Rearrangement of **ALL1** (MLL) in Acute Myeloid Leukemia with Normal Cytogenetics1,2

Michael A. Caligiuri,3,4 Matthew P. Strout,4 David Lawrence, Diane C. Arthur, Maria R. Baer, Feng Yu, Sakari Knuttila, Krzysztof Mrózek, Adam R. Oberkircher, Guido Marcuccii,4 Albert de la Chapelle,4 Erkki Elonen, AnneMarie W. Block, P. Nagesh Rao, Geoffrey P. Herzig, Bayard L. Powell, Tapani Ruutu, Charles A. Schiffer, and Clara D. Bloomfield4


ABSTRACT

Approximately 45% of adults with acute myeloid leukemia (AML) have normal cytogenetics and therefore lack structural abnormalities that can assist in the localization and characterization of molecular defects. The partial tandem duplication of the **ALL1** (MLL) gene has been found in several such cases of AML, yet its frequency and clinical significance are unclear. We performed Southern analysis of the **ALL1** gene in pretreatment samples from 98 AML patients with normal cytogenetics. Eleven of 98 such patients (11%; 95% confidence interval, 6—19%) showed rearrangement of **ALL1** at diagnosis. The partial tandem duplication of **ALL1** was responsible for **ALL1** rearrangement in all such cases examined, making it a frequent molecular defect in adult AML patients with normal cytogenetics. Furthermore, patients with **ALL1** rearrangement had a significantly shorter duration of complete remission when compared to patients without **ALL1** rearrangement (P = 0.01; median, 7.1 versus 23.2 months). This defect defines for the first time a subset of AML patients with normal cytogenetics who have short durations of complete remission and thus require new therapeutic approaches.

INTRODUCTION

Distinctive patterns of chromosomal aberrations occur in approximately 55% of cases of adults with de novo AML5 (1). These abnormalities can identify genes with a role in leukemogenesis, and their presence helps to predict the response to intensive therapy and overall prognosis (1, 2). In the remaining 45% of patients, no clonal cytogenetic abnormality can be found on routine karyotypic analysis. However, in recent studies, a rearranged **ALL1** gene has been observed in a few patients with AML and a normal karyotype (3—5).

Many different balanced translocations in AML involve **ALL1**, a gene located at 11q23, and also termed **MLL**, **HRX**, and **Htrx-1** (6—10). The multiplicity of partner genes that fuse with **ALL1** and their apparent lack of homology with one another (in many instances) have made it difficult to understand how these partners interact with **ALL1** in leukemogenesis. Typically, adults with AML and translocations at 11q23 have an adverse prognosis (1, 11).

We reported an **ALL1** rearrangement in 2 of 19 adults with AML and a normal karyotype (3). The rearrangement was actually a tandem duplication of an internal portion of the **ALL1** gene that spanned exons 2—8, rather than a balanced translocation with another chromosome (12). Two other groups confirmed these results in seven additional cases of AML (4, 5). These findings suggest that **ALL1** may promote leukemogenesis without rearranging with a partner gene from another chromosome. The current study was undertaken to determine the frequency and prognostic significance of **ALL1** rearrangement in 98 patients with AML and normal cytogenetics.

PATIENTS AND METHODS

**Patients.** All patients were adults with de novo AML in whom the karyotype of the diagnostic bone marrow sample was normal (see below). Cryptopreserved cells were available in 88 cases, and DNA from the diagnostic marrow sample was available in 10 cases. Standard French-American-British (FAB) morphological and cytochemical criteria were used (13). Cases were excluded if they had acute promyelocytic leukemia (M3) or if sufficient DNA was not available for Southern analysis. Ninety-eight patients qualified for the study. Informed consent was obtained from all patients according to the guidelines set forth by institutions participating in the study.

