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Novel *KAT6B::NUTM2B* fusion oncogene in congenital acute myeloid leukemia and implications for menin inhibitor therapy

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Author contributions

LW, Y-CL and JMK designed the study. LW and Y-CL supervised the conduction of the project. LB, JER, RWW, MK, SN, SB, Y-CL, LW, LVF and SEK contributed to patient care. Y-CL provided morphology and flow cytometry analyses of patient's samples. VBP analyzed patient WGS and WTS data. JM conducted transcriptomic profiling of patients' samples. RKV, WQ, XM and JL conducted in vitro studies. JMB, MTIII and HC provided material and expertise for conducting in vitro studies. RKV generated tables and figures for the manuscript. RKV and LW wrote the manuscript. All authors reviewed and edited the manuscript.

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Three main figures are present in the manuscript;
Supplementary file: One PDF file consists of two supplementary figures and one supplementary table.

Congenital acute myeloid leukemia (AML) is rare and may initially present as myeloid sarcoma. The most common non-Down syndrome related congenital leukemia is AML, with over half involving *KMT2A* or *KAT6A* fusions[1,2]. *KMT2A*-rearranged infant AML has a poor prognosis, while some cases with *KAT6A* fusions may spontaneously remit[2]. Molecular pathogenesis studies have revealed a functional connection between *KMT2A* and *KAT6A* in transcriptional activation. Both KMT2A and KAT6A fusion proteins drive aberrant transcription and self-renewal in hematopoietic progenitors, notably activating *HOXA* genes[3,4]. Inhibitors targeting the KMT2A/KAT6A transcriptional complex, especially menin inhibitors, have shown therapeutic promise[5,6]. Here, we report the identification of a novel *KAT6B::NUTM2B* fusion, involving the *KAT6A* paralog *KAT6B*, in congenital AML and demonstrate its oncogenic activity and sensitivity to menin inhibition through in vitro study in mouse hematopoietic stem and progenitor cells (mHSPCs). Informed consent for clinical genomics testing was obtained from the patient's legal guardians, and this study was approved by the Institutional Review Board (IRB) at St. Jude Children's Research Hospital (SJCRH). The findings expand the knowledge of *KAT6A/B*-rearranged AML and suggest menin inhibitors as a potential therapy.

The patient presented with blueberry muffin rash at birth. A biopsy of the rash revealed myeloid sarcoma. A bone marrow sample collected at day nine after birth showed 37% blasts, positive for MPO and NSE (Figure 1A), and flow cytometry indicated AML with monocytic differentiation (CD11c, CD64, CD33, HLA-DR, CD123, MPO positive; CD14 loss in most blasts; negative for CD34, CD117, CD133, NG2, CD19, CD3) (Supplementary Figure S1A). No clonal abnormalities or *KMT2A* rearrangement were detected by karyotype or FISH. Bone marrow aspirate (BMA) and skin lesion biopsy samples were collected for molecular diagnosis in CLIA-certified laboratory at SJCRH. The fresh BMA sample was subjected to DNA and RNA extraction followed by Clinical Genomics Testing as previously described[7], including whole genome sequencing (WGS) and whole transcriptome sequencing (WTS). The FFPE tissue of skin lesion biopsy was subjected to

RNA extraction and WTS only. Integrated WGS and WTS analyses identified a cryptic deletion at chromosome region 10q22 resulting in an in-frame *KAT6B::NUTM2B* fusion, preserving the exons encoding the histone acetyltransferase domain of *KAT6B* and most of the coding sequence of *NUTM2B* (Figure 1B). This fusion was the only tumor-acquired likely pathogenic alteration identified and was also detected in the skin rash by WTS. Transcriptomic profiling clustered the case with *KAT6A*- and *KMT2A*-rearranged AML (Figure 1C) and high expression of *HOXA9* and *HOXA10* was observed (Figure 1D). Initial watch-and-wait management was chosen due to possible spontaneous remission[1]. At 4 months of age, disease progressed (44% blasts in bone marrow, hemophagocytosis), prompting standard pediatric induction chemotherapy (Supplementary Figure S1B) and subsequent haploidentical stem cell transplant. Full donor engraftment and MRD-negative marrow by flow cytometry was achieved and sustained for several months post-transplant. Relapse occurred at one year (77.6% blasts, testicular myeloid sarcoma), unfortunately, the patient died at 16 months despite further chemotherapy.

To our knowledge, this patient represents the first reported case in an infant and the fifth case of a myeloid malignancy harboring a *KAT6B* gene fusion, as well as the first reported instance of a *KAT6B::NUTM2B* fusion. The four previously reported cases all carried a *KAT6B::CREBBP* fusion, which is considered a variant of *KAT6A::CREBBP* (Supplementary Table S1). *KAT6A::CREBBP* is a rare but recurrent AML-defining fusion[8], with other *KAT6A* fusion partners (*NCOA2, NCOA3, EP300, LEUTX, ASXL2*) also reported in myeloid malignancies (Supplementary Table S1). Review of infant AML with *KAT6A* fusions shows that over 80% of patients presented with skin lesions (myeloid sarcoma). Bone marrow involvement typically showed morphological features consistent with AML FAB subtype M4 or M5, with erythrophagocytosis observed in up to 50% of cases. Hepatosplenomegaly was frequently present, and up to 30% of patients showed disseminated intravascular coagulation. Spontaneous remission occurred in up to 45% of congenital AML patients with *KAT6A*-rearrangement. Overall, the current case with a novel *KAT6B::NUTM2B* fusion shares clinical features similar to those

observed in infant AML with *KAT6A* fusions; however, despite remaining clinically stable with improvement of skin lesions for approximately 4 months without treatment, the patient ultimately had a poor clinical outcome.

To gain deeper insights into the novel *KAT6B::NUTM2B* fusion, the full-length coding sequence of *KAT6B::NUTM2B* fusion as well as controls (wild-type *KAT6B* and *NUTM2B*) were cloned into MSCV-IRES-GFP (MPG) lentiviral expression vector, respectively, and transduced into C57BL/6J murine bone marrow hematopoietic stem and progenitor cells (mHSPC) to assess the transforming properties of *KAT6B::NUTM2B.* Initially, *Hoxa9* and *Hoxa10* mRNA were assessed in mHSPCs expressing either wild-type *KAT6B* (*KAT6B*-mHSPC) or *KAT6B::NUTM2B (KN*-mHSPC). Consistent with elevated *HOXA9/10* expression observed in the patient's leukemia sample, there was a significant upregulation of *Hoxa9* and *Hoxa10* in *KN*-mHSPCs (Supplementary figure S2B). The mHSPCs transduced with *KAT6B::NUTM2B* or controls were plated in semi-solid methylcellulose-based media for colony forming unit (CFU) assay. Colonies were counted, harvested, and serially replated every 7 days (Figure 2A, I). The *KN*-mHSPCs exhibited a significant and sustained increase in colony formation, with successful serial replating for 4 weeks or longer, in contrast to wild-type *KAT6B* or *NUTM2B,* or empty vector controls (Figure 2B). Considering the *HOXA9/10* activation in the patient's leukemia, *KN*-mHSPCs were treated with SNDX-5613, a clinical-grade menin inhibitor, at three different concentrations over a three-week period (Figure 2A, II and III). We evaluated the sensitivity of *KAT6B::NUTM2B* fusion to SNDX-5613 in comparison with two common fusions in pediatric AML: *RUNX1::RUNX1T1* (9a isoform[9]) serving as a negative control as it is not considered a primary target of menin inhibitors, and *NUP98::KDM5A*, which is associated with *HOXA* activation and sensitivity to menin inhibitors[10], serving as a positive control. An empty vector control was also included. By the end of week three, colony formation of *KN*-mHSPCs was reduced by approximately 90-95% with SNDX-5613 treatment at all three concentrations, *NUP98::KDM5A*-transduced cells also exhibited a dose-dependent reduction in colony formation with SNDX-5613, albeit less

