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**RESEARCH ARTICLES**

**CREBBP Inactivation Promotes the Development of HDAC3-Dependent Lymphomas** ........... 38
Précis: CREBBP loss-of-function mutations accelerate lymphomagenesis by reducing H3K27 acetylation and allowing BCL6/SMRT/HDAC3-mediated repression of key GC B-cell enhancers.
See commentary, p. 14

**The Master Neural Transcription Factor BRN2 Is an Androgen Receptor–Suppressed Driver of Neuroendocrine Differentiation in Prostate Cancer** ............... 54
Précis: BRN2 drives neuroendocrine differentiation and growth of androgen receptor–targeted prostate cancer.

**Tumor Cell–Independent Estrogen Signaling Drives Disease Progression through Mobilization of Myeloid-Derived Suppressor Cells** ............. 72
Précis: Estrogen signaling in myeloid progenitor cells promotes myeloid-derived suppressor cell-mediated immune-suppression and tumor progression, suggesting that estrogen antagonists may be effective in ER+ tumors.
See commentary, p. 17

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Role of KEAP1/NRF2 and TP53 Mutations in Lung Squamous Cell Carcinoma Development and Radiation Resistance ..................86


Précis: Mouse models show that TP53 and KEAP1 mutations drive squamous cell lung cancer growth and radioresistance.

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 ....................... 102


Précis: Ipatasertib was well tolerated and resulted in disease control in a subset of patients with solid tumors, suggesting that ATP-competitive AKT inhibitors may have an improved safety profile compared with allosteric inhibitors.

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ON THE COVER

Jeong and colleagues developed mouse models of lung squamous cell carcinoma (LSCC) driven by Trp53 loss with or without Keap1 loss to further elucidate the role of the KEAP1/NRF2 pathway in LSCC and identify the LSCC cell of origin. Deletion of Trp53 and co-deletion of Trp53 and Keap1 in peripheral lung cells or in tracheal epithelial cells gave rise, respectively, to lung adenocarcinomas or LSCCs, and co-deletion of Trp53 and Keap1 resulted in the development of LSCCs from airway basal stem cells that were more proliferative and more resistant to radiation and oxidative stress, and exhibited decreased intracellular reactive oxygen species compared with Trp53−/− LSCCs. Moreover, KEAP1 mutation status in LSCCs and lung adenocarcinomas could be detected in circulating tumor DNA and predicted patient response to radiotherapy. These findings show how the genetic mouse models of LSCC enabled the identification of the LSCC cell of origin and the characterization of the role of the KEAP1/NRF2 pathway in LSCC. For details, please see the article by Jeong and colleagues on page 86.