

## BREAKING INSIGHTS

- 2145** Highlights from Recent Cancer Literature

## OBITUARY

- 2147** Jimmie C. Holland, MD: In Memoriam (1928–2017)  
David W. Kissane

## REVIEWS

- 2149** Hiding in Plain Sight: Rediscovering the Importance of Noncoding RNA in Human Malignancy  
Kyle P. Feeley and Mick D. Edmonds
- 2159** Resistance to Antibody–Drug Conjugates  
Sara García-Alonso, Alberto Ocaña, and Atanasio Pandiella


## CONTROVERSY AND CONSENSUS

- 2166** Workshop Report for Cancer Research: Defining the Shades of Gy: Utilizing the Biological Consequences of Radiotherapy in the Development of New Treatment Approaches  
 Mansoor M. Ahmed, C. Norman Coleman, Marc Mendonca, Soren Bentzen, Bhadransain Vikram, Stephen M. Seltzer, Dudley Goodhead, Ceferino Obcemea, Radhe Mohan, Kevin M. Prise, Jacek Capala, Deborah Citrin, Gary Kao, Molykutty Aryankalayil, Iris Eke, Jeffrey C. Buchsbaum, Pataje G.S. Prasanna, Fei-Fei Liu, Quynh-Thu Le, Beverly Teicher, David G. Kirsch, DeeDee Smart, Joel Tepper, Silvia Formenti, Daphne Haas-Kogan, David Raben, and James Mitchell

## PRIORITY REPORT

- 2171** Mitotic Phosphorylation of SENP3 Regulates DeSUMOylation of Chromosome-Associated Proteins and Chromosome Stability  
Bo Wei, Chao Huang, Bin Liu, Yang Wang, Nansong Xia, Qiuju Fan, Guo-Qiang Chen, and Jinke Cheng  
*Significance:* Phosphorylation of SENP3 regulates SUMOylation of chromosome-associated proteins to maintain genomic stability during mitosis.

## METABOLISM AND CHEMICAL BIOLOGY


- 2179**  Metabolic Determinants of Sensitivity to Phosphatidylinositol 3-Kinase Pathway Inhibitor in Small-Cell Lung Carcinoma  
Hideki Makinoshima, Shigeki Umemura, Ayako Suzuki, Hiroki Nakanishi, Ami Maruyama, Hibiki Udagawa, Sachiyo Mimaki, Shingo Matsumoto, Seiji Niho, Genichiro Ishii, Masahiro Tsuboi, Atsushi Ochiai, Hiroyasu Esumi, Takehiko Sasaki, Koichi Goto, and Katsuya Tsuchihara  
*Significance:* These findings identify features that determine sensitivity of SCLC to PI3K pathway inhibition and support metabolomics as a tool for finding novel therapeutic biomarkers.

- 2191** RSK Regulates PFK-2 Activity to Promote Metabolic Rewiring in Melanoma  
Thibault Houles, Simon-Pierre Gravel, Geneviève Lavoie, Sejeong Shin, Mathilde Savall, Antoine Méant, Benoit Grondin, Louis Gaboury, Sang-Oh Yoon, Julie St-Pierre, and Philippe P. Roux  
*Significance:* RSK promotes glycolytic metabolism and the growth of BRAF-mutated melanoma by driving phosphorylation of an important glycolytic enzyme.




## MOLECULAR CELL BIOLOGY

- 2205** Nuclear Receptor LRH-1 Functions to Promote Castration-Resistant Growth of Prostate Cancer via Its Promotion of Intratumoral Androgen Biosynthesis  
Lijia Xiao, Yuliang Wang, Kexin Xu, Hao Hu, Zhenyu Xu, Dinglan Wu, Zhu Wang, Wenxing You, Chi-Fai Ng, Shan Yu, and Franky Leung Chan  
*Significance:* These findings not only demonstrate the significant role of the nuclear receptor LRH-1 in the promotion of intratumoral androgen biosynthesis in CRPC via its direct transcriptional control of steroidogenesis, but also suggest targeting LRH-1 could be a potential therapeutic strategy for CRPC management.
- 2219** Demethylation-Induced Overexpression of Shc3 Drives c-Raf–Independent Activation of MEK/ERK in HCC  
Yun Liu, Xinran Zhang, Baicai Yang, Hao Zhuang, Hua Guo, Wen Wei, Yuan Li, Ruibing Chen, Yongmei Li, and Ning Zhang  
*Significance:* Ectopic expression of Shc3 forms a complex with MVP/MEK/ERK to potentiate ERK activation and plays an important role in sorafenib resistance in HCC.

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- 2233** **A DDX31/Mutant-p53/EGFR Axis Promotes Multistep Progression of Muscle-Invasive Bladder Cancer**  
  