prominently than *KN*-mHSPCs. In contrast, no significant change was seen in controls (empty vector or *RUNX1::RUNX1T1*-transduced cells) (Figure 2C). Besides the reduction of clonogenic growth, SNDX-5613 treatment resulted in a significant increase in Gr1 and CD11b positivity and a concomitant decrease in CD117 (cKIT) expression in both *KAT6B::NUTM2B* and *NUP98::KDM5A* transduced mHSPCs, indicating myeloid maturation and loss of stemness (Figure 2D). Additionally, menin inhibition resulted in significantly reduced *Hoxa9/10* mRNA expression (Figure 2E) and morphological changes in *KN*-mHSPCs (Figure 2F).

Both *KAT6A* and *KAT6B* encode histone acetyltransferases (HAT) that are core components of the MOZ/MORF complex[11] and closely interact with the KMT2A (a.k.a. MLL) complex, facilitating histone acetylation and cooperatively promoting transcription of genes regulating hematopoiesis[3]. While wild-type *KAT6A* and *KAT6A* fusions have been functionally characterized, the role of *KAT6B* in hematopoiesis has only recently been recognized[12]. Fusions involving *KAT6A* or *KAT6B* retain 5' exons encoding the MYST (histone acetyltransferase) domain (Figure 3), thereby preserving N-terminal functional domains of KAT6A/B in the resulting chimeric proteins. Notably, nearly all previously reported fusion partners of *KAT6A/B* are transcriptional co-activators (such as *CREBBP*, *EP300*, *NCOA2*, *NCOA3*) or are predicted to possess a transcriptional activation domain (e.g. *LEUTX*), with these activation domains consistently retained as C-terminal regions in the fusion proteins. Consequently, *KAT6A/B* fusions typically contain one or more HAT domains capable of modifying chromatin and activating genes such as the *HOXA* cluster. While *NUTM2B* has been reported in *YWHAE::NUTM2B* fusion in sarcomas, the function of wild-type *NUTM2B* is unclear. Interestingly, a recent study reported that YWHAE::NUTM2B can interact with EP300 and CREBBP[13]. Although the specific functional domain mediating the interaction with EP300/CREBBP was not elucidated in the study of YWHAE::NUTM2B, it raises the possibility that KAT6B::NUTM2B may similarly recruit these co-activators to promote the transcription of *HOXA* genes, akin to *KAT6A/B::NCOA2* fusions.

Previous studies have shown that the KAT6A::NCOA2 fusion protein targets chromatin in a wild-type KMT2A-dependent manner[3]. Menin plays a central role by tethering the KMT2A complex to DNA[6] and recruiting KAT6A/B-fusion proteins[3]. Menin inhibitors have demonstrated therapeutic efficacy in *KMT2A-r* AML[14], and emerging evidence from other *HOXA*-activating AMLs, including *KAT6A*-r[3] and *NUP98*-r AML[10], suggests a similar vulnerability. Consistent with this model, treating *KN*-mHSPCs with menin inhibitor SNDX-5613 impaired colony formation, promoted myeloid differentiation, and reduced *Hoxa9/10* expression, supporting menin dependency in *KAT6B::NUTM2B* leukemogenesis. Our findings align with a previous study on *KAT6A::NCOA2*[11] and further indicate that menin inhibition may hold therapeutic potential against *KAT6A/B*-r AML.

In this study, we report a novel *KAT6B::NUTM2B* fusion in a congenital AML patient whose clinical and transcriptomic features resembled those of *KAT6A::CREBBP*-positive infant AML, indicating a shared mechanism. *KAT6B::NUTM2B* fusion drove oncogenic transformation in vitro, and *KN*-mHSPCs were vulnerable to menin inhibitor, supporting therapeutic potential of menin inhibition for *KAT6B*-r AML. Further studies utilizing primary leukemia samples from AML patients harboring *KAT6A/B*-fusions are required to validate these findings. Given the increasing recognition of resistance to menin inhibitors[15], alternative therapeutic strategies, such as KAT6 inhibitors or combination therapies, should be investigated. Overall, our findings provide critical new insights into the biology of *KAT6B* fusions and nominate a therapeutic strategy for this rare leukemia.

