AITL, NOS, and anaplastic large-cell lymphoma (ALCL) types.[1] Interestingly, whereas *TET2* and *DNMT3A* mutations assessed by targeted resequencing were observed in all 3 categories, although with different frequencies, *IDH2* detected by Sanger sequencing occurred most frequently in AITL (32.8% vs 5% of NOS and 0% of ALCL). Moreover, the previously reported occurrence of *IDH2* mutations at R172 was confirmed, as was the common co-occurrence with *TET2* mutations. These findings are at variance with acute myeloid leukemia and glioblastoma, in which *IDH2* mutations are at R140 and are mutually exclusive of the *TET2* mutations. In particular, the $IDH2^{R172}$-mutated cases showed a distinct GEP among AITLs and the *IDH2*/*TET2* double-mutant cases carried upregulation of T_{FH}-associated genes and downregulation of genes associated with T helper 1 (Th1), Th2, and Th17 phenotypes. These double-mutant AITLs were highly enriched for the signature of $CD4^+$ T cells stimulated by interleukin-12, suggesting a more polarized T_{FH} phenotype. Finally, yet importantly, Wang et al provide experimental evidence that IDH^{R172} mutations produce a significant increase in H3K27me3 and DNA hypermethylation of genes involved in T-cell receptor signaling and T-cell differentiation that likely contribute to lymphomagenesis in AITL. In addition, these findings give a strong rationale for the usage of hypomethylating agents in AITL treatment.

The Wang et al article highlights how sequencing analyses can help dissect apparently homogenous neoplasms using conventional techniques. This study provides new insights on the pathogenesis and subclassification of these tumors as well as on the detection of novel and hopefully more effective therapeutic targets.[1] The latter represent a real need because most PTCLs have a dismal prognosis when treated with current therapies.[5]

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Karol et al, page 1770

ALL and osteonecrosis

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In this issue of *Blood*, Karol et al establish a link between glutamate receptor polymorphisms and osteonecrosis, using a large discovery cohort and 2 validation cohorts. One validation cohort included patients under treatment of acute lymphoblastic leukemia (ALL) and the second is patients receiving glucocorticoid treatment of various other indications.[1] This battered old clinician does not pretend to follow all the mathematics.

Osteonecrosis is the bane of contemporary therapy for ALL in adolescents and young adults, leading to lifelong pain and disability for some.[2] Patients may undergo surgery, such as hip replacement, and obtain symptomatic relief, but artificial hips wear out and must be replaced every 10 to 20 years. These patients may be cured from their leukemia, but we have exchanged one disease for another.

Osteonecrosis appears more common adolescent and young adults, more common in young women than young men, and less common in African Americans. The incidence of symptomatic osteonecrosis varies from 10% to 30% and depends somewhat on the thoroughness of the treating physicians.[1] Pain and loss of range of motion appear prior to any x-ray changes and diagnosis is best made with magnetic resonance imaging (MRI). The course is quite variable, complicating assessment of candidate interventions.

The Children's Oncology Group (COG) decreased dexamethasone in the Delayed Intensification phase from 21 to 14 days (7 days on, 7 days off, and 7 days on), with no erosion of outcome and almost halved the incidence of osteonecrosis.[3] The UKALL 2011 study currently tests a similar intermittent dexamethasone schedule in induction. Results are eagerly awaited.

Hopes that MRI screening would lead to early detection and useful intervention have been confounded by a high incidence of transient marrow edema. Enthusiasm for statins as a preventive agent has gone nowhere. Early surgical intervention remains controversial. Prostaglandins or bisphosphonates to slow progression and ameliorate pain remain anecdotes. Only the seriousness and the urgency of the problem stand unchallenged.[4]

Karol et al find that a polymorphism at single nucleotide polymorphism rs 10989692 near the glutamate receptor GRIN3A locus was associated with a doubling of the incidence of osteonecrosis.[1] The allelic frequency is 0.106, so ~20% of patients have ≥1 affected allele. Using

the discovery cohort of COG white patients, back of the envelope calculations indicate an osteonecrosis incidence of 21.5% for affected patients with G/A or A/A and 10.7% for G/G patients (see Table 1 in Karol et al). The polymorphism accounts for ~17% of cases of osteonecrosis, ~1 case in 6. White patients with the G/G genotype have 109 cases in place of the expected 132 cases, a reduction in incidence from 12.9% to 10.7%, and remain at substantial risk for symptomatic osteonecrosis.

