SUPPLEMENTARY APPENDIX

Multilayer intraclonal heterogeneity in chronic myelomonocytic leukemia

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Patient description. The CMML patient was an 85-year old woman with a past history of ischemic cardiopathy who was referred in January 2012. A monocytosis, which had appeared in 2008, had been neglected for 4 years. At the end of 2011, the occurrence of several infectious events and bone pains induced a dramatic decrease of her performance status, associated with a rapid increase in white blood cell count (22.8 x 10^9/L) with 29% monocytes and a drop in hemoglobin level to 104 g/L and platelet count to 62x10^9/L. Bone marrow investigation showed 12% blast cells including promonocytes, with dysgranulopoiesis, and megakaryocytic hyperplasia and dysplasia. Diagnosis was CMML-2 according to the WHO classification. Flow cytometry analysis of peripheral blood monocytes showed an increase in the classical, $CD14^+$,$CD16^-$ monocyte subset over 94%. Cytogenetic analysis of bone marrow cells was normal. Whole exome sequencing (WES) of peripheral blood monocytes identified 12 gene mutations, including a founding mutation in *KDM6A*, 2 heterozygous mutations in *TET2*, and a $KRAS^{G12D}$ mutation. The patient was treated with Azacytidine, 75mg/m^2 /day, 7 days every 28 days. After 6 cycles, she was classified as partial responder with a dramatic improvement of her blood cell count that had become normal, except a persistent monocytosis at 1.1 x 10^9/L (18% of WBC), with a disappearance of bone marrow blast cell excess but no change in genetic alterations analyzed by WES of sorted monocyte DNA. The treatment was discontinued after 6 cycles, due to poor tolerance. The patient received Hydroxyurea until April 2013, when an increase in bone marrow blast cell count to 19% led to re-introduce Azacytidine treatment that induced a partial response. After 19 cycles however, the disease progressed, her general conditions degraded, and she died after six months of palliative care. The healthy donor was a patient whose bone marrow was collected with informed consent during heap surgery.

Generation of iPSCs from CD34-positive cells. Patient and healthy donor $CD34^+$ cells, collected from bone marrow samples with their informed consent as well as the Institutional review board and the Ethics Committee approvals, were cultured in complete StemPro-34 medium (ThermoFisher Scientific, Villebon-sur-Yvette, France) supplemented with 50 ng/ml stem cell factor (SCF, Peprotech, Neuilly-sur-Seine, France), 1U/ml erythropoietin (EPO, Peprotech), 10 ng/ml interleukin-3 (IL-3, Peprotech), 10 ng/ml interleukin-6 (IL-6, Peprotech), 10 ng/ml Fms-related tyrosine kinase 3 ligand (FLT3LG, Peprotech), 1% non-essential amino acids (NEAA, ThermoFisher Scientific) and 1 mM L-glutamine (ThermoFisher Scientific) for 5 days at 37°C at 5% O_2 to ensure active proliferation before being infected with non-integrated Sendai virus encoding the Yamanaka human reprogramming factors Klf4, Oct4, Sox2, and c-Myc (CytoTune™-iPS 2.0 Sendai Reprogramming Kit, ThermoFisher Scientific) at a multiplicity of infection (MOI) of 5 for 12 hours at 37°C with 4 µg/ml Polybrene (Sigma-Aldrich, Saint-Quentin Fallavier, France). The following day (day 1), cells were centrifuged at 200 x g for 10 min at room temperature and suspended in 0.5 ml $CD34^+$ medium. Two days later, these cells were plated on murine embryonic fibroblast (MEF) inactivated by gamma irradiation (R&DSystems, Lille, France). On day 7, cells were transferred in iPSC medium containing DMEM/F12, GlutaMAX supplement (ThermoFisher Scientific) with 20% of KnockOut Serum Replacement (KSR, ThermoFisher Scientific), 1% nonessential amino acids, 1mM L-glutamine, 0.5mg/ml Penicillin-Streptomycin (ThermoFisher Scientific), 10 ng/ml Basic Fibroblast Growth Factor (bFGF, ThermoFisher Scientific), and 0.1 mM β-Mercaptoethanol (Sigma-Aldrich). This medium was replaced every other day for 3-4 weeks and colonies with human pluripotent stem cell morphology were manually picked and

expanded. An additional iPSC (Co6) was kindly provided by Dr Weiss. [30,31]