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Figure Legends

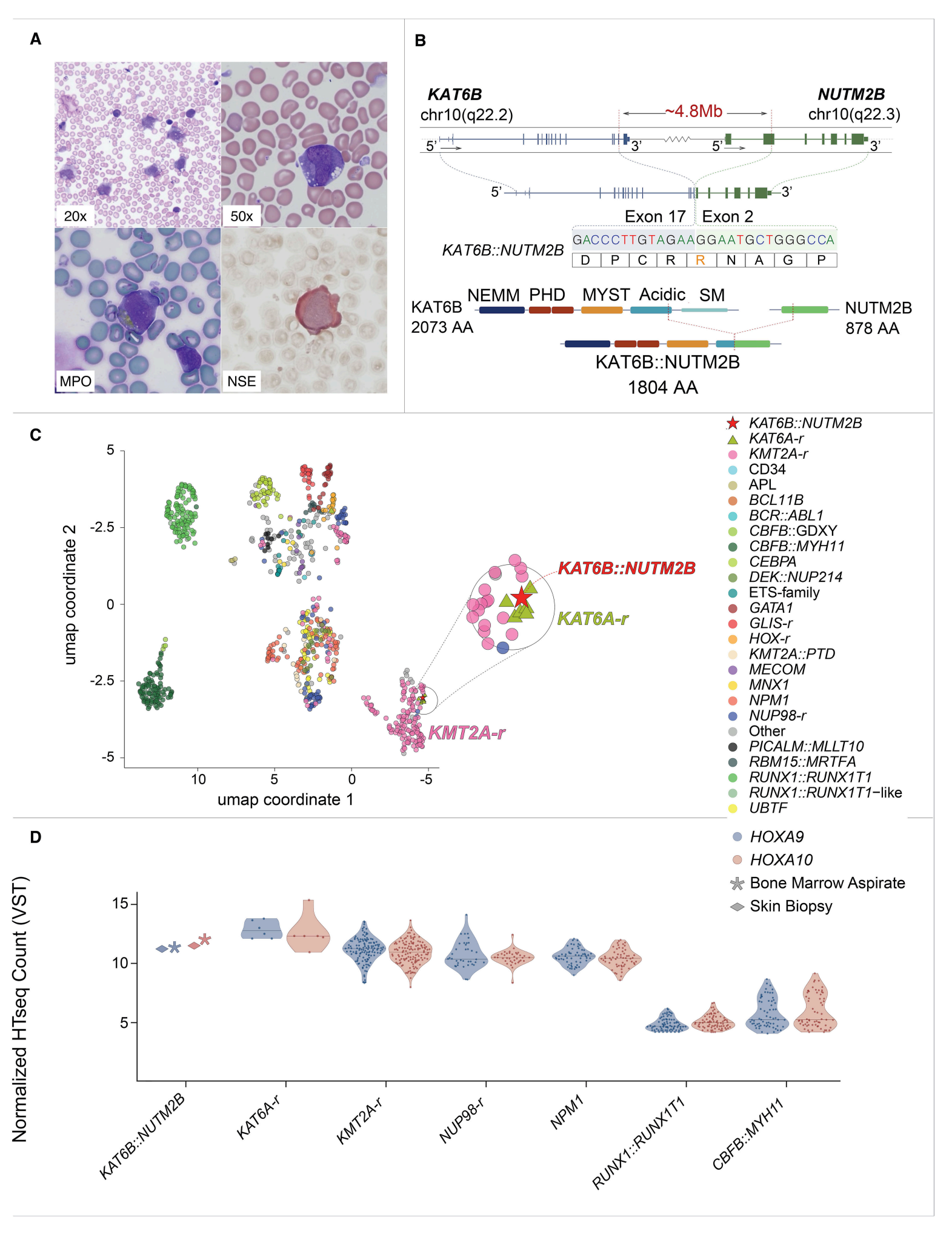
Figure 1. Diagnostic workup of the patient's bone marrow sample. A) Morphology and Immunohistochemical (IHC) staining of diagnostic bone marrow. **Upper:** Wright-Giemsa staining captured at 20x and 50x magnification highlights blasts; **Lower:** IHC staining for MPO and NSE shows reactivity in blasts. **B) Identification of the novel *KAT6B::NUTM2B* fusion in the diagnostic bone marrow sample**. **Upper:** Schema of *KAT6B* (NM_012330) and *NUTM2B* (NM_001278495) gene structures as well as the cryptic deletion of approximately 4.8 Mb in relation to the formation of *KAT6B::NUTM2B* fusion, followed by partial sequence of the *KAT6B::NUTM2B* fusion transcript along with the predicted amino acid sequence. The transcript is an in-frame fusion of *KAT6B* exon 17 to *NUTM2B* exon 2 (mid-exon). **Lower:** Schematic diagrams of KAT6B, NUTM2B and the predicted KAT6B::NUTM2B chimeric proteins with functional domains. NEMM, N-terminal extension of MYST; PHD, plant homeodomain; MYST, histone acetyltransferase domain (HAT); Acidic domain, transcriptional activation and interaction with co-activators; SM, Serine-Methionine-rich region. **C) Global Gene Expression Profiling.** Global gene expression profiling was conducted using UMAP (Uniform Manifold Approximation and Projection) analysis as previously described (doi:10.1038/s41588-023-01640-3). The *KAT6B::NUTM2B*-positive case clustered with the *KAT6A*-r and *KMT2A*-r subtypes by UMAP. The UMAP plot was generated in the context of previously published pediatric AML cohort (n=887, doi:10.1038/s41588-023-01640-3) and cord blood CD34+ cells (n=5). **D) Normalized expression of *HOXA9* and *HOXA10* genes**. Expression levels are shown for the *KAT6B::NUTM2B*-positive patient along with reference cases from selected AML subtypes, including molecular categories known to be associated with *HOXA* activation (*KAT6A-r, KMT2A-r, NUP98-r* and *NPM1-mut*) and that do not have *HOXA* activation (*RUNX1::RUNX1T1* and *CBFB::MYH11*). The reference cases (n=374) were available from St. Jude Cloud (https://www.stjude.cloud) and included in a previously published pediatric AML study cohort

(doi:10.1038/s41588-023-01640-3). Expression values are shown as variance-stabilized counts (VST) derived from HTSeq counts as previously described[7].

Figure 2. In vitro studies with *KAT6B::NUTM2B*-transduced murine bone marrow hematopoietic stem and progenitor cells (mHSPC). A) Schematic depiction of workflow. The GFP+-transduced cells were sorted and plated in methylcellulose for one week (W1). After this initial incubation, cells were divided as follows: (1) to continue colony-forming unit (CFU) assays without (I) and with (II) SNDX-5613 treatment, and (2) to assess the effects of SNDX-5613 treatment in liquid culture (III). **B) Colony forming unit (CFU) assay.** Transduced mHSPCs were plated in triplicate in methylcellulose (2×10^4 cells/35 mm dish). Colonies were counted and serially replated every 7 days. Results from one representative CFU assay are presented, with similar findings observed across multiple independent repeats. EV, empty vector. **C) Impact of SNDX-5613 treatment on colony formation in CFU assay.** Results are shown from a representative experiment (one of four independent replicates) conducted as outlined in Figure 2A-II. Transduced mHSPCs were plated in methylcellulose and treated with SNDX-5613 at 0.3µM, 0.5µM, 1.0µM, respectively, or with 0.1% DMSO (control). Treatment with the indicated concentrations of SNDX-5613 started after the initial one-week incubation in semi-solid culture. The process continued for 3 weeks, with cells replated and treated in fresh methylcellulose every 7 days. Colonies were counted prior to each replating. The x-axis shows time points after 1, 2, and 3 weeks of treatment (T1, T2, T3). The y-axis shows the relative change in colony-forming unit (CFU) counts compared to the DMSO control (% of DMSO control). Error bars represent standard deviation. Statistical significance was assessed using two-sided Welch's t-test. * $p < 0.05$; ** $p < 0.01$; ***$p < 0.001$. **D) Flow cytometry analysis of myeloid differentiation markers.** The mHSPCs transduced with *KAT6B::NUTM2B* and *NUP98::KDM5A*, respectively, were treated with SNDX-5613 at three concentrations or DMSO (control) in liquid culture (RPMI with cytokines) as outlined in figure 2A-III. Results from a representative experiment are depicted. Bar plots display the $\log_2$ fold change in mean fluorescence intensity (MFI) for CD11b, Gr-1 and CD117,