Two patients received no treatment. Induction therapy for 55 patients was cytarabine (200 mg/m2/day for 7 days) and daunorubicin [45 mg/m2/day for 3 days (14—16)]; for 25 patients, it was cytarabine [3 gm/m2 (1.5 gm/m2 if >50 years) every 12 h × 12 doses] and idarubicin [12 mg/m2/day for 3 days (17)]; 8 patients received cytarabine (100 mg/m2/day for 9 days), daunorubicin (50 mg/m2/day for 3 days), and 6-thioguanine [150 mg/m2/day for 9 days (18)]; 6 patients received cytarabine (100—200 mg/m2/day for 7 days) with daunorubicin (30—45 mg/m2/day) or idarubicin (12 mg/m2/day) for 3 days and etoposide (100 mg/m2/day) for 3 days (2 patients); for 2 patients, the treatment was cytarabine (100 mg/m2/day for 9 days), daunorubicin (50 mg/m2/day for 3 days), and 6-thioguanine (150 mg/m2/day for 9 days) followed by cytarabine...
(3 gm/m² every 12 h for 4 doses) and amssacrine [115 mg/m²/day for 5 days (18)]. Of the 68 patients who achieved complete remission on initial treatment, 36 received intensification treatment with high-dose cytarabine (1.5–3 gm/m²), 17 received only etoside (3.6 gm/m²) and cyclophosphamide (200 mg/kg; Ref. 17), 10 received regimens with lower doses of cytarabine (14, 15), 3 patients received no therapy after entering complete remission, and postinduc-
tion therapy was unknown for 1 patient. Three patients underwent allogeneic
bone marrow transplantation in first complete remission.

Cytogenetic Analyses. The definition of a cytogenetic clone and descrip-
tions of karyotypes followed the International System for Human Cytogenetic
Nomenclature (19). For a case to be considered cytogenetically normal, study
of a minimum of 20 marrow metaphases was required.

Fluorescence in situ Hybridization and Comparative Genomic Hybrid-
ization for Detection of +11. Cells from the diagnostic bone marrow of five
patients with ALL+ rearrangement and normal cytogenetics were studied for
+11 by fluorescence in situ hybridization with an a satellite centromeric probe
for chromosome 11 (focus 11ZI; Oncor, Gaithersburg, MD) labeled with
digoxigenin. Bone marrow cells from 12 normal donors were studied as
controls. Hybridization signals were counted in 1000 interphase cells. In one
case, comparative genomic hybridization was performed according to Kallion-
kiemi et al. (20) with modifications (21).

DNA and RNA Preparation. Genomic DNA was extracted using a stan-
dard isolation procedure (22), and total cellular RNA was extracted by thawing
frozen cells and placing them into RNeazol (Biotec Laboratories, Houston,
TX) following the manufacturer's directions.

Southern Analyses. Approximately 8 µg of genomic DNA were digested
to completion with BamHI, HindIII, or EcoRI. The BamHI and EcoRI digests
were hybridized to the B859 and SAS1 probes, respectively (3, 23). HindIII
digests were hybridized to the B859 probe, stripped, and hybridized to the
SAS1 probe. Southern blotting, probe radiolabeling, and autoradiography were
performed by standard techniques (24).

RT-PCR. PCR primer sets 1 and 2 and exact location and sequences, along
with conditions for amplification, have been published (25). Single-round
RT-PCR with outside primers was used for amplification of the partially
duplicated ALL+ fusion transcript in seven ALL+ cases. Amplification prod-
ucts were analyzed by electrophoresis on 1.5% agarose gels stained with
ethidium bromide. All PCR products were directly sequenced to identify the
involved exons and the extent of the duplication.

DNA Sequencing and Sequence Analyses. DNA sequencing was per-
formed with an Applied Biosystems model 373 stretch DNA sequencing
system (Perkin-Elmer Corp., Forest City, CA). The GeneWorks (IntelliGen-
etics, Campbell, CA) computer program was used for sequence analysis.

