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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.
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Tumor Burden Limits Bispecific Antibody Efficacy through T-cell Exhaustion Averted by Concurrent Cytotoxic Therapy ............... 354

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**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.

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**Lysine Demethylase 5A Is Required for MYC-Driven Transcription in Multiple Myeloma** 370


**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** 388


**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.

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**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.