compared to their expression in transduced mHSPCs treated with DMSO control (SNDX-5613 vs. DMSO). Statistical significance was assessed using one-sided Welch's t-test based on the expected direction of change for each marker, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. **E) SNDX-5613 treatment reduced *Hoxa9* and *Hoxa10* expression at the transcriptional level.** The mRNA expression of *Hoxa9* and *Hoxa10* in *KAT6B::NUTM2B*-transduced mHSPCs were significantly downregulated by SNDX-5613 treatment compared with DMSO treatment (control). Cells in liquid culture were harvested after one and two weeks of treatment (T1 and T2, see Figure 2A-III), respectively; results are shown for T2. Bars represent $\log_2$ fold change (SNDX-5613 treated vs. DMSO) for *Hoxa9* and *Hoxa10*. Statistical significance was assessed using one-sided Welch's t-test (expected decrease). **** $p < 0.0001$. **F) Wright-Giemsa stained cytospins of *KAT6B::NUTM2B*-transduced cells** obtained from colony forming unit (CFU) assay harvested after one week of SNDX-5613 treatment (T1) as illustrated in Figure 2A-II.

Figure 3. Schematic representation of KAT6A or KAT6B fusion proteins. Upper panel: KAT6A/B with known fusion junctions associated with different fusion partners. In all chimeric proteins, the N-terminal region of KAT6A/B is retained, including the MYST domain which mediates histone acetyltransferase (HAT) activity. **Lower panel**: C-terminal fusion partners to KAT6A and/or KAT6B reported in literature. Fusion junctions are indicated by red stars. Black boxes highlight retained transcriptional activation domains in all fusion partners. **Abbreviations:** E, exon; NEMM, N-terminal extension of MYST; PHD, plant homeodomain; MYST, histone acetyltransferase domain (HAT); SM, Serine-Methionine-rich region; TAZ1/2, Transcriptional adaptor Zinc-binding domain 1/2; KIX, CREB/Kinase Inducible Domain Interacting Domain; NCBD, Nuclear Coactivator Binding Domain; AD, activation domain; TAD, transactivation domain; ASXH, Asx Homology domain.


