

## BREAKING INSIGHTS

- 4307** Highlights from Recent Cancer Literature

## REVIEWS

- 4309** Mapping and Making Sense of Noncoding Mutations in the Genome  
Jiekun Yang and Mazhar Adli
- 4315** A Tribute to John Mendelsohn: A Pioneer in Targeted Cancer Therapy  
Rakesh Kumar, Marc Van de Vijver, Giampaolo Tortora, Fortunato Ciardiello, Tzipora Goldkorn, Wilson H. Miller, Jr, and Larry Norton

## CANCER RESEARCH HIGHLIGHTS

- 4324** Know Thy PDX Model  
Terrence F. Meehan  
*See related article, p. 4539*

## CONTROVERSY AND CONSENSUS

- 4326**  Recent Developments and Therapeutic Strategies against Hepatocellular Carcinoma  
Mark Yarchoan, Parul Agarwal, Augusto Villanueva, Shuyun Rao, Laura A. Dawson, Josep M. Llovet, Richard S. Finn, John D. Groopman, Hashem B. El-Serag, Satdarshan P. Monga, Xin Wei Wang, Michael Karin, Robert E. Schwartz, Kenneth K. Tanabe, Lewis R. Roberts, Preethi H. Gunaratne, Allan Tsung, Kimberly A. Brown, Theodore S. Lawrence, Riad Salem, Amit G. Singal, Amy K. Kim, Atoosa Rabiee, Linda Resar, Yujin Hoshida, Aiwu Ruth He, Kalpana Ghoshal, Patrick B. Ryan, Elizabeth M. Jaffee, Chandan Guha, Lopa Mishra, C. Norman Coleman, and Mansoor M. Ahmed


## PRIORITY REPORT

- 4331** Temozolomide Sensitizes MGMT-Deficient Tumor Cells to ATR Inhibitors  
Christopher B. Jackson, Seth I. Noorbakhsh, Ranjini K. Sundaram, Aravind N. Kalathil, Sachita Ganesa, Lanqi Jia, Hank Breslin, Danielle M. Burgenske, Oren Gilad, Jann N. Sarkaria, and Ranjit S. Bindra  
*Significance: Monofunctional alkylating agents sensitize MGMT-deficient tumor cells to ATR inhibitors.*

## GENOME AND EPIGENOME

- 4339** Integrative Genomic Characterization Identifies Molecular Subtypes of Lung Carcinoids  
Saurabh V. Laddha, Edaise M. da Silva, Kenneth Robzyk, Brian R. Untch, Hua Ke, Natasha Rekhman, John T. Poirier, William D. Travis, Laura H. Tang, and Chang S. Chan  
*Significance: Integrative genomic analysis of lung carcinoids identifies three novel molecular subtypes with distinct clinical features and provides insight into their distinctive molecular signatures of tumorigenesis, diagnosis, and prognosis.*

## MOLECULAR CELL BIOLOGY

- 4348** Oncogenic MYC Induces the Impaired Ribosome Biogenesis Checkpoint and Stabilizes p53 Independent of Increased Ribosome Content  
Carmen Morcelle, Sandra Menoyo, Francisco D. Morón-Duran, Albert Tauler, Sara C. Kozma, George Thomas, and Antonio Gentilella  
*Significance: Oncogenic MYC induces the impaired ribosome biogenesis checkpoint, which could be potentially targeted for cancer treatment.*
- 4360** Metformin Inhibits Progression of Head and Neck Squamous Cell Carcinoma by Acting Directly on Carcinoma-Initiating Cells  
Xingyu Wu, Huwate Yeerna, Yusuke Goto, Toshinori Ando, Victoria H. Wu, Xuefeng Zhang, Zhiyong Wang, Panomwat Amornphimoltham, Anne N. Murphy, Pablo Tamayo, Qianming Chen, Scott M. Lippman, and J. Silvio Gutkind  
*Significance: Metformin's ability to directly target HNSCC-initiating cells instead of exerting cancer preventive activity based solely on its systemic effects may inform the selection of patients in future precision prevention trials.*
- 4371**  Tumor Angiogenesis Is Differentially Regulated by Phosphorylation of Endothelial Cell Focal Adhesion Kinase Tyrosines-397 and -861  
Ana-Rita Pedrosa, Natalia Bodrug, Jesus Gomez-Escudero, Edward P. Carter, Louise E. Reynolds, Paraskivi Natalia Georgiou, Isabelle Fernandez, Delphine M. Lees, Vassiliki Kostourou, Annika N. Alexopoulou, Silvia Batista, Bernardo Tavora, Bryan Serrels, Maddy Parsons, Thomas Iskratsch, and Kairbaan M. Hodivala-Dilke  
*Significance: Distinct motifs of the focal adhesion kinase differentially regulate tumor blood vessel formation and remodeling.*