Characterization of iPSCs. iPSCs were cultured on irradiated MEFs for 20 passages, then seeded in feeder-free conditions and passaged once a week to yield a cell suspension of small colonies (3-10 cells).[32] Flow cytometry analysis of pluripotency markers was performed with Nanog-PE (N31-355), Oct3/4-PerCP-Cy™5.5 (40/oct-3), Sox2-Alexa Fluor® 647 (245610), SSEA-4-PE (MC813-70), Tra-1-60-FITC (TRA-1-60) and TRA-1-81- Alexa Fluor® 647 (TRA-1-81) from BD Biosciences (Le Pont de Claix, France) (**Table S1**). Teratoma formation was tested by adding 10µM Y-27632 (Miltenyi) to iPSC medium one hour before intramuscular injection of ~2 × 10^6 undifferentiated iPS cells in 140 µL iPSC medium with undiluted Geltrex™ (60 µL, ThermoFisher Scientific) to *NOD/SCID/IL2rγ*$^{-/-}$ mice, following Gustave Roussy laboratory animal care regulations.[33] After 8-12 weeks, tumors were surgically removed, fixed in 4% formaldehyde and stained with hematoxylin and eosin for histological analysis. Karyotype was analyzed by standard GTW banding method. DNA was extracted with QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). Comparative genomic hybridization (CGH) was carried out on Agilent 244K arrays (Agilent Technologies, Santa Clara, CA, USA). PCR-amplified targeted exons were sequenced on a 96-capillary 3130xl DNA Analyzer® (Applied Biosystems, Villebon sur Yvette, France), using ApE® software for analysis.

Generation of hematopoietic progenitor cells (HPCs). A two-dimensional "monolayer" system was used to differentiate iPSCs into $CD34^+CD43^+$ hematopoietic progenitor cells (HPCs).[2] iPSCs at 5-10% confluency in StemMACS iPS-Brew XF medium were transferred into complete hematopoietic differentiation medium supplemented with 5 ng/ml BMP4, 50 ng/ml $VEGF_{165}$ (Peprotech) and 1 µM GSK-3β inhibitor (CHIR99021, Sigma Aldrich). After 2 days, this medium was replaced by serum free medium mixed 1:1 with complete StemPro34 medium and supplemented with 1% nonessential amino acids, 1mM L-glutamine, 0.5mg/ml Penicillin-Streptomycin, 0.1mM β-Mercaptoethanol, 1% Insulin-Transferrin-Selenium (ThermoFisher Scientific), 10% bovine serum albumin (BSA, Hyclone, ThermoFisher Scientific) fraction V, 50 µg/ml ascorbic acid (Sigma Aldrich), 5ng/ml BMP4, 50ng/ml $VEGF_{165}$ and 20ng/ml of bFGF. The hematopoietic differentiation medium was supplemented at day 4 with 50ng/ml $VEGF_{165}$ and 5ng/ml bFGF, at day 6 with 50ng/ml $VEGF_{165}$, 50ng/ml bFGF, 50ng/ml SCF, and 5ng/ml Flt3LG, and at day 8 with 50 ng/ml $VEGF_{165}$, 50ng/ml bFGF, 50ng/ml SCF, 5ng/ml Flt3LG, 10ng/ml Interleukin-6 (IL-6, Peprotech) and 50ng/ml thrombopoietin (TPO, Kirin, Japon). $CD34^+$,$CD43^+$ cells were sorted at day 10 to 16, depending on cell expansion.

Clonogenic assays. 500 µl of $CD34^+$,$CD43^+$ cell suspension (1.25×10^3/ml) in serum free medium were mixed with 2 mL MethoCult H4434 classic (Stem cell technologies, Grenoble, France) before plating 1 mL in duplicate 35-mm dishes.[30] Colonies were scored after 14 days and flow analyses of cells collected in PBS were performed on BD LSRFortessa X-20 cell analyzer. Megakaryocyte progenitors were studied by seeding 3 × 10^3 $CD34^+$,$CD43^+$ cells mixed with 2 ml serum-free fibrin clots in duplicate 35-mm dishes, in the presence of TPO (10 ng/mL) and SCF (50 ng/mL). After 10 days, CFU-Mk colonies were scored after staining with an anti-CD41a monoclonal antibody (BD Pharmingen™, clone HIP8) and a goat anti mouse igG (H+L) alkaline phosphatase conjugate polyclonal antibody (Thermofisher Scientific). All images were obtained with AxioVision 4.6 software.

Liquid cultures: $CD34^+CD43^+$ cells were suspended in serum-free medium supplemented with indicated growth factors (all from Peprotech) for 10 days before flow analysis of cell surface markers (**Table S1**). Cytospin onto Polysine® slides (ThermoFisher Scientific) were stained with May-Grünwald-Giemsa solution (Sigma-Aldrich).

