

## CANCER RESEARCH

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## CANCER RESEARCH HIGHLIGHTS

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## GENOME AND EPIGENOME

**3162** Genetic Variation and Recurrent Haplotypes on Chromosome 6q23-25 Risk Locus in Familial Lung Cancer

Anthony M. Musolf, Claire L. Simpson, Bilal A. Moiz, Claudio W. Pikielny, Candace D. Middlebrooks, Diptasri Mandal, Mariza de Andrade, Michael D. Cole, Colette Gaba, Ping Yang, Ming You, Yafang Li, Elena Y. Kupert, Marshall W. Anderson, Ann G. Schwartz, Susan M. Pinney, Christopher I. Amos, and Joan E. Bailey-Wilson

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

## MOLECULAR CELL BIOLOGY

**3174** mTOR Activation Initiates Renal Cell Carcinoma Development by Coordinating ERK and p38MAPK

Hongguang Wu, Dan He, Soma Biswas, Md Shafiquzzaman, Xin Zhou, Jean Charron, Yibin Wang, Bijaya K. Nayak, Samy L. Habib, Huijuan Liu, and Baojie Li

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.

**3187** Long Noncoding RNA VESTAR Regulates Lymphangiogenesis and Lymph Node Metastasis of Esophageal Squamous Cell Carcinoma by Enhancing VEGFC mRNA Stability

Yali Wang, Weimin Zhang, Wenzhong Liu, Lijie Huang, Yan Wang, Dan Li, Guangchao Wang, Zitong Zhao, Xinming Chi, Yu Xue, Yongmei Song, Xuefeng Liu, and Qimin Zhan

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.

**3200** Inhibition of Jumonji Histone Demethylases Selectively Suppresses HER2<sup>+</sup> Breast Leptomeningeal Carcinomatosis Growth via Inhibition of GMCSF Expression

Arunoday Bhan, Khairul I. Ansari, Mike Y. Chen, and Rahul Jandial

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

**3215** SHP2-Mediated Inhibition of DNA Repair Contributes to cGAS-STING Activation and Chemotherapeutic Sensitivity in Colon Cancer

Bin Wei, Lingyan Xu, Wenjie Guo, Yuanyuan Wang, Jingjing Wu, Xiaofei Li, Xiaomin Cai, Jinbo Hu, Meijing Wang, Qiang Xu, Wen Liu, and Yanhong Gu  
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.

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- 3229**    **EPHB2 Activates  $\beta$ -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/ $\beta$ -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-Mesenchymal Transition in Pancreatic Cancer**  
Adam C. Mueller, Miles Piper, Andrew Goodspeed, Shiv Bhuvane, Jason S. Williams, Shilpa Bhatia, Andy V. Phan, Benjamin Van Court, Kathryn L. Zolman, Brisa Peña, Ayman J. Oweida, Sara Zakem, Cheryl Meguid, Michael W. Knitz, Laurel Darragh, Thomas E. Bickett, Jacob Gadwa, Luisa Mestroni, Matthew R.G. Taylor, Kimberly R. Jordan, Peter Dempsey, M. Scott Lucia, Martin D. McCarter, Marco Del Chiaro, Wells A. Messersmith, Richard D. Schulick, Karyn A. Goodman, Michael J. Gough, Casey S. Greene, James C. Costello, Antonio Galveo Neto, David Lagares, Kirk C. Hansen, Adrie Van Bokhoven, and Sana D. Karam

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, Chun-Jung Ko, 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-Maiques, 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, Ngan-Ming Tsang, Po-Ju Lee, Yun-Hua Sui, Chen-Han Huang, and Tzu-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 Abascal, 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, Mertkaya Aras, Pelin G. Ersan, Sara Serra, Hong Pei, Renee Clift, Qiping Zhao, Kim B. Phan, Lei Huang, Michael J. LaBarre, Xiaoming Li, H. Michael Shepard, Silvia Deaglio, Joel Linden, Christopher D. Thanos, Ozgur 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.

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## TRANSLATIONAL SCIENCE

- 3333** **Inhibition of ATM Induces Hypersensitivity to Proton Irradiation by Upregulating Toxic End Joining**  
Qin Zhou, Michelle E. Howard, Xinyi Tu, Qian Zhu, Janet M. Denbeigh, Nicholas B. Remmes, Michael G. Herman, Chris J. Beltran, Jian Yuan, Patricia T. Greipp, Judy C. Boughey, Liewei Wang, Neil Johnson, Matthew P. Goetz, Jann N. Sarkaria, Zhenkun Lou, and Robert W. Mutter

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 high density ionization.

