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The “Never-Ending” Mouse Models for MLL-Rearranged Acute Leukemia Are Still Teaching Us

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The mixed lineage leukemia (MLL, also known as KMT2A) gene is frequently rearranged in human acute leukemia. Chromosomal rearrangements involving MLL are biologically and molecularly very intriguing because of the unique ability of MLL to “break and fuse” with more than 135 fusion partners, as recently reported by the 2017 MLL Recombinome Consortium.1 MLL fusions are commonly associated with poor disease outcome in infant, pediatric, adult, and therapy-induced acute leukemias. The contribution of MLL fusions to leukemia initiation and evolution, therapy resistance and relapse is still under active investigation. In this issue of HemaSphere, Stavrakopoulou et al report a novel inducible transgenic mouse model of MLL-ENL-driven mixed lineage acute leukemia which reveals that the cell-of-origin and the fusion gene expression level are both critical determinants for lineage acute leukemia which reveals that the cell-of-origin and the MLL-ENL translocations.1,3 Longitudinal genomic studies reveal large the MLL fusions (affecting 11q23) found in acute leukemia indicates that the MLL-AF9, the commonest MLL translocations found in human acute lymphoid and myeloid acute leukemia. The large variety of mixed lineage leukemia (MLL) gene fusions (affecting 11q23) found in acute leukemia indicates that the MLL gene is a hotspot genomic region for chromosomal translocations.1,3 Longitudinal genomic studies reveal large tumor-mutational heterogeneity for secondary driver mutations4 but not for MLL fusions, which are clonal and present in all leukemic cells, thus representing early initiating leukemogenic events.1,3 MLL-rearranged leukemias represent a major subgroup of acute leukemias in infants and pediatric patients but also affect adults (de novo or therapy-related acute leukemia). MLL rearrangements are usually found both in B-cell acute lymphoblastic leukemia (B-ALL) and acute myeloid leukemia (AML) as well as in biphenotypic acute leukemias in which MLL fusions are a hallmark pathogenic event.7 Although there are several clinical and biological factors influencing the long-term prognostic value of MLL rearrangements, the current molecular diagnostic criteria place acute leukemias with 11q23 rearrangements as intermediate/high-risk patients.

Several reasons have contributed to a very dynamic research over the last 10 to 15 years on modeling the leukemogenic impact of MLL fusions. Among these are the unfavorable clinical outcome of these patients, the relatively high frequency of MLL leukemias in children, the prenatal origin of MLL rearrangements in utero during fetal hematopoietic development and the impressively large number of distinct MLL partners eventually contributing to the same (or similar) phenotype. A wide array of transgenic mouse models have been generated for studying the leukemogenic mechanisms of MLL fusions, with special interest in the commonest MLL fusions: MLL-AF4, MLL-ENL, and MLL-AF9, the commonest MLL translocations resulting from the balanced translocations (4;11), t(9;11), and t(11;19), respectively. These available mouse models have proven very useful to further our understanding about the leukemogenic role of MLL fusions; however, they are all somehow subjected to disadvantages which prevent them to faithfully reproduce all the disease phenotypic and latency features. The different experimental strategies, molecular approaches, inducible systems and target cells certainly contributed to the current “controversial” state-of-the-art. Aspects such as the cell-of-origin in which the translocation is specifically induced, the timing and level of MLL fusion expression, the interaction with the bone marrow microenvironment, and the differences between transgenic approaches contribute to the existing diversity of MLL mouse models. The CRISPR/Cas9 system has revolutionized the way to approach functional genomics.6 We envision that the use of more accurate models generated by genome engineering techniques in the appropriate human and mouse target cells will soon transform the field of MLL leukemia biology.
**MLL-AF4(t;4;11) mouse models**