A
20x
50x
MPO
NSE
B
KAT6B
chr10(q22.2)
~4.8Mb
NUTM2B
chr10(q22.3)
5'
3'
5'
3'
5'
3'
Exon 17
Exon 2
KAT6B::NUTM2B
GACCCTTGTAGAAGGAATGCTGGGCCA
D P C R R N A G P
KAT6B
2073 AA
NEMM PHD MYST Acidic SM
NUTM2B
878 AA
KAT6B::NUTM2B
1804 AA
C
umap coordinate 2
umap coordinate 1
KAT6B::NUTM2B
KAT6A-r
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KAT6B::NUTM2B
KAT6A-r
KMT2A-r
CD34
APL
BCL11B
BCR::ABL1
CBFB::GDXY
CBFB::MYH11
CEBPA
DEK::NUP214
ETS-family
GATA1
GLIS-r
HOX-r
KMT2A::PTD
MECOM
MNX1
NPM1
NUP98-r
Other
PICALM::MLLT10
RBM15::MRTFA
RUNX1::RUNX1T1
RUNX1::RUNX1T1−like
UBTF
D
Normalized HTseq Count (VST)
HOXA9
HOXA10
Bone Marrow Aspirate
Skin Biopsy
KAT6B::NUTM2B
KAT6A-r
KMT2A-r
NUP98-r
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RUNX1::RUNX1T1
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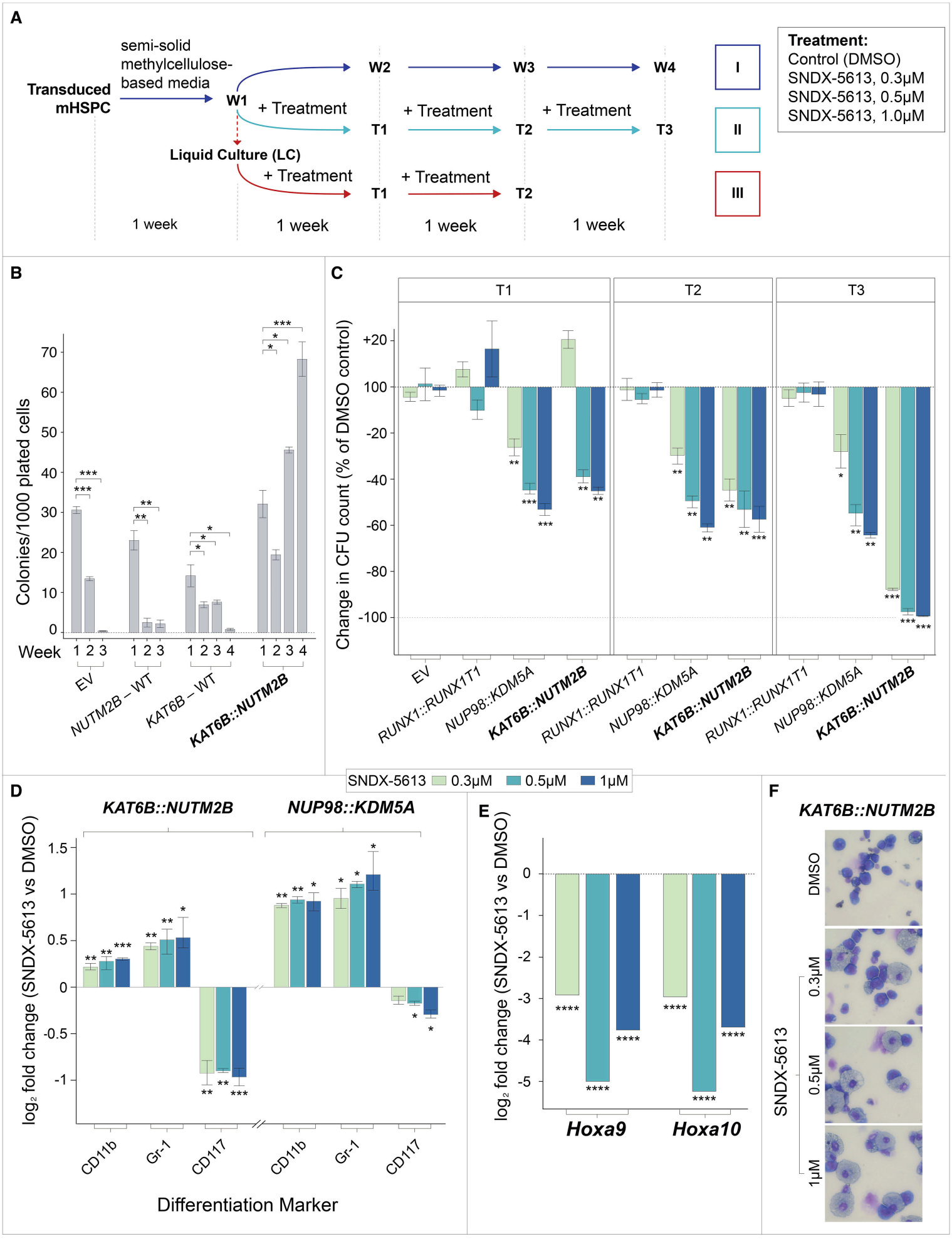
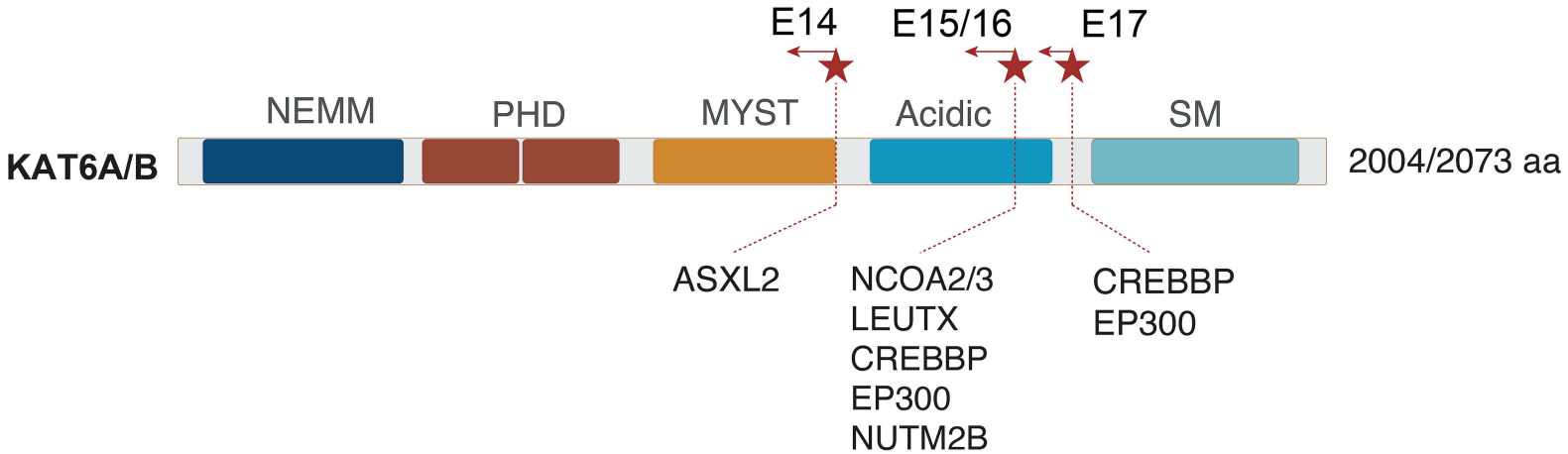
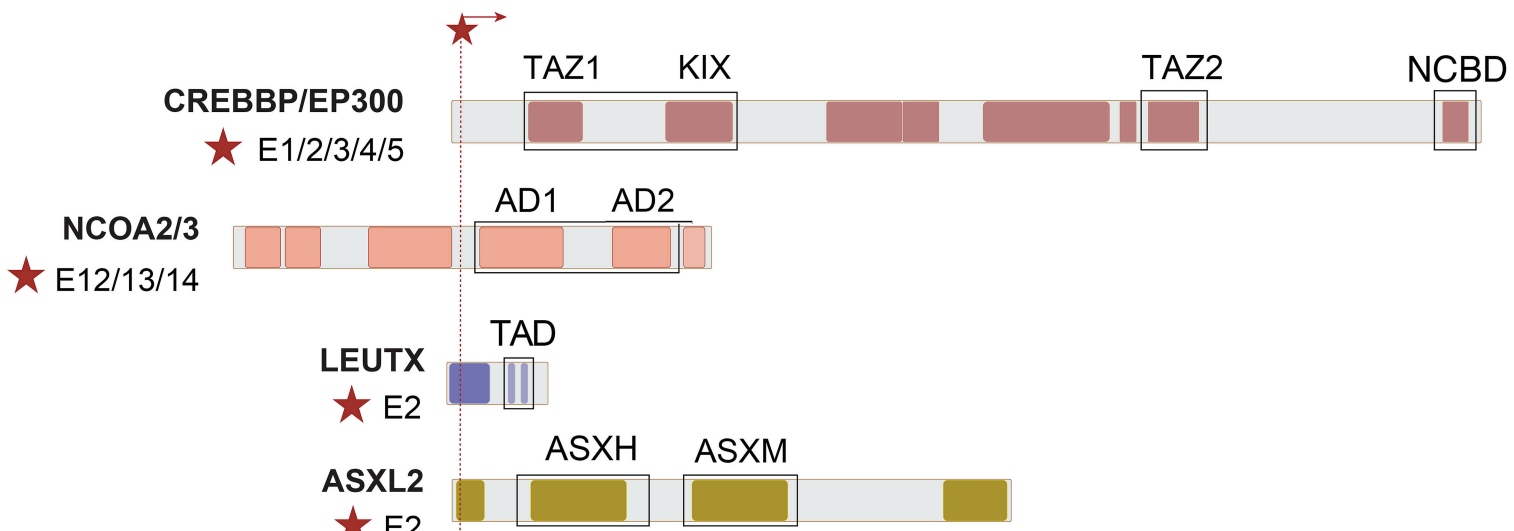
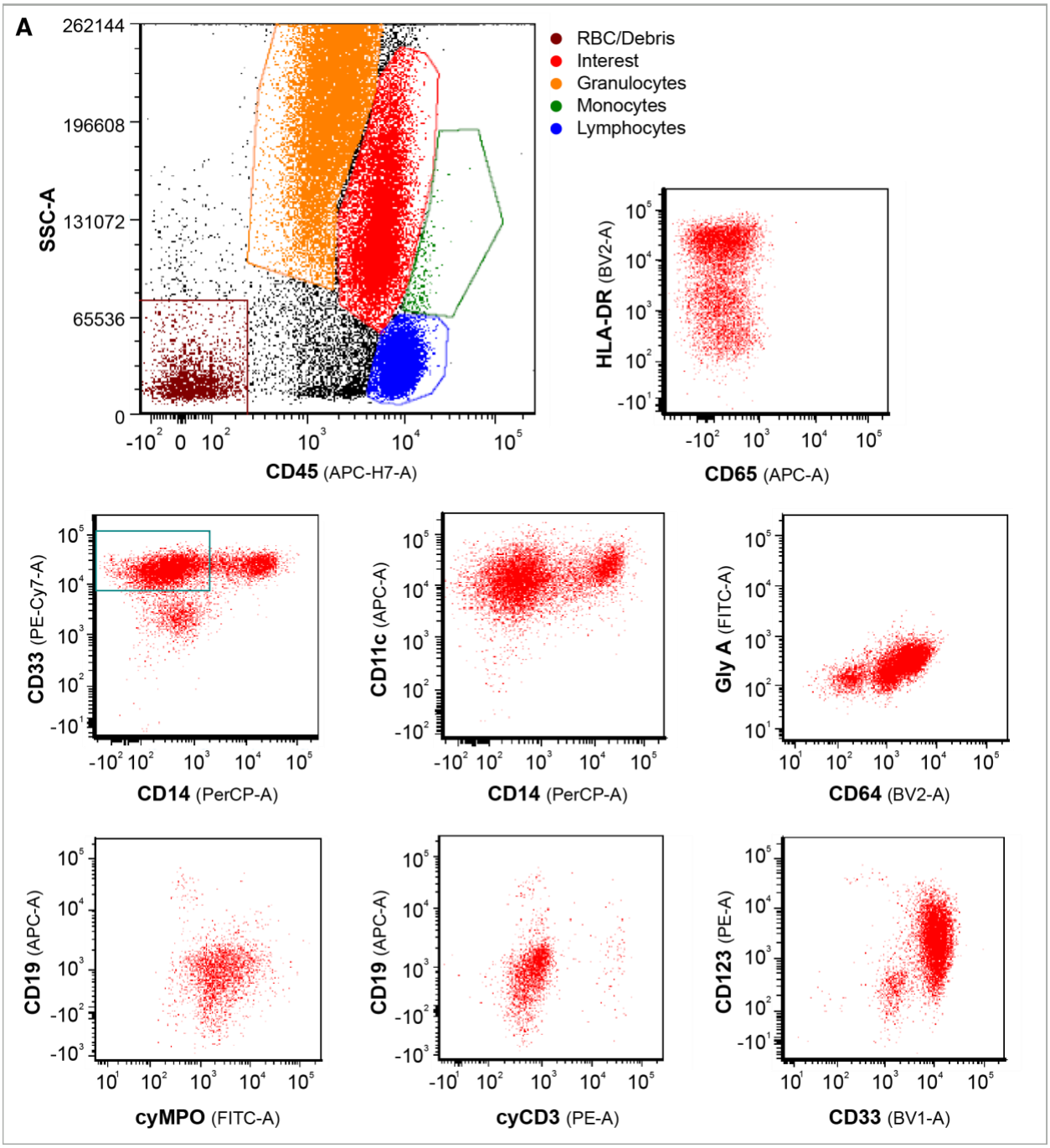

