Acute leukemia: A pediatric perspective

James R. Downing[1,3] and Kevin M. Shannon[2,3]

[1]Department of Pathology, St. Jude Children's Research Hospital, 332 North Lauderdale, Memphis, Tennessee 38105
[2]Department of Pediatrics and Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California 94143
[3]Correspondence: jim.downing@stjude.org (J.R.D.), kevins@itsa.ucsf.edu (K.M.S.)

The spectrum of hematological malignancies differs markedly between children and adults. Moreover, diseases such as acute lymphoblastic leukemia, acute myeloid leukemia, and myelodysplastic syndrome also demonstrate distinct biologic features and responses to treatment between these populations. In this review, we summarize our current understanding of the molecular pathology of acute leukemia and myelodysplastic syndrome, emphasizing areas in which studies in pediatric patients are providing unique insights into the hematopoietic malignancies of adults.

Introduction

Malignancies that arise in the cells of the hematopoietic system are as varied as the individual lineages that comprise this tissue, and can be broadly categorized into acute and chronic leukemias, myelodysplastic and myeloproliferative syndromes, Hodgkin's disease, and the non-Hodgkin's lymphomas. As a result of advances in understanding of both normal hematopoietic development and the molecular pathology of hematopoietic malignancies, significant improvements have occurred in our ability to accurately diagnose, subclassify, and treat these cancers. True treatment successes can be claimed for many of the pediatric acute leukemias and lymphomas (Pui et al., 2001; Weitzman et al., 2002), and for acute promyelocytic leukemia, a specific subtype of acute myeloid leukemia (AML) seen in both the pediatric and adult populations (Warrell, 1996). However, significantly fewer successes have occurred in the treatment of adult patients with hematopoietic malignancies. Moreover, as the frequencies of several of the more common cancer subtypes have steadily decreased during the last two decades, the overall frequency of hematopoietic malignancies has increased, primarily due to increases in the frequency of non-Hodgkin's lymphomas and myeloid leukemias in the adult population (http://www.seer.cancer.gov).

The differences in treatment successes between pediatric and adult hematopoietic malignancies are likely to involve a combination of factors including disease biology, host features, and treatment strategies (Gilliland and Tallman, 2002). One of the most striking aspects of hematopoietic malignancies is the marked difference in the frequency of specific subtypes as a function of age. Although the total number of hematopoietic neoplasms in adults far exceeds the number seen in children, in the pediatric and adolescent population, these malignancies comprise almost 50% of all cancers, whereas in adults, they comprise only 5%–8% (http://www.seer.cancer.gov). In addition, the spectrum of hematopoietic malignancies varies significantly between pediatric and adult patients (Figure 1). Acute lymphoblastic leukemia (ALL) is the most common cancer seen in the pediatric population and accounts for greater than 50% of hematopoietic malignancies in this age group. By contrast, ALL is a relatively rare leukemia subtype in adults, accounting for only 2%–3% of hematopoietic malignancies. Similarly, in children and adolescents, T cell non-Hodgkin's lymphomas (NHLs) are nearly equal in number to those of B cell lineage, whereas in adult patients, B cell NHLs predominate. In addition, in pediatric patients, certain NHL subtypes occur at a high frequency, including Burkitt's and anaplastic large cell lymphoma, whereas in adults the follicular lymphomas predominate, a NHL subtype that is exceedingly rare in pediatric patients. Also, B cell chronic lymphocytic leukemia and multiple myeloma occur almost exclusively in adult patients. Lastly, major differences exist in the overall frequency and subtypes of AML and related myelodysplastic syndromes (MDS), with the incidence of these diseases rising linearly after the age of 40.

The underlying causes for the variation in disease spectrum between pediatric and adult patients are likely to include differences in the stem cell population that are targeted by mutations, the number and type of mutations necessary to induce a fully malignant phenotype, and the internal homeostatic environment of a developing host as compared to that of a fully mature one. The predominance of ALL in pediatric patients may reflect a combination of the existence of a susceptible stem cell population during early and mid-development, and the requirement for only a limited number of mutations in these cells to induce overt disease. Similarly, the low frequency of MDS-related AML in pediatric patients could be secondary to a need for multiple genetic alterations to induce this type of AML.

What lessons can we learn from our expanding knowledge of the underlying molecular pathology of pediatric leukemias and lymphomas, and from the successes we have achieved in their treatment? More importantly, can these lessons lead to future improvements in cure rates for the larger number of adult patients with leukemia and lymphoma? In this article, we focus on the specific aspects of pediatric leukemias that may shed light on some of the acute leukemias seen in adults.

ALL—Differences in both biology and treatment

The major genetic subtypes of pediatric and adult ALL are listed in Table 1. The range of oncogenic mechanisms is similar in the two age groups, and includes enhanced expression of proto-oncogenes (*MYC*, *TAL1*, *LYL1*, and *HOX11*), the expression of translocation-generated fusion oncogenes (*BCR-ABL*, *TEL-AML1*, *E2A-PBX1*, and *MLL* fusions), and alterations in chromosome number including increases and decreases. Studies in a variety of experimental systems have demonstrated that the majority of these lesions are insufficient on their own to generate a full leukemic phenotype (Adams et al., 1985; Hawley et al., 1994; Andreasson et al., 2001; Smith et al., 1999, 2002; Corral et al., 1996). The number and nature of cooperating mutations required to induce a full leukemic phenotype appears to vary depending on the initiating lesions. The early age of disease

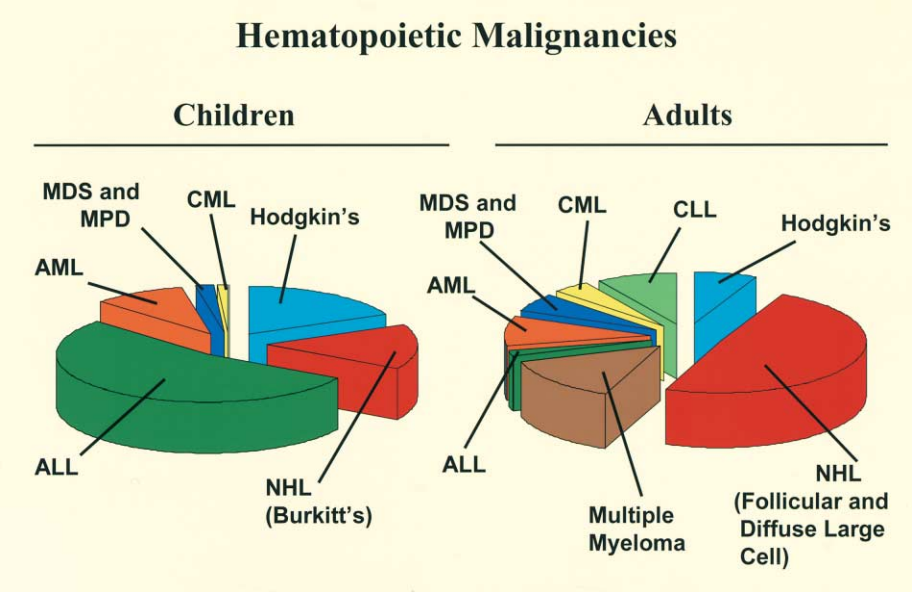

Figure 1. Frequency of the major subtypes of hematopoietic malignancies in pediatric and adult patients

The pie charts show the relative frequency of the major hematopoietic malignancies in children (0 to 19 years) and adults (>19 years). The major leukemia and lymphoma subtypes include chromic myelogenous leukemia (CML), chromic lymphocytic leukemia (CLL), Hodgkin's disease, non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), acute Lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and myeloproliferative disease (MPD).

onset in many children with ALL, and the high rate of disease concordance in monozygotic twins, suggest that some of the initiating lesions are acquired in utero. Indeed, an innovative series of "back-tracking" experiments demonstrated that leukemia-specific translocation breakpoints can be detected in neonatal blood specimens from most children who are diagnosed with ALL during the first decade of life (Ford et al., 1993, 1998; Wiemels et al., 1999). Furthermore, twins that were concordant for the development of ALL frequently shared the same leukemia-associated chromosomal fusion both at birth and when they presented with ALL (Ford et al., 1998). Although these data unequivocally demonstrate that leukemia-associated fusion oncogenes are detectable at birth in many children who later develop ALL, the overall incidence of these abnormalities is unknown, as is the percentage of infants with in utero acquired leukemia-associated translocation such as *MLL-AF4* or *TEL-AML1* that will ultimately develop ALL.

