Précis: Leukemia and nonmalignant clonal hematopoiesis (CH) are indistinguishable by bulk sequencing assays. Here, DNA probes tailored to detect patient-specific oncogenic lesions are combined with multiplex immunophenotyping to definitively resolve leukemia and CH at a single-cell level.

Clinical Significance of Novel Subtypes of Acute Lymphoblastic Leukemia in the Context of Minimal Residual Disease–Directed Therapy ............... 326
Précis: Combining minimal residual disease monitoring with genome analysis demonstrates high-precision risk assessment in newly identified subtypes of pediatric ALL.
See commentary, p. 294

ROBO1 Promotes Homing, Dissemination, and Survival of Multiple Myeloma within the Bone Marrow Microenvironment ....... 338
Précis: ROBO1 mediates multiple myeloma cell–intrinsic growth, as well as adhesion to stromal cells, homing, and engraftment in the bone marrow.

Tumor Burden Limits Bispecific Antibody Efficacy through T-cell Exhaustion Averted by Concurrent Cytotoxic Therapy ............. 354
Précis: Bispecific antibody response in immunocompetent mice with high myeloma burden is transient due to ensuing T-cell exhaustion. Cyclophosphamide pretreatment prevents the exhaustion, enabling complete and durable bispecific antibody responses in animals with advanced disease.

See commentary, p. 297

Lysine Demethylase 5A Is Required for MYC-Driven Transcription in Multiple Myeloma


Précis: KDM5A is required for transcription elongation of Myc target genes in myeloma, and a small-molecule selective inhibitor shows activity in myeloma models.

Hyperthermia Selectively Destabilizes Oncogenic Fusion Proteins


Précis: PML-RARα and other fusion oncoproteins are heat unstable, and prone to aggregation and degradation in hyperthermia. Proof-of-principle patient cases illustrate how this vulnerability may be potentially exploited for therapy of refractory acute promyelocytic leukemia.

See commentary, p. 300

ON THE COVER

In Greek mythology, Sisyphus has tricked death twice and, as a punishment, has been doomed to push a heavy rock uphill, only to run out of steam near the top, where the rock escapes his grip and rolls back down. This cycle, reminiscent of a transient response to therapy followed by a relapse, is futile unless the man would eventually come up with a clever trick to outsmart this destiny. In this issue, Meermeier and colleagues show that in animals with high tumor burden, responses to bispecific T-cell engager (BiTE) antibody therapy of myeloma are limited by exhaustion of T cells. The outcome of this uphill battle can be overturned by the addition of cyclophosphamide, which reduces the tumor load and prevents T-cell exhaustion when combined with BiTE therapy, leading to tumor clearance and long-term protective myeloma-specific immunity. For details, please see the article on page 354 and the accompanying commentary by Louvet, Nadeem, and Smith on page 297.