Whole exome sequencing. Two hundred ng of genomic DNA was sheared with the Covaris S2 system (LGC Genomics / Kbioscience). DNA fragments were end-repaired, extended with an 'A' base on the 3' end, ligated with paired-end adaptors with the Bravo Platform (Agilent) and amplified (six cycles). Exome-containing adaptor-ligated libraries were hybridized for 24h with biotinylated oligo RNA baits, and enriched with streptavidin-conjugated magnetic beads using SureSelect V5 no UTR (Agilent). The final libraries were indexed, pooled and sequenced on Illumina HiSeq-2000 sequencer (Genomic platform, AMMICa, CNRS 3655 & INSERM US23). Raw reads in FASTQ format from each exome sequencing lane were aligned to the reference human genome hg19 (Genome Reference Consortium GRCh37) using BWA 0.5.9 (Burrows–Wheeler Aligner) backtrack algorithm with default parameters. PCR duplicates were removed with Picard (http://picard.sourceforge.net) version 1.76. Local realignment around indels and base quality score recalibration was performed using GATK 2.0.39 (Genome Analysis ToolKit). SNVs and indels were called with VarScan2 somatic 2.3.2. Reads and bases with a Phred-based quality score ≤20 were ignored. Variants with somatic P value below 10−4 (or 10−3 for samples with mean coverage <100 × or contamination >15% in $CD3^+$ control sample) were reported. In addition to the Fisher's exact test of VarScan, we required (variant allele frequency in the tumour sample–variant allele frequency in the normal sample) ≥15% to distinguish somatic from germline variations. Variants were annotated with Annovar. Mutations were searched in 1000G (April 2012) and Exome Sequencing Project (ESP5400). Conservation of the position was predicted by PhyloP and the effect of the mutation was predicted by SIFT, Polyphen2, LRT and MutationTaster. We excluded variants reported in dbSNP version 129, filtered variants located in intergenic, intronic, untranslated regions and non-coding RNA regions, and removed synonymous SNVs and variants with mapping ambiguities.

Genome-wide DNA methylation by Enhanced Reduced Representation Bisulfite Sequencing (ERRBS). DNA was collected from iPSC-derived $CD34^+CD43^+$ cells. High-molecular weight DNA (25 ng) was used to perform the ERRBS assay as described[33] and sequenced on a HiSeq3000 Illumina sequencer.[33] Briefly, 50 bp reads were aligned against a bisulfite-converted human genome (hg19) using Bowtie and Bismark.[34] Downstream analysis was performed using R version 3.0.3, Bioconductor 2.13 and the MethylSig 0.1.3 package.[35] Only genomic regions with coverage between 10 and 500× were used for the downstream analysis. Differentially methylated regions (DMR) were identified by summarizing the methylation status of genomic regions into 25-bp tiles, then identifying regions with absolute methylation difference ≥40% and FDR <5%. DMRs were annotated using chipenrich R package, with function *'nearest_gene'*.[36] This package was also used for gene ontology and pathway analysis from the previously annotated genes. For Correspondence Analysis (COA) and Hierarchical clustering (HC), tiles with the highest Standard Deviation (SD>0.03) were selected. Matrix for HC was calculated with Euclidean distance and was clustered using the Ward's agglomeration method. Exact Binomial Test was performed to compare enrichment of enhancer regions within DMRs compared to Background, which included the whole set of tiles. Heatmap of DMRs was plotted using heatmap.2 function from gplots package (version 3.0.1) with euclidean measure to obtain distance matrix and the complete agglomeration method for clustering. Coordinates for enhancers were defined as described.[33]

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Author contribution

AB generated and analyzed iPSCs in culture, QY, MTM, and MEF performed and analyzed methylation experiments, TD analyzed RNA-seq, PR supervised flow cytometry experiments, VS did cytological analyses, CBN did cytogenetic analysis, AH, LL performed additional experiments, JR and ND did molecular experiments and co-supervised other experiments, WV advised, MEF and LL analyzed the results and corrected the manuscript, ES supervised the study and wrote the MS.

COI disclosure

No author has any conflict to disclose

SUPPLEMENTAL TABLE

Table S1: Antibodies used for flow cytometry analyses of hematopoietic cells and iPSCs.

