
GI (Abdominal pain)	2	1	0	0
Hyperbilirubinemia	3	2	0	0
Febrile neutropenia	3	3	3	0
GU (Metrorrhagia)	1	2	NA	NA
Headache	0	0	0	1
VOD	0	0	0	0

Grading as per the National Institute of Health Common Terminology Criteria for adverse events (CTCAE) version 4.03

Supplementary Table 4 | Cancer-related Genes

Gene symbol	Chromosomal location	Molecular function	Biological process	Cancer association	Leukemia/ lymphoma association	Selected References
SETD2	3p21.31	Histone lysine methyltransferase.	transcriptional regulator	Clear cell renal cell cancer, lung cancer, acute lymphoblastic leukemia, glioma	ALL, AML (frequent), (MLL)	1-3
CUX1	7q22.1	Homeodomain family DNA binding protein.	transcriptional activator/repressor	Colon cancer, pancreatic cancer, breast cancer, glioblastoma	MDS and myeloid neoplasms	4-6
PXN-AS1, PXN	PXN-AS1/PXN: 12q24.23	PXN-AS1: non-protein coding; PXN: Cytoskeletal protein.	PXN-AS1: long non-coding RNA; PXN: involved in focal cell adhesion	PXN-AS1: multiple malignancies, such as pancreatic cancer, glioblastoma; PXN: Promotes tumor invasion	CML: phosphorylation of paxillin by BCR/ABL	7,8
SLX4	16p13.3	Endonuclease.	involved in DNA repair	Breast cancer	Hematopoietic dysfunction, aplastic anemia, childhood leukemia	9-12
NF1	17q11.2	GTPase-activating protein neurofibromin.	Negative regulator of the Ras signal transduction pathway	Hamartoneoplastic syndrome Neurofibromatosis NF1 (benign and malignant tumors)	NF1 associated with JMML (juvenile myelomonocytic leukemia).	13,14
NFIC	19p13.3	DNA-binding protein.	transcription factor	Potential oncogene or tumour suppressor across various cancer models	NFIC reported to be upregulated in AML	15,16
CCDC97	19q13.2	Protein. Function unclear.	unclear	Multiple malignancies	Not described	
POU2F2	19q13.2	Homeobox-containing DNA-binding protein.	transcription factor, activating immunoglobulin gene expression in B-cells	Papillomas, gastric cancer	B- and T-cell lymphoma, follicular lymphoma	17,18
PCM1	8p22	centriolar satellite component protein.	essential for localization of centrosomal proteins, and for anchoring microtubules to the centrosome	Papillary thyroid carcinomas, hematological malignancies	Acute and chronic leukemia, CML, T-cell lymphoma	19,20

PLEKHB1	11q13.4	Protein. Function unclear.	unclear	Multiple malignancies	Not described	
CBFB	16q22.1	regulatory subunit protein, non-DNA binding.	Subunit of a heterodimeric core-binding transcription factor (CBF). Forms CBF with RUNX family proteins.	Hematological malignancies, breast cancer, intestinal cancer	Frequent in acute leukemias, CBF-AML	21
MSL1	17q21.1	MSL1 protein involved in histone H4 acetylation.	Gene activation.	Ovarian cancer	Not described	22
MAP4	3p21.31	Major non-neuronal microtubule-associated protein.	promotes microtubule assembly.	Ovarian Clear Cell Adenocarcinoma	Diffuse large B-cell lymphoma (MALT1-MAP4 fusion)	23,24
NFAT5	16q22.1	DNA binding protein, homodimer.	Transcription factor.	Multiple malignancies	Not described	
PIEZO1	16q24.3	Transmembrane protein.	Component of a mechanically activated ion channel.	Multiple malignancies, such as breast, gastric, bladder, prostate cancer	Not described	25,26
ST13	22q13.2	Adaptor protein.	Mediates the association of heat shock proteins, candidate tumor suppressor gene	Multiple malignancies, such as colon, prostate, pancreatic cancer	B-Cell leukemia and multiple myeloma	27
SLC45A3	1q32.1	Solute carrier family protein.	Coordinates response to hyperosmolarity	Prostate cancer	Not described	28,29
NFATC3	16q22.1	DNA-binding protein.	Regulator of transcriptional activation, oncogenic and tumor-suppressive activities	Multiple malignancies, such as glioma	Lymphoma	30,31

