## BREAKING INSIGHTS

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## REVIEW

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## CANCER RESEARCH HIGHLIGHTS

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## GENOME AND EPIGENOME

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## MOLECULAR CELL BIOLOGY

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This study identifies four genes associated with lung cancer risk, which could help guide future lung cancer prevention and treatment approaches.

Mouse modeling studies show that mTOR activation in combination with inactivation of the p38MAPK-p53/p16 axis initiates renal cell carcinoma that mimics human disease, identifying potential therapeutic targets for RCC treatment.

These findings illustrate the lncRNA-guided regulation of VEGFC mRNA stability via direct RNA–RNA interactions, highlighting a therapeutic target for patients with ESCC with lymphatic metastasis.

HER2+ LC tumors overexpress KDM4A/4C and are sensitive to the Jumonji demethylase inhibitor JIB04, which reduces the viability of primary HER2+ LC cells and increases survival in mouse models.

Dephosphorylation of PARP1 by SHP2 simultaneously suppresses DNA repair and enhances STING pathway-mediated antitumor immunity, highlighting SHP2 activation as a potential therapeutic approach in colon cancer.
3229  EPHB2 Activates β-Catenin to Enhance Cancer Stem Cell Properties and Drive Sorafenib Resistance in Hepatocellular Carcinoma
Hoi Wing Leung, Carmen Oi Ning Leung, Eunice Y. Lau, Katherine Po Sin Chung, Etienne H. Mok, Martina Mang Leng Lei, Rainbow Wing Hei Leung, Man Tong, Vincent W. Keng, Cong Ma, Qian Zhao, Irene Oi Lin Ng, Stephanie Ma, and Terence K. Lee
This study identifies a EPHB2/β-catenin/TCF1 positive feedback loop that augments cancer stemness and sorafenib resistance in HCC, revealing a targetable axis to combat acquired drug resistance in HCC.

TUMOR BIOLOGY AND IMMUNOLOGY

3241  NPM–ALK-Induced Reprogramming of Mature TCR-Stimulated T Cells Results in Dedifferentiation and Malignant Transformation
Jan M. Pawlicki, David L. Cookmeyer, Damian Maseda, John K. Everett, Fang Wei, Hong Kong, Qian Zhang, Hong Y. Wang, John W. Tobias, David M. Walter, Kelly M. Zullo, Sarah Javaid, Amanda Watkins, Mariusz A. Wasik, Frederic D. Bushman, and James L. Riley
This investigation into malignant transformation of T cells uncovers a requirement for TCR triggering, elucidates integral signaling complexes nucleated by NPM–ALK, and delineates dynamic transcriptional changes as a T cell transforms.
See related commentary, p. 3160

3255  Induction of ADAM10 by Radiation Therapy Drives Fibrosis, Resistance, and Epithelial-to-Mesenchyal Transition in Pancreatic Cancer
Targeting a previously unidentified adaptive resistance mechanism to radiation therapy in PDAC tumors in combination with radiation therapy could increase survival of the 40% of PDAC patients with locally advanced disease.
See related commentary, p. 3158

3270  Afatinib Exerts Immunomodulatory Effects by Targeting the Pyrimidine Biosynthesis Enzyme CAD
Hsin-Fang Tu, Chia-Chi Ku, Ching-Tai Lee, Cheng-Fan Lee, Shao-Wei Lan, Hsin-Hsien Lin, Hsin-Ying Lin, Chia-Chi Ku, Der-Yen Lee, I-Chun Chen, Ya-Hui Chuang, Francisco Del Caño-Ochoa, Santiago Ramón-Maques, Chao-Chi Ho, Ming-Shyue Lee, and Geen-Dong Chang
This study elucidates a mechanism of afatinib-mediated immunosuppression and provides new insights into treatment timing for combined targeted therapy and immunotherapy.

3283  Epstein–Barr Virus Induces Adipocyte Dedifferentiation to Modulate the Tumor Microenvironment
Shu-Chen Liu, Ngn-Ming Tsang, Po-Ju Lee, Yun-Hua Sui, Chen-Han Huang, and Tsu-Tung Liu
This study suggests that Epstein–Barr virus hijacks adipocyte lipid metabolism to create a tumor-promoting microenvironment from which reactivation and relapse of infection could potentially occur.

3295  Inhibition of Granulocytic Myeloid-Derived Suppressor Cells Overcomes Resistance to Immune Checkpoint Inhibition in LKB1-Deficient Non–Small Cell Lung Cancer
Rui Li, Ramin Salehi-Rad, William Crosson, Milica Momcilovic, Raymond J. Lim, Stephanie L. Ong, Zi Ling Huang, Tianhao Zhang, Jensen Abascales, Camelia Dumitras, Zhe Jing, Stacy J. Park, Kostyantyn Krysan, David B. Shackelford, Linh M. Tran, Bin Liu, and Steven M. Dubinett
These findings show that accumulation of myeloid-derived suppressor cells in LKB1-deficient non–small cell lung cancer can be overcome via treatment with all-trans-retinoic acid, sensitizing tumors to immunotherapy.

3309  Altering the Microbiome Inhibits Tumorigenesis in a Mouse Model of Oviductal High-Grade Serous Carcinoma
Lixing Chen, Yali Zhai, Yisheng Wang, Eric R. Fearon, Gabriel Núñez, Naohiro Inohara, and Kathleen R. Cho
This study provides strong in vivo evidence for a role of the microbiome in ovarian cancer pathogenesis.