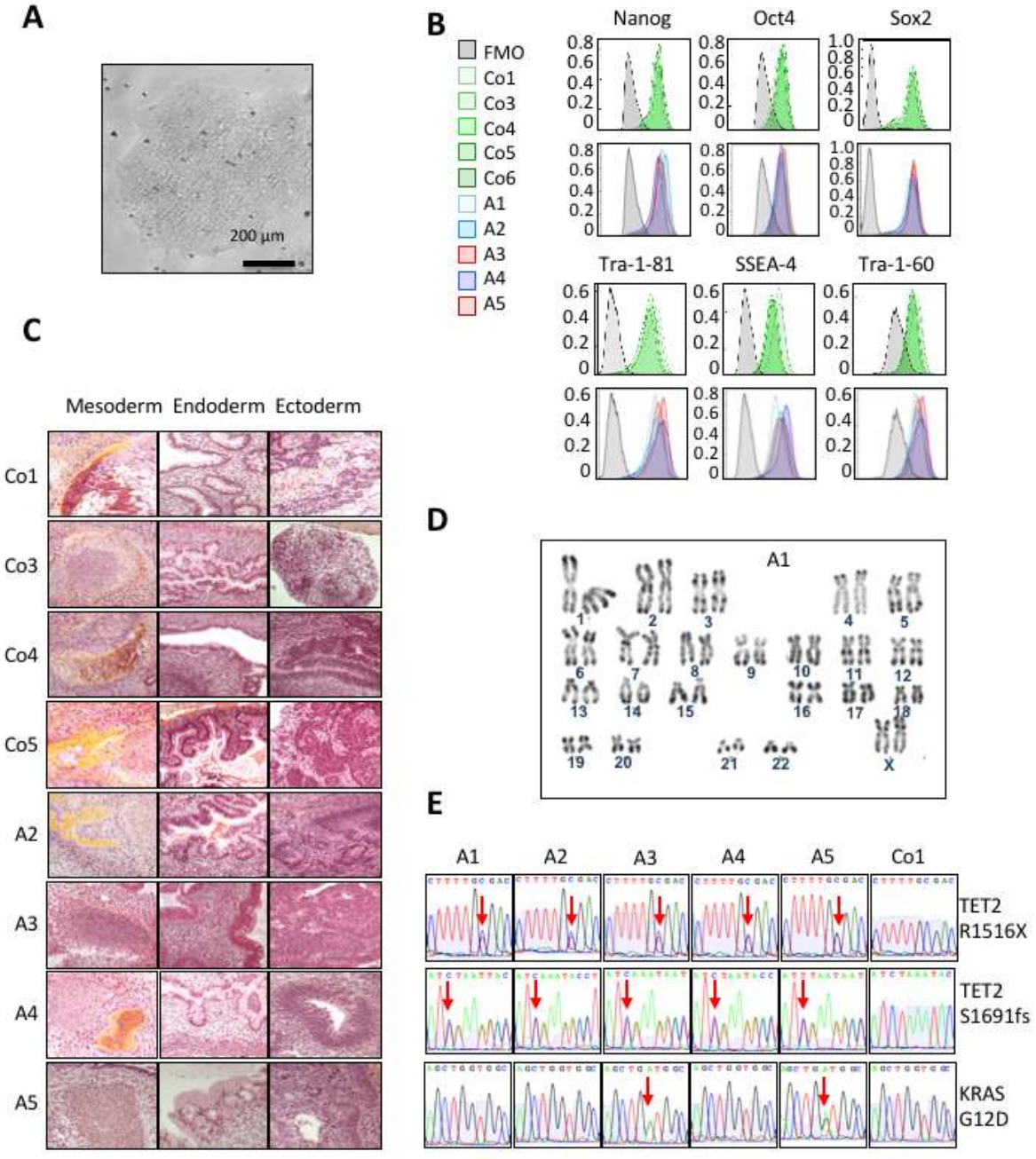
Target	Conjugate	Clone	Provider
CD11b	CD11b-PE	ICRF44	Sony
CD13	CD13-APC-Cy7	WM15	Sony
CD14	CD14-PE	M5E2	Sony
CD14	CD14-APC	M5E2	Sony
CD14	CD14-BUV737	M5E2	BD horizon™
CD15	CD15-BV605	W6D3	Sony
CD16	CD16-BV650	3G8	Sony
CD33	CD33-BV711	WM53	Sony
CD34	CD34-Pe-Cy7	581	Sony
CD36	CD36-APC	5-271	Sony
CD41	CD41-BB515	HIP8	BD horizon™
CD42	CD42-FITC	HIP1	BD horizon™
CD43	CD43-APC	1G10	BD horizon™
CD71	CD71-BV786	M-A712	BD horizon™
CD86	CD86-APC-R700	2331	BD horizon™
CD123	CD123-BV510	6H6	BioLegend
CD163	CD163-PE	GHI/61	BioLegend
CD235a	CD235a-PE	HI264	Sony
Nanog	Nanog-PE,	N31-355	BD Biosciences
Oct3	Oct3/4-PerCP-Cy™5.5	40/oct-3	BD Biosciences
Sox2	Sox2-Alexa Fluor® 647	245610	BD Biosciences
SSEA	SSEA-4-PE	MC813-70	BD Biosciences
Tra-1-60	Tra-1-60-FITC	TRA-1-60	BD Biosciences
Tra-1-81	Tra-1-81-Alexa Fluor®	TRA-1-81	BD Biosciences
HLA-DR	HLA-DR-BUV395	G46-6	BD horizon™
	DAPI solution		BDbiosciences