SPPL2B	19p13.3	Transmembrane protein. Aspartic protease.	Cleaves transmembrane domain of TNF-alpha.	Breast cancer (metastasis)	Not described	32
GNA15	19p13.3	G protein subunit.	Involved in various transmembrane signaling systems.	Small intestine neuroendocrine neoplasia	Not described	33
IKZF2	2q34	Zinc-finger protein.	Hematopoietic-specific transcription factors involved in the regulation of lymphocyte development.	Lymphoid malignancies	B- and T-cell leukemias, AML	34,35
COL4A3 BP (HGNC approved symbol: CERT1)	5q13.3	Kinase 'Goodpasture antigen'.	Phosphorylates type IV collagen	Multiple malignancies, such as breast and lung cancer	Not described	36
RABL6	9q34.3	Small GTPase.	Member of the Ras oncogene family	Breast cancer, osteosarkoma, neuroendocrine tumors	Not described	37-39
KDM6A	Xp11.3	Histone demethylase	Regulates lineage choice in development, tumor suppressor.	Multiple malignancies	T-ALL, AML	40-43
UBR2	6p21.1	E3 ubiquitin ligase UBR2	Regulator in caspase-independent cell death, participate in the N-end rule proteolytic pathway	Multiple malignancies	Lymphoma	44-49

25 integration sites (relative abundance >1%) found within 50 kb of cancer-related genes. Chromosomal location, molecular function and biological process according to databases NCBI (<http://www.ncbi.nlm.nih.gov/gene>) and GeneCards (<http://www.genecards.org>).

Supplementary Table 5 | Summary of Busulfan Exposure and Toxicity in Gene Addition and Gene Editing Trials in β -thalassemia

Trial	Phase	Start	Cumulative Busulfan AUC	Number of Patients	Cases of VOD	Neutrophil Engraftment	Platelet Engraftment	Hospitalization	References
LGG01	1/2	2006	NA (daily target AUC: 4300 $\mu\text{M}^*\text{min}$)	3	NA	NA	NA	NA	⁵⁰
NCT01639690 (MSKCC)	1	2012	39.8-59.7 mg*h/l (median: 50.6)	4	0	16-24d (median: 19)	14-25d (median: 19.5)	20-25d (median: 22)	This manuscript
NCT01745120 (HGB-204)	1/2	2013	49.7-77.5 mg*h/l (median: NA)	18	2	14-30d (median: 18.5)	19-191d (median: 39.5)	NA	⁵¹
NCT02151526 (HGB-205)	1/2	2013	76.7-85.6 mg*h/l (median: NA)	4	0	14-29d (median: 16.5)	20-26d (median: 23)	NA	⁵¹
NCT02906202*/ NCT03207009* (HGB-207/ HGB-212)	3	2016/ 2017	60.9-149.2 mg*h/l (median: 73.1)	31	3	13-38d (median: 25)	20-84d (median: 44)	30-92d (median: NA)	⁵²
NCT03655678* (CLIMB THAL-111)	1/2	2018	73.9-90.3 mg*h/l (median: 82.1)	7	2	20-39d (median: 32)	29-52d (median: 37)	NA	^{53,54}

HSC, hematopoietic stem cell; AUC, area under the curve; cumulative busulfan exposure; cumulative busulfan exposure was calculated by the sum of the daily average busulfan AUCs published; NA, not applicable; mPBC, mobilized peripheral blood cells; * interim results.

Supplementary Table 6 | Summary of Top Integration Sites in Whole Blood in Gene-Addition Trials in β -thalassemia

Trial	MSK trial				HGB-204/HGB-205 trials				Globe trial	
Patient ID	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1102	Patient 1103	Patient 1201	Patient 1202	Patient 1	Patient 4
Timepoint	Y7	Y6	Y6	Y4.5	Y2	Y2	Y2	Y2	Y2	Y1.5
Top1	SLC25A33	MSRB3	SSH2	UBR2	SART3	NBR1	CAPN1	POLA2	AHNAK	RNF216
Top2	PRKCB	SLX4	MAP4	COL4A3BP	TTYH1	AKT2	AARSD1	DNAH1	MOB3A	ARFGEF1
Top3	SETD2	FLRT2	C6orf106	EGFEM1P	HN1L	LINC00470	SLC27A1	FCHSD2	XKR3	FAM208B
Top4	STRBP	CCDC97	SNX37	KDM6A	SUPT3H	PIK3CG	APPBP2	TMEM66	CCDC88A	PTPRA
Top5	CUX1	ADAM22	CBFB	GOLPH3L	PHF16	MLLT3	ILF3	CBFB	GPATCH8	DNAJC8
Top6	NF1	ZFAND6	C6orf106	SLC22A11	OR1A1	CASC5	NT5C2	HMGA2	MUM1	EIF4G3
Top7	POC1A	NFIC	PLEKHB1	GNA15	SGK493	EHMT1	MGA	AKAP13	PDE4DIP	MROH1
Top8	TFCP2	NF1	LOC101927237	USP48	MARK2	NSD1	BAX	C11orf49	ISY1	STXBP3
Top9	GJC1	PCM1	NDUFS4	MIA2	RAVER2	CYTH1	DOLPP1	POLA2	BBX	CEL
Top10	STIL	MGA	SLC22A11	POLQ	EYA3	BLVRB	UBA3	TMEM55A	CAPN1	LOC101927817
Reference	This manuscript				51				55	