The translocation between chromosomes 4 and 11, t(4;11), which fuses MLL to the AF4 gene, is the most common genetic-chromosomal alteration found in infant leukemia and is associated with a particularly dismal prognosis.\(^6\)\(^,\)\(^10\) It mostly manifests itself as B-ALL; however, as other MLL-rearranged leukemias, can also appear biphenotypic, with patient blast cells coexpressing lymphoid and myeloid markers. Importantly, it has the capacity to undergo lineage switching, from B-ALL to AML, following either conventional chemotherapy-based treatment or immunotherapy with CD19-specific chimeric antigen receptor-modified T cells (CAR-T cells).\(^11\) Understanding the lineage preference and plasticity of MLL-rearranged leukemias and how this is influenced by the properties of the cell-of-origin and the specific MLL is thus of utmost importance for the design of successful treatment strategies.

Recent sequencing studies have revealed MLL-AF4+ infant B-ALL to be one of the most silent mutational landscapes without no other recurrent genetic abnormalities apart from the initiating t (4;11) translocation.\(^12\) Despite this seemingly genetic simplicity, it has proven to be extremely difficult to model MLL-AF4+ leukemia in mice. The first attempt involved a straight knock-in of the human AF4 gene into the mouse MLL locus; however, despite considerable embryonic lethality, the surviving mice developed hematological malignancies only after a very long latency, and without an acute leukemia phenotype, eventually succumbing to lymphoid and myeloid hyperplasias and, most commonly, B cell lymphomas.\(^13\) An alternative model was based on the in vitro technology and allowed cell lineage-specific expression of MLL-AF4 via Cre recombinase-mediated inversion of human AF4 within the mouse MLL locus, creating an MLL-AF4 fusion.\(^14\) Interestingly, targeting MLL-AF4 expression to the T cell and the B cell lineage produced a B cell malignancy in both cases, thus demonstrating a clear B lymphoid bias; however, disease was once again a more mature B lymphoma that developed after a long latency. Using the same mouse model, but initiating MLL-AF4 expression already in the first definitive hematopoietic cells generated during development, thus more closely recreating conditions in the infant disease, Barrett et al.\(^15\) were able to describe the preleukemic prenatal stages and the lymphoid-primed multipotent progenitor (LMPP) as the likely cell-of-origin, which was also highlighted in the present study by Stavropoulou et al\(^16\)\(^,\)\(^2\) as a potential cell-of-origin for MLL-ENL. However, embryonic expression of MLL-AF4 in this model did not shorten disease latency and did not result in acute leukemia development. An acute leukemia phenotype with a much shorter latency was achieved in the conditional Mxl-Cre-induced model generated in the Armstrong lab.\(^16\) Around 30% of the mice developed AML, while approximately 40% succumbed to ALL, albeit with a slightly more mature pre-B phenotype. Using this model, the authors were able to highlight H3K79 methylation as a hallmark for MLL-AF4 leukemia.

Despite the valuable knowledge gained from these genetic models, their failure to faithfully recapitulate the human disease suggests that they are missing crucial elements. B-ALL has generally been challenging to model in murine models. One possible explanation may be that there are fundamental differences in lymphoid development between mice and humans. This notion has recently received a lot of support in a study where mouse progenitor cells transduced with a human-mouse MLL-AF4 construct induced AML upon transplantation, while human progenitors transduced with the same construct were able to initiate pro-B ALL.\(^17\) Other crucial factors may include contributing immune stimuli which is somewhat supported by the stronger phenotype observed in the model that relies on poly I:C injections for fusion gene expression,\(^18\) which is known to induce an inflammatory response. The stromal microenvironment may also play an important role in leukemia initiation as indicated by the detection of the t(4;11) translocation and fusion transcript in a subset of stromal cells from leukemia patients.\(^19\) A model like the one published by Stavropoulou\(^2\) would lend itself particularly well to addressing this question as the timing and level of fusion gene expression can be tightly regulated in any cell type.