What is the nature of these cooperating mutations in childhood ALL, and how are they acquired? Greaves has proposed a provocative hypothesis—that lymphoid proliferation in response to viral illnesses directly or indirectly provides additional "hits" that contribute to the development of ALL (Greaves, 1996). While this idea is consistent with the age-adjusted peak incidence of ALL, there is no direct evidence that supports it.

Table 1. Acute lymphoblastic leukemia

Leukemia subtype	Pediatric	Adult
T cell		
TAL1 Ip32	6%	12%
HOX11L2 5q35	2%	1%
LYL1 19p13	1.5%	2%
HOX11 10q24	0.5%	6%
B cell		
Hyperdiploidy > 50 chromosomes	25%	6%
Hypodiploidy < 45 chromosomes	1%	1%
TEL-AML1 t(12;21)	22%	2%
MLL rearrangements (t[4;11], t[11;19], t[9;11], etc.)	8%	10%
E2A-PBX1 t(1;19)	5%	3%
BCR-ABL t(9;22)	3%	30%
MYC t(8;14), t(2;8), t(8;22)	2%	4%
Others	24%	23%

With modern chemotherapeutic regimens, approximately 80% of children with ALL are cured (Pui et al., 2001; Gaynon et al., 2000). This is in marked contrast to adult ALL, where much lower cure rates are achieved despite the use of myeloablative regimens with hematopoietic stem cell transplantation in many patients who enter remission (Thomas et al., 2001; Annino et al., 2002; Linker et al., 2002). What might explain these dramatic differences? First, many adult patients have unfavorable biologic features at diagnosis. For example, *BCR-ABL* fusions are strongly associated with chemoresistant leukemia in all age groups, but are much more prevalent in adults with ALL than in pediatric cases (~30% versus <5%, see Table 1) (Radich, 2001). By contrast, leukemias with *TEL-AML1* translocations, which are frequently cured with chemotherapy alone, are more common in children (Romana et al., 1995; Shurtleff et al., 1995; McLean et al., 1996). A second factor that may be important involves the nature of both the susceptible target cell and the spectrum of cooperating mutations. In particular, the intrauterine origin of pediatric ALL raises the possibility that substantial functional differences exist between the leukemia-initiating cell in children and adults, as has been shown for hematopoietic stem cells derived from umbilical cord blood versus adult bone marrow (Gluckman, 2000). Furthermore, if viral infections play a role in the acquisition of cooperating events in pediatric ALL but not in the corresponding adult leukemias, the spectrum of these mutations may differ between childhood and adult cases. Intrinsic differences in either the leukemia-initiating cell or the nature of secondary mutations that occur in pediatric versus adult ALL could, in turn, modulate responses to chemotherapeutic agents.

Differences in the way in which pediatric and adult patients with ALL are treated is a third possible factor that might influence cure rates. While limited data address this issue, an intriguing preliminary report found that adolescents with ALL enrolled on Children's Cancer Group protocols had a superior outcome compared to similar age patients who were treated according to a concurrent Cancer and Leukemia Group B regimen designed for adult patients (Stock et al., 2000). These data raise the impor-

Table 2. World Health Organization (WHO) classification

Acute myeloid leukemia (AML)
AML with recurrent cytogenetic abnormalities
AML with multilineage dysplasia
AML and MDS, therapy related
AML not otherwise categorized
Acute leukemia of ambiguous lineage
Myelodysplastic syndromes (MDS)
Refractory anemia
Refractory anemia with ringed sideroblasts
Refractory anemia with multilineage dysplasia
Refractory anemia with excess blasts
MDS associated with isolated del(5q) chromosome abnormalities
MDS unclassifiable
Myelodysplastic/myeloproliferative disease
Chronic myelomonocytic leukemia
Atypical chronic myeloid leukemia
Juvenile myelomonocytic leukemia
Myelodysplastic/myeloproliferative unclassifiable

tant possibility that the higher intensity therapy used by pediatric oncologist to treat ALL patients may in part be responsible for the better outcome seen in patients treated on their protocols. Additional studies will be required to verify this possibility.

A major challenge that remains for both pediatric and adult ALL is to identify patients at diagnosis or early during treatment who are destined to relapse, especially since relapsed ALL is largely refractory to salvage regimens. Two complementary technologies are being harnessed for this purpose. The first of these is expression microarray analysis, which has the potential to identify gene expression patterns in diagnostic specimens that portend a high probability of relapse (Ferrando et al., 2002; Yeoh et al., 2002). Distinguishing patients who are likely to relapse is confounded by the fact that specific leukemia-associated fusion genes such as *TEL-AML1* and *E2A-PBX* have global effects on gene expression that must first be accounted for when considering relapse risk. However, when subgroups of pediatric ALL specimens with the same chromosomal translocations were examined, it was possible to identify groups of genes whose expression correlated with later disease relapse (Yeoh et al., 2002). Additional data are essential to confirm these preliminary findings in both pediatric and adult patients, and to decipher the influence of different treatment regimens on the predictive value of gene expression patterns. A number of groups are exploring either flow cytometry or polymerase chain reaction (PCR)-based strategies to detect rare residual leukemia cells in patients that are in morphologic remission. Recent studies in pediatric ALL have established that detecting certain levels of residual leukemia early in therapy correlated with a high risk of relapse (Coustan-Smith et al., 2002; Cave et al., 1998; Gaynon et al., 1997). An important question for clinical investigation involves whether intensifying therapy in ALL patients who are in morphologic remission but have high levels of minimal residual disease will alter the outcome of the disease. Several ongoing clinical trials are beginning to prospectively address this issue. By contrast, gene expression and minimal residual disease techniques might ultimately allow clinical oncologists to reduce the doses of mutagenic drugs administered to patients with ALL that have highly favorable biologic features.

Lastly, Imatinib, also known as STI-571 and Gleevec, is a small molecule inhibitor of the BCR-ABL kinase that has demonstrated impressive efficacy in patients with chronic myelogenous leukemia (CML) (Druker, 2002; Druker et al., 2001). Moreover, treatment with Imatinib induces transient remissions in many CML patients with lymphoid blast crisis (Kantarjian et al., 2002; Sawyers et al., 2002), and thus represents a promising approach for improving the outcome of adults and children with BCR-ABL-positive ALL. However, the rapid emergence of Imatinib resistant clones in BRC-ABL-positive ALL (Gorre et al., 2001; Shah et al., 2002) suggests that effective use of this drug in ALL will require its delivery in combination with other agents, including possibly other BCR-ABL inhibitors that are directed to a separate region of the ABL kinase.

The spectrum of acute myeloid leukemias and the myelodysplastic syndromes

AML is defined as a clonal expansion of myeloid blasts that comprise ≥20% of the nucleated cells in the bone marrow or blood. By contrast, MDS is defined as a clonal hematopoietic stem cell disease that is characterized by dysplasia and ineffective hematopoiesis in one or more of the myeloid lineages. Often the dysplasia is accompanied by an increase in myeloblasts; however, these cells account for less than 20% of the total. From both a biological and clinical perspective, AML and MDS are heterogeneous diseases, consisting of many recognized morphologic and biological subtypes. A number of different classification schemes have been proposed over the years to assist in accurately diagnosing clinically relevant disease subtypes. One of the most recent classifications is that sponsored by the World Health Organization (WHO) (Vardiman et al., 2002). The relevant parts of the WHO classification scheme that are germane to our discussion are shown in Table 2.

