

## BREAKING INSIGHTS

- 1577 Highlights from Recent Cancer Literature

## GENOME AND EPIGENOME

- 1579 Integrative Genomic Analysis Predicts Causative Cis-Regulatory Mechanisms of the Breast



Cancer-Associated Genetic Variant rs4415084

Yi Zhang, Mohith Manjunath, Shilu Zhang, Deborah Chasman, Sushmita Roy, and Jun S. Song

*Significance:* Unification of GWAS results with information from high-throughput genomic and epigenomic profiles provides a direct link between common genetic variants and measurable molecular perturbations.

## METABOLISM AND CHEMICAL BIOLOGY

- 1592 Pyruvate Dehydrogenase PDH-E1 $\beta$  Controls Tumor Progression by Altering the Metabolic Status of Cancer Cells

Ryo Yonashiro, Kayoko Eguchi, Masaki Wake, Norihiko Takeda, and Koh Nakayama

*Significance:* This seminal study offers a mechanistic explanation for why glycolysis is aberrantly activated in normoxic cancer cells, offering insights into this long-standing hallmark of cancer termed the Warburg effect.

- 1604 Polyol Pathway Links Glucose Metabolism to the Aggressiveness of Cancer Cells

Annemarie Schwab, Aarif Siddiqui, Maria Eleni Vazakidou, Francesca Napoli, Martin Böttcher, Bianca Menchicchi, Umar Raza, Özge Saatçı, Angela M. Krebs, Fulvia Ferrazzi, Ida Rapa, Katja Dettmer-Wilde, Maximilian J. Waldner, Arif B. Ekici, Suhail Ahmed Kabeer Rasheed, Dimitrios Mouggiakakos, Peter J. Oefner, Ozgur Sahin, Marco Volante, Florian R. Greten, Thomas Brabletz, and Paolo Ceppi

*Significance:* A glucose-transforming pathway in TGF $\beta$ -driven epithelial-to-mesenchymal transition provides novel mechanistic insights into the metabolic control of cancer differentiation.

## MOLECULAR CELL BIOLOGY

- 1619 Keratin 19 Expression in Hepatocellular Carcinoma Is Regulated by Fibroblast-Derived HGF via a MET-ERK1/2-AP1 and SP1 Axis

Hyungjin Rhee, Hye-Young Kim, Ji-Hye Choi, Hyun Goo Woo, Jeong Eun Yoo, Ji Hae Nahm, Jin-Sub Choi, and Young Nyun Park

*Significance:* These findings reveal KRT19 expression in hepatocellular carcinoma is regulated by cross-talk between cancer-associated fibroblasts and HCC cells, illuminating new therapeutic targets for this aggressive disease.

- 1632 MBD2 Ablation Impairs Lymphopoiesis and Impedes Progression and Maintenance of T-ALL

Mi Zhou, Kuangguo Zhou, Ling Cheng, Xing Chen, Jue Wang, Xiao-Min Wang, Yingchi Zhang, Qilin Yu, Shu Zhang, Di Wang, Liang Huang, Mei Huang, Ding Ma, Tao Cheng, Cong-Yi Wang, Weiping Yuan, and Jianfeng Zhou

*Significance:* This study highlights a methylated DNA binding protein as a candidate therapeutic target to improve the treatment of T-cell acute lymphoblastic leukemias, as a new starting point for developing epigenetic therapy in this and other lymphoid malignancies.

- 1643 Forkhead Box F2 Suppresses Gastric Cancer through a Novel FOXF2-IRF2BPL- $\beta$ -Catenin Signaling Axis

Akira Higashimori, Yujuan Dong, Yanquan Zhang, Wei Kang, Geicho Nakatsu, Simon S.M. Ng, Tetsuo Arakawa, Joseph J.Y. Sung, Francis K.L. Chan, and Jun Yu

*Significance:* FOXF2-mediated upregulation of the E3 ligase IRF2BPL drives ubiquitylation and degradation of  $\beta$ -catenin in gastric cancer, blunting Wnt signaling and suppressing carcinogenesis.