Molecular and Clinical Definitions. To be considered ALL+, DNA from
the diagnostic bone marrow sample had to show rearrangement of ALL+
by Southern analysis using the B859 probe. In our laboratory, the B859 probe
is able to detect a rearrangement of ALL+ when the rearranged gene is present in
≥10% of the cells in a sample. The percentage of leukemic blasts in the
diagnostic bone marrow samples used for Southern analysis in this study
ranged from 31–96%. Complete remission was defined by the criteria estab-
lished by the National Cancer Institute conference on AML (26). Duration of
complete remission was measured from the date of documented complete
remission to the date of AML relapse; patients were censored at the date they
were last known to be in complete remission, date of bone marrow transplan-
tation during first complete remission, or at the date of death if they died with
no evidence of AML. Overall survival was measured from the date of entry
into the treatment study until date of death. For analysis of survival, only
patients alive at last follow-up were censored. The median follow-up for the 34
patients whose complete remission duration was censored was 22 months, with

Fig. 1. Partial tandem duplication of the ALL+ gene. A, the normal ALL+ gene consists of at least 36 exons (vertical lines and boxes) and introns (horizontal line between exons).
Restriction enzyme sites used in the Southern analysis of ALL+ gene rearrangement are indicated: E, EcoRI; B, BamHI; and H, HindIII. The SAS1 genomic probe hybridizes to a region
of intron 1 that is immediately 5' of exon 2, allowing for the detection of genomic rearrangements involving this region of ALL+. The B859 cDNA probe hybridizes to exons 5–11,
allowing for the detection of genomic rearrangements involving this region of ALL+. B, rearrangement of ALL+ can be detected with the B859 probe, and partial duplication can be
confirmed using the SAS1 probe. In this example, there is a duplication of exons 2–6, and the unique genomic fusion of intron 6 with intron 1 is indicated by the junction of the black
horizontal bar with the white horizontal bar. After complete digestion of genomic DNA with the HindIII restriction enzyme, SAS1 and B859 each hybridize to two distinct germ-line
fragments. Both probes also hybridize to the same rearranged fragment, indicating the genomic fusion of these two regions. C, partial duplication can be confirmed by RT-PCR
amplification of the expressed mRNA fusion transcript. Outside primers from primer set 1 (25) in exons 5 and 3 are indicated by the black triangles.
**RESULTS**

**Molecular Analyses.** The 98 patients with AML and normal cytogenetics had a median age of 53 years (range, 18–84 years), and 54% were women. Probes for Southern hybridization, designated B859 and SAS1, have been described previously (3, 23). The B859 probe is an 859-bp BamHI fragment of ALL1 cDNA derived from exons 5–11 of the ALL1 gene. Using a BamHI or HindIII digestion of DNA, the probe detects virtually all rearrangements that occur in the breakpoint cluster region of the ALL1 gene (3, 29). The SAS1 probe detects rearrangements of ALL1 that occur in the partial tandem duplication of ALL1 involving exon 2 in all 20 cases. For this reason, a rearrangement of ALL1 detected by both the B859 and SAS1 probes by Southern analysis is probably diagnostic of a partial tandem duplication (Fig. 1B).

In three cases, rearrangement of ALL1 by Southern analysis was inferred. In two cases, the duplication of ALL1 spanned exons 2—8. In each of the seven cases in which the partial duplication was detected by single-round RT-PCR, the sequence of the unique fusion was found to be in frame.

RNA was not available from patient 2 for RT-PCR, and genomic cloning was not successful. However, in this case, we demonstrated rearrangement of ALL1 by Southern analysis using the B859 and SAS1 probes (Table 1). In 7 cases reported here, plus 13 others in which ALL1 was found to be rearranged by Southern analysis with both B859 and SAS1 (4, 5, 25), cloning and sequencing showed a partial tandem duplication of ALL1 involving exon 2 in all 20 cases. For this reason, a rearrangement of ALL1 detected by both the B859 and SAS1 probes by Southern analysis is probably diagnostic of a partial tandem duplication (Fig. 1B).