A
semi-solid methylcellulose-based media
Transduced mHSPC
W1
W2
W3
W4
+ Treatment
T1
T2
T3
Liquid Culture (LC)
1 week
Treatment:
Control (DMSO)
SNDX-5613, 0.3μM
SNDX-5613, 0.5μM
SNDX-5613, 1.0μM
I
II
III
B
Colonies/1000 plated cells
Week
EV
NUTM2B – WT
KAT6B – WT
KAT6B::NUTM2B
C
T1
T2
T3
Change in CFU count (% of DMSO control)
EV
RUNX1::RUNX1T1
NUP98::KDM5A
KAT6B::NUTM2B
SNDX-5613 0.3μM 0.5μM 1μM
D
KAT6B::NUTM2B
NUP98::KDM5A
log2 fold change (SNDX-5613 vs DMSO)
CD11b
Gr-1
CD117
Differentiation Marker
E
log2 fold change (SNDX-5613 vs DMSO)
Hoxa9
Hoxa10
F
KAT6B::NUTM2B
DMSO
SNDX-5613
0.3μM
0.5μM
1μM

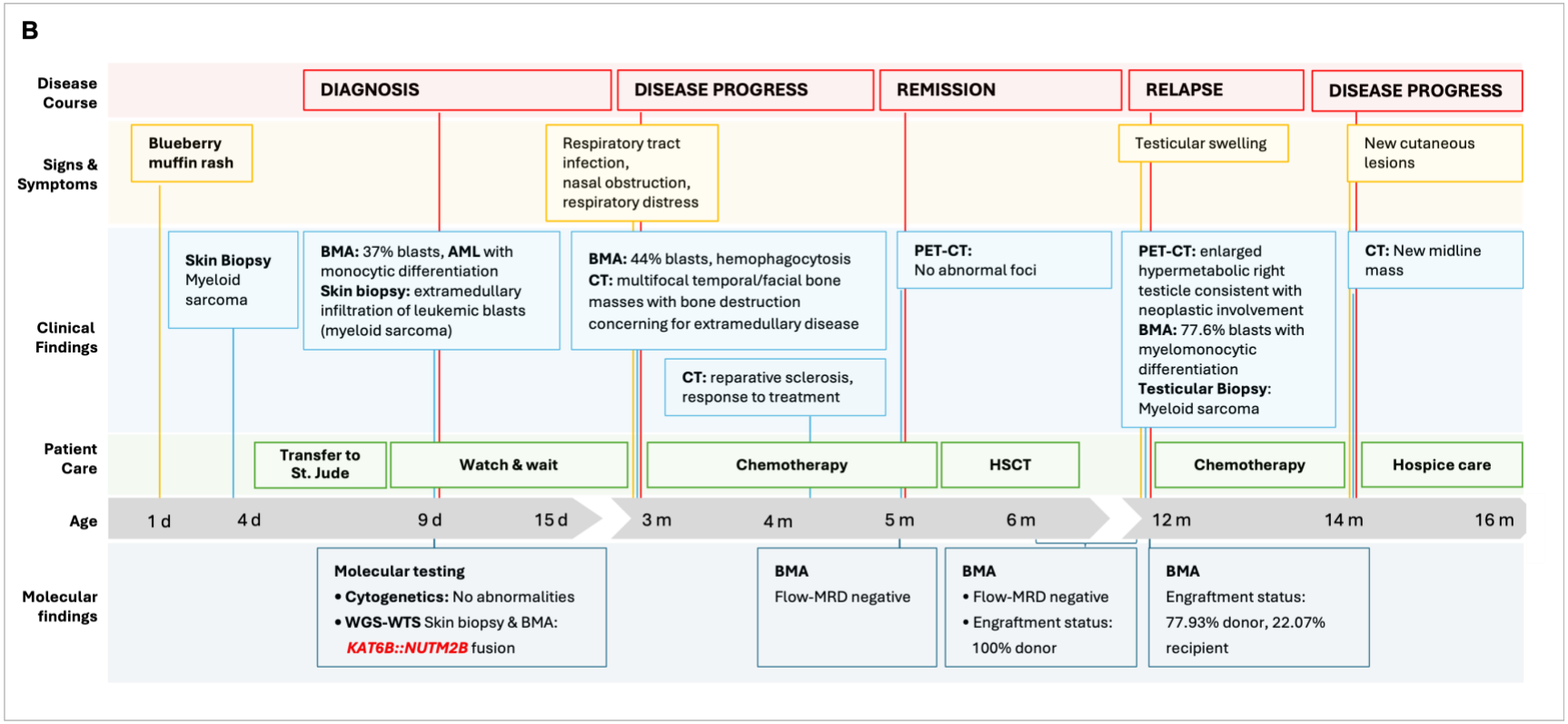

E14
E15/16
E17
NEMM
PHD
MYST
Acidic
SM
KAT6A/B
2004/2073 aa
ASXL2
NCOA2/3
LEUTX
CREBBP
EP300
NUTM2B
CREBBP
EP300


TAZ1
KIX
TAZ2
NCBD
CREBBP/EP300
E1/2/3/4/5
AD1
AD2
NCOA2/3
E12/13/14
TAD
LEUTX
E2
ASXH
ASXM
ASXL2
E2

Supplementary Figure S1

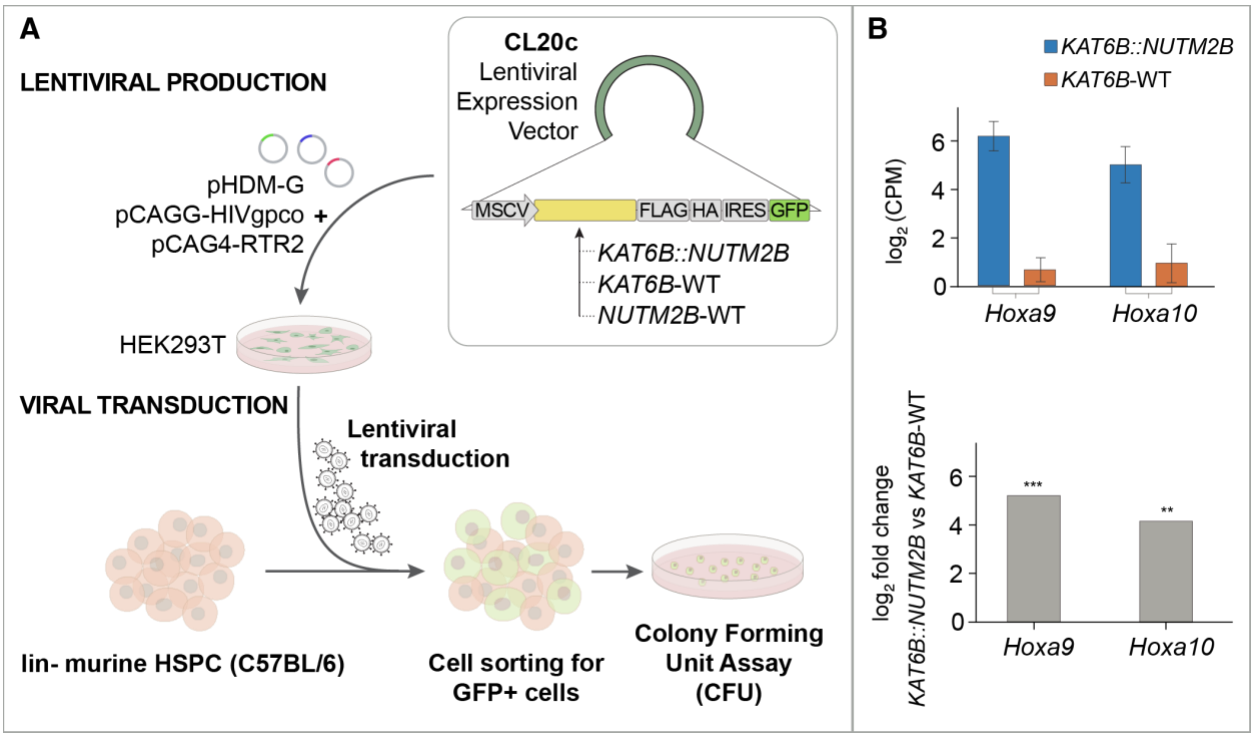


Supplementary Figure S1. Immunophenotypic characterization of patient's leukemia and the time course of the patient's disease. A) Immunophenotypic feature of the bone marrow aspirate sample collected at initial diagnostic work-up at St. Jude Children's Research Hospital. Expression of selected CD (cell differentiation) markers by flow cytometry analysis. Blasts are positive for monocytic markers CD64 and CD11c, but loss of CD14 expression is observed in the majority of blasts (green rectangle). Blasts are also positive for MPO, CD123 and HLA-DR, but negative for CD19 and cyCD3.



Supplementary Figure S1. B) The time course of the patient's disease since birth. Clinical signs and symptoms are shown in orange boxes, and pathology and imaging findings are shown in bright blue boxes. Patient management, including therapeutic interventions, is depicted in green boxes. Chemotherapy administered at disease progression consisted of Induction I (cytarabine, daunorubicin, etoposide and gemtuzumab) and Induction II (idarubicin and cytarabine), followed by haploidentical HSCT. At relapse, the patient received two cycles of azacitidine, gemtuzumab, and venetoclax. Molecular diagnostic results and disease monitoring are summarized at the bottom. **Abbreviations:** BMA, bone marrow aspirate; d/o, days old; HSCT, hematopoietic stem cell transplantation; m/o, months old; MRD, measurable residual disease; WGS, whole genome sequencing; WTS, whole transcriptome sequencing

Supplementary Figure S2



Supplementary Figure 2. In vitro cell model: Mouse hematopoietic stem and progenitor cells (mHSPCs) transduced with expression constructs, recapitulating *Hoxa9/10* dysregulation by *KAT6B::NUTM2B* fusion. A) Construction of wild-type *KAT6B* (*KAT6B*-WT), wild-type *NUTM2B* (*NUTM2B*-WT) and *KAT6B::NUTM2B* expression vectors and schematic of transduction and Colony Forming Unit (CFU) Assay. Coding sequences of human *KAT6B* (NM_012330), *NUTM2B* (NM_001278495) and *KAT6B::NUTM2B* fusion were synthesized and cloned into pENTR/D-TOPO Gateway entry vector (K240020, Thermo Fisher) by GenScript (Piscataway NJ) then transferred into MSCV-IRES-GFP (MPG) vector using Gateway LR clonase II enzyme system (Invitrogen, Waltham, MA, USA). For the generation of lentivirus, one million HEK293T cells were plated in each well of a 6-well plate for 24 h, then transiently co-transfected with lentiviral packaging helper plasmids pHDM-G, pCAGG-HIVgpco, pCAG4-RTR2 and the plasmid of interest at a 1:1 ratio. Transfections were carried out using either FuGene HD (Promega, Madison, WI, USA) or Lipofectamine (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. After an incubation period of 48 h, the supernatant containing the lentivirus was collected for transduction of mice hematopoietic stem and progenitor cells (mHSPCs) isolated from bone marrow sample obtained from C57BL/6 mice (EastSep™ Mouse Hematopoietic Progenitor Cell Isolation Kit, STEMCELL TECHNOLOGIES™) followed by colony forming unit (CFU) assay. **B) *Hoxa9* and *Hoxa10* expression at the**

transcriptional level. Upper: Expression levels of *Hoxa9* and *Hoxa10* in *KAT6B::NUTM2B* and *KAT6B*-WT transduced mHSPCs; Lower: Relative expression of *Hoxa9* and *Hoxa10* in *KAT6B::NUTM2B* transduced mHSPCs compared to *KAT6B*-WT transduced cells (*KAT6B::NUTM2B vs. KAT6B*-WT). *** $p<0.001$, ** $p<0.01$.