Cancer related genes highlighted in bold; Y, year.

Supplementary Table 7 | Primary and Secondary Objectives

Primary objective: Evaluation of safety

Occurrence of insertional oncogenesis

Generation of a replication-competent lentivirus (RCL)

Safety of a low dose non-myeloablative conditioning regimen

Secondary objective: evaluation of efficacy

Level of engraftment of transduced CD34+ cells

Biological activity of the globin vector, as measured by:

- presence and expression of the transduced β -globin transgene in peripheral blood cells; and in hematopoietic progenitor cells in bone marrow
- The frequency of palliative transfusions subsequent to transplantation.

Supplementary Table 8 | HbF and HPFH

Patient ID	Patient 1	Patient 2	Patient 3	Patient 4
HbF (%) pre conditioning	1.2%	Not measurable	13.1%	4.6%
HbF (%) max post infusion	3.2% (7 months)	15.5% (4 months)	21.8% (14 months)	12.7% (3months)
HbF (%) Last follow-up	0.4%	1.1%	11.2%	2.6%
HPFH polymorphisms	- AGCA at Positions -222 to -225, ^A gamma (heterozygous)	- AGCA at Positions -222 to -225, ^A gamma (heterozygous)	<i>BCL11A</i> (rs11886868 T/C, rs1427407 G/T, rs10189857 A/G) <i>HBS1L-MYB</i> (rs9399137 C/T)	- AGCA at Positions -222 to -225, ^A gamma (homozygous)

HPFH, Hereditary persistence of fetal hemoglobin; - AGCA, Deletion of four nucleotides, AGCA, at positions -225 to -222, this deletion is reported as a polymorphism that determines a very slight increase in HbF 1-3%. *BCL11A* and *HBS1L-MYB*, non-deletional polymorphisms in *BCL11A* (chromosome 2p16) and intergenic region *HBS1L-MYB* (chromosome 6q23).

Supplementary Table 9 a | Patient 1
Transfusion requirements over time

Months pre/post infusion	Transfusion volume (ml/kg/year)	Hb pre transfusion (g/dl)	Mean daily decrease in Hb (%)
-60	191.56	9.21	1,13
-48	203.17	9.33	1,16
-36	214.53	9.38	1,22
-24	213.44	9.33	1,22
-12	192.31	9.14	1,22
0	230.88	9.32	1,46
12	160.5	8.19	1,42
24	197.14	8.91	1,39
36	148.22	9.11	1,38
48	231.51	9.,35	1,48
60	204.44	9.72	1,09
72	219	9.5	1,16
84	209.43	8.8	1.11
96	181.74	9.33	1.19

Supplementary Table 9 b | Patient 2
Transfusion requirements over time

Months pre/post infusion	Transfusion volume (ml/kg/year)	Hb pre transfusion (g/dl)	Mean daily decrease in Hb (%)
-60	221.54	9.68	1.29
-48	225.16	9.64	1.25
-36	201.27	9.16	1.18
-24	221.22	9.52	1.08
-12	198.35	9.4	1.17
0	246.58	9.76	1.22
12	107.64	8.23	1.4
24	41.49	7.63	1.34
36	38.14	7.62	1.29
48	91.73	8.27	0.68
60	131.2	9.24	0.74
72	123.34	9.25	0.63
84	110.09	8.87	0.74
96	101.35	9.09	0.62