**Statistical Analyses.** Pretreatment factors were compared between ALL1+ and ALL1− patients. The Fisher’s exact two-tailed test and the Mann-Whitney test were used to compare binary and uncensored continuous data, respectively. Multiple comparison adjustment was used for the analysis of FAB based on the Bonferroni inequality (27). The log-rank test was used to analyze differences in distributions for complete remission duration. Because the overall survival curves cross, the modified Kolmogorov-Smirnov test rather than the log-rank test was used to test for a difference in survival distribution (28). The level of statistical significance used in all cases was 0.05, and all tests were two-tailed.

The 98 cases, 11 (11%; 95% confidence interval, 6–19%) showed evidence of a rearranged ALL1 gene (*i.e.,* ALL1+) in both BamHI and HindIII digests (Fig. 2). Of the 11 cases in which the B859 probe detected a rearranged ALL1 gene, a SAS1 probe hybridization of an EcoRI digest also demonstrated the rearrangement in 8 cases (Table 1).

Seven of the 11 ALL1+ cases were further characterized by a single round of RT-PCR (Fig. 1C and Fig. 3), and 1 additional case was characterized (patient 101) by genomic cloning. In all eight cases, we found the partial tandem duplication of ALL1 by DNA sequencing (Table 1). Six cases had duplications that spanned exons 2–6, and in two cases, the duplication of ALL1 spanned exons 2–8. In each of the seven cases in which the partial duplication was detected by single-round RT-PCR, the sequence of the unique fusion was found to be in frame.

A minimum of 1 month and a maximum of 89 months. The median follow-up time for the 39 patients whose overall survival duration was censored was 27 months with a minimum of 2 months and a maximum of 90 months.

**Table 1 Results of molecular analysis**

<table>
<thead>
<tr>
<th>Unique patient number</th>
<th>B859 analysis</th>
<th>SAS1 analysis</th>
<th>RT-PCR analysis</th>
<th>Duplicated region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 8</td>
</tr>
<tr>
<td>2+</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 8</td>
</tr>
<tr>
<td>101</td>
<td>Positive</td>
<td>Positive</td>
<td>Not done</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>104</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 8</td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 8</td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 8</td>
<td></td>
</tr>
<tr>
<td>161</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 8</td>
<td></td>
</tr>
<tr>
<td>166</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 8</td>
<td></td>
</tr>
<tr>
<td>176</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 6</td>
</tr>
<tr>
<td>211</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Exon 2 to exon 6</td>
</tr>
<tr>
<td>300</td>
<td>Positive</td>
<td>Positive</td>
<td>Not done</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>

a No material available.

b Reported in Refs. 3 and 12.

c Reported in Ref. 3.

...
Table 2 Comparison of adults with de novo AML and normal cytogenetics with (ALL1+) and without (ALL1−) rearrangement of ALL1

<table>
<thead>
<tr>
<th></th>
<th>ALL1+ (n = 11)</th>
<th>ALL1− (n = 87)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median yrs)</td>
<td>41</td>
<td>53</td>
<td>0.51</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>82</td>
<td>51</td>
<td>0.06</td>
</tr>
<tr>
<td>FAB classification (%)</td>
<td>100</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>M1</td>
<td>18</td>
<td>19</td>
<td>1.0</td>
</tr>
<tr>
<td>M2</td>
<td>64</td>
<td>42</td>
<td>0.21</td>
</tr>
<tr>
<td>M4</td>
<td>18</td>
<td>28</td>
<td>0.72</td>
</tr>
<tr>
<td>M5</td>
<td>0</td>
<td>7</td>
<td>1.0</td>
</tr>
<tr>
<td>Percentage of bone marrow blasts (median)</td>
<td>66</td>
<td>69</td>
<td>0.94</td>
</tr>
<tr>
<td>Minimum percentage</td>
<td>31</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Maximum percentage</td>
<td>93</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>WBCs x 10^9/mm^3 (median)</td>
<td>38</td>
<td>29</td>
<td>0.35</td>
</tr>
<tr>
<td>Percent peripheral blood blasts (median)</td>
<td>66</td>
<td>52</td>
<td>0.49</td>
</tr>
<tr>
<td>Percent with Auer rods</td>
<td>56</td>
<td>52</td>
<td>1.0</td>
</tr>
<tr>
<td>Platelet count—cells x 10^3/mm^3 (median)</td>
<td>59</td>
<td>68</td>
<td>0.71</td>
</tr>
<tr>
<td>Median hemoglobin (g/dl)</td>
<td>9.4</td>
<td>9.1</td>
<td>0.88</td>
</tr>
<tr>
<td>Treatment protocol (%)</td>
<td>0.2- ALL1+(n=7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB 8525®</td>
<td>9</td>
<td>4</td>
<td>0.38</td>
</tr>
<tr>
<td>CALGB 8923®</td>
<td>18</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>CALGB 9022®, 9222®</td>
<td>18</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>DS 91-20®, 94-26®</td>
<td>27</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>AML 86®</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Complete remission rate (%)</td>
<td>70</td>
<td>71</td>
<td>1.0</td>
</tr>
<tr>
<td>Median complete remission duration (mo)</td>
<td>7.1</td>
<td>23.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Median survival (mo)</td>
<td>13.8</td>
<td>20.1</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Reported in Ref. 14.  
* Reported in Ref. 15.  
* Reported in Ref. 16.  
* Reported in Ref. 17.  
* Reported in Ref. 18.