Although AML and MDS in their classic forms are easily distinguished from one another, the diseases can be conceptualized to represent a continuum of pathogenic entities (Figure 2). At one extreme sits the AMLs that arise without any evidence of a preceding MDS and show minimal dysplasia outside of the myeloid lineage. This subtype of AML is characterized by the presence of recurrent chromosomal translocations or rearrangements that encode chimeric oncoproteins, including AML1-ETO, CBFβ-MYH11, PML-RARα, and MLL fusions. The incidence of these specific leukemia subtypes is relatively constant throughout life. At the other extreme sits the AMLs that arise in patients with a preceding history of MDS. In fact, for many subtypes of MDS, progression to AML is the natural course of the disease. The incidence of both MDS and the AMLs that arise in these patients increases linearly with age with a mean age of onset >65. In between these two extremes exists an overlapping spectrum of entities from AMLs that lack either recurrent cytogenetic abnormalities or evidence of dysplasia to acute myeloid leukemias with multilineage dysplasia. The latter subgroup, although lacking a preceding history of MDS, closely resembles leukemias that arise in MDS patients, including having the presence of complex cytogenetic abnormalities, such as –7/del(7q), –5/del(5q), +8, +21, and 3q26 abnormalities.

AMLs with recurrent cytogenetic abnormalities

The underlying pathology and clinical outcome of the AMLs with

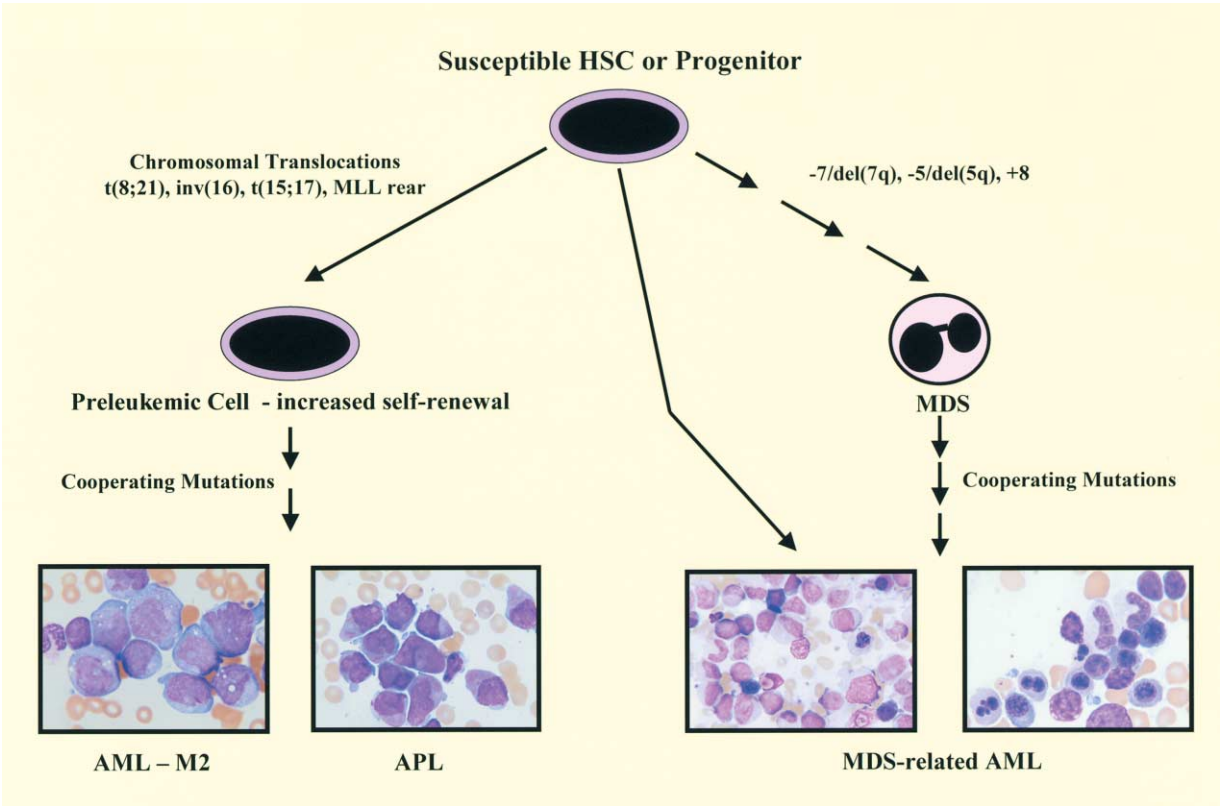

Figure 2. A conceptual model of the pathogenesis of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and MDS-related AML

Hematopoietic stem cells (HSC) or committee progenitors are formed early in development and persist throughout life. These cells are likely to vary in their biologic properties with age, and thus during ontogeny may also vary in their susceptibility to different oncogenic events. The acquisition of certain chromosomal translocations or rearrangements results in the production of fusion oncoproteins that typically result in the enhanced self-renewal capacity of HSC and their committed progenitors. The cells serve as a silent prelukemic population that can acquire other cooperating mutations leading to the formation of an overt leukemic clone. Two examples of this subtype of leukemia are t(8;21)-containing AML with M2 morphology (AML-M2) and t(15;17)-containing acute promyelocytic leukemia (APL). By contrast, myelodypslastic syndrome (MDS) is thought to arise through the acquisition of multiple mutations. Once established, the myelodyplastic stem cell can continue to undergo additional genetic and epigenetic changes, which in a substantial percentage of cases will lead to the development of overt AML. MDS-related AML can also occur without a preceding history of MDS. Shown are examples of the type of cellular morphology seen in a case of MDS-related AML.

recurrent cytogenetic abnormalities appear to be similar in pediatric and adult patients. The chromosomal rearrangements that define many of these leukemias encode chimeric transcription factors that directly alter the normal repertoire of expressed genes that regulate the formation, self-renewal, and differentiation of hematopoietic stem cells and their progeny. Prominent among these pathways are those controlled by the AML1/CBFβ transcription factor complex (Speck and Gilliland, 2002; Lorsbach and Downing, 2001), the HOX developmental proteins (Look, 1997), and the retinoic acid receptor (Grignani et al., 1994).

Experiments in strains of mice engineered to express the *CBFβ-MYH11* (Castilla et al., 1996, 1999), *AML1-ETO* (Yuan et al., 2001; Higuchi et al., 2002), *MLL-AF9* (Corral et al., 1996; Dobson et al., 1999), and *PML-RARα* (He et al., 1997) fusion genes in hematopoietic cells strongly support the idea that these oncoproteins are insufficient to induce a full leukemic phenotype. Instead, expression of these fusion proteins appears to alter the growth and differentiation of HSC generating a "preleukemia" population of cells that are then susceptible to the acquisition of cooperating mutations to induce AML. The initial expression of the translocation-encoded fusion proteins appears to provide only a minimal to modest growth advantage that is not detectable clinically. Nevertheless, recent studies have demonstrated that cells expressing translocation-encoded chimeric transcripts can be detected in the normal bone marrows of patients who are in long-term remission from their leukemia (Miyamoto et al., 1996, 2000) and in neonatal blood spots from some patients that eventually develop AML (Mahmoud et al., 1995; Gale et al., 1997; Ford et al., 1998; Wiemels et al., 2002).