Table S2: Correlation between differentially expressed genes and differentially methylated regions in topologically-associated domains identified using publicly available coordinates in CMML compared to control iPSCs. (provided as an independent supplemental Excel sheet)

SUPPLEMENTAL FIGURES

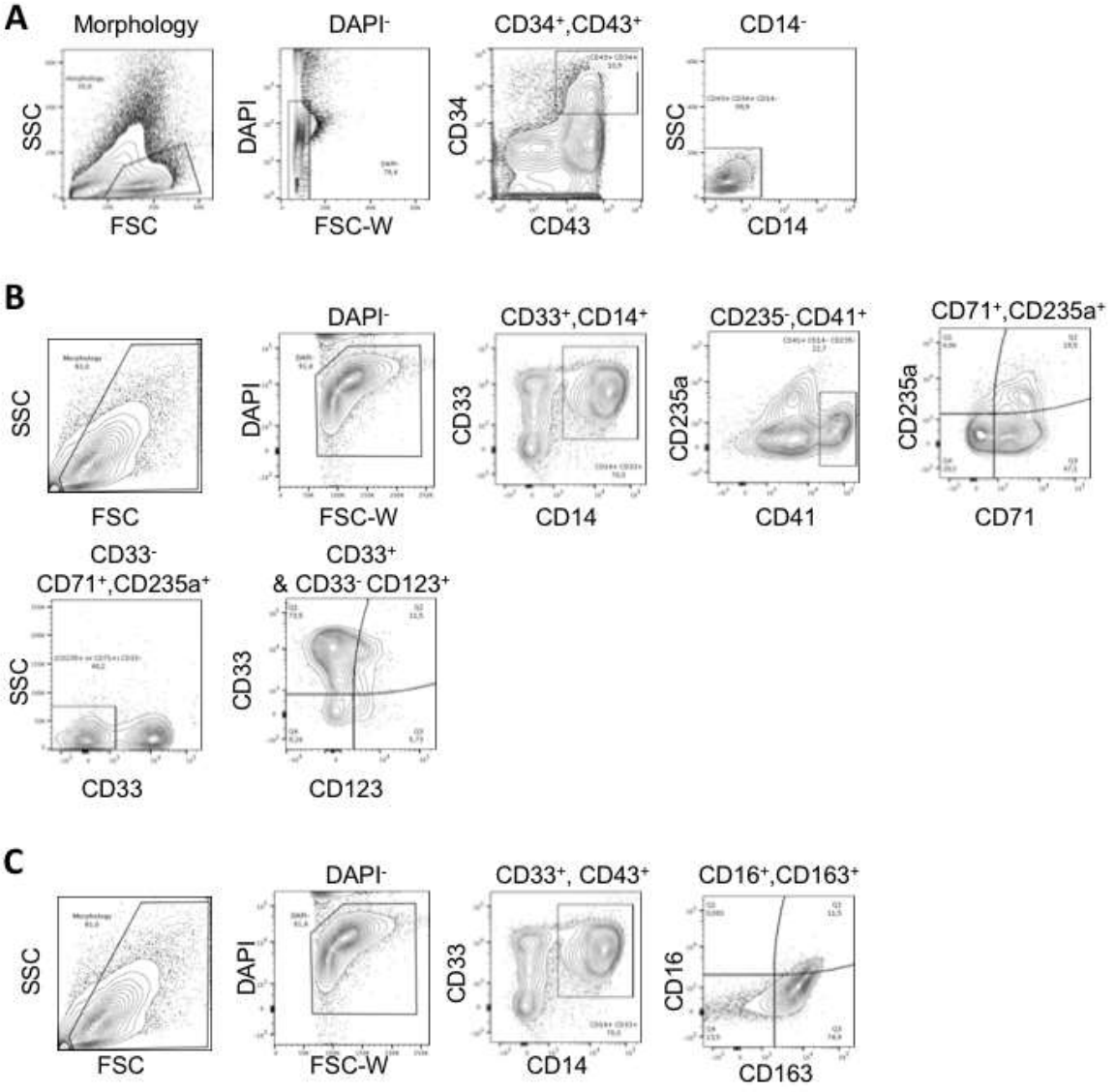
Supplemental Figure 1. Characterization of iPSCs. A. Light microscopy visualization of an iPSC (A4) is shown. Scale bar 200 μm; **B.** Flow cytometry analysis of intracellular (Nanog, Oct4, Sox2) and extracellular (Tra-1-81, SSEA-4, Tra-1-60) pluripotency markers by flow cytometry in each selected clone; **C**. H&E staining of teratomas developed in NSG mice injected subcutaneously with indicated clones, showing mesoderm, including bone and cartilage (Co1, Co4, Co5, A2, A4) or cartilage alone (Co3, A3, A5), endoderm, including intestinal-like mucin-secreting cells in every clone, and ectoderm, showing neural tubes in every clone but Co3 (glial nodule); **D.** Cytogenetic analysis of A1 clone, provided as an example, showing the lack of chromosomal aberration; **E.** Sanger sequencing of *TET2* and *KRAS* genes, showing $TET2^{R1516X}$ and $TET2^{S1691fs}$ mutations in every clone A and a $KRAS^{G12D}$ mutation in only two of them (A3 and A5).