demonstrated with the B859 probe but not with SAS1. In one case (patient 104), further analysis was not possible. In the second case (patient 176), a partial tandem duplication of ALL1 was not detected by RT-PCR. The third case (patient 161) had a partial duplication of ALL1 spanning exons 2–6, but genomic cloning revealed that the breakpoint within intron 1 was almost 20 kb 5’ of the SAS1 site (data not shown). Thus, a negative result with the ALL1 probe does not exclude that a rearranged ALL1 detected with B859 by Southern analysis is due to partial duplication. If we count the detection of rearrangement of ALL1 with both B859 and SAS1 probes as diagnostic of a partial tandem duplication, then duplications of ALL1 occurred in 9 of the 11 ALL1+ cases of AML with normal cytogenetics (Table 1).

The majority of patients with AML and +11 as the sole cytogenetic abnormality have a partial tandem duplication of ALL1 (25). We performed fluorescence in situ hybridization using a chromosome 11 probe in five cases from the current study with direct evidence for the duplication (patients 1, 2, 144, 146, and 166) and in patient 176. We found no evidence of +11, and in an additional case (patient 104) studied by comparative genomic hybridization, no DNA copy number changes were observed in chromosome 11 or in any other chromosome. RNA was isolated from diagnostic bone marrow samples of 63 patients who lacked ALL1 rearrangement by Southern analysis. None of these samples amplified a product by single-round RT-PCR as was performed on the ALL1+ patients.

**Correlation of Molecular Findings with Clinical Features.** Clinical characteristics of the 11 ALL1+ patients were not significantly different from the 87 AML patients with normal cytogenetics who did not rearrange ALL1 (i.e., ALL1−). The ALL1+ patients had a median age of 41 years (range, 22–77 years), and nine were female. Two cases were FAB M1, seven cases were M2, and two were M4. Both patients with M4 (patients 166 and 211) had direct evidence of partial tandem duplication. All except for patient 2 received induction chemotherapy, and seven of those treated achieved complete remission. The median duration of complete remission (7 months) was relatively short compared to a recent report (14), with only patient 101 remaining in continuous complete remission at 80 months. This patient received eight intensive cycles of combination chemotherapy including two induction cycles with cytarabine (100 mg/m^2/day for 9 days), daunorubicin (50 mg/m^2/day for 3 days), and 6-thioguanine (150 mg/m^2/day for 9 days; Ref. 18). Median survival for ALL1+ patients (14 months) was also relatively short compared to a recent report (14).