## TUMOR BIOLOGY AND IMMUNOLOGY

- 1657 CCR5 Governs DNA Damage Repair and Breast Cancer Stem Cell Expansion

Xuanmao Jiao, Marco A. Velasco-Velázquez, Min Wang, Zhiping Li, Hallgeir Rui, Amy R. Peck, James E. Korkola, Xuelian Chen, Shaohua Xu, James B. DuHadaway, Sandra Guerrero-Rodríguez, Sankar Addya, Daniela Sicoli, Zhaomei Mu, Gang Zhang, Andres Stucky, Xi Zhang, Massimo Cristofanilli, Alessandro Fatatis, Joe W. Gray, Jiang F. Zhong, George C. Prendergast, and Richard G. Pestell


*Significance:* This study offers a preclinical rationale to reposition CCR5 inhibitors to improve the treatment of breast cancer, based on their ability to enhance the tumor-specific activities of DNA-damaging chemotherapies administered in that disease.

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- 1672** **Antiestrogen Therapy Increases Plasticity and Cancer Stemness of Prolactin-Induced ER $\alpha$ <sup>+</sup> Mammary Carcinomas**  
Michael P. Shea, Kathleen A. O'Leary, Saja A. Fakhraldeen, Vincent Goffin, Andreas Friedl, Kari B. Wisinski, Caroline M. Alexander, and Linda A. Schuler  
*Significance:* This study suggests that treatment of a subset of ER $\alpha$ <sup>+</sup> breast cancers with antiestrogen therapies may not only fail to slow growth but promote aggressive behavior by evoking tumor cell plasticity and regenerative CSC activity.
- 1685** **Downregulation of Membrane Trafficking Proteins and Lactate Conditioning Determine Loss of Dendritic Cell Function in Lung Cancer**  
Nicoletta Caronni, Francesca Simoncello, Francesca Stafetta, Corrado Guarnaccia, Juan Sebastian Ruiz-Moreno, Bastian Opitz, Thierry Galli, Veronique Proux-Gillardeaux, and Federica Benvenuti  
*Significance:* These findings provide insight into the cell-intrinsic and cell-extrinsic mechanisms that cause loss of presentation of tumor-specific antigens in lung cancer tissues.
- 1700** **Tumor–Stroma IL1 $\beta$ -IRAK4 Feedforward Circuitry Drives Tumor Fibrosis, Chemoresistance, and Poor Prognosis in Pancreatic Cancer**  
Daoxiang Zhang, Lin Li, Hongmei Jiang, Qiong Li, Andrea Wang-Gillam, Jinsheng Yu, Richard Head, Jingxia Liu, Marianna B. Ruzinova, and Kian-Huat Lim  
*Significance:* Targeting the IL1 $\beta$ -IRAK4 signaling pathway potentiates the effect of chemotherapy in pancreatic cancer.
- 1713** **Targeting the SphK1/S1P/S1PR1 Axis That Links Obesity, Chronic Inflammation, and Breast Cancer Metastasis**  
Masayuki Nagahashi, Akimitsu Yamada, Eriko Katsuta, Tomoyoshi Aoyagi, Wei-Ching Huang, Krista P. Terracina, Nitai C. Hait, Jeremy C. Allegood, Junko Tsuchida, Kizuki Yuza, Masato Nakajima, Manabu Abe, Kenji Sakimura, Sheldon Milstien, Toshifumi Wakai, Sarah Spiegel, and Kazuaki Takabe  
*Significance:* These findings offer a preclinical proof of concept that signaling by a sphingolipid may be an effective target to prevent obesity-related breast cancer metastasis.
- 1726** **XIAP Regulation by MNK Links MAPK and NF $\kappa$ B Signaling to Determine an Aggressive Breast Cancer Phenotype**  
Myron K. Evans, Michael C. Brown, Joseph Geradts, Xuhui Bao, Timothy J. Robinson, Mohit Kumar Jolly, Peter B. Vermeulen, Gregory M. Palmer, Matthias Gromeier, Herbert Levine, Michael A. Morse, Steven J. Van Laere, and Gayathri R. Devi  