Despite the silent mutational landscape, activating mutations in the RAS pathway have been commonly observed in MLL-AF4 + patients; however, these were subclonal and often disappeared at relapse.\(^2\)\(^2\) According to a recent KRAS mutation proved unable to initiate leukemia in a lentiviral MLL-AF4 transplant model, but was shown to enhance engraftment and extramedullary hematopoiesis.\(^2\)\(^1\) The current MLL-ENL study by Stavropoulou also detected an activating KRAS signature in the leukemia-propagating population suggesting that RAS pathway activation, despite not being essential, is nevertheless an important contributing factor. What sets MLL-AF4 apart from other MLL-rearranged leukemias is a possible role for the reciprocal fusion, AF4-MLL. It is expressed in a large proportion of patients, but not all, arguing against an essential function, which is supported by a recent study in which it was shown to enhance engraftment, but was unable to initiate disease.\(^2\)\(^2\) While there have been some important advances and discoveries recently, a genetic mouse model for MLL-AF4+ infant B-ALL in which all stages from prenatal initiation can be studied via disruption of normal fetal hematopoiesis to full-blown early onset pro-B ALL in vivo has not yet been generated. Uncovering the missing elements may highlight important therapeutic targets.

Table 1 summarizes current mouse models available for MLL-AF4+ acute leukemia.

**MLL-ENL/t(11;19) mouse models**

Mixed-lineage leukemia—eleven-nineteen-leukemia translocation, known as t(11;19)/MLL-ENL is found in both adult and pediatric B and T-ALL and also in adult AML, in this case being associated with favorable or intermediate prognosis. MLL-ENL is more common in B-ALL than AML and in contrast to MLL-AF4 and MLL-AP9, it is the only 11q23 abnormality found in T-ALL. An important feature of MLL-ENL is the ability to cause lineage reassignment and switch between AML and ALL by reprogramming the transcriptome of MLL-ENL+ cells.\(^2\)\(^3\)\(^,\)\(^2\)\(^4\)

To address how MLL-ENL specifies leukemia phenotype and outcome, different in vivo mouse models have been described. The MLL-ENL translocator mouse which carries the chromosomal rearrangement after Cre-loxP-mediated recombination, was crossed with different lineage-specific Cre lines to express MLL-ENL in different compartments, such as HSC (Lmo2-Cre), B/T progenitors (Rag1-Cre), T cells (Lck-Cre), and B cells (CD19-Cre). These translocator models evidenced that targeted cells influence leukemic development and not all compartments could initiate leukemia.\(^2\)\(^3\)\(^,\)\(^2\)\(^4\) For example, MLL-ENL expression in B cells did not result in a malignant phenotype.\(^2\)\(^2\) Later on, studies using tamoxifen or doxycycline-inducible expression of MLL-ENL (iMLL-ENL) in distinct hematopoietic populations were performed to fine-tune the dosage and restrict the window
of protein expression.\(^{26,27}\) When different populations from Col1a1\(-\)tetO-MLL-ENL mice were isolated and transplanted into DOX-treated mice, AML leukemia developed from multiple progenitors (GMLP, pGM, committed myeloid progenitors (GMP), and common lymphoid progenitors (CLP)) but not from HSC, MPP or PreMeg/E.\(^{27,28}\) Now, a novel inducible MLL-ENL mouse model reported that hematopoietic stem and early multipotent precursor cells (LT-HSC, LMPP, MMP, and CMP) rather than GMP could act as cell-of-origin and give rise to a biphenotypic leukemia.\(^2\)