See related commentary, p. 3156

- 3347** **Pharmacological Disruption of the Notch1 Transcriptional Complex Inhibits Tumor Growth by Selectively Targeting Cancer Stem Cells**

**AC** 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.

- 3358** **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.

- 3374** **Small-Molecule Natural Product Physachenolide C Potentiates Immunotherapy Efficacy by Targeting BET Proteins**

Poonam Tewary, Alan D. Brooks, Ya-Ming Xu, E.M. Kithsiri Wijeratne, Ashley L. Babyak, Timothy C. Back, Raj Chari, Christine N. Evans, Curtis J. Henrich, Thomas J. Meyer, Elijah F. Edmondson, Maria T. Prudente de Aquino, Thanigaivelan Kanagasabai, Anil Shanker, A.A. Leslie Gunatilaka, and Thomas J. Sayers

These findings demonstrate that PCC selectively sensitizes cancer cells to immune-mediated cell death, potentially improving the efficacy of cancer immunotherapies.

- 3387** **Peripheral Nerve Resident Macrophages and Schwann Cells Mediate Cancer-Induced Pain**

**AC** 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 intraneural macrophages.

- 3402** **Hexavalent TRAIL Fusion Protein Eftozanermin Alfa Optimally Clusters Apoptosis-Inducing TRAIL Receptors to Induce On-Target Antitumor Activity in Solid Tumors**

**AC** Darren C. Phillips, Fritz G. Buchanan, Dong Cheng, Larry R. Solomon, Yu Xiao, John Xue, Stephen K. Tahir, Morey L. Smith, Haichao Zhang, Deborah Widomski, Vivek C. Abraham, Nan Xu, Zhihong Liu, Li Zhou, Enrico DiGiammarino, Xin Lu, Nandini Rudra-Ganguly, Bruce Trela, and Susan E. Morgan-Lappe

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.

## CONVERGENCE AND TECHNOLOGIES

- 3415** **Spectral Endoscopy Enhances Contrast for Neoplasia in Surveillance of Barrett's Esophagus**

Dale J. Waterhouse, Wladyslaw Januszewicz, Sharib Ali, Rebecca C. Fitzgerald, Massimiliano di Pietro, and Sarah E. Bohndiek

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.

## CORRECTIONS

- 3426** **Correction: Cyclophosphamide and Vinorelbine Activate Stem-Like CD8<sup>+</sup> T Cells and Improve Anti-PD-1 Efficacy in Triple-Negative Breast Cancer**

- 3427** **Correction: CXCR4 in Tumor Epithelial Cells Mediates Desmoplastic Reaction in Pancreatic Ductal Adenocarcinoma**

Toshihiro Morita, Yuza Kodama, Masahiro Shiokawa, Katsutoshi Kuriyama, Saiko Marui, Takeshi Kuwada, Yuko Sogabe, Tomoaki Matsumori, Nobuyuki Kakiuchi, Teruko Tomono, Atsushi Mima, Tatsuki Ueda, Motoyuki Tsuda, Yuki Yamauchi, Yoshihiro Nishikawa, Yojiro Sakuma, Yuji Ota, Takahisa Maruno, Norimitsu Uza, Takashi Nagasawa, Tsutomu Chiba, and Hiroshi Seno

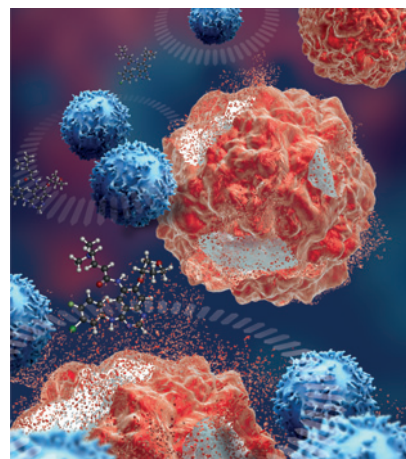
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## ABOUT THE COVER

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<sup>+</sup> T lymphocyte proliferation, which rebounded following long-term treatment, suggesting an immunomodulatory effect of afatinib on CD8<sup>+</sup> T lymphocytes. Sequential treatment with afatinib then anti-PD1 immunotherapy could enhance therapeutic efficacy by promoting the proliferation of tumor-infiltrating CD8<sup>+</sup> 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.



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