Supplementary Table 9 c | Patient 3
Transfusion requirements over time

Months pre/post infusion	Transfusion volume (ml/kg/year)	Hb pre transfusion (g/dl)	Mean daily decrease in Hb (%)
-60	177.8	10.1	1.2
-48	176.4	10.3	1.1
-36	175.2	10.3	1.2
-24	182.8	10.3	1.1
-12	171	10.2	1.1
0	191.2	10.2	1.2
12	171.9	9.3	1.1
24	166.2	9.9	0.9
36	170.9	9.6	0.9
48	175	9.6	0.8
60	198.4	10	0.9
72	212	10	0.9
84	169	10.4	0.7

Supplementary Table 9 d | Patient 4
Transfusion requirements over time

Months pre/post infusion	Transfusion volume (ml/kg/year)	Hb pre transfusion (g/dl)	Mean daily decrease in Hb (%)
-36	265.68	9.13	1.59
-24	267.93	9.17	1.61
-12	268.68	9.3	1.62
0	274.19	9.34	1.63
12	145.36	8.52	1.62
24	183.68	8.73	1.07
36	184.92	9.16	1.15
48	185.52	9.21	0.97
60	183.14	8.9	1.25
72	156.57	8.14	1.15

Supplementary Table 10 | Integration Site Samples Metadata

GTSP	Time point	Pt	Cell Type	Total Reads	Inferred Cells	Unique Sites	Gini	Chao1	Shannon	Pielou	UC50
GTSP4268	D0	1	CD34+	39,687	1,452	1,443	0.006	104,189	7.27	1	718
GTSP1699	M54	1	WB	390,529	1,392	838	0.333	2,280	6.45	0.959	190
GTSP1393	Y3	1	WB	918,125	1,606	1,019	0.304	3,141	6.7	0.967	244
GTSP2180	Y5	1	WB	802,067	2,395	1,363	0.358	3,539	6.9	0.956	289
GTSP3310	Y6	1	WB	423,243	5,911	1,968	0.532	3,467	6.95	0.917	234
GTSP3437	Y7	1	WB	546,205	925	509	0.358	1,094	5.95	0.955	112
GTSP1395	M42	2	WB	824,102	1,876	1,095	0.362	3,135	6.6	0.944	224
GTSP3622	M53	2	WB	417,569	1,321	708	0.388	1,733	6.17	0.94	136
GTSP1701	Y4	2	WB	322,345	2,896	1,220	0.48	2,395	6.49	0.914	167
GTSP2181	Y5	2	WB	794,730	7,402	2,078	0.59	3,812	6.78	0.887	187
GTSP3311	Y6	2	WB	389,410	7,131	1,905	0.601	3,396	6.66	0.882	166
GTSP4269	D0	3	CD34+	21,320	1,783	1,660	0.064	11,522	7.39	0.997	769
GTSP1599	M42	3	WB	370,340	689	557	0.166	2,130	6.23	0.986	213
GTSP3626	M75	3	WB	1,001,616	744	508	0.284	2,666	5.96	0.957	137
GTSP3309	Y5	3	WB	275,417	260	198	0.221	2,765	5.08	0.96	69
GTSP3438	Y6	3	WB	524,064	847	516	0.317	1,246	5.98	0.957	126
GTSP0886	D0	4	CD34+	325,929	941	852	0.088	5,807	6.71	0.994	382
GTSP0890	D0	4	CD34+	512,004	9,934	9,626	0.03	171,156	9.16	0.999	4,660
GTSP4270	D0	4	CD34+	13,208	616	616	0	190,036	6.42	1	309
GTSP4185	M70	4	WB	942,615	119	71	0.373	681	3.78	0.886	12
GTSP3306	Y3	4	WB	468,354	4,021	743	0.712	1,175	5.16	0.78	23
GTSP3308	Y4	t4	WB	460,687	3,600	699	0.73	1,364	4.93	0.753	16
GTSP3440	Y4.5	t4	WB	358,613	779	238	0.598	459	4.51	0.824	17

GTSP, internal tracking number; Pt, patient; WB, whole blood; Total Reads, total number of sequence reads; Inferred Cells, inferred number of cells queried from SonicAbundance; Unique Sites, the number of integration sites recovered after dereplication; Chao1, minimum population size inferred from sharing among replicates; Gini, the asymmetry of clonal distribution; Shannon, the diversity summarized as the Shannon index; UC50, and the number of unique clones making up the top 50% of the sample abundance.

