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

Authors

Rebecca K. Voss,[1] Wenqing Qi,[1] La'Ron Browne,[2] Ruth W. Wang'ondu,[2] Mahsa Khanlari,[1] Jing Ma,[1] Xuefei Ma,[1,3] Josi Lott,[4] Juan M. Barajas,[1] Melvin Thomas III,[1] Victor B. Pastor Loyola,[1] Hui Cao,[1] Larissa V. Furtado,[1] Swati Naik,[5] Sakshi Bami,[6] Seth E. Karol,[2] Jeffrey E. Rubnitz,[2] Jeffery M. Klco,[1] Yen-Chun Liu[1] and Lu Wang[1]

[1]Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN, USA; [2]Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA; [3]Department of Laboratory Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [4]Center of Excellence in Leukemia Studies, St. Jude Children's Research Hospital, Memphis, TN, USA; [5]Department of Bone Marrow Transplant and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, TN, USA and [6]Department of Hematology/Oncology, St Jude Affiliate Clinic, Our Lady of the Lake Children's Hospital, Baton Rouge, LA, USA

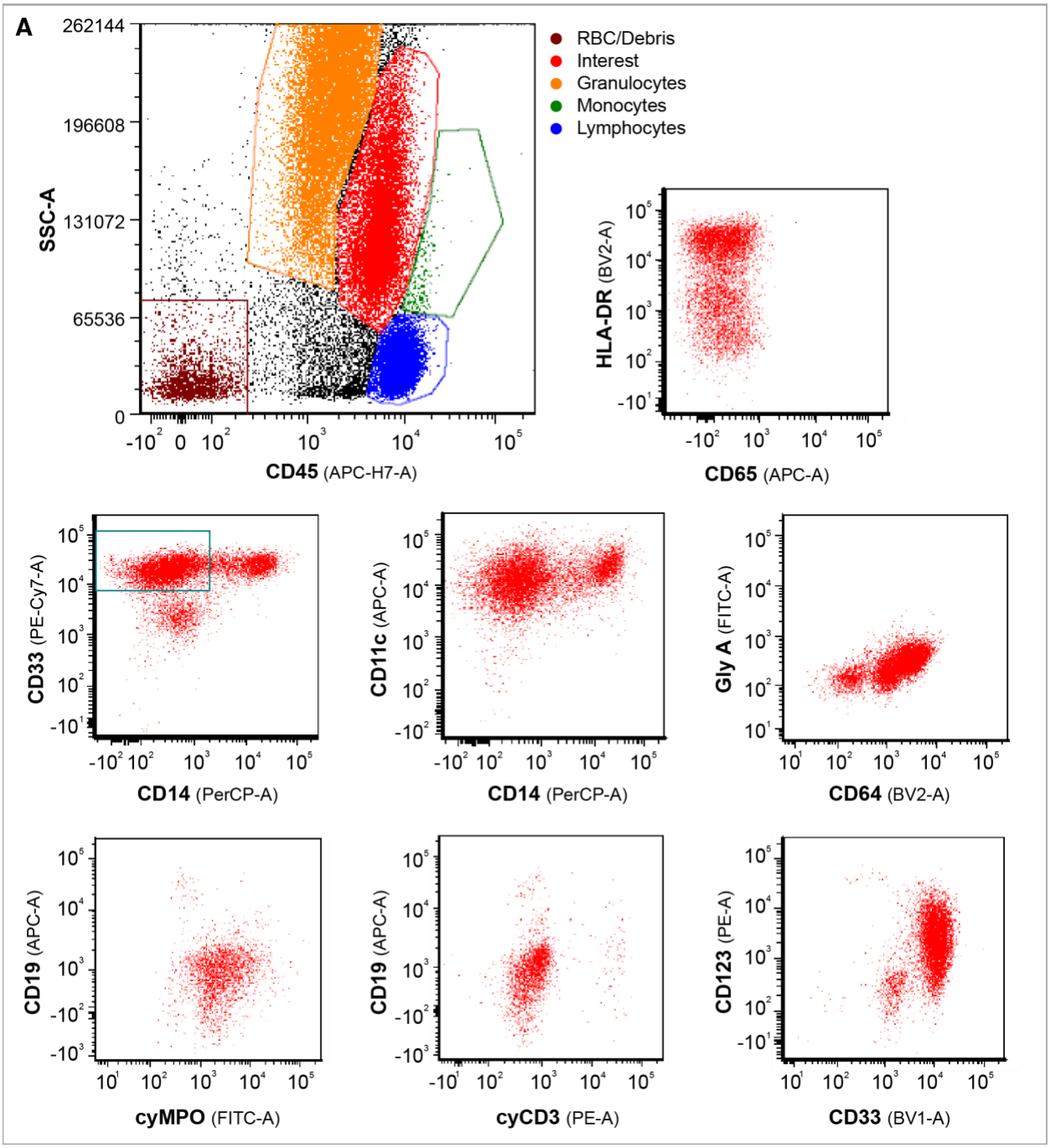
Correspondence:
L. WANG - Lu.Wang2@stjude.org
Y-C. LIU - Yen-Chun.Liu@stjude.org