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- 4387** SCF<sup>FBXW7</sup>/GSK3 $\beta$ -Mediated GFI1 Degradation Suppresses Proliferation of Gastric Cancer Cells  
Xiaoling Kuai, Long Li, Ran Chen, Kangjunjie Wang, Min Chen, Binghai Cui, Yuxue Zhang, Junqiang Li, Hongwen Zhu, Hu Zhou, Jianfei Huang, Jun Qin, Zhiwei Wang, Wenyi Wei, and Daming Gao

*Significance:* These findings demonstrate the oncogenic role of the transcription factor GFI1 and the tumor suppressive function of FBXW7 in gastric cancer.

- 4399** Glucocorticoid Receptor Signaling Activates TEAD4 to Promote Breast Cancer Progression  
Lingli He, Liang Yuan, Yang Sun, Pingyang Wang, Hailin Zhang, Xue Feng, Zuoyun Wang, Wenxiang Zhang, Chuanyu Yang, Yi Ariel Zeng, Yun Zhao, Ceshi Chen, and Lei Zhang

*Significance:* This study provides new insight into the role of glucocorticoid signaling in breast cancer, with potential for clinical translation.

- 4412** Single-Cell Analysis Reveals a Preexisting Drug-Resistant Subpopulation in the Luminal Breast Cancer Subtype

Marta Prieto-Vila, Wataru Usuba, Ryou-u Takahashi, Iwao Shimomura, Hideo Sasaki, Takahiro Ochiya, and Yusuke Yamamoto

*Significance:* This study highlights the role of breast cancer intratumor heterogeneity in drug resistance at a single-cell level.

- 4426** APE1 Upregulates MMP-14 via Redox-Sensitive ARF6-Mediated Recycling to Promote Cell Invasion of Esophageal Adenocarcinoma

Heng Lu, Ajaz A. Bhat, Dunfa Peng, Zheng Chen, Shoumin Zhu, Jun Hong, Selma Maacha, Jin Yan, David J. Robbins, M. Kay Washington, Abbes Belkhir, and Wael El-Rifai

*Significance:* This study demonstrates the association between oxidative stress and the development and metastatic behavior of esophageal adenocarcinoma.

## TUMOR BIOLOGY AND IMMUNOLOGY

- 4439** CXCR7 Reactivates ERK Signaling to Promote Resistance to EGFR Kinase Inhibitors in NSCLC

Jeffrey H. Becker, Yandi Gao, Margaret Soucheray, Ines Pulido, Eiki Kikuchi, María L. Rodríguez, Ritu Gandhi, Aranzazu Lafuente-Sanchis, Miguel Aupí, Javier Alcácer Fernández-Coronado, Paloma Martín-Martorell, Antonio Cremades, José M. Galbis-Caravajal, Javier Alcácer, Camilla L. Christensen, Patricia Simms, Ashley Hess, Hajime Asahina, Michael P. Kahle, Fatima Al-Shahrouh, Jeffrey A. Borgia, Agustín Lahoz, Amelia Insa, Oscar Juan, Pasi A. Jänne, Kwok-Kin Wong, Julian Carretero, and Takeshi Shimamura

*Significance:* Increased expression of the chemokine receptor CXCR7 constitutes a mechanism of resistance to EGFR TKI in patients with non-small cell lung cancer through reactivation of ERK signaling.

