# CANCER RESEARCH
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These findings suggest that targeting acetate metabolism through ACS52 inhibitors has the potential to safely and effectively treat a wide range of patients with cancer.
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Zhaoji Liu, Linchong Sun, Yongping Cai, Shengqi Shen, Tong Zhang, Nana Wang, Gongwei Wu, Wenhao Ma, Shi-Ting Li, Caixin Suo, Yijie Hao, Wei-Dong Jia, Gregg L. Semenza, Ping Gao, and Huafeng Zhang
This study defines the opposing roles and clinical relevance of MBD2a and MBD2c, two MBD2 alternative splicing products, in hypoxia-driven breast cancer metastasis.

1279 MEK Inhibition Reverses Aberrant Signaling in Melanoma Cells through Reorganization of NRas and BRAF in Self Nanoclusters
Oren Yakovian, Julia Sajman, Rand Arafeh, Yair Neve-Oz, Michal Alon, Yardena Samuels, and Eilon Sherman
Nanoscale 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.

1293 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.

1302 Systematic Analysis of Intronic miRNAs Reveals Cooperativity within the Multicomponent FXR Locus to Promote Colon Cancer Development
Zhi Hao Kwok, Bin Zhang, Xiao Hong Chew, Jianhong Ou, Bin Deng, Lihua J. Zhu, Neil Johnson, and Jennifer A. Calvo
This study illustrates the functional relationships between individual components of multigenic loci in regulating cancer progression.

1321 USP24 Is a Cancer-Associated Ubiquitin Hydrolase, Novel Tumor Suppressor, and Chromosome Instability Gene Deleted in Neuroblastoma
Tibor Bedekovics, Sajjad 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 Kumarasamy, Paris Vail, Ram Nambiar, Agnieszka K. Witkiewicz, and Erik S. Knudsen
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1359 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, Jijun 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

1375 Enhanced Antitumor Immunity via Endocrine Therapy Prevents Mammary Tumor Relapse and Increases Immune Checkpoint Blockade Sensitivity
Gonzalo R. Sequeira, Ana Sabores, Tomás Dalotto-Moreno, Ramiro M. Perrotta, Gabriela Patacini, Silvia I. Vanzulli, Maria L. Polo, Derek C. Radisky, Carol A. Sartorius, Virginia Novaro, Caroline A. Lamb, Gabriel A. Rabinovich, Derek C. Radisky, Carol A. Sartorius, Virginia Novaro, Caroline A. Lamb, Gabriel A. Rabinovich, Mariana Salatino, and Claudia Lanari
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
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.