The number and type of cooperating mutations may vary significantly between individual subtypes of AML. In addition, the exact nature of cooperating mutations that can act with the translocation-encoded fusion proteins remains to be defined. Moreover, whether the specific constellation of cooperating mutations will differ between patients that respond to standard therapy and are cured and those that eventually relapse remains unknown. Recent insights into the nature of cooperating mutations have emerged from a number of lines of investigation. Rare patients with CML have been identified that have acquired chromosomal translocations including the t(8;21) and t(3;21) prior to undergoing a blast transformation to AML (Kojima et al., 1999; Gilliland et al., 1990). Similarly, a patient with chronic myelomonocytic leukemia that expressed the

t(5;12)-encoded TEL-PDGFRβ fusion protein acquired a t(8;21) prior to progressing to AML (Golub et al., 1994). In each case, AML appeared to develop as a result of the cooperation between an activated tyrosine kinase and a translocation-encoded chimeric transcription factor. More recently, activating mutations in the FLT3 receptor tyrosine kinase, including internal duplications of the juxtamembrane regions and point mutations within the kinase domain, have been identified in approximately 25% of AMLs (Nakao et al., 1996; Yamamoto et al., 2001). Similarly, a high frequency of activating mutations have been detected in *NRAS, KRAS,* and *C-KIT* (Kiyoi et al., 1999; Beghini et al., 2000), primarily in leukemias with alterations of the AML1/CBFβ transcription complex (the so-called core binding factor leukemias).

These observations suggest that alterations in tyrosine kinase signaling pathways may be an obligate step in leukemogensis. This, in turn, raises the more provocative possibility that specific small molecule inhibitors against activated kinases may prove to be valuable therapeutic modalities in all AML patients. Bolstered by the clinical success of Imatinib in treating CML, a number of inhibitors of the FLT-3 kinase have recently been developed. In preclinical studies, these compounds appear to specifically inhibit the growth of some leukemia cells that contain activating mutations in this receptor kinase (Kelly et al., 2002; Levis et al., 2002; Sawyers, 2002; Weisberg et al., 2002). Additional examples of directed therapy that are being pursued in this subclass of AMLs are the use of all trans retinoic acid and arsenic trioxide to treat acute promyelocytic leukemias (APL) that express a PML-RARα fusion protein or its variants and the use of histone deacetylase inhibitors to treat a broader spectrum of AMLs. These topics have been recently reviewed by others (Ferrara et al., 2001; Marks et al., 2001; Fenaux et al., 2001).

MDS and MDS-related AMLs: Lessons learned from the pediatric diseases

MDS and MDS-related AML are relatively rare diseases in the pediatric population, but are much more common in adults. Moreover, as a group they respond very poorly to contemporary treatment, with 5 year overall survival rates for the so-called high-risk MDS-related AML falling below 10% (Oosterveld et al., 2002). Hampering progress in treating MDS and MDS-related AML is our relatively limited understanding of the molecular pathology that underlies these diseases. Although commonly deleted DNA segments have been identified on 5q31 and 7q22 that likely harbor myeloid tumor suppressors (Kratz et al., 2001; Lai et al., 2001), the target gene(s) of the –7/del(7q) and –5/del(5q) remain unknown. Similarly, the genes that are critical for the biological effects resulting from specific chromosomal trisomies remain to be identified. Can any insights be gained from the analysis of those rare cases of MDS and MDS-related AML that arise in children and adolescents?

Although MDS is uncommon in the pediatric age group, the majority of cases share clinical, laboratory, and morphologic features with one of the recognized subtypes of adult MDS and are readily classified into one of the defined categories (Table 2). Pediatric patients with this "adult type" MDS are typically older at diagnosis (>5 years old) (Luna-Fineman et al., 1999). The remaining children with MDS demonstrate a mixed pattern of myeloproliferation, dysplasia, and hepatosplenomegaly in association with abnormal peripheral blood counts (most frequently leukocytosis, anemia, and thombocytopenia). Cytogenetic analysis reveals monosomy 7 in about 25% of patients. These disorders have historically been called "juvenile chronic myelogenous leukemia," "infantile monosomy 7 syndrome," and "chronic myelomoncytic leukemia" by different authors (Luna-Fineman et al., 1995, 1999). In the 1990s, an international working group proposed that the term "juvenile myelomonocytic leukemia" (JMML) be applied to cases that fulfill a defined set of clinical and laboratory criteria. This nomenclature has been adopted widely, and JMML has been assigned to a new diagnostic category with chronic myelomoncytic leukemia (CMML) within the new WHO classification (Table 2). A distinctive biologic feature of JMML is a selective hypersensitive pattern of colony forming unit granulocyte macrophage (CFU-GM) growth in response to the cytokine granulocyte-macrophage colony stimulating factor (GM-CSF) (Emanuel et al., 1991).

Approximately 30% of children with MDS or MDS-related AML have a recognizable genetic predisposition to leukemia such as neurofibromatosis 1 (NF1), Fanconi Anemia, or severe congenital neutropenia. These associations may provide a starting point for elucidating genes and growth control pathways that may be critical in adult MDS and MDS-related AML.

JMML, NF1, and hyperactive Ras

Children (but not adults) with NF1 show a 200- to 500-fold increase in the incidence of myeloid malignancies, particularly JMML (Stiller et al., 1994). The *NF1* gene encodes neurofibromin, a GTPase-activating protein (GAP) that negatively regulates Ras output by accelerating GTP hydrolysis on Ras (Boguski and McCormick, 1993; Donovan et al., 2002). Genetic and biochemical analysis has shown that *NF1* and its murine homolog *(Nf1)* function as tumor suppressor genes in myeloid leukemogenesis by negatively regulating Ras signaling (Bollag et al., 1996; Jacks et al., 1994; Side et al., 1997). Furthermore, identification of oncogenic *RAS* mutations in a substantial percentage of JMML samples from children without NF1 disease further implicates hyperactive Ras in this disease (Kalra et al., 1994). Although homozygous inactivation of *Nf1* is lethal in embryonic life, adoptive transfer of these mutant cells consistently induces a JMML-like disorder in irradiated recipient mice (Largaespada et al., 1996). Further studies in which fetal liver cells doubly mutant at the *Gmcsf* and *Nf1* loci were transferred into irradiated *Gmcsf*$^{-/-}$ or wild-type recipients have underscored the central role of aberrant GM-CSF signaling in initiating and maintaining this myeloid leukemia in vivo (Birnbaum et al., 2000). Together, these studies of children with JMML and of *Nf1* mutant mice have contributed novel insights regarding how aberrant Ras signaling and hematopoietic growth factors cooperate to initiate and maintain leukemogenesis.

Fanconi anemia (FA)

FA is an autosomal recessive disorder characterized by multiple congenital anomalies and progressive bone marrow failure, and is associated with a high frequency of MDS and AML in late childhood and adolescence. A hallmark of FA cells is hypersensitivity to genetic damage induced by DNA-crosslinking agents such as mitomycin C, and to a lesser extent by ionizing radiation. FA is a heterogeneous disease at the molecular level with seven distinct complementation groups identified. The genes for six of these complementation groups have been recently cloned, resulting in the emergence of a fascinating story on the interaction of the different FA proteins in a DNA repair pathway (Taniguchi and Dandrea, 2002; Stewart and Elledge, 2002). DNA damage activates the FA complex (consisting of Fanconi proteins A, C, G, and F), leading to the monoubiquitination of the

FANCD2 protein (Garcia-Higuera et al., 2001). The modified FANCD2 protein, in turn, relocalizes in the nucleus to sites of DNA repair where it directly interacts with the breast cancer susceptibility protein, BRCA1. Furthermore, the FNCD2 protein is phosphorylated by the ATM protein kinase in response to ionizing radiation, linking the Fanconi pathway to this checkpoint response (Taniguchi et al., 2002). Lastly, mutations in the *BRCA2* gene, a DNA repair enzyme, were shown to be the underlying abnormality in FA patients that were previously assigned to complementation group B and D1 (Howlett et al., 2002). These data establish a defect in DNA repair as the underlying abnormality in FA. Determining why FA patients primarily develop AML is an important experimental priority. Moreover, since MDS and AML in FA patients resemble the sporadic forms of these diseases, it will be important to ascertain if acquired mutations in components of the FA pathway are involved in the pathogenesis of these myeloid malignancies in adults.

