not have a decreased proportion of naive $CD4^+$ T cells seen in previous studies[3,4,6] that could have at least explained the decreased levels of CXCR4 expression.

Cytokine therapies (IL-2 and IFNγ) have been used to improve proliferation, increase survival of T cells, and facilitate clearance of infections with variable success in cases of ICL. The lack of clinical benefit, despite substantial $CD4^+$ T-cell expansions with IL-2 therapy in HIV infection, has taught us that cytokine-induced $CD4^+$ T-cell increases are not always clinically meaningful. Reversal of a specific T-cell defect in ICL would be a reasonable objective. Defects in chemokine receptors or signaling may thus represent a plausible immunotherapeutic target not investigated to date. Both IL-2 as shown here and IL-7 can up-regulate CXCR4 expression,[7] so it will be important to determine whether the results of this study can be reproduced in other cohorts and whether clinical outcome correlates with these laboratory measurements. In conclusion, Scott-Algara et al have opened up a new area of investigation in ICL, both from the pathogenesis and etiology standpoint and from the therapeutic perspective. More data are needed to validate these findings in other cohorts and to further evaluate potential underlying genetic defects or soluble factors that may be responsible for these observations.

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● ● ● LYMPHOID NEOPLASIA

Comment on Kühnl et al, page 3737

Getting to the root of (it) ALL

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As shown in an elegant study of patients treated on GMALL trials in this issue of *Blood*, Kühnl and colleagues report that the *Brain And Acute Leukemia Cytoplasmic* (*BAALC*) gene provides a new marker identifying a population of B-lineage ALL patients whose cells express an immature leukemic phenotype and whose outcome is associated with a poor overall response to standard therapy.[1]

The overall survival of adults with acute lymphoblastic leukemia (ALL), in sharp contrast with childhood ALL, has not changed significantly over the past 3 decades, with 5-year survival rates between 30% and 40%.[2] For far too long the therapy of ALL in adults has been based on largely arbitrary and non-biologic prognostic factors. With the exception of the Philadelphia chromosome, treatment decisions have usually been based on age, white cell count at presentation, time to achievement of complete remission (CR), and immunophenotype. This has been in contrast to treatment of patients with acute myeloid leukemia (AML), where cytogenetics have been at the core of therapy for more than 25 years and molecular targeting has come into place over the past 15 years. Thus, it is often difficult to define the prognosis of patients with ALL, leading to either undertreatment or overtreatment.

Age remains the single most important prognostic factor determining outcome. However, this is likely to be, at least in part, a surrogate for intrinsic unfavorable biologic features, such as the Philadelphia chromosome, and is also driven by the inherent inability to tolerate the intensive therapies considered crucial for the management of adults with ALL.[3] High white blood cell (WBC) count at presentation, another time-honored prognostic factor, is also associated with known poor prognostic features, such as t(4;11)(q21;q23). Conversely, aberrations such as the t(12;21)(p13;q22), known to confer a better prognosis, are associated with low WBC counts. Apart from the "Burkitt leukemia" mature B-cell ALL, morphology has had no prognostic value in ALL. Time to CR, shorter or longer than 4 weeks, has been used in therapeutic stratification for several decades, although the significance of this has not been demonstrated in a recent very large trial.[4] Detection of minimal residual disease at various time points is becoming increasingly incorporated into the management of adult ALL and, much like childhood ALL, is likely to be a mainstay in the future determination of the appropriateness of intense therapies in this disease, such as allogeneic hematopoietic stem cell transplantation.[5] Although immunophenotyping has been considered crucial in the classification of ALL, its discriminatory impact on prognosis and therapy has been marginal and often conflicting. It is only with the detection of specific molecular abnormalities present in either T- or B-lineage ALL, or specific molecular targeting, such as monoclonal antibodies for B-lineage ALL or novel drugs for T-lineage ALL, such as nelarabine, that immunophenotyping is likely to have a significant role in the management of ALL. Only recently have cytogenetics been recognized as having a major role in the classification of Philadelphia chromosome–negative ALL in adults. In addition to the previously recognized t(9;22)(q34;q11), an analysis from the UKALLXII/ECOG2993 study, with the largest prospective cytogenetic database, has

