**Cancer Discovery**

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**In This Issue**  
Highlighted research articles ........................................ 1325

**News in Brief**  
Important news stories affecting the community ............. 1330

**News in Depth**  
TMB Faces Validation Hurdles ....................................... 1334

**Research Watch**  
Selected highlights of recent articles of exceptional significance from the cancer literature .............. 1335

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**Research Brief**  
Distinct Colorectal Cancer-Associated APC Mutations Dictate Response to Tankyrase Inhibition ......................... 1358

** précis:** The locations of mutations in APC, which hyperactivate WNT signaling and are common in colorectal cancers, dictate whether tankyrase inhibition can restore normal WNT signaling.

**Research Articles**  
Combination Olaparib and Temozolomide in Relapsed Small-Cell Lung Cancer ........ 1372

** précis:** A phase I/II clinical trial of the PARP inhibitor olaparib with the DNA-alkylating agent temozolomide in small-cell lung cancer provided preliminary evidence of efficacy, and a co-clinical trial using patient-derived xenografts revealed possible biomarkers for response.

**See commentary, p. 1340**

Tumor Genomic Profiling Guides Patients with Metastatic Gastric Cancer to Targeted Treatment: The VIKTORY Umbrella Trial ............ 1388

** précis:** Biomarker-based treatment of patients with gastric cancer was associated with an improved overall response rate, and patients with MET amplifications who received savolitinib exhibited especially promising responses.

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**Views**  
**In The Spotlight**

Temozolomide plus PARP Inhibition in Small-Cell Lung Cancer: Could Patient-Derived Xenografts Accelerate Discovery of Biomarker Candidates? .... 1340

J.M. Pacheco and L.A. Byers

**See article, p. 1372**

Single-Cell RNA Sequencing Reveals a Developmental Hierarchy in Langerhans Cell Histiocytosis ................. 1343

T.A. Gruber

**See article, p. 1406**

Bringing Oncohistones into the Fold ......................... 1346

J.F. Sarthy and S. Henikoff

**See article, p. 1438**

**Mini Review**  
Tumor Microenvironment Dynamics in Clear-Cell Renal Cell Carcinoma ................... 1349

L. Vuong, R.R. Kotecha, M.H. Voss, and A.A. Hakimi

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For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/CDNews.
Epigenomics and Single-Cell Sequencing Define a Developmental Hierarchy in Langerhans Cell Histiocytosis. 1406


Précis: Single-cell analysis of Langerhans cell histiocytosis lesions revealed cellular and molecular heterogeneity suggestive of a developmental hierarchy shared among lesions. See commentary, p. 1343

The Mechanism of Anti–PD-L1 Antibody Efficacy against PD-L1−Negative Tumors Identifies NK Cells Expressing PD-L1 as a Cytolytic Effector 1422

W. Dong, X. Wu, S. Ma, Y. Wang, A. P. Nalin, Z. Zhu, J. Zhang, D. M. Benson, K. He, M. A. Caligiuri, and J. Yu

Précis: The counterintuitive response of some PD-L1− tumors to anti–PD-L1 therapy may be a result of PD-L1 expression on natural killer (NK) cells, which can be triggered by contact between NK cells and myeloid leukemia cells.

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A Mutation in Histone H2B Represents a New Class of Oncogenic Driver 1438


Précis: Mutations in the bodies of core histone proteins recur in cancers; the most common one (H2B176G) destabilizes nucleosomes, increases chromatin accessibility, alters gene expression, and increases proliferation of normal epithelial cells. See commentary, p. 1346

Altered Nuclear Export Signal Recognition as a Driver of Oncogenesis 1452


Précis: Recurrent and lineage-specific mutations in the nuclear-export receptor XPO1 alter the distribution of proteins in the nucleus and cytoplasm and promote oncogenesis in vitro and in vivo.

ON THE COVER

Taylor and colleagues found that recurrent and lineage-specific mutations in exportin-1 (XPO1)—the protein predominantly responsible for nuclear export of proteins 40 kDa and larger—change how proteins are distributed in the nucleus and cytoplasm. These mutations also increased tumor growth in mouse xenotransplantation experiments and promoted oncogenesis in a conditional knock-in mouse model. Altered protein export was also observed in a B-cell precursor leukemia cell line; some differentially exported proteins included participants in the K63-ubiquitination, TLR4, and NFκB pathways. Both in vitro and in vivo, the tested XPO1 mutation caused increased sensitivity to treatment with selinexor, an XPO1 inhibitor. For details, please see the article by Taylor and colleagues on page 1452.