Beke A, Laplane L *et al.*, Supplemental Figure 1.



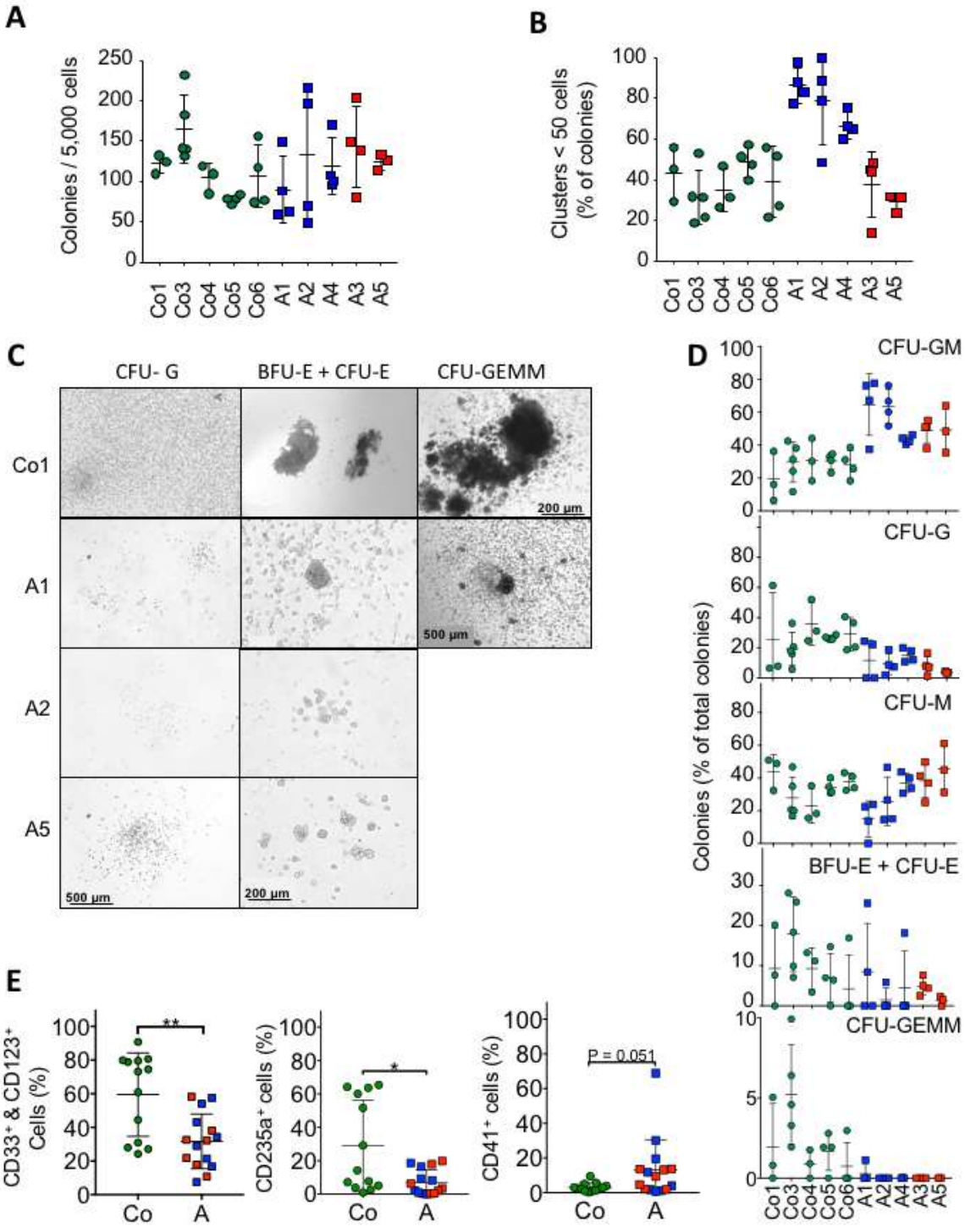
Supplemental Figure 2: Flow cytometry analysis and sorting of hematopoietic cells generated by iPSCs differentiation. **A**. Gating strategy used to identify hematopoietic stem and progenitor cells generated by differentiation of iPSCs; after labeling with antibodies targeting CD14, CD34, and CD43 and with DAPI, hematopoietic cells were roughly selected on morphological parameters before excluding DAPI- doublets using FSC-width and selecting $CD34^+$ $CD43^+$ cells, of which only CD14-negative cells were sorted in a sterile tube with 0.5 ml of medium. **B**. Gaiting strategy used to identify differentiated hematopoietic cells after labeling with 12 antibodies targeting CD11b, CD13, CD14, CD16, CD33, CD34, CD41, CD42, CD71, CD123, CD163 and CD235a and with DAPI. Hematopoietic cells were selected on morphological parameters before excluding DAPI-labeled cells. Cells of the monocytic lineage, which expressed CD33 and CD14, were counted and excluded from subsequent analyses. Cells of the megakaryocytic lineage expressing CD41 but not CD235a were counted and excluded from subsequent analysis. Cells of the erythroid lineage were identified as those expressing CD235a or CD71 but not CD33, counted, and excluded from subsequent analysis. The remaining cells expressing CD33 were considered as granulocytes whereas those expressing CD123 were counted as myeloid progenitors. **C**. Gaiting strategy to identify $CD16^+$, $CD163^+$ macrophages in the $CD14^+$ cell population. Hematopoietic cells were labeled with antibodies targeting CD14, CD16, CD33, and CD163 and stained with DAPI. Hematopoietic cells were selected on morphological parameters, DAPI-labeled cells were excluded, and cells of the monocyte lineage expressing both CD33 and CD14 were selected. These cells were separated in four subsets based on CD16 and CD163 expression, namely $CD16^-$ $CD163^-$, $CD16^+$ $CD163^-$, $CD16^-$ $CD163^+$ and $CD16^+$ $CD163^+$ cells.