*Significance:* Signaling by the MNK kinase is essential in inflammatory breast cancer, and it can be targeted to inhibit XIAP-NF $\kappa$ B signaling and the aggressive phenotype of this malignancy.
- 1739** **STAT3/PIAS3 Levels Serve as "Early Signature" Genes in the Development of High-Grade Serous Carcinoma from the Fallopian Tube**  
Uksha Saini, Adrian A. Suarez, Shan Naidu, John J. Wallbillich, Kristin Bixel, Ross A. Wanner, Jason Bice, Raleigh D. Kladney, Jenny Lester, Beth Y. Karlan, Paul J. Goodfellow, David E. Cohn, and Karuppaiyah Selvendiran  
*Significance:* Concomitant gain of pSTAT3 Tyr705 and loss of PIAS3 appear critical for initiation and development of high-grade serous carcinoma.
- 1751** **miR-508 Defines the Stem-like/Mesenchymal Subtype in Colorectal Cancer**  
Ting-Ting Yan, Lin-Lin Ren, Chao-Qin Shen, Zhen-Hua Wang, Ya-Nan Yu, Qian Liang, Jia-Yin Tang, Ying-Xuan Chen, Dan-Feng Sun, Witold Zgodzinski, Marek Majewski, Piotr Radwan, Ilona Kryczek, Ming Zhong, Jinxian Chen, Qiang Liu, Weiping Zou, Hao-Yan Chen, Jie Hong, and Jing-Yuan Fang  
*Significance:* These results define a key functional determinant of a stem-like/mesenchymal subtype of colorectal cancers and a candidate therapeutic target for its treatment.
- 1766** **Myeloma Cells Are Activated in Bone Marrow Microenvironment by the CD180/MD-1 Complex, Which Senses Lipopolysaccharide**  
Jiro Kikuchi, Yoshiaki Kuroda, Daisuke Koyama, Naoki Osada, Tohru Izumi, Hiroshi Yasui, Takakazu Kawase, Tatsuo Ichinohe, and Yusuke Furukawa  
*Significance:* This study describes a novel mechanism by which myeloma cells are regulated in the bone marrow, where drug resistance and dormancy can evolve after treatment, with potential therapeutic implications for treating this often untreatable blood cancer.
- 1779** **Metformin-Induced Reduction of CD39 and CD73 Blocks Myeloid-Derived Suppressor Cell Activity in Patients with Ovarian Cancer**  
 Lifeng Li, Liping Wang, Jieyao Li, Zhirui Fan, Li Yang, Zhen Zhang, Chaoqi Zhang, Dongli Yue, Guohui Qin, Tengfei Zhang, Feng Li, Xinfeng Chen, Yu Ping, Dan Wang, Qun Gao, Qianyi He, Lan Huang, Hong Li, Jianmin Huang, Xuan Zhao, Wenhua Xue, Zhi Sun, Jingli Lu, Jane J. Yu, Jie Zhao, Bin Zhang, and Yi Zhang  
*Significance:* The antitumor activity of an anti-diabetes drug is attributable to reduced immunosuppressive activity of myeloid-derived tumor suppressor cells.
- 1792** **TRIM59 Promotes Gliomagenesis by Inhibiting TC45 Dephosphorylation of STAT3**  
Youzhou Sang, Yanxin Li, Lina Song, Angel A. Alvarez, Weiwei Zhang, Deguan Lv, Jianming Tang, Feng Liu, Zhijie Chang, Shigetsugu Hatakeyama, Bo Hu, Shi-Yuan Cheng, and Haizhong Feng  
*Significance:* These findings identify a novel component of the EGFR/STAT3 signaling axis in the regulation of glioma tumorigenesis.

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## TRANSLATIONAL SCIENCE

**1805**  **PHD3 Controls Lung Cancer Metastasis and Resistance to EGFR Inhibitors through TGF $\alpha$**

Higinio Dopeso, Hui-Ke Jiao, Angel M. Cuesta, Anne-Theres Henze, Liane Jurida, Michael Kracht, Amparo Acker-Palmer, Boyan K. Garvalov, and Till Acker

*Significance:* This study links the oxygen sensor PHD3 to metastasis and drug resistance in cancer, with implications for therapeutic improvement by targeting this system.