Supplementary Table 11 | Clusters of integration sites in pooled patient samples pre- and post-infusion

Chr.	Start	End	Width	Sites: 6 years	Sites: Pre-infusion	Cluster Source	Nearby genes of interest
chr1	28994617	29066014	71398	6	0	T6	EPB41
chr1	155475830	155523663	47834	8	1	T6	ASH1L
chr2	42641725	43533854	892130	15	2	T6	
chr3	47678397	48030376	351980	17	9	T6	
chr3	51600444	52257778	657335	8	1	T6	
chr8	144227307	145061045	833739	0	57	T0	
chr9	137284409	137364400	79992	6	0	T6	EXD3, NRARP
chr11	65903017	66101385	198369	0	36	T0	
chr12	8702107	9689590	987484	15	10	T6	
chr12	50561540	50888906	327367	13	7	T6	
chr15	41688228	41956383	268156	14	8	T6	
chr16	581878	1534701	952824	3	65	T0	
chr16	15259791	16053684	793894	16	2	T6	
chr16	28163642	28452684	289043	9	0	T6	
chr17	42360682	42374061	13380	6	0	T6	STAT3
chr17	81593009	81881897	288889	1	39	T0	
chr19	2260306	3127896	867591	21	13	T6	
chr19	10102708	10223830	121123	0	31	T0	DNMT1
chr19	11998654	12656008	657355	16	12	T6	

Chr., chromosome; Sites, number of integration sites at 6 years follow-up or pre-infusion; Cluster Source, T0 indicates pretransplant, T6 is after ~6 years.

Supplementary Table 12 | Gene Ontology Analysis of Integration Site Distributions in pooled patient samples pre- and six years post infusion

Function	GO	p.value	T0 GO	T0 no GO	T6 GO	T6 no GO	Corr p.value
mitochondrion	GO:0005739	0.00638647	0.0674229	0.9325771	0.05591736	0.94408264	0.11883687
extracellular exosome	GO:0070062	0.0069904	0.1010989	0.8989011	0.1154278	0.8845722	0.11883687
protein serine/threonine kinase activity	GO:0004674	0.02398025	0.0358738	0.9641262	0.04334157	0.95665843	0.20647289
endosome	GO:0005768	0.0243827	0.04601205	0.95398795	0.05434539	0.94565461	0.20647289
signal transduction	GO:0007165	0.03036366	0.07671039	0.92328961	0.0869077	0.9130923	0.20647289
cellular response to DNA damage stimulus	GO:0006974	0.05986914	0.04792627	0.95207373	0.04109589	0.95890411	0.29591157
RNA binding	GO:0003723	0.06092297	0.11159163	0.88840837	0.1015046	0.8984954	0.29591157
proteolysis	GO:0006508	0.07945869	0.02984757	0.97015243	0.02470245	0.97529755	0.32340841
protein homodimerization activity	GO:0042803	0.08560811	0.03417228	0.96582772	0.03974848	0.96025152	0.32340841
DNA binding	GO:0003677	0.12357621	0.13590925	0.86409075	0.12688075	0.87311925	0.40618093
chromosome	GO:0005694	0.13743202	0.04679192	0.95320808	0.04132046	0.95867954	0.40618093
cytosol	GO:0005829	0.14335798	0.36830911	0.63169089	0.35616438	0.64383562	0.40618093
intracellular membrane-bounded organelle	GO:0043231	0.18261927	0.06196384	0.93803616	0.05636649	0.94363351	0.47761962
kinase activity	GO:0016301	0.19699184	0.05303084	0.94696916	0.05816304	0.94183696	0.47840875
endoplasmic reticulum	GO:0005783	0.25075567	0.07529245	0.92470755	0.07006512	0.92993488	0.56837951
integral component of plasma membrane	GO:0005887	0.29738482	0.04360156	0.95639844	0.04738379	0.95261621	0.60724712
protein transport	GO:0015031	0.30362356	0.04870613	0.95129387	0.05254884	0.94745116	0.60724712
Golgi apparatus	GO:0005794	0.38468953	0.08933002	0.91066998	0.09364473	0.90635527	0.69838239
intracellular signal transduction	GO:0035556	0.45623218	0.03034385	0.96965615	0.03256232	0.96743768	0.69838239
cytoplasmic vesicle	GO:0031410	0.47844223	0.0450195	0.9549805	0.0424433	0.9575567	0.69838239
nucleolus	GO:0005730	0.4785997	0.05083304	0.94916696	0.04805749	0.95194251	0.69838239
nuclear speck	GO:0016607	0.48134902	0.03417228	0.96582772	0.03637997	0.96362003	0.69838239