- 4453** LINE-1 Retrotransposition Promotes the Development and Progression of Lung Squamous Cell Carcinoma by Disrupting the Tumor-Suppressor Gene FGGY

Rui Zhang, Fan Zhang, Zeguo Sun, Pengpeng Liu, Xiao Zhang, Yingnan Ye, Beiqi Cai, Martin J. Walsh, Xiubao Ren, Xishan Hao, Weijia Zhang, and Jinpu Yu

*Significance:* LINE-1-FGGY is a prognosis predictive biomarker and potential therapeutic target to overcome local immune evasion in lung squamous cell carcinoma.

- 4466** Dysregulated Tgfb $\beta$ 2/ERK-Smad4/SOX2 Signaling Promotes Lung Squamous Cell Carcinoma Formation

Yanxiao Wang, Xiaohong Tan, Yuling Tang, Chong Zhang, Jiaqian Xu, Jian Zhou, Xuan Cheng, Ning Hou, Wenjia Liu, Guan Yang, Yan Teng, and Xiao Yang

*Significance:* This study sheds new light on the mechanisms underlying lung SCC formation driven by mutated Kras.

- 4480** PPAR $\delta$  Mediates the Effect of Dietary Fat in Promoting Colorectal Cancer Metastasis

Dingzhi Wang, Lingchen Fu, Jie Wei, Ying Xiong, and Raymond N. DuBois

*Significance:* These findings show that PPAR $\delta$  contributes to colorectal cancer metastasis by expanding the CSC population, indicating that antagonists that target PPAR $\delta$  may be beneficial in treating colorectal cancer.

## TRANSLATIONAL SCIENCE

- 4491** Poly (ADP) Ribose Glycohydrolase Can Be Effectively Targeted in Pancreatic Cancer

Aditi Jain, Lebaron C. Agostini, Grace A. McCarthy, Saswati N. Chand, AnnJosette Ramirez, Avinoam Nevler, Joseph Cozzitorto, Christopher W. Schultz, Cinthya Yabar Lowder, Kate M. Smith, Ian D. Waddell, Maria Raites-Gurevich, Chani Stossel, Yulia Glick Gorman, Dikla Atias, Charles J. Yeo, Jordan M. Winter, Kenneth P. Olive, Talia Golan, Michael J. Pishvaian, Donald Ogilvie, Dominic I. James, Allan M. Jordan, and Jonathan R. Brody

*Significance:* PARC is a potential target in pancreatic cancer as a single-agent anticancer therapy or in combination with current standard of care.

- 4503** Mesenchymal Stem Cell-Mediated Delivery of an Oncolytic Adenovirus Enhances Antitumor Efficacy in Hepatocellular Carcinoma

A-Rum Yoon, JinWoo Hong, Yan Li, Ha Chul Shin, Hyunah Lee, Hyun Soo Kim, and Chae-Ok Yun

*Significance:* Mesenchymal stem cells enable delivery of an oncolytic adenovirus specifically to the tumor without posing any risk associated with systemic administration of naked virions to the host.

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## CONVERGENCE AND TECHNOLOGIES

**4515** DNA–SWCNT Biosensors Allow Real-Time Monitoring of Therapeutic Responses in Pancreatic Ductal Adenocarcinoma

Santanu Bhattacharya, Xun Gong, Enfeng Wang, Shamit K. Dutta, Joseph R. Caplette, Manki Son, Freddy T. Nguyen, Michael S. Strano, and Debabrata Mukhopadhyay

*Significance:* A novel biosensor is used to detect intratumoral hydrogen peroxide, allowing real-time monitoring of responses to chemotherapeutic drugs.