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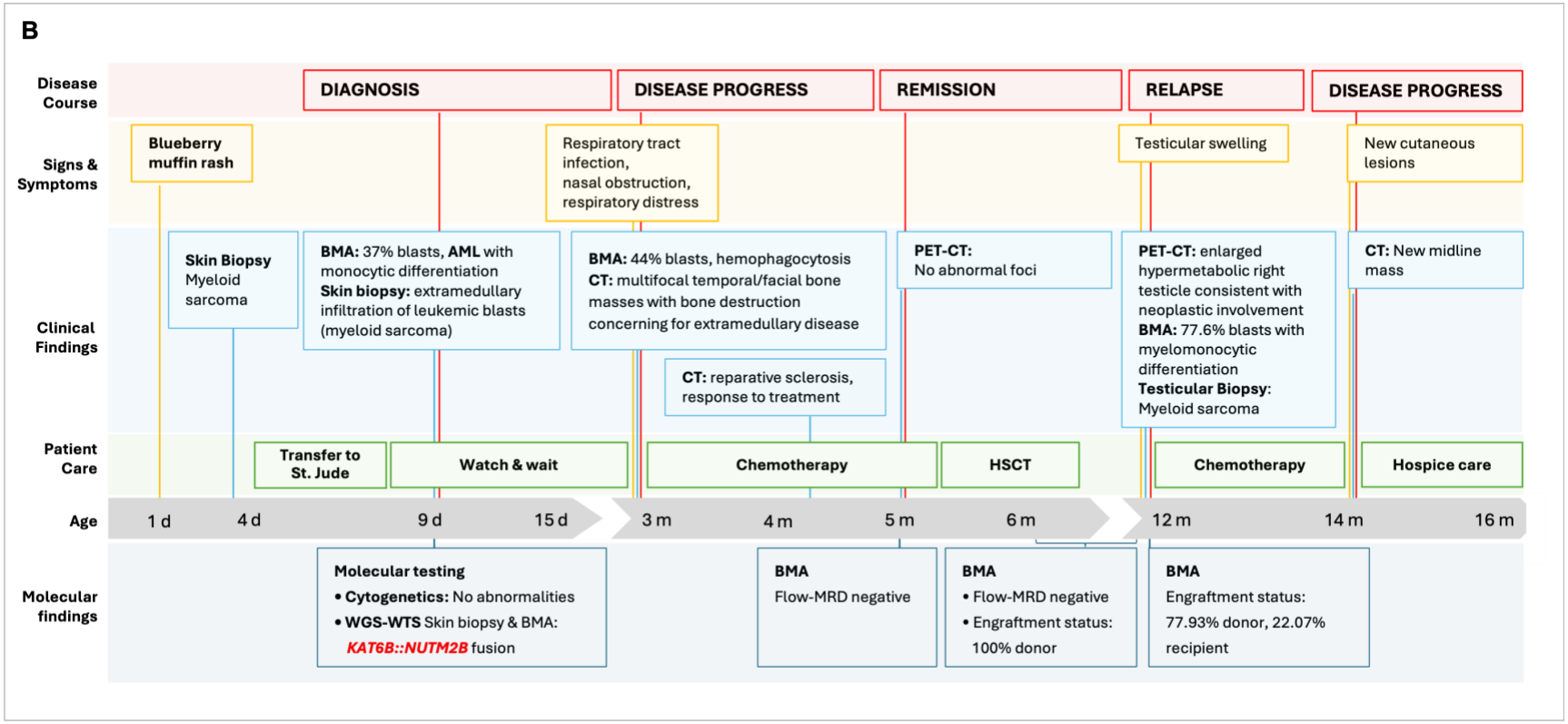
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Supplementary Figure S1

