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**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
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**Harnessing Mitochondrial Mutations to ATAC Clonal Evolution in CLL** .......................... 2965
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### Reviews

**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

### 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.

**Multimomic Analysis of Lung Tumors Defines Pathways Activated in Neuroendocrine Transformation** .......... 3028
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 modulators in tumors that enhanced natural killer cell and CD8 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 Extraphepatic Biliary Cancer                                                                  3158


Précis: A humanized animal model predicts clonal evolution and therapeutic vulnerabilities in myeloproliferative neoplasms.
CANCER DISCOVERY CONTENTS

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

Rf-Mycl Gene Fusion Drives Tumorigenesis and Metastasis in a Mouse Model of Small Cell Lung Cancer
Précis: The first genetically engineered mouse model expressing the Rf-Mycl 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.

ON THE COVER
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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