Congenital neutropenia

Severe congenital neutropenia (SCN) refers to a group of constitutional disorders of myelopoiesis characterized by low blood neutrophil counts and recurrent infections (Zeidler and Welte, 2002). Pharmacologic doses of recombinant human granulocyte colony stimulating factor (G-GSF) enhance neutrophil production in most patients, and this alleviates many of the life-threatening complications of SCN. With longer survival and close observation, evolution to MDS and AML has been observed in 10%–15% of children with SCN, including occasional patients who never received recombinant G-CSF (Banerjee and Shannon, 2001). Clonal evolution is associated with *RAS* mutations and monosomy 7 in some patients (Kalra et al., 1995); however, the most fascinating molecular alteration is the acquisition of somatic mutations in the G-CSF receptor, which truncate the carboxyl terminus. Heterologous expression of these mutant receptors in myeloid cell lines promotes growth, blocks maturation, and impairs apoptosis (Dong et al., 1995). However, studies in transgenic mice suggest that mutations in the G-CSF receptor are insufficient to initiate leukemogenesis. Recently, mutations in the neutrophil elastase *(ELA2)* gene have been implicated as a cause of SCN (Ancliff et al., 2001). SCN thus provides another example in which an inherited predisposition interacts with a growth factor receptor-signaling cascade in leukemogenesis.

Down syndrome (DS)

Infants and children with DS have a 14-fold increase in the overall rate of leukemia (Arceci, 2002). Although ALL is more prevalent than AML, the ratio of lymphoid to myeloid leukemia is about 6:4 versus 4:1 in the general population. In addition, some infants with DS develop clinical features of AML that resolve spontaneously over time, which is referred to as transient myeloproliferative disease (TMD). This term is misleading as TMD does not resolve in some infants, while others go on to develop AML after a period of remission. Cases of AML in patients with DS frequently are classified as megakaryoblastic (M7). Recently, somatic mutations were identified in the transcription factor *GATA1* in leukemias from children with DS (Wechsler et al., 2002). It will be of interest to ascertain if these mutations are invariably associated with leukemia or are also found in some infants with TMD. Furthermore, DS provides a novel opportunity to begin to address how an extra copy of a critical gene (or genes) located on chromosome 21 interacts with other events to promote leukemogenesis.

Although our understanding of the pathogenesis of MDS and MDS-related AML remains in its infancy, some of the recently acquired insights gained from studies of both the pediatric and adult diseases are starting to translate into novel therapeutic approaches. The prominent role of RAS alterations in both congenital and sporadic cases of MDS and MDS-related AML suggest that inhibitors against this pathway may be of benefit. Recently, a specific inhibitor of the Ras processing enzyme farnesyl transferase has been tested in a murine model of JMML characterized by hyperactive Ras (Mahgoub et al., 1999). Whether this will prove beneficial in treating patients with these diseases remains to be determined. Other recent findings are likely to influence the therapeutic approaches that will be used to treat these diseases. Prominent among these observations is the finding of an increased frequency of MDS and MDS-related AMLs in patients with congenital syndromes that render them hypersensitive to DNA damage. Accumulating data from both congenital and acquired cases of MDS-related AML raises the possibility that these diseases have as part of their underlying pathogenesis an enhanced mutation rate secondary to alterations in normal DNA damage response pathways. If this is true, we will need to take this possibility into account when devising therapeutic strategies.

Conclusions

The insights gained through the coordinated efforts to study the biology and therapy of pediatric ALL, AML, and inherited syndromes that predispose to these diseases are providing important insights in the underlying biology of these malignancies in both pediatric and adult patients. Moreover, this information is starting to influence the way patients are treated. In their accompanying focus article on embryonal malignancies, Maris and Denny emphasize the interrelationship between developmental processes and childhood cancer (Maris and Denny, 2002 [this issue of *Cancer Cell*]). As described above, this comparison extends to the pediatric leukemias. The point-counterpoint comparisons between pediatric and adult leukemias should continue to provide fertile ground upon which we can expand our understanding of the molecular pathology of these cancers.

Acknowledgments

Our collaborative research in leukemogenesis is supported by NIH grant CA84221. We also wish to acknowledge funding provided by NIH grants CA40046 and CA72614, U.S. Army Neurofibromatosis Research grant DAMD17, and American Cancer Society grant RSG-96-104-06-LIB (all to K.M.S.), and by NIH grants P01 CA71907-06, a Cancer Center CORE Grant CA-21765, and by the American Lebanese and Syrian Associated Charities (ALSAC) of St. Jude Children's Research Hospital (to J.R.D.).

References

Adams, J.M., Harris, A.W., Pinkert, C.A., Corcoran, L.M., Alexander, W.S., Cory, S., Palmiter, R.D., and Brinster, R.L. (1985). The c-myc oncogene driven by immunoglobulin enhancers induces lymphoid malignancy in transgenic mice. Nature *318*, 533–538.

Ancliff, P.J., Gale, R.E., Liesner, R., Hann, I.M., and Linch, D.C. (2001). Mutations in the ELA2 gene encoding neutrophil elastase are present in most patients with sporadic severe congenital neutropenia but only in some patients with the familial form of the disease. Blood *98*, 2645–2650.

Andreasson, P., Schwaller, J., Anastasiadou, E., Aster, J., and Gilliland, D.G. (2001). The expression of ETV6/CBFA2 (TEL/AML1) is not sufficient for the transformation of hematopoietic cell lines in vitro or the induction of hematologic disease in vivo. Cancer Genet. Cytogenet. *130*, 93–104.

Annino, L., Vegna, M.L., Camera, A., Specchia, G., Visani, G., Fioritoni, G., Ferrara, F., Peta, A., Ciolli, S., Deplano, W., et al. (2002). Treatment of adult

acute lymphoblastic leukemia (ALL): long-term follow- up of the GIMEMA ALL 0288 randomized study. Blood *99*, 863–871.

Arceci, R.J. (2002). Down syndrome, transient myeloproliferative syndrome, and leukemia: bridging development and neoplasia. J. Pediatr. Hematol. Oncol. *24*, 1.

Banerjee, A., and Shannon, K.M. (2001). Leukemic transformation in patients with severe congenital neutropenia. J. Pediatr. Hematol. Oncol. *23*, 487–495.

Birnbaum, R.A., O'Marcaigh, A., Wardak, Z., Zhang, Y.Y., Dranoff, G., Jacks, T., Clapp, D.W., and Shannon, K.M. (2000). Nf1 and Gmcsf interact in myeloid leukemogenesis. Mol. Cell *5*, 189–195.

Beghini, A., Peterlongo, P., Ripamonti, C.B., Larizza, L., Cairoli, R., Morra, E., and Mecucci, C. (2000). C-kit mutations in core binding factor leukemias. Blood *95*, 726–727.

Boguski, M., and McCormick, F. (1993). Proteins regulating Ras and its relatives. Nature *366*, 643–653.

Bollag, G., Clapp, D.W., Shih, S., Adler, F., Zhang, Y., Thompson, P., Lange, B.J., Freedman, M.H., McCormick, F., Jacks, T., and Shannon, K. (1996). Loss of *NF1* results in activation of the Ras signaling pathway and leads to aberrant growth in murine and human hematopoietic cells. Nat. Genet. *12*, 144–148.