integral component of membrane	GO:0016021	0.48139738	0.18674229	0.81325771	0.19155625	0.80844375	0.69838239
metal ion binding	GO:0046872	0.4929758	0.22034739	0.77965261	0.21536043	0.78463957	0.69838239
nucleotide binding	GO:0000166	0.56447775	0.1235732	0.8764268	0.12014372	0.87985628	0.74548188
apoptotic process	GO:0006915	0.57100726	0.04005672	0.95994328	0.04199416	0.95800584	0.74548188
cytoskeleton	GO:0005856	0.60856344	0.0899681	0.9100319	0.08735684	0.91264316	0.74548188
G protein-coupled receptor signaling pathway	GO:0007186	0.61671766	0.0248139	0.9751861	0.02335504	0.97664496	0.74548188
Golgi membrane	GO:0000139	0.6358522	0.04119107	0.95880893	0.04289243	0.95710757	0.74548188
endoplasmic reticulum membrane	GO:0005789	0.66136003	0.0494151	0.9505849	0.04760835	0.95239165	0.74954137
transmembrane transport	GO:0055085	0.69054983	0.02367955	0.97632045	0.02245677	0.97754323	0.7530018
neutrophil degranulation	GO:0043312	0.70870758	0.02637363	0.97362637	0.02739726	0.97260274	0.7530018
ion transport	GO:0006811	0.90611481	0.02183623	0.97816377	0.02133393	0.97866607	0.93357284
perinuclear region of cytoplasm	GO:0048471	0.96715109	0.04558667	0.95441333	0.04581181	0.95418819	0.96715109

GO, gene ontology ID; T0 indicates pretransplant, T6 is after ~6 years. All p values significant only before correction for multiple comparisons.

References

1. Aymard, F., *et al.* Transcriptionally active chromatin recruits homologous recombination at DNA double-strand breaks. *Nat Struct Mol Biol* **21**, 366-374 (2014).
2. Luco, R.F., *et al.* Regulation of alternative splicing by histone modifications. *Science* **327**, 996-1000 (2010).
3. Skucha, A., Ebner, J. & Grebien, F. Roles of SETD2 in Leukemia-Transcription, DNA-Damage, and Beyond. *Int J Mol Sci* **20**(2019).
4. Ramdzan, Z.M. & Nepveu, A. CUX1, a haploinsufficient tumour suppressor gene overexpressed in advanced cancers. *Nat Rev Cancer* **14**, 673-682 (2014).
5. McNerney, M.E., *et al.* CUX1 is a haploinsufficient tumor suppressor gene on chromosome 7 frequently inactivated in acute myeloid leukemia. *Blood* **121**, 975-983 (2013).
6. Aly, M., *et al.* Distinct clinical and biological implications of CUX1 in myeloid neoplasms. *Blood Adv* **3**, 2164-2178 (2019).
7. Yan, J., Jia, Y., Chen, H., Chen, W. & Zhou, X. Long non-coding RNA PXN-AS1 suppresses pancreatic cancer progression by acting as a competing endogenous RNA of miR-3064 to upregulate PIP4K2B expression. *J Exp Clin Cancer Res* **38**, 390 (2019).
8. Salgia, R., *et al.* CRKL links p210BCR/ABL with paxillin in chronic myelogenous leukemia cells. *J Biol Chem* **270**, 29145-29150 (1995).
9. Kim, Y., *et al.* Mutations of the SLX4 gene in Fanconi anemia. *Nat Genet* **43**, 142-146 (2011).
10. Yamamoto, K.N., *et al.* Involvement of SLX4 in interstrand cross-link repair is regulated by the Fanconi anemia pathway. *Proc Natl Acad Sci U S A* **108**, 6492-6496 (2011).
11. Spinella, J.F., *et al.* Whole-exome sequencing of a rare case of familial childhood acute lymphoblastic leukemia reveals putative predisposing mutations in Fanconi anemia genes. *BMC Cancer* **15**, 539 (2015).
12. Arias-Salgado, E.G., *et al.* Genetic analyses of aplastic anemia and idiopathic pulmonary fibrosis patients with short telomeres, possible implication of DNA-repair genes. *Orphanet J Rare Dis* **14**, 82 (2019).
13. Brodeur, G.M. The NF1 gene in myelopoiesis and childhood myelodysplastic syndromes. *N Engl J Med* **330**, 637-639 (1994).
14. Chan, R.J., Cooper, T., Kratz, C.P., Weiss, B. & Loh, M.L. Juvenile myelomonocytic leukemia: a report from the 2nd International JMML Symposium. *Leuk Res* **33**, 355-362 (2009).
15. Fane, M., Harris, L., Smith, A.G. & Piper, M. Nuclear factor one transcription factors as epigenetic regulators in cancer. *Int J Cancer* **140**, 2634-2641 (2017).
16. Alanazi, B., *et al.* Integrated nuclear proteomics and transcriptomics identifies S100A4 as a therapeutic target in acute myeloid leukemia. *Leukemia* **34**, 427-440 (2020).

