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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

RESEARCH BRIEF Distinct Colorectal Cancer-Associated APC Mutations Dictate Response to Tankyrase Inhibition 1358

E.M. Schatoff, S. Goswami, M.P. Zafra, M. Foronda, M. Shusterman, B.I. Leach, A. Katti, B.J. Diaz, and L.E. Dow

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



A.F. Farago, B.Y. Yeap, M. Stanzione, Y.P. Hung, R.S. Heist, J.P. Marcoux, J. Zhong, D. Rangachari, D.A. Barbie, S. Phat, D.T. Myers, R. Morris, M. Kem, T.D. Dubash, E.A. Kennedy, S.R. Digumarthy, L.V. Sequist, A.N. Hata, S. Maheswaran, D.A. Haber, M.S. Lawrence, A.T. Shaw, M. Mino-Kenudson, N.J. Dyson, and B.J. Drapkin

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.

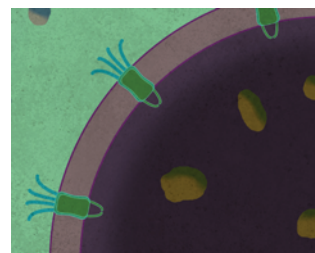
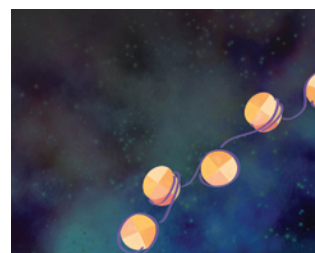
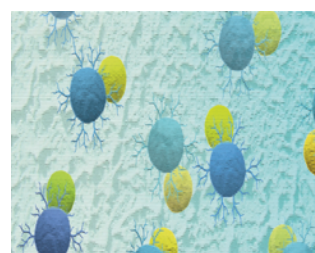
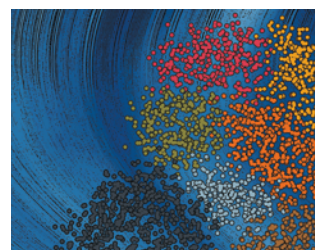
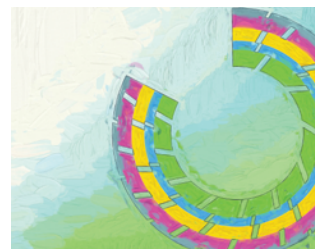
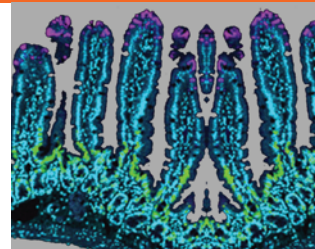
See commentary, p. 1340

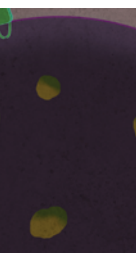
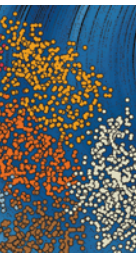
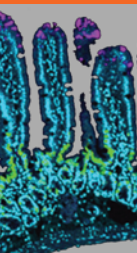
Tumor Genomic Profiling Guides Patients with Metastatic Gastric Cancer to Targeted Treatment: The VIKTORY Umbrella Trial 1388



J. Lee, S.T. Kim, K. Kim, H. Lee, I. Kozarewa, P.G.S. Mortimer, J.I. Odegaard, E.A. Harrington, J. Lee, T. Lee, S.Y. Oh, J.-H. Kang, J.H. Kim, Y. Kim, J.H. Ji, Y.S. Kim, K.E. Lee, J. Kim, T.S. Sohn, J.Y. An, M.-G. Choi, J.H. Lee, J.M. Bae, S. Kim, J.J. Kim, Y.W. Min, B.-H. Min, N.K.D. Kim, S. Luke, Y.H. Kim, J.Y. Hong, S.H. Park, J.O. Park, Y.S. Park, H.Y. Lim, A.A. Talasaz, S.J. Hollingsworth, K.-M. Kim, and W.K. Kang

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.





Epigenomics and Single-Cell Sequencing Define a Developmental Hierarchy in Langerhans Cell Histiocytosis 1406



F. Halbritter, M. Farlik, R. Schwentner, G. Jug, N. Fortelny, T. Schnöller, H. Pisa, L.C. Schuster, A. Reinprecht, T. Czech, J. Gojo, W. Holter, M. Minkov, W.M. Bauer, I. Simonitsch-Klupp, C. Bock, and C. Hutter

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

R.L. Bennett, A. Bele, E.C. Small, C.M. Will, B. Nabat, J.A. Oyer, X. Huang, R.P. Ghosh, A.T. Grzybowski, T. Yu, Q. Zhang, A. Riva, T.P. Lele, G.C. Schatz, N.L. Kelleher, A.J. Ruthenburg, J. Liphardt, and J.D. Licht

Précis: Mutations in the bodies of core histone proteins recur in cancers; the most common one (H2B^{E76K}) 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



J. Taylor, M. Sendino, A.N. Gorelick, A. Pastore, M.T. Chang, A.V. Penson, E.I. Gavrilu, C. Stewart, E.M. Melnik, F. Herrejon Chavez, L. Bitner, A. Yoshimi, S.C.-W. Lee, D. Inoue, B. Liu, X.J. Zhang, A.R. Mato, A. Dogan, M.G. Kharas, Y. Chen, D. Wang, R.K. Soni, R.C. Hendrickson, G. Prieto, J.A. Rodriguez, B.S. Taylor, and O. Abdel-Wahab

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.