Castilla, L.H., Wijmenga, C., Wang, Q., Stacy, T., Speck, N.A., Eckhaus, M., Marin-Padilla, M., Collins, F.S., Wynshaw-Boris, A., and Liu, P.P. (1996). Failure of embryonic hematopoiesis and lethal hemorrhages in mouse embryos heterozygous for a knock-in leukemia gene CBFβ-MYH11. Cell *87*, 687–696.

Castilla, L.H., Garrett, L., Adya, N., Orlic, D., Dutra, A., Anderson, S., Owens, J., Eckhaus, M., Bodine, D., and Liu, P.P. (1999). The fusion gene cbfb-MYH11 blocks myeloid differentiation and predisposes mice to acute myelomonocytic leukaemia. Nat. Genet. *23*, 144–146.

Cave, H., van der Werff ten Bosch, J., Suciu, S., Guidal, C., Waterkeyn, C., Otten, J., Bakkus, M., Thielemans, K., Grandchamp, B., and Vilmer, E. (1998). Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. European Organization for Research and Treatment of Cancer–Childhood Leukemia Cooperative Group. N. Engl. J. Med. *339*, 591–598.

Corral, J., Lavenir, I., Impey, H., Warren, A.J., Forster, A., Larson, T.A., Bell, S., McKenzie, A.N., King, G., and Rabbitts, T.H. (1996). An Mll-AF9 fusion gene made by homologous recombination causes acute leukemia in chimeric mice: a method to create fusion oncogenes. Cell *85*, 853–861.

Coustan-Smith, E., Sancho, J., Behm, F.G., Hancock, M.L., Razzouk, B.I., Ribeiro, R.C., Rivera, G.K., Rubnitz, J.E., Sandlund, J.T., Pui, C.H., and Campana, D. (2002). Prognostic importance of measuring early clearance of leukemic cells by flow cytometry in childhood acute lymphoblastic leukemia. Blood *100*, 52–58.

Dobson, C.L., Warren, A.J., Pannell, R., Forster, A., Lavenir, I., Corral, J., Smith, A.J., and Rabbitts, T.H. (1999). The mll-AF9 gene fusion in mice controls myeloproliferation and specifies acute myeloid leukaemogenesis. EMBO J. *18*, 3564–3574.

Dong, F., Brynes, R., Tidow, N., Welte, K., Lowenberg, B., and Touw, I. (1995). Mutations in the gene for the granulocyte colony stimulating factor receptor in patients with acute myeloid leukemia preceded by severe congenital neutropenia. N. Engl. J. Med. *333*, 487–493.

Donovan, S., Shannon, K.M., and Bollag, G. (2002). GTPase activating poteins: critical regulators of intracellular signaling. Biochim. Biophys. Acta *1602*, 23–45.

Druker, B.J. (2002). Perspectives on the development of a molecularly targeted agent. Cancer Cell *1*, 31–36.

Druker, B.J., Talpaz, M., Resta, D.J., Peng, B., Buchdunger, E., Ford, J.M., Lydon, N.B., Kantarjian, H., Capdeville, R., Ohno-Jones, S., and Sawyers, C.L. (2001). Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N. Engl. J. Med. *344*, 1031–1037.

Emanuel, P.D., Bates, L.J., Castleberry, R.P., Gualtieri, R.J., and Zuckerman, K.S. (1991). Seletive hypersensitivity to granulocyte-macrophage colony stimulating factor by juvenile chronic myeloid leukemia hematopoietic progenitors. Blood *77*, 925–929.

Fenaux, P., Chomienne, C., and Degos, L. (2001). All-trans retinoic acid and chemotherapy in the treatment of acute promyelocytic leukemia. Semin. Hematol. *38*, 13–25.

Ferrando, A.A., Neuberg, D., Staunton, J., Loh, M.L., Huard, C., Raimondi, S., Behm, F., Pui, C.H., Downing, J.R., Gilliland, D.G., et al. (2002). Gene expression signatures define novel oncogenic pathways in T-cell acute lymphoblastic leukemia. Cancer Cell *1*, 75–87.

Ferrara, F.F., Fazi, F., Bianchini, A., Padula, F., Gelmetti, V., Minucci, S., Mancini, M., Pelicci, P.G., Lo, C.F., and Nervi, C. (2001). Histone deacetylase-targeted treatment restores retinoic acid signaling and differentiation in acute myeloid leukemia. Cancer Res. *61*, 2–7.

Ford, A.M., Ridge, S.A., Cabrera, M.E., Mahmoud, H., Steel, C.M., Chan, L.C., and Greaves, M. (1993). In utero rearrangements in the trithorax-related oncogene in infant leukaemias. Nature *363*, 358–360.

Ford, A.M., Bennett, C.A., Price, C.M., Bruin, M.C., van Wering, E.R., and Greaves, M. (1998). Fetal origins of the TEL-AML1 fusion gene in identical twins with leukemia. Proc. Natl. Acad. Sci. USA *95*, 4584–4588.

Gale, K.B., Ford, A.M., Repp, R., Borkhardt, A., Keller, C., Eden, O.B., and Greaves, M.F. (1997). Backtracking leukemia to birth: identification of clonotypic gene fusion sequences in neonatal blood spots. Proc. Natl. Acad. Sci. USA *94*, 13950–13954.

Garcia-Higuera, I., Taniguchi, T., Ganesan, S., Meyn, M.S., Timmers, C., Hejna, J., Grompe, M., and D'Andrea, A.D. (2001). Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. Mol. Cell *7*, 249–262.

Gaynon, P.S., Desai, A.A., Bostrom, B.C., Hutchinson, R.J., Lange, B.J., Nachman, J.B., Reaman, G.H., Sather, H.N., Steinherz, P.G., Trigg, M.E., et al. (1997). Early response to therapy and outcome in childhood acute lymphoblastic leukemia: a review. Cancer *80*, 1717–1726.

Gaynon, P.S., Trigg, M.E., Heerema, N.A., Sensel, M.G., Sather, H.N., Hammond, G.D., and Bleyer, W.A. (2000). Children's cancer group trials in childhood acute lymphoblastic leukemia: 1983–1995. Leukemia *14*, 2223–2233.

Gilliland, D.G., Patterson, E.J., Rosenthal, D.S., and Tantravahi, R. (1990). Multiple clones with (3;21) translocation in a case of Ph-positive chronic myelogenous leukemia during relapse after allogeneic bone marrow transplantation. Cancer Genet. Cytogenet. *47*, 55–60.

Gilliland, D.G., and Tallman, M.S. (2002). Focus on acute leukemias. Cancer Cell *1*, 417–420.

Gluckman, E. (2000). Current status of umbilical cord blood hematopoietic stem cell transplantation. Exp. Hematol. *28*, 1197–1205.

Golub, T.R., Barker, G.F., Lovett, M., and Gilliland, D.G. (1994). Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. Cell *77*, 307–316.

Gorre, M.E., Mohammed, M., Ellwood, K., Hsu, N., Paquette, R., Rao, P.N., and Sawyers, C.L. (2001). Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science *293*, 876–880.

Greaves, M.F. (1996). Infant leukaemia biology, aetiology and treatment. Leukemia *10*, 372–377.

Grignani, F., Fagioli, M., Alcalay, M., Longo, L., Pandolfi, P.P., Donti, E., Biondi, A., Lo, C.F., and Pelicci, P.G. (1994). Acute promyelocytic leukemia: from genetics to treatment. Blood *83*, 10–25.

Hawley, R.G., Fong, A.Z., Lu, M., and Hawley, T.S. (1994). The HOX11 homeobox-containing gene of human leukemia immortalizes murine hematopoietic precursors. Oncogene *9*, 1–12.

