ABSTRACT

From its beginnings two decades ago with the analysis of chromosomal translocation breakpoints, research into the molecular pathogenesis of acute lymphoblastic leukemia (ALL) has now progressed to the large-scale resequencing of candidate oncogenes and tumor suppressor genes in the genomes of ALL cases blocked at various developmental stages within the B- and T-cell lineages. In this review, we summarize the findings of these investigations and highlight how this information is being integrated into multistep mutagenesis cascades that impact specific signal transduction pathways and synergistically lead to leukemic transformation. Because of these advances, fueled by improved technology for mutational analysis and the development of small-molecule drugs and monoclonal antibodies, the future is bright for a new generation of targeted therapies. Best illustrated by the successful introduction of imatinib mesylate, these new treatments will interfere with disordered molecular pathways specific for the leukemic cells, and thus should exhibit much less toxicity and fewer long-term adverse effects than currently available therapeutic modalities.

INTRODUCTION

Great strides have been made in the understanding of the molecular pathophysiology of acute lymphoblastic leukemia (ALL). The cloning and characterization of recurrent chromosomal translocations has allowed the identification of genes critical for the leukemogenic process. Furthermore, the presence of particular translocations often has prognostic importance and can be used to stratify patients into those who require more-intensive therapy. The use of gene expression analysis to characterize the differences in gene expression between leukemias with different chromosomal aberrations has solidified the notion that specific chromosomal abnormalities specify unique leukemias. More recently, mutations in specific signaling molecules have been identified in B-precursor and T-precursor ALL that might be targeted with small molecule inhibitors. These developments have generated much excitement about the possibility for development of therapies that are designed based on the specific genetic aberrations present in individual leukemias. This review will outline some of the more recent findings delineating the molecular genetics of ALLs. Although the review is divided into adult, childhood, and infant ALL, data are accumulating in which similar molecular defects share similar pathophysiology across the different age groups. Molecular pathophysiology will be described in the age group in which the genetic abnormalities are the most common.

CHILDHOOD ALL

B-Precursor ALL

B-precursor ALL is the most common form of acute leukemia in children and thus represents the most common malignancy of childhood. As a group, children diagnosed with B-precursor ALL have a good prognosis. Recent treatment protocols from groups in Europe and the United States demonstrate an event-free survival of
approximately 80% for children between the ages of 1 and 18 years. While this represents a remarkable improvement over the dismal cure rates only 30 years ago, most believe that further improvement will require the development of new therapeutic approaches—approaches that will likely come from a better understanding of the molecular pathophysiology of leukemia. Furthermore, long-term adverse effects remain a troublesome problem for the increasing numbers of survivors of childhood leukemia.

Recurrent chromosomal abnormalities are a hallmark of lymphoblastic leukemias and provide insight into the molecular mechanisms of leukemogenesis. The most common translocation found in childhood B-precursor ALL is the t(12;21)(p13;q22). Although standard karyotypic analysis does not identify most TEL-AML1 translocations, molecular techniques demonstrate the presence of this translocation in approximately 25% of childhood ALL (Fig 1). Microarray-based gene expression studies have shown that TEL-AML1–rearranged ALLs represent a unique biologic subset of B-precursor ALL. Elegant epidemiologic data demonstrating the presence of the TEL-AML1 translocation in neonatal blood spots shows that the translocation is present in blood cells at birth, up to 5 to 10 years before the development of leukemia. These data provide convincing evidence that the TEL-AML1 translocation is the initiating event in this leukemia.

The TEL-AML1 fusion protein generated by the t(12;21) contains the basic helix-loop-helix domain of TEL, fused to the DNA-binding and transactivation domains of AML1. Both the TEL and AML1 genes are found in other leukemia-associated translocations. TEL was originally cloned as a fusion partner of the platelet-derived growth factor receptor β gene (PDGFRβ) encoded by the t(5;12) in chronic myelomonocytic leukemia and is found in other translocations associated with genes such as MN1, ABL, and EVI1 in AML, and with JAK2 in T-ALL. AML1 is the DNA-binding component of the AML1/CBFβ transcription factor complex, the most frequent target of myeloid-associated translocations, including the t(8;21), t(3;21), and inv(16). The prominent role of AML1 (also known as RUNX1) in the pathogenesis of human leukemias is reinforced by the identification of inherited or acquired mutations in AML1 in acute myelogenous leukemias (AMLs); and the presence of genomic amplifications of the AML1 locus in childhood ALL.