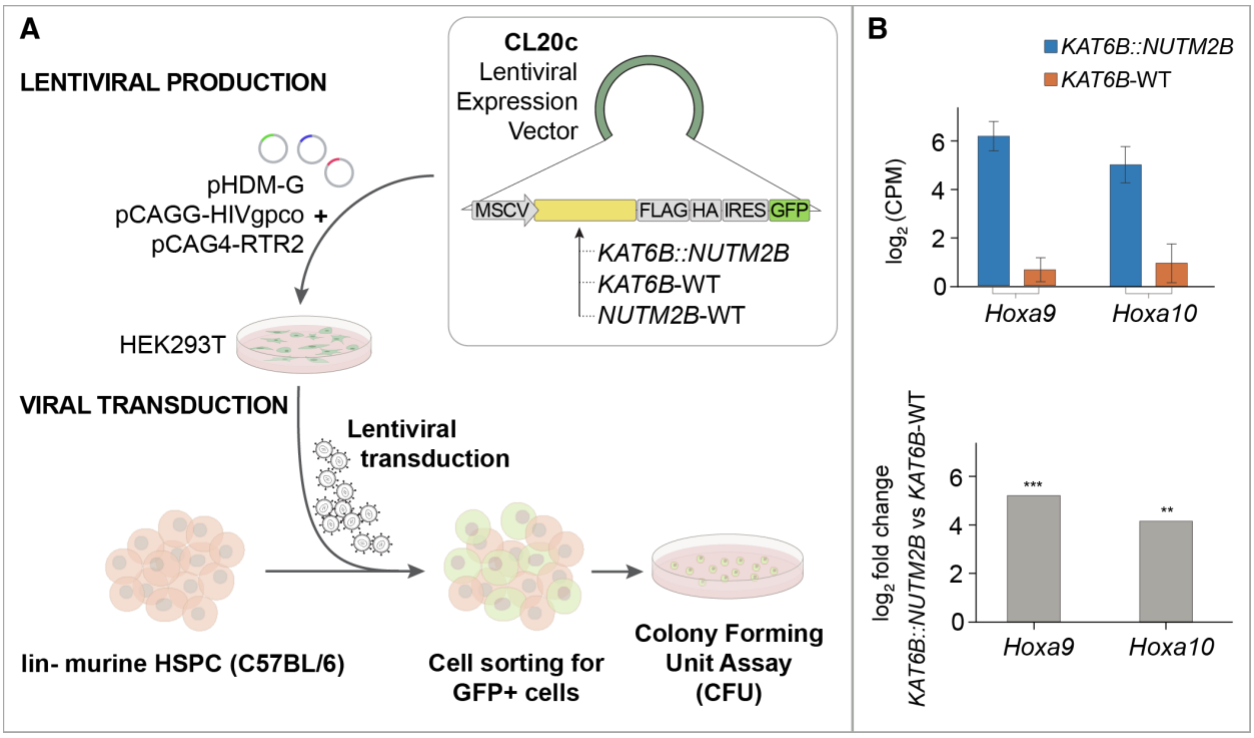


Supplementary Figure S1. Immunophenotypic characterization of patient's leukemia and the time course of the patient's disease. A) Immunophenotypic feature of the bone marrow aspirate sample collected at initial diagnostic work-up at St. Jude Children's Research Hospital. Expression of selected CD (cell 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*