He, L.Z., Tribioli, C., Rivi, R., Peruzzi, D., Pelicci, P.G., Soares, V., Cattoretti, G., and Pandolfi, P.P. (1997). Acute leukemia with promyelocytic features in PML/RARalpha transgenic mice. Proc. Natl. Acad. Sci. USA *94*, 5302–5307.

Higuchi, M., O'Brien, D., Kumaravelu, P., Lenny, N., Yeoh, E.J., and Downing, J.R. (2002). Expression of a conditional AML1-ETO oncogene bypasses embryonic lethality and establishes a murine model of human t(8;21) acute myeloid leukemia. Cancer Cell *1*, 63–74.

Howlett, N.G., Taniguchi, T., Olson, S., Cox, B., Waisfisz, Q., Die-Smulders, C., Persky, N., Grompe, M., Joenje, H., Pals, G., et al. (2002). Biallelic inactivation of BRCA2 in Fanconi anemia. Science *297*, 606–609.

Jacks, T., Shih, S., Schmitt, E.M., Bronson, R.T., Bernards, A., and Weinberg, R.A. (1994). Tumorigenic and developmental consequences of a targeted *Nf1* mutation in the mouse. Nat. Genet. *7*, 353–361.

Kalra, R., Paderanga, D., Olson, K., and Shannon, K.M. (1994). Genetic analysis is consistent with the hypothesis that *NF1* limits myeloid cell growth through p21^{ras}. Blood *84*, 3435–3439.

Kalra, R., Dale, D., Freedman, M., Bonilla, M.A., Weinblatt, M., Ganser, A., Bowman, P., Abish, S., Priest, J., Olson, K., et al. (1995). Malignant transformation in patients with congenital neutropenia during treatment with recombinant granulocyte colony stimulating factor. Blood *86*, 4579–4586.

Kantarjian, H.M., Cortes, J., O'Brien, S., Giles, F.J., Albitar, M., Rios, M.B., Shan, J., Faderl, S., Garcia-Manero, G., Thomas, D.A., et al. (2002). Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood *99*, 3547–3553.

Kelly, L.M., Yu, J.C., Boulton, C.L., Apatira, M., Li, J., Sullivan, C.M., Williams, I., Amaral, S.M., Curley, D.P., Duclos, N., et al. (2002). CT53518, a novel selective FLT3 antagonist for the treatment of acute myelogenous leukemia (AML). Cancer Cell *1*, 421–432.

Kiyoi, H., Naoe, T., Nakano, Y., Yokota, S., Minami, S., Miyawaki, S., Asou, N., Kuriyama, K., Jinnai, I., Shimazaki, C., et al. (1999). Prognostic implication of FLT3 and N-RAS gene mutations in acute myeloid leukemia. Blood *93*, 3074–3080.

Kojima, K., Yasukawa, M., Ishimaru, F., Dansako, H., Matsuo, Y., Kimura, Y., Nawa, Y., Hara, M., and Harada, M. (1999). Additional translocation (8;21)(q22;q22) in a patient with Philadelphia-positive chronic myelogenous leukaemia in the blastic phase. Br. J. Haematol. *106*, 720–722.

Kratz, C.P., Emerling, B.M., Donovan, S., Laig-Webster, M., Taylor, B.R., Thompson, P., Jensen, S., Banerjee, A., Bonifas, J., Makalowski, W., et al. (2001). Candidate gene isolation and comparative analysis of a commonly deleted segment of 7q22 implicated in myeloid malignancies. Genomics *77*, 171–180.

Lai, F., Godley, L.A., Joslin, J., Fernald, A.A., Liu, J., Espinosa, R., 3rd, Zhao, N., Pamintuan, L., Till, B.G., Larson, R.A., et al. (2001). Transcript map and comparative analysis of the 1.5-Mb commonly deleted segment of human 5q31 in malignant myeloid diseases with a del(5q). Genomics *71*, 235–245.

Largaespada, D.A., Brannan, C.I., Jenkins, N.A., and Copeland, N.G. (1996). *Nf1* deficiency causes Ras-mediated granulocyte-macrophage colony stimulating factor hypersensitivity and chronic myeloid leukemia. Nat. Genet. *12*, 137–143.

Levis, M., Allebach, J., Tse, K.F., Zheng, R., Baldwin, B.R., Smith, B.D., Jones-Bolin, S., Ruggeri, B., Dionne, C., and Small, D. (2002). A FLT3-targeted tyrosine kinase inhibitor is cytotoxic to leukemia cells in vitro and in vivo. Blood *99*, 3885–3891.

Linker, C., Damon, L., Ries, C., and Navarro, W. (2002). Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. J. Clin. Oncol. *20*, 2464–2471.

Look, A.T. (1997). Oncogenic transcription factors in the human acute leukemias. Science *278*, 1059–1064.

Lorsbach, R.B., and Downing, J.R. (2001). The role of the AML1 transcription factor in leukemogenesis. Int. J. Hematol. *74*, 258–265.

Luna-Fineman, S., Shannon, K., and Lange, B.J. (1995). Childhood monosomy 7: Epidemiology, biology and mechanistic implications. Blood *85*, 1985–1999.

Luna-Fineman, S., Shannon, K.M., Atwater, S.K., Davis, J., Masterson, M., Ortega, J., Sanders, J., Steinherz, P., Weinberg, V., and Lange, B.J. (1999). Myelodysplastic and myeloproliferative disorders of childhood: a study of 167 patients. Blood *93*, 459–466.

Mahgoub, N., Taylor, B.R., Gratiot, M., Kohl, N.E., Gibbs, J.B., Jacks, T., and Shannon, K.M. (1999). In vitro and In vivo effects of a farnesyltransferase inhibitor on Nf1-deficient hematopoietic cells. Blood *94*, 2469–2476.

Mahmoud, H.H., Ridge, S.A., Behm, F.G., Pui, C.H., Ford, A.M., Raimondi, S.C., and Greaves, M.F. (1995). Intrauterine monoclonal origin of neonatal concordant acute lymphoblastic leukemia in monozygotic twins. Med. Pediatr. Oncol. *24*, 77–81.

Maris, J.M., and Denny, C.T. (2002). Focus on embryonal malignancies. Cancer Cell *2*, this issue, 447–450.

Marks, P.A., Richon, V.M., Breslow, R., and Rifkind, R.A. (2001). Histone deacetylase inhibitors as new cancer drugs. Curr. Opin. Oncol. *13*, 477–483.

McLean, T.W., Ringold, S., Neuberg, D., Stegmaier, K., Tantravahi, R., Ritz, J., Koeffler, H.P., Takeuchi, S., Janssen, J.W., Seriu, T., et al. (1996). TEL/AML-1 dimerizes and is associated with a favorable outcome in childhood acute lymphoblastic leukemia. Blood *88*, 4252–4258.

Miyamoto, T., Nagafuji, K., Akashi, K., Harada, M., Kyo, T., Akashi, T., Takenaka, K., Mizuno, S., Gondo, H., Okamura, T., et al. (1996). Persistence of multipotent progenitors expressing AML1/ETO transcripts in long-term remission patients with t(8;21) acute myelogenous leukemia. Blood *87*, 4789–4796.

Miyamoto, T, Weissman, I., and Akashi, K. (2000). AML1/ETO-expressing hematopoietic stem cells in acute myelogenous leukemia with 8;21 chromosomal translocation. Proc. Natl. Acad. Sci. USA *97*, 7521–7526.

Nakao, M., Yokota, S., Iwai, T., Kaneko, H., Horiike, S., Kashima, K., Sonoda, Y., Fujimoto, T., and Misawa, S. (1996). Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia *10*, 1911–1918.

