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### VIEWS

**In The Spotlight**

**Untangling the Role of Polycomb Complexes in Chemotherapy Resistance**

C. Duy and A. Melnick

*See article, p. 1376*

**Is ctDNA the Road Map to the Landscape of the Clonal Mutational Evolution in Drug Resistance? Lessons from the PALOMA-3 Study and Implications for Precision Medicine**

R. Schiff and R. Jeselsohn

*See article, p. 1390*

**Inhibition of HIF1α Signaling: A Grand Slam for MDS Therapy?**

J. Chen and U. Steidl

*See article, p. 1438*

### MINI REVIEW

**Mouse Models for Cancer Immunotherapy Research**

B. Olson, Y. Li, Y. Lin, E.T. Liu, and A. Patnaik

### RESEARCH BRIEFS

**Combined Analysis of Antigen Presentation and T-cell Recognition Reveals Restricted Immune Responses in Melanoma**


**Précis:** Neoantigen prediction and HLA peptidomics identifies tumor-associated antigens and neoantigens in 16 melanomas from 7 patients and reveals a limited set of neoantigens responsible for antitumor immune responses.

### RESEARCH ARTICLES

**Targeting the MTF2–MDM2 Axis Sensitizes Refractory Acute Myeloid Leukemia to Chemotherapy**


*Précis:* MTF2 is downregulated by promoter hypermethylation in AML, resulting in loss of MDM2 transcriptional repression, reduced p53 expression, and resistance to standard induction chemotherapy.

*See commentary, p. 1348*

**The Genetic Landscape and Clonal Evolution of Breast Cancer Resistance to Palbociclib plus Fulvestrant in the PALOMA-3 Trial**


*Précis:* Longitudinal analysis of samples from patients with estrogen receptor-positive breast cancer identified the mechanisms of resistance and clonal evolution to fulvestrant and palbociclib.

*See commentary, p. 1352*

**Prediction of DNA Repair Inhibitor Response in Short-Term Patient-Derived Ovarian Cancer Organoids**


*Précis:* Functional profiling of DNA repair in 33 patient-derived organoids from 22 patients with high-grade serous ovarian cancer combined with genomic analysis identified targetable DNA damage repair defects.
Crebbp Loss Drives Small Cell Lung Cancer and Increases Sensitivity to HDAC Inhibition .................................. 1422
Précis: Loss of the tumor suppressor CREBBP results in loss of histone acetylase-mediated activation of genes that suppress epithelial-to-mesenchymal transition in small cell lung cancer.

Pathobiological Pseudohypoxia as a Putative Mechanism Underlying Myelodysplastic Syndromes ............. 1438
Précis: Hypoxia-independent activation of HIF1α is necessary and sufficient for development of myelodysplastic syndromes, suggesting the HIF1α pathway as a potential therapeutic target.

Cholinergic Signaling via Muscarinic Receptors Directly and Indirectly Suppresses Pancreatic Tumorigenesis and Cancer Stemness ............... 1458
Précis: CHRML1-dependent parasympathetic nerve signaling inhibits pancreatic tumor growth by suppressing expansion of myeloid cells and cancer stem cells and by inhibiting EGFR/MAPK and PI3K/AKT pathway activation.

Multiple Routes to Oncogenesis Are Promoted by the Human Papillomavirus–Host Protein Network .............. 1474
Précis: Integration of the HPV-human protein–protein interaction network with tumor mutation profiles uncovers oncogene HPV interactions that phenocopy recurrent mutations in HPV-negative cancers.

Corrections
Correction: A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors ........... 1490
Correction: Phase I Dose-Escalation Study of Taselisib, an Oral PI3K Inhibitor, in Patients with Advanced Solid Tumors .................. 1491

ON THE COVER
Hill and colleagues profiled DNA-repair activity to discover potential therapeutic vulnerabilities in 33 organoid cultures derived from 22 patients with high-grade serous ovarian cancer (HGSC). The majority of HGSC organoids exhibited functional homologous recombination (HR) and were insensitive to agents targeting HR defects including the PARP inhibitor olaparib. Although genetic alterations predicted to affect HR occurred more frequently, only 2 of 34 organoid cultures were olaparib-sensitive, indicating a lack of functional HR. Replication fork instability occurred in 61% of tested cultures and was linked to sensitivity to carboplatin, prexasertib, and VE-822. Combining prexasertib with carboplatin or gemcitabine could induce fork instability and replication stress in fork-stable lines. Together, these findings indicate that functional organoid profiling in concert with genomic analysis may aid the discovery of targetable DNA damage repair defects in patients with HGSC. For details, please see the article by Hill and colleagues on page 1404.
## CANCER DISCOVERY

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