## IN THIS ISSUE

Highlighted research articles .................. 187

### VIEWS

**Obituary**

Honoring Emil J. Freireich: A Visionary Medical Cancer Researcher—March 21, 1927–February 1, 2021 ........ 190

H.M. Kantarjian

**In The Spotlight**

Toward More Complete Prognostication for Patients with Clonal Hematopoiesis .... 192

B. Spitzer and R.L. Levine

See article, p. 226

Toward Artificial Intelligence–Driven Pathology Assessment for Hematologic Malignancies .... 195

O. Elemento

See article, p. 238

Non-oncogene Addiction to SIRT5 in Acute Myeloid Leukemia .... 198

M. Li and A.M. Melnick

See article, p. 266

### REVIEW

An Evolutionary Approach to Clonally Complex Hematologic Disorders .................... 201

E. Schwenger and U. Steidl

### RESEARCH ARTICLES

**Large-scale Identification of Clonal Hematopoiesis and Mutations Recurrent in Blood Cancers .... 226**


**Précis:** Mutation hotspots are determined from 48 hematologic malignancy studies, which allows for calculating the prevalence rate of clonal hematopoiesis at hotspots within noncancer cohorts; the results from this study could be used for blood cancer risk assessment.

See commentary, p. 192

**Machine Learning of Bone Marrow Histopathology Identifies Genetic and Clinical Determinants in Patients with MDS ........... 238**


**Précis:** Histopathology features extracted by machine learning can identify MDS stage, prognosis, and genetic lesions, linking tissue morphology to underlying genetics and offering new tools for improved clinical evaluation for MDS.

See commentary, p. 195

**Avadomide Induces Degradation of ZMYM2 Fusion Oncoproteins in Hematologic Malignancies .... 250**


**Précis:** Translocations involving ZMYM2 result in oncogenic fusion proteins in AML. This article shows that thalidomide and its analogues target ZMYM2 and its fusions to cereblon-mediated proteolysis and impede growth of ZMYM2 fusion–driven leukemias.

**Dissecting Clonal Hematopoiesis in Tissues of Patients with Classic Hodgkin Lymphoma ....... 216**


**Précis:** In situ genetic composition of classical Hodgkin lymphoma tumors, normal lymph node tissue, and blood dissects contributions of clonal hematopoiesis to malignant lymphoma

**In situ** genetic composition of classical Hodgkin lymphoma tumors, normal lymph node tissue, and blood dissects contributions of clonal hematopoiesis to malignant lymphoma.
The presence of somatic mutations in a fraction of blood cells, termed clonal hematopoiesis (CH), is associated with increased risk of blood cancers. With a few exceptions, the exact relationships between CH and hematologic malignancies remain uncharted. A broad conceptual framework encompassing clonal relationships in cancer evolution is laid out in a review article by Schwenger and Steidl on page 201. The article on page 216 by Venanzi and colleagues dissects CH contributions to Hodgkin lymphoma in the blood lineage, tumor cells, and their microenvironment. Certain mutations with known oncogenic properties are especially common in CH. Conversely, studies of CH are often limited to a panel of these predetermined hotspots. Genomic analysis by Feusier and colleagues (page 226) expands the catalog of mutations recurrent in blood cancer and in CH. Cover images by Katie Vicari and Doug Smock.

SIRT5 Is a Druggable Metabolic Vulnerability in Acute Myeloid Leukemia ........................................ 266

Précis: CRISPR screen identifies SIRT5 as a metabolic vulnerability in AML but not in healthy hematopoietic cells. SIRT5 controls mitochondrial and glutamine metabolic pathways in AML. SIRT5 genetic or pharmacologic inhibition triggers apoptosis and delays leukemia progression, pointing to its potential as a therapeutic target for AML.
See commentary, p. 198