**1820** **Fc-Mediated Anomalous Biodistribution of Therapeutic Antibodies in Immunodeficient Mouse Models**

Sai Kiran Sharma, Andrew Chow, Sebastien Monette, Delphine Vivier, Jacob Pourat, Kimberly J. Edwards, Thomas R. Dilling, Dalya Abdel-Atti, Brian M. Zeglis, John T. Poirier, and Jason S. Lewis

*Significance:* Fc/Fc $\gamma$ R-mediated immunobiology of the experimental host is a key determinant to preclinical in vivo tumor targeting and efficacy of therapeutic antibodies.

**1833** **microRNA-1246 Is an Exosomal Biomarker for Aggressive Prostate Cancer**

Divya Bhagirath, Thao Ly Yang, Nathan Bucay, Kirandeep Sekhon, Shahana Majid, Varahram Shahryari, Rajvir Dahiya, Yuichiro Tanaka, and Sharanjot Saini

*Significance:* Dysregulation of exosomal miRNAs in aggressive prostate cancer leads to alteration of key signaling pathways associated with metastatic prostate cancer.

**1845** **Selective mTORC2 Inhibitor Therapeutically Blocks Breast Cancer Cell Growth and Survival**

Thomas A. Werfel, Shan Wang, Meredith A. Jackson, Taylor E. Kavanaugh, Meghan Morrison Joly, Linus H. Lee, Donna J. Hicks, Violeta Sanchez, Paula Gonzalez Ericsson, Kameron V. Kilchrist, Somtochukwu C. Dimobi, Samantha M. Sarett, Dana M. Brantley-Sieders, Rebecca S. Cook, and Craig L. Duvall

*Significance:* This study describes a nanomedicine to effectively inhibit the growth regulatory kinase mTORC2 in a preclinical model of breast cancer, targeting an important pathogenic enzyme in that setting that has been undruggable to date.

## CONVERGENCE AND TECHNOLOGIES

**1859** **Investigating Low-Velocity Fluid Flow in Tumors with Convection-MRI**

Simon Walker-Samuel, Thomas A. Roberts, Rajiv Ramasawmy, Jake S. Burrell, Sean Peter Johnson, Bernard M. Siow, Simon Richardson, Miguel R. Gonçalves, Douglas Pendse, Simon P. Robinson, R. Barbara Pedley, and Mark F. Lythgoe

*Significance:* A noninvasive method for measuring low-velocity fluid flow caused by raised fluid pressure can be used to assess changes caused by therapy.

**1873** **In Silico Evaluation of Pharmacokinetic Optimization for Antimitogram-Based Clinical Trials**

Skerdi Haviari, Benoit You, and Michel Tod

*Significance:* This work offers a method to reduce the number of patients needed for a clinical trial to prove the hypothesized benefit of a drug to progression-free survival, possibly easing opportunities to evaluate combinations.

## LETTER TO THE EDITOR

**1883** **Charting the Future of Cancer Health Disparities Research—Letter**

Philip E. Castle

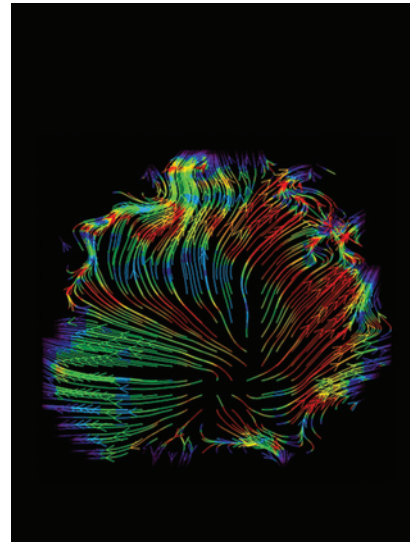
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## ABOUT THE COVER

Interstitial fluid pressure is typically raised in solid tumors, which can affect drug delivery. Using magnetic resonance imaging, a technique called convection-MRI was developed that has been used to noninvasively study low-velocity, extravascular fluid flow in tumors. This image shows fluid velocity streamlines, measured *in vivo* with convection-MRI, that emanate from the tumor center and radiate outwards, and that are consistent with elevated, central fluid pressure. For details, see article by Walker-Samuel and colleagues on page 1859.



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