**Fig 1.** Chromosomal abnormalities in acute lymphoblastic leukemia. The relative frequencies of chromosomal aberrations found in lymphoblastic leukemias are shown for (A) adult and (B) childhood (right) acute lymphoblastic leukemias. The groups are divided into early B-cell lineage and early T-cell lineage.
Although the mechanisms of leukemogenesis induced by TEL-AML1 remains obscure, recent data have demonstrated the importance of both TEL and AML1 for normal hematopoiesis, thus suggesting that the presence of the TEL-AML1 fusion protein leads to disordered hematopoietic development as a critical component. Tel-deficient mice die at approximately day 11 of embryogenesis associated with defective yolk sac angiogenesis, thus establishing Tel as an important regulator of development.

Recently, studies in mice using conditional inactivation of Tel alleles have shown that Tel is required for definitive hematopoiesis. In addition, the observation that loss of the normal TEL allele frequently accompanies TEL-AML1 fusion in ALL cases suggests that the leukemogenic effects of TEL-AML1 could be mediated, at least in part, through loss of function of the normal TEL protein. The absence of definitive hematopoiesis in mice lacking either AML1 or CBFβ further supports an essential role for the AML1-CBFβ complex in normal hematopoiesis.

TEL-AML1 expression is associated with an excellent prognosis, with event-free survival rates approaching 90%. In addition, the favorable prognostic impact of TEL-AML1 is independent of age and leukocyte count and was consistently favorable among patients treated on several different protocols. Thus, TEL-AML1 expression identifies a large subset of B-precursor ALL patients who may be candidates for less-intensive therapy.

Another common chromosomal aberration found in B-precursor ALL is the presence of more than 46 chromosomes (hyperdiploid ALL). As with TEL-AML1–rearranged ALL, gene expression studies demonstrated that hyperdiploid ALL represents a separate genetically defined subset of B-precursor ALL. But, the lack of a recurrent abnormality in specific genes identifiable by karyotypic analysis has prevented the identification of initiating events in this leukemia. Potential insight into the mechanism of leukemogenesis in hyperdiploid ALL came recently when activating mutations in the receptor tyrosine kinase FLT3 were identified in approximately 20% of hyperdiploid ALL. This finding is intriguing not only in that it points to activated tyrosine kinases as potential oncogenes in hyperdiploid ALL, but also in that it suggests that small-molecule tyrosine kinase inhibitors might be of benefit to patients with this leukemia. Given that patients with hyperdiploid ALL have an extremely good prognosis with event-free survival rates near 90%, it will be a challenge to determine how to incorporate such therapeutics into treatment regimens.

The t(1;19)(q23;p13) encoding the E2A-PBX fusion protein is present in about 6% of all B-precursor ALLs and in 25% of cases with a preB (cytoplasmic immunoglobulin-positive) immunophenotype. The t(1;19) (q23;p13) fuses the transactivation domain of the bHLH transcription factor E2A on chromosome 19, to the homeobox (HOX) gene PBX1 on chromosome 1. E2A contains a bHLH domain responsible for sequence-specific DNA binding and dimerization, and plays a critical role in lymphocyte development. Given that E2A-deficient mice show significant defects in lymphoid development and the t(1;19) impairs one copy of the E2A locus, loss of E2A function may contribute to leukemogenesis in this subtype of ALL. Furthermore, given the clear role of HOX genes in leukemogenesis, and the ability of PBX1 to alter HOX gene dependent regulatory programs, dysregulation of PBX1 function likely contributes to leukemogenesis.

**T-Precursor ALL**

bHLH, HOX, and other developmental genes. Transcription factor genes are the preferred targets of chromosomal translocations in the acute T-cell leukemias. Notable examples include the bHLH genes MYC, TAL1(SCL), and LYL1, which are essential for the development of other lineages such as erythroid cells (TAL1), but with the exception of MYC, they are not normally expressed in T-lymphoid cells. When rearranged near enhancers within the TCRβ-chain locus on chromosome 7, band q34, or the αβ-chain locus on chromosome 14, band q11, these regulatory genes become active, and their protein products bind inappropriately to the promoter or enhancer elements of downstream target genes.