Beke A, Laplane L *et al.*, Supplemental Figure 2



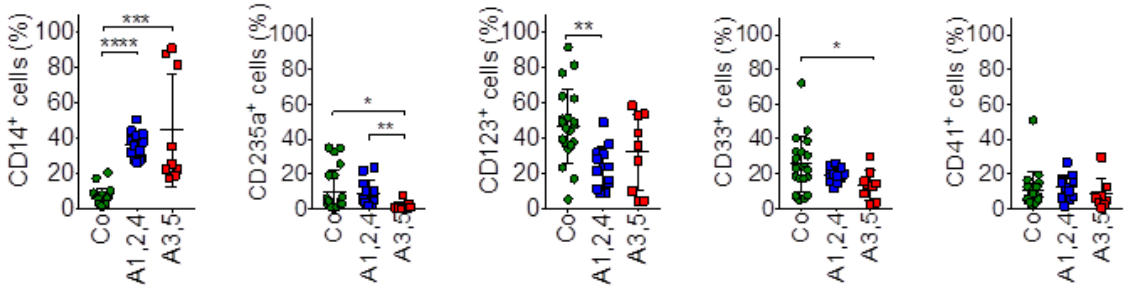
Supplemental figure 3. Hematopoietic cells generated from CMML-derived iPSCs are biased toward the monocyte lineage. Details of results shown on Figure 1 are depicted**. A.** Total number of colonies generated by plating 5,000 iPSC-derived $CD34^{+}CD43^{+}$ hematopoietic cells in methylcellulose for 14 days; Kruskal-Wallis test; **B**. Fraction of clusters, as defined by colonies < 50 cells, among colonies; Kruskal-Wallis test; **C**. Representative CFU-G (colony-forming unit-granulocyte), erythroid colonies (CFU-E: colony-forming unit-erythroid and BFU-E: burst-forming unit-erythroid) and CFU-GEMM (colony-forming unit-granulocyte-erythroid-monocyte-megakaryocyte) generated by indicated iPSCs and visualized by light microscopy. Scale bars indicate magnification; Kruskal-Wallis test; **D**. Fraction of indicated colonies among colonies shown in A. **E.** Fractions of $CD33^{+}$ or $CD123^{+}CD14^{-}CD41^{-}CD235a^{-}$ cells (upper panel), $CD235a^{+}CD41^{-}CD14^{-}$ cells (middle panel) and $CD41^{+}CD14^{-}$ cells (lower panel) in cells collected from colonies grown in methylcellulose from control- or CMML- iPSC-derived hematopoietic cells; Mann-Whitney test. Bars indicate mean +/- SD. * $P<0.05$; **, $P<0.01$.

Beke A, Laplane L *et al.*, Supplemental Figure 3



Supplemental figure 4. Functional heterogeneity of patient iPSC-derived hematopoietic cells. The panels correspond to Figure 3 E-J panel after removal of all experiments in which cell viability was below 90%; Kruskal-Wallis test. * P<0.05: **, P<0.01; *** P<0.001; **** P<0.0001.