Supplementary Table S1. Summary of reported cases with *KAT6A/B* fusions in infant AML/myeloid sarcoma and additional cases with other *KAT6A* or *KAT6B* fusion partners not observed in infant patients.

Fusion partner	No. of cases	Age at DX	Diagnosis	BM-Blast	FAB classification	Karyotype	Clinical signs & symptoms	Clinical course	Reference
KAT6A::CREBBP	26*	median ~1 month (1 day-12 months) *	AML, myeloid sarcoma	52% (med.)	M4, M5	*See original publication*	Cutaneous lesions in 82%, disseminated intravascular coagulation in 30% and erythrophagocytosis in 50% of infants for whom data was available	7 of 26 cases with spontaneous remission, 4 of whom relapsed	*Coenen et al., Blood (2013)*
KAT6A::CREBBP	1**	<1 month	Myeloid sarcoma	NA	M4	*NA*	Cutaneous lesions, hemophagocytosis, hepatosplenomegaly	Deceased	*Francianne Gomes Andrade et al., Revista Brasileira de Hematologia e Hemoterapia (2016)*
KAT6A::CREBBP	1	<1 month	Myeloid sarcoma + BM involvement	35%	M4	46,XX (fusion identified by FISH)	Cutaneous lesions, hepatosplenomegaly	Spontaneous remission after 5 months	*Barrett R, et al. Pediatr Blood Cancer. (2017)*
KAT6A::EP300	1	Newborn	Myeloid sarcoma, AML	44%	M5b	46,XX,t(8;12;22)(p11.2;q24.1;q13)[15]/46,XX[5]	Cutaneous lesions	Spontaneous remission within 3 months	*Ikawa, Y., et al Leukemia & Lymphoma (2018).*
KAT6A::EP300	1	1 month	Myeloid sarcoma	NA	*NA*	*NA*	Cutaneous lesions	Spontaneous remission	*Hosahalli Vasanna, et al. Medicine (2023)*
KAT6A::NCOA2	1	7 months	Myeloid sarcoma, AML	46%	M4/5	46,XX,t(1;20)(q21;q21.3),-8, der(21)t(1;21) (q21;q22),+mar[16]/46,XX,idem,add(6)(q27)[4]	Cutaneous lesions (scalp)	Relapse pre HSCT, death 5 months after diagnosis	*Koduru, Prasad R. et al. Journal of Pediatric Hematology/Oncology (2017)*
KAT6A::LEUTX	1	2 weeks	Myeloid sarcoma, AML	37.2%	M4/5	*NA*	Cutaneous lesions, hepatosplenomegaly, thrombocytopenia, leukocytosis	Death within 5 days of diagnosis under chemotherapy, leukemic infiltration of lung and heart	*Sramkova, L. et al., Pediatr Blood Cancer (2020)*
KAT6A::LEUTX	1	3 months	Myeloid sarcoma, AML	26%	M4	46,XX,t(8;19)(p11.2;q13.3)[16]/46,XX [4]	Cutaneous lesions, hepatosplenomegaly, thrombocytopenia, leukocytosis	Remission after chemotherapy	*Eason, Ashley C., et al. Case Reports in Hematology (2019)*

KAT6A::LEUTX	1	8 months	AML	72%	M5a	46,XY,t(8;19)(p11;q13.2)[8]/46,XY, t(8;19),1,+1q[22]/46,XY, t(8;19),-16,+16q+[6]	Hepatosplenomegaly, enlarged lymph nodes, disseminated intravascular coagulation, erythrophagocytosis	Death after bone marrow transplantation due to veno-occlusive disease	*A. Brizard et al., Leukemia Research (1988)*
KAT6A::ASXL2	1	6 years	tMDS	5%	*NA*	46,XY,del(8)(p21)[17]/46,XY[3]	*NA*	Initial diagnosis: AML M2 with t(8;21)(q22;q22)/ *RUNX1::RUNX1T1* at age 4; relapsed at age 5 (*RUNX1::RUNX1T1*); developed hypocellular dysplasia at age 6 with new t(2;8)(p23;p11.2)/ *KAT6A::ASXL2* and persistent *RUNX1::RUNX1T1*; died of infectious complications	*Imamura et al., Genes Chromosom. Cancer (2003)*
KAT6A::NCOA3	1	75 years	AML	91%	M5	46,XX,t(8;20)(p11;q13)[23]	Splenomegaly, disseminated intravascular coagulation.	Treatment with hydroxyurea + low dose cytosine arabinoside, no remission achieved and patient passed from intracerebral hemorrhage within 3 months of diagnosis	*Murati et al., British Journal of Hematology (2004)*
KAT6B::CREBBP	1	4 years	AML	94%	M5a	47,XX,der(7) t(7;10)(p13;p11), +8, der(10)t(7;10)(p13;p11)t(10;16)(q22;p13), der(16)t(10;16)(q22;p13)[19]/46,XX[6]	*NA*	Patient treated according to NOPHO-93	*Panagopoulos I. et al., Hum Mol Genet. (2001)*
KAT6B::CREBBP	1	52 years	tMDS	1.8%	*NA*	46,XX,t(10;16)(q22;p13)[18]/46,XX[2]	*NA*	History of AML-M1, 95% BM blasts, normal Karyotype, treated with intensive chemotherapy ~1.5years prior to diagnosis of tMDS. Treatment of tMDS: Supportive management, progress to 21% blasts after 9 months, no monocytic differentiation	*Kojima K. et al. British Journal of Haematology (2003)*
KAT6B::CREBBP	1	84 years	AML	89%	M5b	46,XY,t(10;16)(q22;p13)	*NA*	no curative therapy, death one month after diagnosis	*Vizmanos, J.L. et al. Genes Chromosom. Cancer (2003)*
KAT6B::CREBBP	1	*NA*	AML	*NA*	M4	46,XX,t(10;16)(q21;p13),t(11;17)(q23;q21)	*NA*		*Murati, A. et al. British Journal of Haematology (2004)*

* Twenty-six of 62 cases in this study cohort were congenital/infant AML (case IDs: 3, 4, 16, 17, 19, 21, 23, 28, 29, 34, 35, 37, 38, 40, 41, 43, 46, 47, 48, 51, 52, 55, 59, 60, 61, 62)
** One of 5 cases in this study cohort showed *KAT6A::CREBBP*