A useful model of aberrant transcription factor expression in T-ALL is provided by TAL1 activation due to the t(1;14) or to an intragenic deletion upstream of the gene, changes that characterize as many as one fourth of all cases of childhood T-ALL. Because the TAL1 protein forms a pentameric DNA-binding complex with E2A, LMO2, GATA1 and LDB1, its ectopic expression in T cells might be expected to activate specific sets of target genes that are normally quiescent in T-cell progenitors. Alternatively, TAL1 might be leukemogenic via a dominant-negative effect, since overexpression of TAL1 can lead to a functional inactivation of E2A homodimers or E2A-HEB heterodimers, presumably by sequestering E2A in the aforementioned pentameric complex. This model is supported by the observations that E2A-deficient mice develop T-ALL, and that mice expressing the E2A inhibitor Id in the thymus also develop T-ALL. Moreover, mice that express TAL1 mutant proteins able to heterodimerize with E2A, but unable to bind DNA, develop a form of T-ALL that is indistinguishable from that produced by the full-length SCL protein.

In addition to genes encoding bHLH proteins, additional classes of regulatory genes are rearranged near TCR loci, including those encoding the proteins LMO1...
(formerly known as RBTN1 or TTG1) and LMO2 (formerly known as RBTN2 or TTG2) within the cysteine-rich LIM family.58,59 Although present in high concentrations in the central nervous system,60 these proteins are only minimally expressed or absent altogether in T cells and their progenitors. Both LMO1 and LMO2 possess zinc-finger-like structures in their LIM domains but lack the DNA-binding domains common to other transcription factors in this family, suggesting that the LIM domain functions in protein–protein rather than protein–DNA interactions. Conceivably, it could even mediate the action of other transcription factors, as indicated by the ability of LMO2 to bind to the bHLH protein TAL1 in vitro.61,62 Moreover, LMO1 induces thymic lymphomas in transgenic mice whose thymocytes bear the LMO1 gene under the control of a proximal Lck promoter.63 In this context, inappropriate expression of a LIM family protein appears to have selectively transformed a rare subset of CD8+, CD4+, CD3+ thymocytes. The t(11;14)(p15;q11) and t(11;14)(p13;q11) are thought to affect similar T-cell developmental pathways by inducing ectopic expression of either LMO1 or LMO2.

In a recent gene therapy trial in infants with X-linked severe combined immune deficiency due to underproduction of the common gamma subunit of the interleukin (IL) -2 receptor, two children whose immune systems had been reconstituted successfully using a retroviral vector carrying a cDNA for the common y chain gene have developed T-ALL. Strikingly, the malignant cells from both of these patients showed that the retroviral particle had integrated near the LMO2 gene, leading to its overexpression in the malignant lymphoblasts.64-66 This observation indicates that LMO2 can be activated iatrogenically by the nearby insertion of a highly active retroviral promoter, as well as by chromosomal translocation.

HOX11, HOX11L2, and also major HOX genes complete the list of developmental genes that are inappropriately placed under the control of TCR loci. Located on chromosome 10, band q24,67-70 HOX11 encodes a homeo-domain transcription factor that can bind DNA and trans-activate specific target genes.71 It is most closely related to Hlx, a murine homeobox gene expressed in specific hematopoietic cell lineages and during mouse embryogenesis, and it is distantly related to the antennapedia homeobox genes of Drosophila, which regulate segment-specific gene expression along the anteroposterior axis of the fly embryo.73 A specific role of HOX11 in mammalian development was demonstrated by homozygous disruption of this gene, which blocked the formation of the spleen in otherwise normal mice.74 In the mouse, Hox11 is normally expressed in specific regions of the branchial arches and ectoderm of the pharyngeal pouches of the developing hindbrain, as well as from a single site corresponding to the splanchnic mesoderm beginning on embryonic day 11.5.74 Because the nervous system develops normally in these mice, the roles of Hox11 proteins in branchial arch and hindbrain structures appear to be compensated for by other transcription factors expressed by the cells; however, the role of Hox11 in cellular organization at the site of splenic development is absolutely essential for the genesis of this organ. Lymphoid and other types of hematopoietic cells, normally lacking expression of Hox11 proteins, were not affected by loss-of-function mutations in this gene, except for the presence of asplenia-related Howell-Jolly bodies in circulating erythrocytes. Activation of HOX11 expression by chromosomal translocations, either the t(10;14)(q24;q11) or the t(7;10)(q35;q24), in developing T cells must therefore interfere with normal regulatory cascades to promote malignant transformation. Interestingly, HOX11 expression by T-ALL blasts is associated with a favorable prognosis in children treated with modern intensive therapy, possibly because these leukemias have a gene expression signature reflecting an arrest at the early cortical thymocyte stage with downregulation of anti-apoptotic proteins such as BCL2 and BCLXL.4

