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RESEARCH BRIEF  Overcoming PD-1 Blockade Resistance with CpG-A Toll-Like Receptor 9 Agonist Vidutolimod in Patients with Metastatic Melanoma ...........  2998
Précis: Intratumoral vidutolimod (CpG-A TLR9 agonist) together with pembrolizumab overcomes PD-1 blockade resistance in 25% of patients with metastatic melanoma with manageable toxicities in a phase I trial.
See commentary, p. 2960

RESEARCH ARTICLES  Genomes for Kids: The Scope of Pathogenic Mutations in Pediatric Cancer Revealed by Comprehensive DNA and RNA Sequencing ....  3008
Précis: Analysis of data from the Genomes for Kids research study reveals the value of three-platform whole-genome, whole-exome, and RNA sequencing in identifying clinically and biologically relevant lesions in pediatric cancer.

Multiomic Analysis of Lung Tumors Defines Pathways Activated in Neuroendocrine Transformation .................  3028

For Whom the Bell Tolls? A Toll-Like Receptor 9 Agonist’s Journey from Vaccine Adjuvant to Promising Agent in Anti–PD-1–Resistant Melanoma .................  2960
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A Tale of Two Histologies: Dissecting the Biology of Lineage Transformation in Lung Cancer .................  2962
C.B. Meador and C.M. Lovly
See article, p. 3028

Harnessing Mitochondrial Mutations to ATAC Clonal Evolution in CLL .................  2965
L.K. Hilton and D.W. Scott
See article, p. 3048

Detecting Liquid Remnants of Solid Tumors: Circulating Tumor DNA Minimal Residual Disease ....  2968
E.J. Moding, B.Y. Nabet, A.A. Alizadeh, and M. Diehn

Clonal Hematopoiesis: From Mechanisms to Clinical Intervention .................  2987
T. Köhnke and R. Majeti

REviews
and improved response to checkpoint therapy through derepression of ERVs and dsRNA stress, hyperploidy, and cell death.

Accessibility and CNV changes, reveals insight as natural barcodes, and, along with chromatin dynamics, highlights formation in a pathway as a therapeutic target to inhibit transformation in EGFR-mutant lung adenocarcinoma.

See commentary, p. 2962

Longitudinal Single-Cell Dynamics of Chromatin Accessibility and Mitochondrial Mutations in Chronic Lymphocytic Leukemia Mirror Disease History .......................... 3048


Précis: Single-cell analysis of serial chronic lymphocytic leukemia (CLL) samples highlights the potential of mitochondrial DNA mutations as natural barcodes, and, along with chromatin accessibility and CNV changes, reveals insight into the clonal evolution of CLL.

See commentary, p. 2965

AKT Degradation Selectively Inhibits the Growth of PI3K/PTEN Pathway–Mutant Cancers with Wild-Type KRAS and BRAF by Destabilizing Aurora Kinase B ........ 3064


Précis: AKT depletion using a degrader proved superior to kinase inhibition due to sustained repression of AKT signaling and destabilization of AURKB, leading to induction of G2/M arrest, hyperploidy, and cell death.

Pharmacologic Activation of p53 Triggers Viral Mimicry Response Thereby Abolishing Tumor Immune Evasion and Promoting Antitumor Immunity ....... 3090


Précis: Reactivation of p53 by MDM2 inhibitors potentiates anticancer immune surveillance through derepression of ERVs and dsRNA stress, resulting in induction of the interferon pathway and improved response to checkpoint therapy.

Cholesterol Auxotrophy as a Targetable Vulnerability in Clear Cell Renal Cell Carcinoma ......................... 3106


Précis: Multi-omic analyses of clear cell renal cell carcinoma revealed a strict exogenous cholesterol dependency as a novel therapeutic strategy by limiting cholesterol availability and/or inhibiting a key cholesterol transporter.

A Humanized Animal Model Predicts Clonal Evolution and Therapeutic Vulnerabilities in Myeloproliferative Neoplasms ............................................. 3126


Précis: A patient-derived xenograft system was developed that enables engraftment of primary cells from patients with myelofibrosis (MF) and transmission of phenotypes, such as bone marrow fibrosis, and genotypes including MF driver mutations in mice with expression of human myeloid promoting cytokines.

Tumor Microenvironment–Derived R-spondins Enhance Antitumor Immunity to Suppress Tumor Growth and Sensitize for Immune Checkpoint Blockade Therapy ........................................... 3142


Précis: Bioinformatic analysis coupled with in vivo studies identified R-spondins as immunotherapeutic modifiers in tumors that enhanced natural killer cell and CDB+ T-cell antitumor immunity, inhibited tumor progression, and sensitized cells to anti–PD-1 therapy.

Genetic Screens Identify a Context-Specific PI3K/p27kip1 Node Driving Extrahepatic Biliary Cancer .......................................................... 3158

Précis: Genetic screening in a mouse model of biliary cancer revealed Pik3ca activation but not oncogenic Kras activation as critical for transformation and tumor formation and additionally reveals the context-and tissue-specific nature of oncogenic drivers.

Blocking Short-Form Ron Eliminates Breast Cancer Metastases through Accumulation of Stem-Like CD4+ T Cells That Subvert Immunosuppression

S.-C.A. Lai, H. Gundlapalli, H.A. Ekiz, A. Jiang, E. Fernandez, and A.L. WelM

Précis: Inhibition of a specific isoform of RON receptor tyrosine kinase (SF-RON) recruits stem-like CD4 T cells to the metastatic site and promotes strong antitumor immune responses that severely restrict growth of breast cancer metastases.

Actinomycin D Targets NPM1c-Primed Mitochondria to Restore PML-Driven Senescence in AML Therapy


Précis: Oncogenic NPM1c mutations prime acute myeloid leukemia cells for mitochondrial targeting by actinomycin D, which restores PML nuclear bodies—driven senescence and is synergistic with venetoclax to induce tumor clearance.

Rif-Myc1 Gene Fusion Drives Tumorigenesis and Metastasis in a Mouse Model of Small Cell Lung Cancer


Précis: The first genetically engineered mouse model expressing the Rif-Myc1 fusion protein indicated the ability of this fusion to promote transformation and tumorigenesis of small cell lung cancer as well as increase metastatic potential to an array of different sites.

In addition to its tumor suppressor gene function, p53 has been shown to contribute to silencing of repetitive elements including endogenous retrovirus (ERV) long terminal repeat sequences. Zhou, Singh, and colleagues made the unexpected observation that upon p53 activation through pharmacologic inhibition of its negative regulator MDM2, ERV expression was increased due to increased p53 occupancy on ERV promoters and p53-mediated suppression of LSD1 and DNMT1, two major ERV repressors. ERV derepression following MDM2 inhibition contributed to double-stranded RNA stress leading to type I/III interferon (IFN) expression, antigen processing/presentation, and increased T-cell infiltration. Additionally, dual treatment with an anti-PD-1 antibody along with an MDM2 inhibitor markedly reduced tumor growth in a poorly immunogenic murine model of melanoma as compared with checkpoint therapy alone. An augmentation of IFN signaling and immune cell recruitment was also observed in patients who received an MDM2 inhibitor. For more information, see the article by Zhou, Singh, and colleagues on page 3090.

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