identified high-risk cohorts in adults. This includes those with t(4;11)(q24.1;q32), t(8;14)(q24.1;q32), low hypodiploidy, near triploidy, and a complex karyotype. In contrast, patients with hyperdiploidy or with a del(9p) had a significantly improved outcome.[6] Molecular markers in ALL, demonstrated to be of prognostic significance, have mostly been described only in the past 5 years. These include the transcription factor Erg or the expression of HOX11L2, which are reported to be associated with an adverse outcome in T-cell ALL.[7] It has also been recognized that high BAALC expression is associated with an inferior prognosis in T-cell ALL.[8] Similarly, a Notch1/FBXW7 mutation was identified in a large subgroup with a more favorable outcome among adults with T-lineage ALL.[9]

The importance of the present report in this issue of *Blood* by Kühnl et al is the determination of a significant molecular prognostic factor in a large study of more than 350 patients with B-lineage ALL.[1] The high BAALC expression predicted for a primary resistance or an overall poor response in the entire cohort and, most importantly, in the subgroups who did not express bcr-abl or MLL-AF4. It also turned out that high BAALC expression occurred significantly more often in older patients, providing another biological reason for the poor prognosis of ALL with increasing age. Similarly, high BAALC expression was significantly associated with a high WBC count at presentation, once again providing a more biological rationale for the poor prognosis in this group.

Whereas the poor prognosis of patients with B-lineage ALL, whose cells express bcr-abl fusion protein or the translocation t(4;11)(q21;q23) with the MLL-AF4 fusion protein, has been well established,[10] patients lacking such abnormalities have been considered as standard risk. And herein lies the challenge. Without doubt, the most potent antileukemic therapy for ALL is allogeneic transplantation; however, its use is limited by the attendant transplantation-related mortality. The ability to better define the risk/benefit ratio for individual patients is often elusive in the absence of cytogenetic or molecular determinants. The report by Kühnl and colleagues, together with the other known cytogenetic and molecular prognostic factors, should go a long way toward digging deeper and finally getting closer to a more biologic classification for adults with ALL.

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● ● ● PLATELETS & THROMBOPOIESIS

Comment on Schwertz et al, page 3801

Platelets in bloom

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Beginning with initial observations a century ago,[1] the complex events involved in platelet production from megakaryocytes have been characterized with increasing precision during the past decade.[2-4] In this issue of *Blood*, Schwertz and colleagues add surprising new findings that elucidate the probable terminal event of thrombopoiesis, that is, the duplication of human blood platelets.[5] Their experiments were conducted ex vivo in microdrops, as well as in suspension and whole blood cultures. The implication of their report is that platelet replication may also occur in the circulation and during platelet storage under blood-banking conditions.

Multinucleated megakaryocytes in the bone marrow stroma extend long, tubular cytoplasmic projections ("proplatelets") between endothelial cells into the lumina of marrow sinusoids. While anchored to the megakaryocyte within the sinusoids, or after shear-induced breakage, the proplatelets use microtubular rearrangements at their tips to produce and release mature platelets into the circulation.[1-4] These platelets normally circulate for about 10 days.

Although devoid of a nucleus and the capacity to transcribe new mRNA, each platelet produced by this mechanism retains a robust capacity to cleave and activate precursor forms of mRNA. These precursor mRNAs, previously transcribed in the polyploid nuclei of a megakaryocyte progenitor, are then transported through the megakaryocyte's extended cytoplasmic proplatelet stalks to nascent platelet "buds" at the tips of the stalks.[2-4] Each mature platelet that escapes into the circulation continues to process its composition of precursor mRNAs and to translate the resulting functional mRNAs into proteins.[6,7] Included among the platelet-translated proteins identified so far are glycoprotein αIIbβ3, cyclooxygenase-1 and -2 isoforms, components of the spliceosome complex involved in precursor mRNA intron removal, proapoptosis and antiapoptosis factors, plasminogen activator inhibitor-1, P-selectin, and tissue factor.[5-7]

In their report, Schwertz et al demonstrate that human platelets also retain the essential molecular components and synthetic capacity that enables them to replicate within a few