Karol et al are impressive for their sample size and scientific rigor. They present compelling arguments for biological plausibility. However, no prior genome-wide association study investigation has linked glutamate receptor genetic variations and osteonecrosis. A variety of other plausible polymorphisms have been inconsistently implicated with similar hazard ratios, involving PAI-1, glucocorticoid metabolism, antifolate pharmacodynamics, fibrinolysis, and lipid and albumin homeostasis.[5-8] Few candidate polymorphisms appear in >1 report. As with all retrospective studies, prospective confirmation is needed.[9]

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● ● ● LYMPHOID NEOPLASIA

Comment on Song et al, page 1813

Restoring Ikaros's wings to solve a leukemia maze

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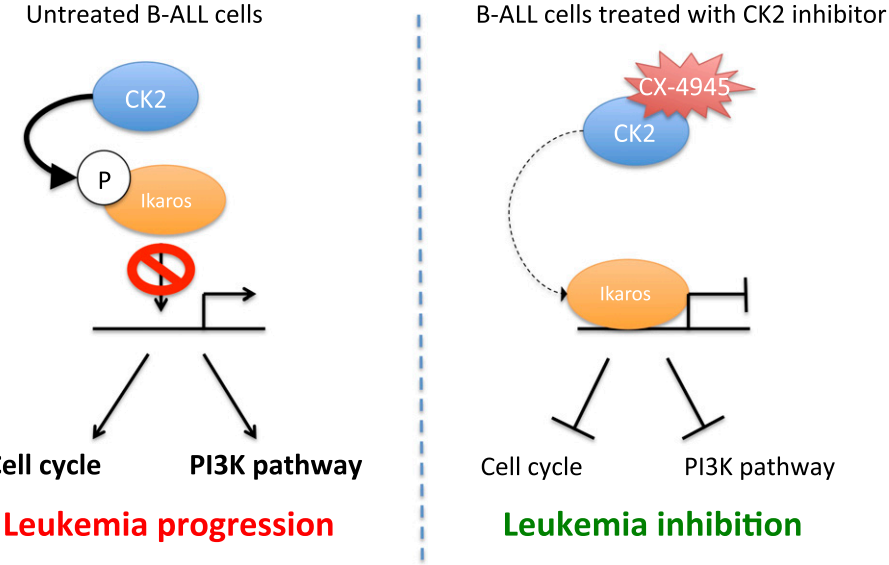
In this issue of *Blood*, Song et al show that tumor suppressor activity of Ikaros is achieved though repression of cell cycle and phosphatidylinositol-3 (PI3) kinase pathway genes and can be reactivated through pharmacologic inhibition of casein kinase 2 (CK2) to eradicate disease in high-risk B-cell acute lymphoblastic leukemia (B-ALL).[1]

B-ALL is the most common leukemia diagnosed during childhood. Although frontline risk-adapted chemotherapies have improved overall survival, nearly 20% of children and >50% of adults relapse.[2] Therefore, this disease remains one of the leading causes of leukemia death. In recent years, extensive genomic profiling has led to better classification and understanding of high-risk B-ALL.[3] Elucidation of the mechanisms involving these genetic alterations in the pathogenesis of B-ALL could lead to the design of specific therapies for the most refractory subgroups.

Among these genetic alterations, the *IKZF1* gene encoding the Ikaros transcription factor



The two "wings" of Ikaros in B-ALL suppression. (Right) In B-ALL cells, CK2 activity is increased and results in Ikaros phosphorylation that prevents its binding to DNA and regulation of cell cycle and PI3K pathway genes. (Left) On treatment with the specific CK2 inhibitor CX-4945, Ikaros is no longer phosphorylated and can actively repress its target genes, leading to leukemia inhibition.