17. Li, H., *et al.* Mutations in linker histone genes HIST1H1 B, C, D, and E; OCT2 (POU2F2); IRF8; and ARID1A underlying the pathogenesis of follicular lymphoma. *Blood* **123**, 1487-1498 (2014).
18. Hoefnagel, J.J., *et al.* Expression of B-cell transcription factors in primary cutaneous B-cell lymphoma. *Mod Pathol* **19**, 1270-1276 (2006).
19. Murati, A., *et al.* PCM1-JAK2 fusion in myeloproliferative disorders and acute erythroid leukemia with t(8;9) translocation. *Leukemia* **19**, 1692-1696 (2005).
20. Reiter, A., *et al.* The t(8;9)(p22;p24) is a recurrent abnormality in chronic and acute leukemia that fuses PCM1 to JAK2. *Cancer Res* **65**, 2662-2667 (2005).
21. Opatz, S., *et al.* The clinical mutanome of core binding factor leukemia. *Leukemia* **34**, 1553-1562 (2020).
22. Peedicayil, A., *et al.* Risk of ovarian cancer and inherited variants in relapse-associated genes. *PLoS One* **5**, e8884 (2010).
23. Zhang, S., Deen, S., Storr, S.J., Yao, A. & Martin, S.G. Expression of Syk and MAP4 proteins in ovarian cancer. *J Cancer Res Clin Oncol* **145**, 909-919 (2019).
24. Murga Penas, E.M., *et al.* A novel fusion of the MALT1 gene and the microtubule-associated protein 4 (MAP4) gene occurs in diffuse large B-cell lymphoma. *Genes Chromosomes Cancer* **45**, 863-873 (2006).
25. De Felice, D. & Alaimo, A. Mechanosensitive Piezo Channels in Cancer: Focus on altered Calcium Signaling in Cancer Cells and in Tumor Progression. *Cancers (Basel)* **12**(2020).
26. Han, Y., *et al.* Mechanosensitive ion channel Piezo1 promotes prostate cancer development through the activation of the Akt/mTOR pathway and acceleration of cell cycle. *Int J Oncol* **55**, 629-644 (2019).
27. Sossey-Alaoui, K., Kitamura, E., Head, K. & Cowell, J.K. Characterization of FAM10A4, a member of the ST13 tumor suppressor gene family that maps to the 13q14.3 region associated with B-Cell leukemia, multiple myeloma, and prostate cancer. *Genomics* **80**, 5-7 (2002).
28. Esgueva, R., *et al.* Prevalence of TMPRSS2-ERG and SLC45A3-ERG gene fusions in a large prostatectomy cohort. *Mod Pathol* **23**, 539-546 (2010).
29. Palanisamy, N., *et al.* Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. *Nat Med* **16**, 793-798 (2010).
30. Urso, K., *et al.* NFATc3 controls tumour growth by regulating proliferation and migration of human astrogloma cells. *Sci Rep* **9**, 9361 (2019).
31. Glud, S.Z., *et al.* A tumor-suppressor function for NFATc3 in T-cell lymphomagenesis by murine leukemia virus. *Blood* **106**, 3546-3552 (2005).
32. Cho, Y., *et al.* Intramembrane proteolysis of an extracellular serine protease, epithin/PRSS14, enables its intracellular nuclear function. *BMC Biol* **18**, 60 (2020).