Oosterveld, M., Muus, P., Suciu, S., Koller, C., Verhoef, G., Labar, B., Wijermans, P., Aul, C., Fiere, D., Selleslag, D., et al. (2002). Chemotherapy only compared to chemotherapy followed by transplantation in high risk myelodysplastic syndrome and secondary acute myeloid leukemia; two parallel studies adjusted for various prognostic factors. Leukemia *16*, 1615–1621.

Pui, C.H., Campana, D., and Evans, W.E. (2001). Childhood acute lymphoblastic leukamia—current status and future perspectives. Lancet *2*, 597–607.

Radich, J.P. (2001). Philadelphia chromosome-positive acute lymphocytic leukemia. Hematol. Oncol. Clin. North Am. *15*, 21–36.

Romana, S.P., Poirel, H., Leconiat, M., Flexor, M.A., Mauchauffe, M., Jonveaux, P., Macintyre, E.A., Berger, R., and Bernard, O.A. (1995). High frequency of t(12;21) in childhood B-lineage acute lymphoblastic leukemia. Blood *86*, 4263–4269.

Sawyers, C.L. (2002). Finding the next Gleevec: FLT3 targeted kinase inhibitor therapy for acute myeloid leukemia. Cancer Cell *1*, 413–415.

Sawyers, C.L., Hochhaus, A., Feldman, E., Goldman, J.M., Miller, C.B., Ottmann, O.G., Schiffer, C.A., Talpaz, M., Guilhot, F., Deininger, M.W., et al. (2002). Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood *99*, 3530–3539.

Shah, N.P., Nicol, J.M., Nagar, B., Gorre, M., Paquette, R., Kuryian, J., and Sawyers, C.L. (2002). Multiple Bcr-Abl kinase domina mutations confer resistance to the tyrosine kinase inhibitor imatinib in chronic phase or blast crisis chronic myeloid leukemia. Cancer Cell *2*, 117–125.

Shurtleff, S.A., Buijs, A., Behm, F.G., Rubnitz, J.E., Raimondi, S.C., Hancock, M.L., Chan, G.C., Pui, C.H., Grosveld, G., and Downing, J.R. (1995). TEL/AML1 fusion resulting from a cryptic t(12;21) is the most common genetic lesion in pediatric ALL and defines a subgroup of patients with an excellent prognosis. Leukemia *9*, 1985–1989.

Side, L., Taylor, B., Cayouette, M., Connor, E., Thompson, P., Luce, M., and Shannon, K. (1997). Homozygous inactivation of the NF1 gene in bone marrow cells from children with neurofibromatosis type 1 and malignant myeloid disorders. N. Engl. J. Med. *336*, 1713–1720.

Smith, K.S., Rhee, J.W., Naumovski, L., and Cleary, M.L. (1999). Disrupted differentiation and oncogenic transformation of lymphoid progenitors in E2A-HLF transgenic mice. Mol. Cell. Biol. *19*, 4443–4451.

Smith, K.S., Rhee, J.W., and Cleary, M.L. (2002). Transformation of bone marrow B-cell progenitors by E2A-HLF requires coexpression of BCL-2. Mol. Cell. Biol. *22*, 7678–7687.

Speck, N.A., and Gilliland, D.G. (2002). Core-binding factors in haematopoiesis and leukaemia. Nat. Rev. Cancer *2*, 502–513.

Stewart, G., and Elledge, S.J. (2002). The two faces of BRCA2, a FANCtastic discovery. Mol. Cell *10*, 2–4.

Stiller, C.A., Chessells, J.M., and Fitchett, M. (1994). Neurofibromatosis and

childhood leukemia/lymphoma: A population-based UKCCSG study. Br. J. Cancer *70*, 969–972.

Stock, W., Sather, H., Dodge, R.K., Bloomfield, C.D., Larson, R.A., and Nachman, J. (2000). Outcome of adolescents and young adults with acute lymphoblastic leukemia (ALL): A comparison pf Children's Cancer Group (CCG) and Cancer and Leukemia Group B (CALGB) regimens. Blood *96*, 2009a.

Taniguchi, T., and Dandrea, A.D. (2002). Molecular pathogenesis of fanconi anemia. Int. J. Hematol. *75*, 123–128.

Taniguchi, T., Garcia-Higuera, I., Xu, B., Andreassen, P.R., Gregory, R.C., Kim, S.T., Lane, W.S., Kastan, M.B., and D'Andrea, A.D. (2002). Convergence of the fanconi anemia and ataxia telangiectasia signaling pathways. Cell *109*, 459–472.

Thomas, X., Danaila, C., Le, Q.H., Sebban, C., Troncy, J., Charrin, C., Lheritier, V., Michallet, M., Magaud, J.P., and Fiere, D. (2001). Long-term follow-up of patients with newly diagnosed adult acute lymphoblastic leukemia: a single institution experience of 378 consecutive patients over a 21-year period. Leukemia *15*, 1811–1822.

Vardiman, J.W., Harris, N.L., and Brunning, R.D. (2002). The World Health Organization (WHO) classification of the myeloid neoplasms. Blood *100*, 2292–2302.

Warrell, R.P., Jr. (1996). Pathogenesis and management of acute promyelocytic leukemia. Annu. Rev. Med. *47*, 555–565.

Wechsler, J., Greene, M., McDevitt, M.A., Anastasi, J., Karp, J.E., Le Beau, M.M., and Crispino, J.D. (2002). Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. Nat. Genet. *32*, 148–152.

Weisberg, E., Boulton, C., Kelly, L.M., Manley, P., Fabbro, D., Meyer, T., Gilliland, D.G., and Griffin, J.D. (2002). Inhibition of mutant FLT3 receptors in leukemia cells by the small molecule tyrosine kinase inhibitor PKC412. Cancer Cell *1*, 433–443.

Weitzman, S., Suryanarayan, K., and Weinstein, H.J. (2002). Pediatric non-Hodgkin's lymphoma: clinical and biologic prognostic factors and risk allocation. Curr. Oncol. Rep. *4*, 107–113.

Wiemels, J.L., Cazzaniga, G., Daniotti, M., Eden, O.B., Addison, G.M., Masera, G., Saha, V., Biondi, A., and Greaves, M.F. (1999). Prenatal origin of acute lymphoblastic leukaemia in children. Lancet *354*, 1499–1503.

Wiemels, J.L., Xiao, Z., Buffler, P.A., Maia, A.T., Ma, X., Dicks, B.M., Smith, M.T., Zhang, L., Feusner, J., Wiencke, J., et al. (2002). In utero origin of t(8;21) AML1-ETO translocations in childhood acute myeloid leukemia. Blood *99*, 3801–3805.

Yamamoto, Y., Kiyoi, H., Nakano, Y., Suzuki, R., Kodera, Y., Miyawaki, S., Asou, N., Kuriyama, K., Yagasaki, F., Shimazaki, C., et al. (2001). Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. Blood *97*, 2434–2439.

Yeoh, E.J., Ross, M.E., Shurtleff, S.A., Williams, W.K., Patel, D., Mahfouz, R., Behm, F.G., Raimondi, S.C., Relling, M.V., Patel, A., et al. (2002). Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. Cancer Cell *1*, 133–143.

Yuan, Y., Zhou, L., Miyamoto, T., Iwasaki, H., Harakawa, N., Hetherington, C.J., Burel, S.A., Lagasse, E., Weissman, I.L., Akashi, K., and Zhang, D.E. (2001). AML1-ETO expression is directly involved in the development of acute myeloid leukemia in the presence of additional mutations. Proc. Natl. Acad. Sci. USA *98*, 10398–10403.

Zeidler, C., and Welte, K. (2002). Kostmann syndrome and severe congenital neutropenia. Semin. Hematol. *39*, 82–88.