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Oren Yakovian, Julia Sajman, Rand Arafeh, Yair Neve-Oz, Michal Alon, Yardena Samuels, and Eilon Sherman

Nano-scale dynamic organization of WT and mutant NRas relative to Braf serves as a regulatory mechanism for NRas signaling and may be a viable therapeutic target for its sensitivity to MEKi.

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These findings establish roles for PLK1 as a potent proto-oncogene and a CIN gene and provide insights for the development of effective treatment regimens across PLK1-overexpressing and CIN-positive cancers.

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Zhi Hao Kwok, Bin Zhang, Xiao Hong Chew, Jia Jia Chan, Velda Teh, Henry Yang, Dennis Kappel, and Yvonne Tay

Our study illustrates the functional relationships between individual components of multigenic loci in regulating cancer progression.

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### 1321 USP24 is a Cancer-Associated Ubiquitin Hydrolase, Novel Tumor Suppressor, and Chromosome Instability Gene Deleted in Neuroblastoma
Tibor Bedekovics, Sajid Hussain, Ying Zhang, Asma Ali, Young J. Jeon, and Paul J. Galardy

This study identifies the chromosome instability gene USP24 as frequently deleted in neuroblastoma and provides important insight into the pathogenesis of this aggressive childhood cancer.

### 1332 Differential Regulation of Cancer Progression by CDK4/6 Plays a Central Role in DNA Replication and Repair Pathways
Meiou Dai, Julien Boudreault, Ni Wang, Sophie Poulet, Girija Daliah, Gang Yan, Alaa Moamer, Sergio A. Burgos, Siham Sabri, Suhad Ali, and Jean-Jacques Lebrun

In-depth transcriptomic analysis identifies cyclin-dependent kinases CDK4 and CDK6 as regulators of metastasis through distinct signaling pathways and reveals the DNA replication/repair pathway as central in promoting these effects.

### 1347 Functional Determinants of Cell Cycle Plasticity and Sensitivity to CDK4/6 Inhibition
Vishnu Kumasasamy, Paris Vail, Ram Nambiar, Agnieszka K. Witkiewicz, and Erik S. Knudsen

This work provides a mechanistic insight toward understanding the functional roles of multiple cell cycle regulators that drive plasticity and sensitivity to CDK4/6 inhibition.

### 1353 Plk1 Induces Chromosomal Instability and Overrides Cell-Cycle Checkpoints to Drive Tumorigenesis

These findings establish roles for PLK1 as a potent proto-oncogene and a CIN gene and provide insights for the development of effective treatment regimens across PLK1-overexpressing and CIN-positive cancers.

### 1361 A Positive Feedback Loop of AKR1C3-Mediated Activation of NF-κB and STAT3 Facilitates Proliferation and Metastasis in Hepatocellular Carcinoma
Qingqing Zhou, Wei Tian, Zhiyuan Jiang, Tingting Huang, Chao Ge, Tengfei Liu, Fangyu Zhao, Taoyang Chen, Ying Cui, Hong Li, Ming Yao, Jinjun Li, and Hua Tian

These findings elucidate a novel AKR1C3-driven signaling loop that regulates proliferation and metastasis in HCC, providing potential prognostic and therapeutic targets in this disease.

## TUMOR BIOLOGY AND IMMUNOLOGY

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Antiprogestin therapy induces immunogenic tumor cell death in PRA-overexpressing tumors, eliciting an adaptive immune memory response that protects mice from future tumor recurrence and increases sensitivity to PD-L1 blockade.

### 1388 Replication Gaps Underlie BRCA Deficiency and Therapy Response
Nicholas J. Panzarino, John J. Kraus, Ke Cong, Min Peng, Michelle Mosquera, Sumeet U. Nayak, Samuel M. Bond, Jennifer A. Calvo, Mihir B. Doshi, Matt Bere, Jianhong Ou, Bin Deng, Lihua J. Zhu, Neil Johnson, and Sharon B. Cantor

This study suggests that ssDNA replication gaps are fundamental to the toxicity of genotoxic agents and underlie the BRCA-cancer phenotype “BRCAness,” yielding promising biomarkers, targets, and opportunities to resensitize refractory disease.

See related Commentary, p. 1214
Dual Inhibition of MEK and AXL Targets Tumor Cell Heterogeneity and Prevents Resistant Outgrowth Mediated by the Epithelial-to-Mesenchymal Transition in NSCLC
Jessica M. Konen, B. Leticia Rodriguez, Aparna Padhye, Joshua K. Ochieng, Laura Gibson, Lixia Diao, Natalie W. Fowlkes, Jared J. Fradette, David H. Peng, Robert J. Cardnell, Jeffrey J. Kovacs, Jing Wang, Lauren A. Byers, and Don L. Gibbons
This study shows that a novel combination of MEK and AXL inhibitors effectively bypasses EMT-mediated drug resistance in KRAS/p53-mutant non–small cell lung cancer by targeting EMT subpopulations, thereby preventing tumor cell survival.

Targeting the IRAK1–S100A9 Axis Overcomes Resistance to Paclitaxel in Nasopharyngeal Carcinoma
Lizhen Liu, Sailan Liu, Peng Deng, Yujing Liang, Rong Xiao, Lin-Quan Tang, Jinghong Chen, Qiu-Yan Chen, Peiyong Guan, Shu-Mei Yan, Xiangliang Huang, Jing Han Hong, Jianfeng Chen, Yichen Sun, Bin Tean Teh, Qiang Yu, Hai-Qiang Mai, and Jing Tan
Deregulation of the IRAK1–S100A9 axis correlates with poor prognosis, contributes to chemoresistance in nasopharyngeal carcinoma, and can be targeted by pacritinib to overcome chemoresistance in nasopharyngeal carcinoma.

ABOUT THE COVER
Cancer is a heterogeneous disease with extensive genetic complexity. The circles in the middle represent a normal cell with germline variations. In cancer, germline variants can affect the tumor mutational burden, both of which contribute to the emergence of different types of cancer cells. For details, see article by Sun and colleagues on page 1230.