In addition, the HOX11L2 gene, located at chromosomes 5 band q35, has been found to be activated by translocation near the BCL11B locus as a result of the t(5;14)(q35;q32), or by fusion to the TCRB locus as a result of the t(5;14)(q35;q11). Although neither of these translocations is commonly recognized with use of conventional cytogentic techniques, almost 20% of childhood T-ALL patients demonstrated a HOX11L2 gene translocation by fluorescence in situ hybridization.75 Although some studies have suggested that T-ALL patients whose lymphoblasts overexpress HOX11L2 have a poor prognosis, this finding appears to be eliminated in children who receive more-intensive therapy.76

More recently, a new recurrent translocation has been recognized that targets and dysregulates expression from the whole HOXA cluster.77 Thus, this translocation mimics the global HOXA gene dysregulation characteristic of T-ALLs with MLL gene fusions, as discussed in the next section. Gene expression analysis demonstrates that this subgroup shares aspects of the gene expression signature characteristic of HOX11- and HOX11L2-overexpressing T-ALLs.

Fusion genes in T-ALL. Although most chromosomal translocations in T-ALL patients lead to inappropriate activation of structurally intact cellular proto-oncogenes such as MYC, TAL1, HOX11 or LMO2, some can produce fusion genes. MLL-ENL fusion results from the translocation t(11;19)(q23;p13), and is associated with acute myeloid leukemia, B-cell precursor ALL, and T-ALL. Strikingly, in one series, all 11 T-ALL patients with the MLL-ENL fusion became long-term survivors, suggesting that this rearrangement is associated with a good prognosis.78 Gene expression array analysis showed that these cases overexpress major
HOX genes such as HOXA9 as well as MEIS1, resembling the expression signature identified in B-lineage leukemias with MLL fusion genes. The CALM-AF10 fusion gene was initially identified in the U937 cell line, which was established from a patient with histiocytic lymphoma and shown to differentiate along the macrophage lineage in vitro. Subsequently, CALM-AF10 was found in patients with a wide spectrum of hematologic malignancies, but most commonly in patients with T-ALL. CALM-AF10 fusions were identified in 12 (9%) of 131 consecutive patients with T-ALL. Of note, all of the patients with CALM-AF10 fusions had either immature T-cell lymphoblasts that expressed no TCR genes or γΔ-positive lymphoblasts. None of the patients with CALM-AF10 fusions expressed TCRα/β, suggesting that such fusions are restricted to the TCRγδ lineage.

NOTCH1 gene mutations in T-ALL. Very rare cases of T-ALL harbor chromosomal translocations that produce a truncated and activated form of NOTCH1, a gene that normally encodes a transmembrane receptor, as shown in Figure 2, that is involved in the regulation of normal T-cell development and may other tissues during embryologic development. The NOTCH-1 protein is generated as a pro-protein that is synthesized and then cleaved into a heterodimer by a furin-like protease. This heterodimer migrates to the cell membrane where signals from its ligands, which consist of Delta-Serrate-Lag2 family proteins, lead to further cleavages, including a final step catalyzed by the enzyme gamma-secretase. This final step generates an intracellular NOTCH protein, which translocates to the nucleus and forms a complex with the CSL protein and Mastermind cofactors to initiate transcription. NOTCH-1 had previously been shown to be truncated and activated by a rare t(7;9) in T-cell ALL and the same activated fragment was shown to induce T-cell ALL in mouse models. To uncover more frequent types of NOTCH1-activating mutations, we tested several T-cell leukemia cell lines with a drug known to inhibit gamma-secretase and found evidence of cell-cycle arrest that was subsequently proven to be NOTCH-1 specific. We were able to identify specific mutations in sequences encoding both the heterodimerization and PEST domains of NOTCH1 in these cell lines, and subsequently in over 50% of primary patient T-cell ALL samples, including samples from all of the molecular subtypes of T-cell leukemia (Fig 3).

INFANT ALL

Leukemias bearing translocations involving chromosome 11q23 are found in leukemic blasts from > 70% of leukemias in patients younger than 1 year of age whether the immunophenotype is designated AML or ALL. Some infant leukemias express antigens characteristic of both lymphoblasts and monoblasts, and are sometimes designated acute biphenotypic leukemias. Infants diagnosed with ALL harboring an 11q23 rearrangement have a particularly poor prognosis as compared to other children with ALL. The association of 11q23 rearrangements with either ALL or AML is unique in that most other translocations tend to be associated with leukemias of a particular hematopoietic lineage. These observations prompted the name mixed-lineage leukemia (MLL) for the gene on 11q23.