The presenting clinical and laboratory data in the 11 ALL1+ patients and the 87 ALL1− patients were similar, and there were no remarkable differences in treatment (Table 2). The complete remission rate was similar for both groups of patients. Postinduction regimens were also similarly distributed between the two groups. However, the seven ALL1+ patients who achieved complete remission had shorter durations of complete remission compared to the 61 ALL1− patients (P = 0.01; median, 7.1 versus 23.2 months; Fig. 4). One ALL1+ patient was in complete remission at 2 years, whereas 16 ALL1− patients were in complete remission at 2 years. The difference in 2-year survival did not reach statistical significance (P = 0.06; median, 13.8 versus 20.1 months).

**DISCUSSION**

We screened DNA from the diagnostic bone marrow of 98 adults with de novo AML and normal cytogenetics by Southern analysis with the B859 probe, a genomic probe that detects virtually all rearrangements that occur within the breakpoint cluster region of the ALL1 gene (3, 29). In 11%, ALL1 was rearranged; the estimated proportion of such cases in 6–19%, based on the 95% confidence interval. Moreover, the partial tandem duplication of ALL1 was detected in all nine ALL1+ cases with adequate material for additional molecular analysis.

We and others (4) found the partial tandem duplication of ALL1 in AML of the FAB M1, M2, M4, and M5 subtypes with normal cytogenetics. This suggests that the duplication can occur along several lineages of myeloid differentiation or before lineage commitment and then contributes to leukemogenesis during the early stages of myeloid or monocytic differentiation. There is considerable structural and functional evidence to suggest that the wild-type ALL1 may encode a transcription factor that regulates morphogenesis and hematopoiesis (30, 31). However, the mechanism by which the partial tandem duplication may contribute to leukemogenesis is unknown. Se-
quencing analysis has, thus far, always revealed the unique fusion of exons in the partial tandem duplication of ALL1 to be in-frame, suggesting that the resultant mRNA is capable of being translated into a full-length protein. The region of ALL1 that is tandemly duplicated contains both DNA binding and DNA methyltransferase motifs (30). The tandem duplication may exert a dominant-negative effect, as has been described for other transcription factors involved in leukemogenesis (32, 33).

The data presented in this report suggest that ALL1+ patients may have a shortened duration of complete remission after intensive chemotherapy compared to patients with de novo AML and normal cytogenetics who lack this genetic defect. To our knowledge, rearrangement of ALL1 and its association with the partial duplication of ALL1 is the first consistent genetic alteration reported in de novo AML adult patients with normal cytogenetics that imparts an adverse prognosis after intensive chemotherapy. However, the results of our report will require confirmation with a prospective study that includes larger numbers of patients. The current study suggests that, like structural cytogenetic abnormalities that have prognostic significance in adult de novo AML, molecular tools may be useful in the absence of cytogenetic abnormalities to unveil genetic alterations that have prognostic significance.

The ALL1+ patients that did achieve complete remission did so with various postinduction therapies. The one ALL1+ patient who continues in complete remission received a unique intensive multidrug multicycle postintensification regimen. Should a prospective assessment for ALL1 rearrangement demonstrate a significantly shortened overall survival in ALL1+ patients, serious consideration might then be given to this type of intensification or to allogeneic stem cell transplantation. Alternatively, autologous stem cell transplantation that uses a purging technique to eliminate disease may provide a novel technique for ex vivo bone marrow purging. Blood, 88: 731—741, 1996.

ACKNOWLEDGMENTS

We are indebted to Christine Wick for preparation of the manuscript; Linda Regal, Laurie Ann Ford, Ritva Keskimäki, and Arja Asummaa for assistance with data collection; and Pamela Evans and Eileen Healey for tissue procurement. We thank our colleagues at Roswell Park Cancer Institute, the University of Helsinki, and the Cancer and Leukemia Group B for assisting in the study and management of the patients in this report. We thank Dr. Carlo Croce for the B859 and SASI probes.

REFERENCES


Rearrangement of \textit{ALL1} (\textit{MLL}) in Acute Myeloid Leukemia with Normal Cytogenetics

Michael A. Caligiuri, Matthew P. Strout, David Lawrence, et al.