**4524** Molecular Profiling Establishes Genetic Features Predictive of the Efficacy of the p110 $\beta$  Inhibitor KIN-193

Isha Sethi, Zhenying Cai, Thomas M. Roberts, and Guo-Cheng Yuan

*Significance:* These findings provide new insights into molecular signatures associated with sensitivity of the p110 $\beta$  inhibitor KIN-193, which may provide a useful guide for developing precise treatment methods for cancer.

## POPULATION AND PREVENTION SCIENCE

**4532** The HPV16 Genome Is Stable in Women Who Progress to *In Situ* or Invasive Cervical Cancer: A Prospective Population-Based Study

Laila-Sara Arroyo-Mühr, Camilla Lagheden, Emilie Hultin, Carina Eklund, Hans-Olov Adami, Joakim Dillner, and Karin Sundström

*Significance:* These findings show there is no genomic variation over time in HPV16 infections progressing to cervical cancer, which could influence risk stratification of women when screening for cervical cancer and inform HPV vaccination strategies.

## RESOURCE REPORT

**4539** Integrative Pharmacogenomics Analysis of Patient-Derived Xenografts

Arvind S. Mer, Wail Ba-Alawi, Petr Smirnov, Yi X. Wang, Ben Brew, Janosch Ortmann, Ming-Sound Tsao, David W. Cescon, Anna Goldenberg, and Benjamin Haibe-Kains

*Significance:* A computational platform for PDX data analysis reveals consistent gene and pathway activity across passages and confirms drug response prediction biomarkers in PDX.

See related commentary, p. 4324

## CORRECTIONS

**4551** Correction: Antibody-Targeted Chemotherapy for the Treatment of Melanoma

Wendy K. Nevala, Sarah A. Buhrow, Daniel J. Knauer, Joel M. Reid, Elena A. Atanasova, and Svetomir N. Markovic

**4552** Correction: Androgen Receptor Is the Key Transcriptional Mediator of the Tumor Suppressor SPOP in Prostate Cancer

Chuandong Geng, Kimal Rajapakshe, Shrijal S. Shah, John Shou, Vijay Kumar Eedunuri, Christopher Foley, Warren Fiskus, Mahitha Rajendran, Sue Anne Chew, Martin Zimmermann, Richard Bond, Bin He, Cristian Coarfa, and Nicholas Mitsiades

## RETRACTION

**4553** Retraction: MIG-7 Controls COX-2/PGE2-Mediated Lung Cancer Metastasis

Ming-Yi Ho, Shu-Mei Liang, Shao-Wen Hung, and Chi-Ming Liang



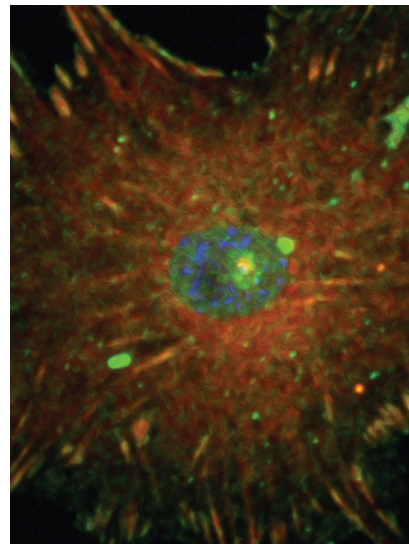
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## ABOUT THE COVER

FAK is a ubiquitously expressed nonreceptor tyrosine kinase that regulates several endothelial cell processes important for angiogenesis, including motility and proliferation. This work describes the differential roles of endothelial cell FAK phosphorylation at tyrosines-397 and -861 for tumor angiogenesis *in vivo*. Using immunofluorescence, the authors found that different nonphosphorylatable tyrosine mutations within endothelial cell FAK, namely Y397 and Y861, have different binding abilities to phosphorylated Src. While loss of FAK-Y397 phosphorylation impairs binding of FAK to p-Src, loss of FAK-Y861 phosphorylation does not affect binding to p-Src at focal adhesion sites as shown in this image. For details see article by Pedrosa and colleagues on page 4371.



# Cancer Research

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