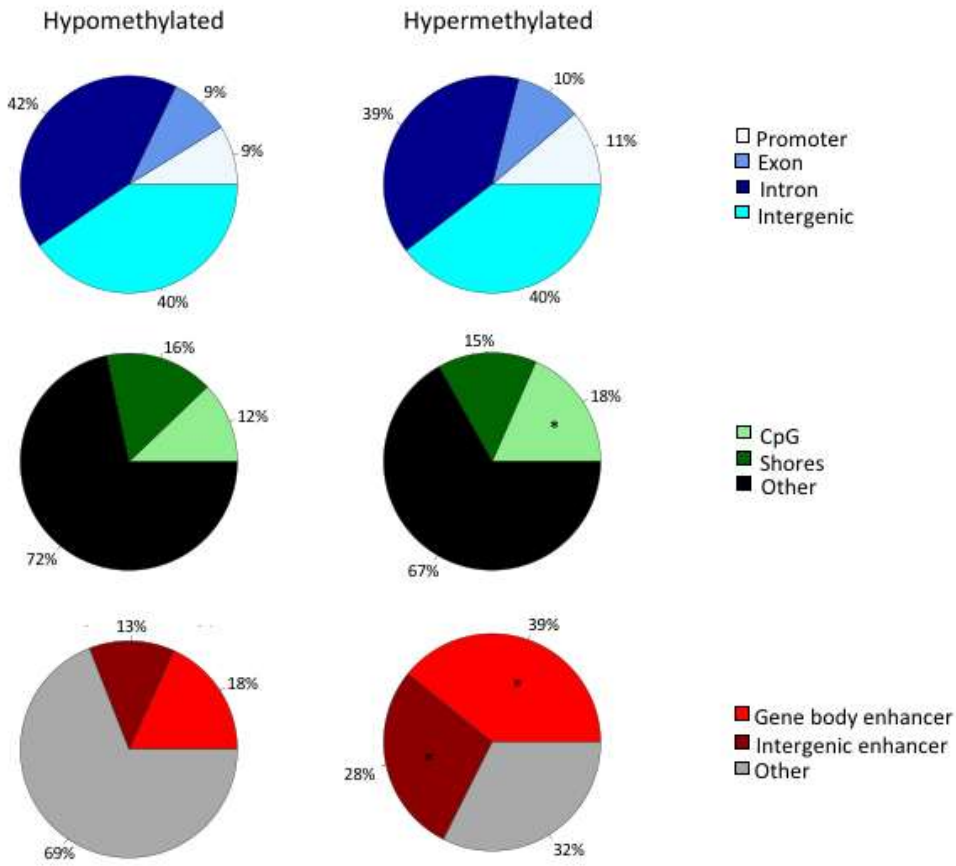
Beke A, Laplane L *et al.*, supplemental Figure 4.



Supplemental figure 5. Methylation profile in CD34^{+} cells derived from CMML versus control iPSCs.
A. Genomic distribution of DMRs separated into hyper and hypomethylated regions in CMML-iPSCs. Star, significance by binomial test (P<0.001); **B.** Transcription factor motifs enriched in DMRs between control- and CMML-iPSCs.

Beke A, Laplane L *et al.*, Supplemental Figure 5.

A



B

Total Target Sequences = 6511, Total Background Sequences = 1116455

Rank	Motif	Name	P-value	log P-pvalue	q-value (Benjamini)	# Target Sequences with Motif	% of Targets Sequences with Motif	# Background Sequences with Motif	% of Background Sequences with Motif
1		ERG(ETS)/VCaP-ERG-ChIP-Seq(GSE14097)/Homer	1e-386	-8.908e+02	0.0000	2615.0	40.16%	199175.6	17.84%
2		Etv2(ETS)/ES-ER71-ChIP-Seq(GSE59402)/Homer(0.967)	1e-288	-6.636e+02	0.0000	1652.0	25.37%	108538.0	9.72%
3		ETS1(ETS)/Jurkat-ETS1-ChIP-Seq(GSE17954)/Homer	1e-268	-6.186e+02	0.0000	1811.0	27.81%	131337.0	11.76%
4		ETV1(ETS)/GIST48-ETV1-ChIP-Seq(GSE22441)/Homer	1e-253	-5.831e+02	0.0000	2426.0	37.25%	213734.9	19.14%
5		EWS:ERG-fusion(ETS)/CADO_ES1-EWS:ERG-ChIP-Seq(SRA014231)/Homer	1e-237	-5.475e+02	0.0000	1049.0	16.11%	56145.5	5.03%