Given that MLL-ENL-initiated ALL was never observed in mice, Ugale et al investigated the impact of inducible MLL-ENL expression in lymphoid progenitors. They hypothesized that MLL-ENL fails to initiate ALL owing to either fundamental differences in lymphoid development between species or the requirement of additional cooperating mutations in MLL-ENL+ cells. When different B and T cell developmental stages were isolated from iMLL-ENL mice and transplanted into DOX-treated recipients, only T-cell DN1 progenitors and B-cell progenitors (BLP) gave rise to AML, likely due to their latent myeloid potential. If MLL-ENL fusion was coexpressed with an active KRAS mutant form (KRAS\(^{G^{12D}}\)), appearance of GMLP-initiated AML leukemia was accelerated. Addressing the impact of sequential acquisition of oncogenic hits revealed that the mutation order determines leukemia phenotype. Thus, a T-ALL was observed when KRAS\(^{G^{12D}}\) preceded MLL-ENL whereas a myeloid leukemia was more common when MLL-ENL preceded KRAS\(^{G^{12D}}\).\(^{27}\)

In spite of these studies, the nature of the leukemia initiating cell (LIC) still remains controversial and not all MLL-ENL-associated leukemia phenotypes observed in humans could be recapitulated in mice. Differences in MLL-ENL expression levels between the knock-in approaches could explain these discrepancies since MLL-ENL leukemogenic capacity requires fusion expression levels above those of the endogenous MLL1 gene.\(^7\) It is likely that both lineage potential of the target cells and MLL-ENL expression levels are key determinants for establishing leukemia phenotype. Additionally, factors influencing the lineage choice in LIC cells could exist and be elusive for MLL-rearranged leukemias. Nonetheless, these mouse models proved useful for initial drug screening studies as reported in the Ara-C induced leukemia remission in MLL-ENL/Lmo2-Cre translocator mice.\(^{2,5}\) Their refinement will contribute better in vivo MLL mouse models for preclinical drug testing. Finally, despite a silent genetic landscape in infant MLL-rearranged B-ALL in which only mutations in PI3K-RAS signaling pathways were found\(^{12}\) a whole-genome mutational landscape of MLL-ENL+ leukemias has not been analyzed in a patient cohort sufficiently large as to reveal recurrent cooperating mutations that could be functionally explored in these mouse models. Table 2 summarizes current mouse models available for MLL-ENL+ acute leukemia.

### MLL-AF9/t(9;11) mouse models

Translocation t(9;11) results in the expression of MLL-AF9 fusion protein found in both B-ALL and AML in infants and children, and AML in adults.\(^{29}\) MLL-AF9 leukemia is associated with extramedullary tumor infiltration, frequent relapses and variable prognosis depending on the age of the patient and phenotype of the leukemia, being intermediate risk (childhood) or intermediate-high (adulthood) prognosis in AMLs, and overall poor prognosis for childhood B-ALL.\(^{30}\) MLL-AF9-induced leukemia has been easier to model in vivo in comparison to other MLL-rearranged leukemias, mimicking phenotype and latency of the human disease quite accurately, which has allowed an extensive research of the biology of this disease. Besides retroviral models where the fusion oncogene is introduced into the target cells by viral vectors with an uncontrolled expression-integration, numerous mouse models have been developed to recreate a more physiological initiation of the disease.

The first attempt to recreate MLL-AF9 translocation in mice was performed by the Rabbits’ lab using a targeting vector encoding for Mll (exon 8)-AF9 (human sequence) fusion was inserted by homologous recombination into mouse ES cells in the endogenous MLL gene, thus being expressed at physiological levels.\(^{31}\) Extensive characterization of the chimeric and heterozygous mice showed that they recapitulate a human AML disease with the similar expansion of immature myeloid cell populations, macroscopically symptoms, and organ infiltration. Interestingly, 2 out of 24 chimeric mice developed B-ALL, similar to the proportion (~10%) of MLL-AF9+ B-ALL described for