The MLL-AF4 gene generated by the t(4;11)(q21;q23) was cloned in the early 1990s. MLL-AF4 encodes a protein of 2304 amino acids, with the NH2-terminal 1439 amino acids derived from MLL on chromosome 11, and COOH-terminal 865 amino acids from the AF4 gene on chromosome 4. Subsequently, more than 40 different translocations have been identified, all of which produce a fusion protein possessing the NH2-terminal of MLL fused to COOH-terminus of the fusion partner. Although MLL translocations can be found in either ALL or AML, particular translocations are associated with hematopoietic lineage with the t(4;11) found most often in ALL and the t(9;11)(p21;q23) AML. But this specificity is not absolute in that the t(9;11) is also frequently identified in blasts designated as ALL. The association of particular translocations with a specific immunophenotype suggests that the fusion partner plays a role, but the molecular details of this association are unclear.

The MLL gene encodes a 3969 amino acid DNA-binding protein that possesses multiple protein motifs including an NH2-terminal DNA binding domain, transcriptional activation and repression domains, and a COOH-terminal SET domain that contains histone methyltransferase activity. Of interest, the MLL protein is
cleaved into two subunits by a recently identified novel protease. Analysis of Mll knockout mice suggests that Mll plays an important role in development and hematopoiesis through maintenance of appropriate homeotic (Hox) gene expression. The ability of Mll to regulate Hox gene expression suggests that its role in both hematopoiesis and leukemogenesis may be mediated by altering patterns of Hox gene expression. Multiple studies have demonstrated the ability of Hox genes to induce leukemia in mice, and the t(7;11)(p15;p15) translocation found in some human acute myeloid leukemias results in a fusion of the HOXA9 gene to the nucleoporin NUP98. Given the apparent importance of Hox genes in leukemogenesis, it seems likely that translocations involving MLL, a known regulator of Hox genes, alters expression of Hox genes that are critical for leukemogenesis.

We recently found the receptor tyrosine kinase FLT3 to be highly expressed in MLL-rearranged ALL as compared with other acute leukemias. This prompted further assessment of FLT3 in this disease, in which we found approximately 20% of MLL-rearranged ALL samples to possess activating mutations in the activation loop region. These data support the idea that leukemogenic fusion proteins such as MLL fusions cooperate with activated kinases to promote leukemogenesis (Fig 4). Furthermore, FLT3 inhibitors appear to have activity against MLL-rearranged and hyperdiploid ALL, in vitro and in murine models. Clinical trials to assess the efficacy of FLT3 inhibitors in MLL-rearranged ALL are in development.

FIG 4. Multi step pathogenesis of MLL-rearranged lymphoblastic leukemias. MLL translocations induce self-renewal in hematopoietic progenitors as a first step in leukemogenesis. The presence of FLT3 mutations in MLL-rearranged ALLs support activation of FLT3 or other kinases as cooperating events in this disease. Clinical trials designed to assess the efficacy of FLT3 inhibitors in MLL-rearranged ALL are being developed.
B-ALL have a poor prognosis. Due to this poor prognosis with standard ALL-directed chemotherapy, bone marrow transplantation is often recommended for patients in first remission. This is one of the few situations where bone marrow transplant is clearly beneficial for children with ALL in first remission.

**T-Precursor ALL**

As noted in the T-Precursor ALL subsection in Childhood ALL, the activation of oncogenic transcription factors defines distinct molecular subsets of T-ALL with prognostic significance in children. We studied cryopreserved lymphoblasts collected at diagnosis from 52 adults with T-ALL to determine whether overexpression of these oncogenes is of comparable importance in the pathogenesis and treatment responses of adults with T-ALL. We found that the molecular pathways leading to adult T-ALL were very similar to those identified in childhood T-ALL, except that HOX11 was expressed by 33% of adult T-ALL cases, compared with only 3% of T-ALLs arising in children (Fig 1). In addition, HOX11L2 overexpression was under-represented in adult T-ALL compared with childhood cases (5% vs 20% of cases; Fig 1). As in children, adults T-ALLs with aberrant expression of HOX11 had a significantly better leukemia-specific survival rate than did those without this feature. Thus, we propose that patients with HOX11+ T-ALL could be treated effectively with regimens of intensive chemotherapy and spared from the toxicity associated with very intensive therapy followed by rescue with autologous or allogeneic stem cell transplantation.