3319  Targeting Adenosine with Adenosine Deaminase 2 to Inhibit Growth of Solid Tumors
Lin Wang, Luz M. Londono, Jessica Cowell, Ozge Saatci, Merktaya Aras, Pelin G. Ersan, Sara Serra, Hong Pei, Renee Clift, Qingping Zhao, Kim B. Phan, Lei Huang, Michael J. LaBarre, Xiaoming Li, H. Michael Shepard, Silvia Deaglio, Joel Linden, Christopher D. Thanos, Orgur Sahin, and Caglar Cekic
This study identifies ADA2 as a prognostic factor associated with prolonged cancer patient survival and introduces the potential of enzymatic removal of adenosine with engineered ADA2 for cancer immunotherapy.
Inhibition of ATM Induces Hypersensitivity to Proton Irradiation by Upregulating Toxic End Joining
Coadministration of an ATM inhibitor rewires DNA repair machinery to render cancer cells uniquely hypersensitive to DNA damage induced by the proton Bragg peak, which is characterized by higher density ionization.

Pharmacological Disruption of the Notch1 Transcriptional Complex Inhibits Tumor Growth by Selectively Targeting Cancer Stem Cells
Annamil Alvarez-Trotta, William Guerrant, Luisana Astudillo, Mohini Lahiry, Giulia Diluvio, Elena Shersher, Hugo Kaneku, David J. Robbins, Darren Orton, and Anthony J. Capobianco
This study showcases the first Notch1-selective inhibitor that suppresses tumor growth with limited toxicity by selectively ablating cancer stem cells.

Recruitment of KMT2C/MLL3 to DNA Damage Sites Mediates DNA Damage Responses and Regulates PARP Inhibitor Sensitivity in Cancer
Antao Chang, Liang Liu, Justin M. Ashby, Dan Wu, Yanan Chen, Stacey S. O’Neill, Shan Huang, Juan Wang, Guanwen Wang, Dongmei Cheng, Xiaoming Tan, W.J. Petty, Boris C. Pasche, Rong Xiang, Wei Zhang, and Peiqing Sun
This study uncovers a critical role for KMT2C in DDR via direct recruitment to DNA damage sites, identifying high-frequency KMT2C/D mutations as biomarkers for response to PARP inhibition in cancer.

Small-Molecule Natural Product Physachenolide C Potentiates Immunotherapy Efficacy by Targeting BET Proteins
These findings demonstrate that PCC selectively sensitizes cancer cells to immune-mediated cell death, potentially improving the efficacy of cancer immunotherapies.

Peripheral Nerve Resident Macrophages and Schwann Cells Mediate Cancer-Induced Pain
Francesco De Logu, Matilde Marini, Lorenzo Landini, Daniel Souza Monteiro de Araujo, Niccolò Bartalucci, Gabriela Trevisan, Gennaro Bruno, Martina Marangoni, Brian L. Schmidt, Nigel W. Bunnett, Pierangelo Geppetti, and Romina Nassini
Schwann cell TRPA1 sustains cancer pain through release of M-CSF and oxidative stress, which promote the expansion and the proalgesic actions of intraneuronal macrophages.

Hexavalent TRAIL Fusion Protein Eftozanermin Alfa Optimally Clusters Apoptosis-Inducing TRAIL Receptors to Induce On-Target Antitumor Activity in Solid Tumors
This study describes the activity of a hexavalent TRAIL-receptor agonistic fusion protein in preclinical models of solid tumors that mechanistically distinguishes this molecular entity from other TRAIL-based therapeutics.

Spectral Endoscopy Enhances Contrast for Neoplasia in Surveillance of Barrett’s Esophagus
The results of this pilot first-in-human clinical trial demonstrate the potential of spectral endoscopy to reveal disease-associated vascular changes and to provide high-contrast delineation of neoplasia in the esophagus.

Correction: Cyclophosphamide and Vinorelbine Activate Stem-Like CD8+ T Cells and Improve Anti-PD-1 Efficacy in Triple-Negative Breast Cancer

Correction: CXCR4 in Tumor Epithelial Cells Mediates Desmoplastic Reaction in Pancreatic Ductal Adenocarcinoma
Toshihiro Morita, Yuzo Kodama, Masahiro Shikokawa, Katsutoshi Kuriyama, Saiko Marui, Takeshi Kuwada, Yuko Sogabe, Tomoaki Matsumori, Nobuyuki Kakiuchi, Teruko Tomono, Atsushi Mima, Tatsuki Ueda, Motoyuki Tsuda, Yuki Yamauchi, Yoshiiro Nishikawa, Yojiro Sakuma, Yuji Ota, Takahisa Maruno, Norimitsu Uza, Takashi Nagasawa, Tsutomu Chiba, and Hiroshi Seno
ABOUT THE COVER

Results from clinical trials of EGFR tyrosine kinase inhibitors (TKI) and immunotherapy indicate that the combination remains inadequate for inducing long-term remission. The study by Tu and colleagues demonstrated that early treatment with EGFR TKI afatinib suppressed human CD8⁺ T lymphocyte proliferation, which rebounded following long-term treatment, suggesting an immunomodulatory effect of afatinib on CD8⁺ T lymphocytes. Sequential treatment with afatinib then anti-PD1 immunotherapy could enhance therapeutic efficacy by promoting the proliferation of tumor-infiltrating CD8⁺ T lymphocytes. The image depicts the impact of timing of afatinib treatment on effective killing of tumor cells (red) by T lymphocytes (blue). For details, see article by Tu and colleagues on page 3270.