### Table 1: Summary of MLL-AF4 Mouse Models

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cre Line</th>
<th>Disease Phenotype (LIC)</th>
<th>Average Latency</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLL-AF4 constitutive knock-in</td>
<td>NA</td>
<td>Lymphoid and myeloid hyperplasia</td>
<td>520 d</td>
<td>Chen et al(^{13})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-cell lymphoma (most common)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MPD-like myeloid leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enythroblast leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLL-AF4 conditional invertor</td>
<td>Lmo2-Cre (HSC)</td>
<td>Embryonic lethal</td>
<td>NA</td>
<td>Metzler et al(^{14})</td>
</tr>
<tr>
<td></td>
<td>Rag1-Cre (B, T cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lck-Cre (T cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD19-Cre (B cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vav-Cre (all definitive hematopoietic cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE-Cadherin-Cre (hemogenic endothelium + all definitive hematopoietic cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLL-AF4 conditional knock-in</td>
<td>Miu1-Cre</td>
<td>Pre-B ALL or AML</td>
<td>152 d</td>
<td>Krivtsov et al(^{16})</td>
</tr>
<tr>
<td>MLL-AF4 transgenic</td>
<td>NA</td>
<td>Pro-B ALL or lymphoma</td>
<td>144 d</td>
<td>Tamai and Inokuchi(^{20})</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, HSC = hematopoietic stem cells, MPD = myeloproliferative disorder, NA = not applicable.
patients with a t(9;11).29 Using the same model, Kersey’s lab assessed the potential of endogenous Mll-AF9 to transform phenotypically defined populations (HSC, CLP, CMP, and GMP) and to initiate leukemia.33 They showed that both HSCs and CMPs could be immortalized in vitro and transformed in vivo by MLL-AF9 so AML was initiated even when a low number of MLL-AF9+ cells were transplanted. In contrast, committed myeloid progenitors (CMP) were somehow refractory to MLL-AF9 transformation and a large number of MLL-AF9+ cells had to be transplanted for leukemia initiation. GMP progenitors could not be immortalized by MLL-AF9 so far, indicating they are not target cells for such a fusion. In addition, the Rabbitts’ lab developed a conditional knock-in mouse model to address which is the cell-of-origin of this disease.34 This model consisted in a translocator mice where a loxP sequence was included at the desired breaking point in the sequences of both Mll and Af9 genes, promoting their recombination upon Cre expression. To specifically promote the recombination in particular cell types, this translocator model was bred with specific Cre-models (Lmo2-Cre, expressing Cre enzyme in the HSC compartment and Lck-Cre expressing Cre in the T-cell compartment).33 Contrarily to the Mll-Enl model described above, the Mll-Af9 model was unable to recapitulate hematological malignancies when Mll-Af9 was expressed in the T cell compartment. However, when expressed into more primitive cells/HSCs, a myeloproliferative disorder (MPD)-like myeloid leukemia was observed, underlying the importance of the cell-of-origin for the oncogenic fusion to drive a specific leukemia development/phenotype.

Inducible transgenic models allow for temporal control of transgene expression. An inducible MLL-AF9 (human sequence) model was developed previously in the Schwaller’s lab,19 similar to the iMLL-ENL model reported in this issue of HemaSphere.2 In the iMLL-AF9 study, authors recreated AML in mice upon doxycycline administration, showing that the leukemic cells become oncogene-addicted, since the disease regressed after doxycycline removal, demonstrating that MLL-AF9 is necessary for AML maintenance. They also investigated the cell-of-origin of MLL-AF9-induced AML using purified LT-HSCs and GMPs populations. Both populations gave rise to AML after doxycycline induction but with different latencies. Resulting AML showed a primitive progenitor phenotype, cytotoxic drug resistance and a stemness and migration gene signature. They also observed a subtype of LT-HSCs-derived AML (LT-HSCs-early-AMl), arising from a more immature HSC phenotype, enriched for LICs and more aggressive than LT-HSCs-late- and GMP-derived AML.

