—Photogravure—

Establishment of MLL/AF4 Transgenic Mice with the Phenotype of Lymphoblastic Leukemia or Lymphoma

Hayato Tamai and Koiti Inokuchi
Department of Hematology, Nippon Medical School

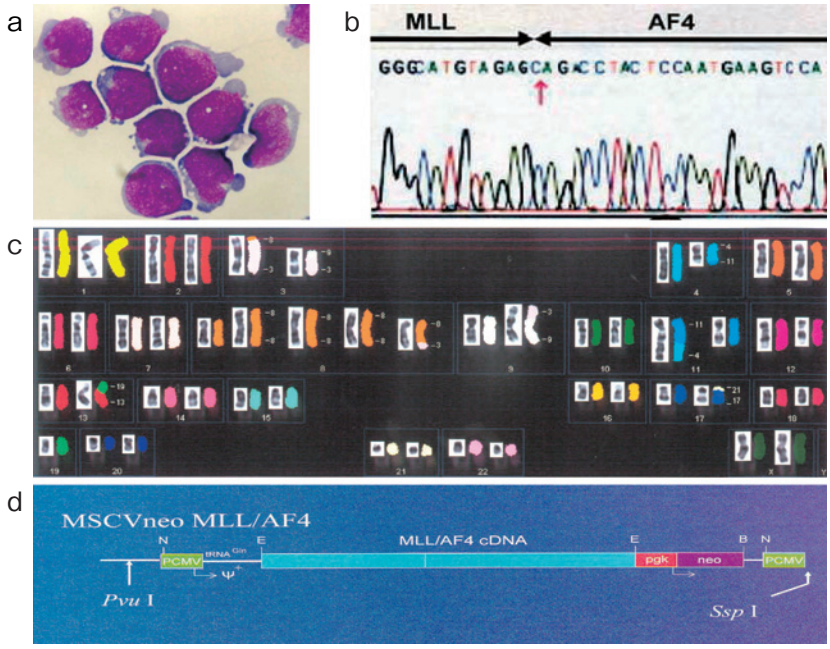

Fig. 1

Acute lymphoblastic leukemia (ALL) with MLL/AF4 fusion is a common leukemia in infants and has a poor prognosis[1]. Research into the molecular mechanisms underlying MLL/AF4-positive ALL has been hampered by the absence of the complete complementary DNA of MLL/AF4 **(Fig. 1)** and a good animal model. To develop a murine model of MLL/AF4-positive ALL more similar to human MLL/AF4-positive ALL, we established MLL/AF4 transgenic mice through overexpression of a human-derived MLL/AF4 fusion gene[2] **(Fig. 1 and 2)**.

In our newly established MLL/AF4 transgenic mice, lymphoma developed 12 months after birth. Infiltrating lymphoid cells were found in the liver, lungs, kidneys, and spleen and consisted of a pro-B-cell (CD45R+ CD43+ CD19−) lineage[2]. Leukemic change appeared after a long latency period (median, 14 months). Abnormal lymphocytes (more than 30%) and severe anemia were found in the peripheral blood of MLL/AF4 transgenic mice[2]. Western blot analysis showed that HoxA9 and S100A6 in MLL/AF4 transgenic mouse were up-regulated compared with those in wild-type C57BL/6 mice[3]. Thus, we succeeded in establishing MLL/AF4 transgenic mice that reflect the MLL/AF4 leukemogenicity of humans. Enhancement of HoxA9 and S100A6 expression may be involved in MLL/AF4-associated leukemogenesis[3]. The present transgenic mice will be useful for studying the molecular mechanisms of leukemogenesis and for developing new therapies for MLL/AF4-positive ALL.

Correspondence to Koiti Inokuchi, Department of Hematology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

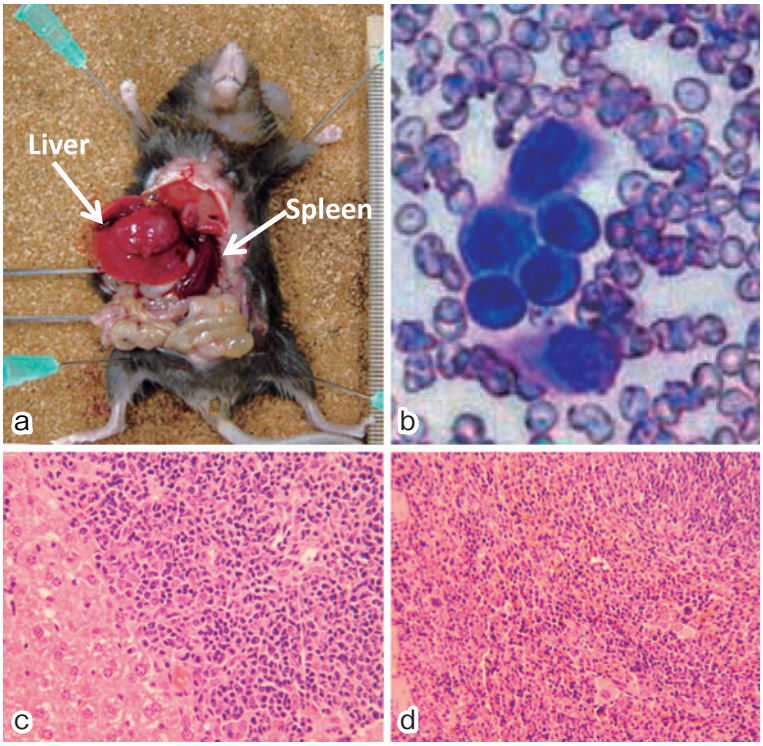

Fig. 2

Conflict of Interest: The authors have no conflicts of interest to declare.

Fig. 1 Molecular analysis of the MLL/AF4-positive cell line and construction of the vector for creating MLL/AF4 transgenic mice
(a) The MLL/AF4 cell line was established from a 44-year-old woman with ALL. Wright-Giemsa staining. (b) Direct sequence of the breakpoint of the cloned MLL/AF4 complementary DNA. (c) Spectral karyotyping analysis of the MLL/AF4-positive cell line showed t(4;11)(q21;q23). (d) Schematic diagram of the MSCVneoMLL/AF4 vector constructed for injection. The MLL/AF4 complementary DNA was introduced into a pMSCVneo vector. Transgenic mice were established by microinjecting pMSCVneoMLL/AF4 into the pronuclei of eggs from C57BL/6N Crj mice.

Fig. 2 The expression phenotype of the established MLL/AF4 transgenic mice. (a) The MLL/AF4 transgenic mice showed hepatosplenomegaly. (b) ALL cells in the peripheral blood of MLL/AF4 transgenic mice with the phenotype of lymphoblastic leukemia or lymphoma (leukemia/lymphoma). (c) Leukemia/lymphoma cells had infiltrated the liver. (d) Diffuse infiltration of leukemia/lymphoma cells was observed in the spleen.

References

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3. Tamai H, Miyake K, Yamaguchi H, et al.: AAV8 vector expressing IL24 efficiently suppresses tumor growth mediated by specific mechanisms in MLL/AF4-positive ALL model mice. Blood 2012; 119: 64–71.

E-mail: inokuchi@nms.ac.jp Journal Website (http://www.nms.ac.jp/jnms/)