33. Zanini, S., *et al.* GNA15 expression in small intestinal neuroendocrine neoplasia: functional and signalling pathway analyses. *Cell Signal* **27**, 899-907 (2015).
34. Nakase, K., *et al.* Overexpression of novel short isoforms of Helios in a patient with T-cell acute lymphoblastic leukemia. *Exp Hematol* **30**, 313-317 (2002).
35. Chan, S.M. The Making of a Leukemic Stem Cell: A Novel Role for IKZF2 in AML Stemness and Differentiation. *Cell Stem Cell* **24**, 5-6 (2019).
36. Revert, F., *et al.* Selective targeting of collagen IV in the cancer cell microenvironment reduces tumor burden. *Oncotarget* **9**, 11020-11045 (2018).
37. Montalbano, J., Jin, W., Sheikh, M.S. & Huang, Y. RBEL1 is a novel gene that encodes a nucleocytoplasmic Ras superfamily GTP-binding protein and is overexpressed in breast cancer. *J Biol Chem* **282**, 37640-37649 (2007).
38. Tang, H., *et al.* RBEL1 is required for osteosarcoma cell proliferation via inhibiting retinoblastoma 1. *Mol Med Rep* **13**, 1275-1280 (2016).
39. Hagen, J., *et al.* RABL6A promotes G1-S phase progression and pancreatic neuroendocrine tumor cell proliferation in an Rb1-dependent manner. *Cancer Res* **74**, 6661-6670 (2014).
40. Wang, L. & Shilatifard, A. UTX Mutations in Human Cancer. *Cancer Cell* **35**, 168-176 (2019).
41. Schulz, W.A., Lang, A., Koch, J. & Greife, A. The histone demethylase UTX/KDM6A in cancer: Progress and puzzles. *Int J Cancer* **145**, 614-620 (2019).
42. Van der Meulen, J., *et al.* The H3K27me3 demethylase UTX is a gender-specific tumor suppressor in T-cell acute lymphoblastic leukemia. *Blood* **125**, 13-21 (2015).
43. van Haften, G., *et al.* Somatic mutations of the histone H3K27 demethylase gene UTX in human cancer. *Nat Genet* **41**, 521-523 (2009).
44. An, J.Y., *et al.* UBR2 of the N-end rule pathway is required for chromosome stability via histone ubiquitylation in spermatocytes and somatic cells. *PLoS One* **7**, e37414 (2012).
45. Kume, K., *et al.* Role of N-end rule ubiquitin ligases UBR1 and UBR2 in regulating the leucine-mTOR signaling pathway. *Genes Cells* **15**, 339-349 (2010).
46. Kwon, Y.T., *et al.* Female lethality and apoptosis of spermatocytes in mice lacking the UBR2 ubiquitin ligase of the N-end rule pathway. *Mol Cell Biol* **23**, 8255-8271 (2003).
47. Tasaki, T., Sriram, S.M., Park, K.S. & Kwon, Y.T. The N-end rule pathway. *Annu Rev Biochem* **81**, 261-289 (2012).
48. Villa, E., *et al.* The E3 ligase UBR2 regulates cell death under caspase deficiency via Erk/MAPK pathway. *Cell Death Dis* **11**, 1041 (2020).
49. Zhang, G., Lin, R.K., Kwon, Y.T. & Li, Y.P. Signaling mechanism of tumor cell-induced up-regulation of E3 ubiquitin ligase UBR2. *FASEB J* **27**, 2893-2901 (2013).

50. Cavazzana-Calvo, M., *et al.* Transfusion independence and HMGA2 activation after gene therapy of human beta-thalassaemia. *Nature* **467**, 318-322 (2010).
51. Thompson, A.A., *et al.* Gene Therapy in Patients with Transfusion-Dependent beta-Thalassemia. *N Engl J Med* **378**, 1479-1493 (2018).
52. Schneiderman, J., *et al.* Interim Results from the Phase 3 Hgb-207 (Northstar-2) and Hgb-212 (Northstar-3) Studies of Betibeglogene Autotemcel Gene Therapy (LentiGlobin) for the Treatment of Transfusion-Dependent β -Thalassemia. *Biology of Blood and Marrow Transplantation* **26**, S87-S88 (2020).
53. Frangoul, H., *et al.* Safety and Efficacy of CTX001 in Patients with Transfusion-Dependent β -Thalassemia and Sickle Cell Disease: Early Results from the Climb THAL-111 and Climb SCD-121 Studies of Autologous CRISPR-CAS9-Modified CD34+ Hematopoietic Stem and Progenitor Cells. *Blood* **136**, 3-4 (2020).
54. Frangoul, H., *et al.* CRISPR-Cas9 Gene Editing for Sickle Cell Disease and beta-Thalassemia. *N Engl J Med* **384**, 252-260 (2021).
55. Markt, S., *et al.* Intrabone hematopoietic stem cell gene therapy for adult and pediatric patients affected by transfusion-dependent α -thalassemia. *Nat Med* **25**, 234-241 (2019).