### Table 2
Summary of MLL-ENL Mouse Models

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cre Line</th>
<th>Disease Phenotype (LIC)</th>
<th>Average Latency</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLL-Enl translocator model by LoxP/Cre-mediated recombination</td>
<td>Lmo2-Cre (HSC)</td>
<td>Myeloproliferative-disease-like myeloid leukemia</td>
<td>120 d</td>
<td>Forster et al24</td>
</tr>
<tr>
<td></td>
<td>Lck-Cre (T cells)</td>
<td>Either lymphoid or myeloid neoplasia</td>
<td>550 d</td>
<td>Drynan et al23</td>
</tr>
<tr>
<td></td>
<td>Lmo2-Cre (HSC)</td>
<td>Myeloid leukemia</td>
<td>120-180 d</td>
<td>Cano et al35</td>
</tr>
<tr>
<td></td>
<td>Lck-Cre (T cells)</td>
<td>AML and ALL</td>
<td>170 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rag1-Cre (B, T cells)</td>
<td>Myeloid-like leukemia</td>
<td>550 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD19-Cre (B cells)</td>
<td>No phenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen-inducible MLL-ENL-ERTm inserted at the endogenous locus</td>
<td>NA</td>
<td>Long latency MPD with progression to AML upon DDR inhibition</td>
<td>229-140 d (primary recipients)</td>
<td>Takacova et al26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>165-140 d (secondary recipients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX-inducible MLL-ENL inserted at the Col1a1 locus under tetracycline-regulated control (Col1a1-tetO-MLL/ENL)</td>
<td>NA</td>
<td>AML when expressed from progenitors, but not from HSC</td>
<td>EFS: 5-30 wk depending on targeted cell transplanted (GMLP &lt; pGM &lt; CLP &lt; GMP)</td>
<td>Ugale et al27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AML (T progenitors: DN1–DN3)</td>
<td>DNI: 9-14 wk post-transplant</td>
<td>Ugale et al28</td>
</tr>
<tr>
<td>DOX-inducible MLL-ENL inserted at the Gata1 locus under tetracycline-regulated control (Gata1-terO-MLL/ENL)</td>
<td>NA</td>
<td>AML (BLP and Hardy fractions B–F)</td>
<td>BLP: 20 wk post-transplant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KrasG12D upon in vitro Tal-Cre recombination</td>
<td>AML (GMLP with simultaneous hits)</td>
<td>Only MLL-ENL: 100 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T-ALL (GMLP with sequential hits: KrasG12D first and MLL-ENL later)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MLL × KrasG12D; 31 d</td>
<td>Only KrasG12D; 143 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX-inducible MLL-ENL inserted at the Hprt locus under tetracycline-regulated control (Mll-ENL)</td>
<td>NA</td>
<td>Biphenotypic mixed lineage leukemia</td>
<td></td>
<td>Stavropoulou et al29</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, BLP = B cell progenitors, CLP = common lymphoid progenitor, CMP = committed myeloid progenitors, DDR = DNA damage response, DOX = doxycycline, EFS = event-free survival, ERTm = estrogen binding domain of estrogen receptor, GMLP = granulocyte-monocyte-lymphoid progenitor, GMP = granulocyte and macrophage progenitor, HSC = hematopoietic stem cell, LIC = leukemia-initiating cells, LMPP = lymphoid-primed multipotent progenitor, MPD = myeloproliferative disorder, NA = not applicable, pGM = pregranulocyte-monocyte progenitor.
In conclusion, MLL-AF9 mouse models have been able to recapitulate the main features including phenotype and latency of human ALL and AML using different mouse models expressing either a chimeric (mouse–human) or a human version of the fusion gene. Humanized models based on retro or lentiviral gene delivery into human HSC followed by xenotransplantation into immunosuppressed mice have also been developed in order to better mimic the biology of the human MLL-AF9+ leukemia, but similar transgene expression levels caveats were reported. Cutting-edge genome editing (TALEN and CRISPR/Cas9) strategies are currently been explored as more accurate mechanisms to recreate the allele-specific exact translocation process, with the advantages of reproducing endogenous expression levels and also reciprocal translocations. These models will, without hesitation, continue providing more precise experimental tools for modeling MLL-rearranged leukemia. Table 3 summarizes current mouse models available for MLL-AF9+ acute leukemia.

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