**Small-Molecule Inhibitors of Tyrosine Kinase Receptors**

Tyrosine kinases are recognized as valid therapeutic targets in multiple types of cancer including leukemia, and inhibition of constitutively active kinases has clear therapeutic benefit. Kinase inhibition is highly successful in the treatment of chronic myelogenous leukemia (CML), in which imatinib mesylate, a small-molecule inhibitor of the BCR-ABL kinase, is remarkably effective. Imatinib induces complete hematologic remission in approximately 95% of patients, and complete cytogenetic responses in approximately 75% of patients with chronic phase CML. Imatinib also has significant activity in patients with BCR-ABL+ ALL, in which remission is frequently achieved with imatinib alone. Unfortunately these responses are transient, with most patients experiencing a relapse of their disease within months. The transient nature of the responses has prompted a number of clinical trials in adults and children in which imatinib will be incorporated into multi-agent chemotherapy for patients with BCR-ABL+ ALL. These early trials combining imatinib and chemotherapy are of significant interest; it is likely that other kinase inhibitors currently in development for both leukemias and other cancers also will need to be combined with either chemotherapy or other targeted therapy because resistance to single-kinase inhibitors is becoming an expected outcome. Because multiple inhibitors are in clinical development, the imatinib trials will provide the groundwork for future combinations.

**Small-Molecule Inhibitors of the NOTCH Pathway**

As noted in the T-Precursor ALL subsection in Childhood ALL, we recently identified mutations involving the extracellular NOTCH1 heterodimerization domain or C-terminal PEST domain in the majority of human T-ALLs, including leukemias from all of the previously defined molecular oncogenic subtypes. The mutations cause increased NOTCH1 signaling, and T-ALL cell lines bearing such mutations are growth arrested by NOTCH pathway inhibitors. These findings greatly expand the role of activated NOTCH1 in the molecular pathogenesis of human T-ALL, and provide a strong rationale for targeted therapies of this disease that interfere with NOTCH signaling because mutationally activated forms of NOTCH1 are still dependent on enzymatic cleavage for activity. On the basis of these findings, a novel clinical trial of a potent NOTCH pathway inhibitor has been opened recently at the Dana-Farber Cancer Institute to target specifically the NOTCH pathway in children and adults with relapsed or refractory T-ALL or T-lymphoblastic lymphoma.

**CONCLUSIONS**

Molecular studies of recurrent genetic abnormalities found in ALL blasts have provided tremendous insights into molecular pathogenesis. The discovery and ongoing characterization of fusion oncogenes encoded by chromosomal translocations provides a foundation upon which the study of leukemogenesis continues to build. Recent studies assessing gene expression profiles of lymphoblastic leukemias have demonstrated convincingly the dividing of cases into biologic subsets, and in some cases identified potential therapeutic targets that are under investigation. Finally, the identification of aberrant signaling pathways represents a fertile ground of future study, given the proven success of small molecule tyrosine kinase inhibitors like imatinib mesylate for the treatment of leukemia. The incorporation of such targeted agents into ALL treatment represents a major focus for clinicians and scientists involved in the study of ALL, and the addition of such therapies should improve the therapeutic index for ALL therapy.

**Acknowledgment**

We thank Eric Smith and Adolfo Ferrando for help in designing figures. We would also like to thank Jason Berman and Doris Dodson for help with editing and references. Finally, we would like to dedicate this review to the
memory of the late Stanley J. Korsmeyer, a beloved col-
gle, friend and mentor, for his enduring contributions to the understanding of leukemia biology and treatment.

**Authors’ Disclosures of Potential Conflicts of Interest**

The authors indicated no potential conflicts of interest.
MYC. Proc Natl Acad Sci U S A 83:6636-6640, 1986
81. Kobayashi H, Hosoda F, Maseki N, et al: Hematologic malignancies with the t(10;11) (p13;q21) have the same molecular event and a variety of morphologic or immunophenotypic features. Genes Chromosomes Cancer 20:253-259, 1997
88. Kimberly WT, Eslir WP, Ye W, et al: Notch and the amyloid precursor protein are cleaved...
by similar gamma-secretase(s). Biochemistry 42: 137-144, 2003