Kei Daizumoto, Tetsuro Yoshimaru, Yosuke Matsushita, Tomoya Fukawa, Hisanori Uehara, Masaya Ono, Masato Komatsu, Hiro-omi Kanayama, and Toyomasa Katagiri  
*Significance:* DDX31 cooperates with mutp53 and EGFR to promote progression of muscle invasive bladder cancer.
- 2248** **Oncogenic Kinase-Induced PKM2 Tyrosine 105 Phosphorylation Converts Nononcogenic PKM2 to a Tumor Promoter and Induces Cancer Stem-like Cells**  
Zhifen Zhou, Min Li, Lin Zhang, Hong Zhao, Özgür Şahin, Jing Chen, Jean J. Zhao, Zhou Songyang, and Dihua Yu  
*Significance:* These findings reveal PKM2 promotes tumorigenesis by inducing cancer stem-like cell properties and clarify the paradox of PKM2's dichotomous functions in tumor progression.
- 2262** **Proteolytic Release of the p75<sup>NTR</sup> Intracellular Domain by ADAM10 Promotes Metastasis and Resistance to Anoikis**  
Xin Bao, Jianbo Shi, Furong Xie, Zengying Liu, Jingshuang Yu, Wantao Chen, Zhiyuan Zhang, and Qin Xu  
*Significance:* These findings identify the ADAM10-p75<sup>NTR</sup> ICD-TRAF6-NFκB signaling axis as a potential candidate for cancer therapy.
- 2277** **A Soft Microenvironment Protects from Failure of Midbody Abscission and Multinucleation Downstream of the EMT-Promoting Transcription Factor Snail**  
Allison K. Simi, Alisya A. Anlaş, Melody Stallings-Mann, Sherry Zhang, Tiffany Hsia, Magdalena Cichon, Derek C. Radisky, and Celeste M. Nelson  
*Significance:* These findings reveal tissue stiffening during tumorigenesis synergizes with oncogenic signaling to promote genomic abnormalities that drive cancer progression.
- 2290** **2-Hydroxyglutarate-Mediated Autophagy of the Endoplasmic Reticulum Leads to an Unusual Downregulation of Phospholipid Biosynthesis in Mutant IDH1 Gliomas**  
Pavithra Viswanath, Marina Radoul, Jose Luis Izquierdo-Garcia, Wei Qiang Ong, Hema Artee Luchman, J. Gregory Cairncross, Bo Huang, Russell O. Pieper, Joanna J. Phillips, and Sabrina M. Ronen  
*Significance:* Downregulation of phospholipid biosynthesis via ER-phagy is essential for proliferation and clonogenicity of mutant IDH1 gliomas, a finding with immediate therapeutic implications.

## TUMOR BIOLOGY AND IMMUNOLOGY

- 2305** **SPON2 Promotes M1-like Macrophage Recruitment and Inhibits Hepatocellular Carcinoma Metastasis by Distinct Integrin-Rho GTPase-Hippo Pathways**  
  
  
Yan-Li Zhang, Qing Li, Xiao-Mei Yang, Fang Fang, Jun Li, Ya-Hui Wang, Qin Yang, Lei Zhu, Hui-Zhen Nie, Xue-Li Zhang, Ming-Xuan Feng, Shu-Heng Jiang, Guang-Ang Tian, Li-Peng Hu, Ho-Young Lee, Su-Jae Lee, Qiang Xia, and Zhi-Gang Zhang  
*Significance:* Matricellular protein SPON2 acts as an HCC suppressor and utilizes distinct signaling events to perform dual functions in HCC microenvironment.
- 2318** **A Distinct Oncogenerative Multinucleated Cancer Cell Serves as a Source of Stemness and Tumor Heterogeneity**  
  
David Díaz-Carballo, Sahitya Saka, Jacqueline Klein, Tobias Rennkamp, Ali H. Acikelli, Sascha Malak, Holger Jastrow, Gunther Wennemuth, Clemens Tempfer, Inge Schmitz, Andrea Tannapfel, and Dirk Strumberg  
*Significance:* P1 oncogenerative cell entities express low levels of CSC markers, which are characteristic of their histological origin.
- 2332** **IRAK1 Augments Cancer Stemness and Drug Resistance via the AP-1/AKR1B10 Signaling Cascade in Hepatocellular Carcinoma**  
Bowie Y. Cheng, Eunice Y. Lau, Hoi-Wing Leung, Carmen Oi-Ning Leung, Nicole P. Ho, Shilpa Gurung, Lily K. Cheng, Chi Ho Lin, Regina Cheuk-Lam Lo, Stephanie Ma, Irene Oi-Lin Ng, and Terence K. Lee  
*Significance:* IRAK4/IRAK1/AP-1/AKR1B10 signaling pathway regulates cancer stemness and drug resistance and may be a novel therapeutic target in HCC.
- 2343** **Expression of Adipocyte/Macrophage Fatty Acid-Binding Protein in Tumor-Associated Macrophages Promotes Breast Cancer Progression**  
Jiaqing Hao, Fei Yan, Yuwen Zhang, Ashley Triplett, Ying Zhang, Debra A. Schultz, Yanwen Sun, Jun Zeng, Kevin A.T. Silverstein, Qi Zheng, David A. Bemlohr, Margot P. Cleary, Nejat K. Egilmez, Edward Sauter, Shujun Liu, Jill Suttles, and Bing Li  
*Significance:* These findings identify A-FABP as a functional marker for protumor macrophages, thus offering a new target for tumor immunotherapy.

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**2356** FOXO Transcription Factors Both Suppress and Support Breast Cancer Progression

Marten Hornsveld, Lydia M.M. Smits, Maaïke Meerlo, Miranda van Amersfoort, Marian J.A. Groot Koerkamp, Dik van Leenen, David E.A. Kloet, Frank C.P. Holstege, Patrick W.B. Derksen, Boudewijn M.T. Burgering, and Tobias B. Dansen

*Significance:* FOXO proteins are not solely tumor suppressors but also support tumor growth and metastasis by regulating a multitude of cellular processes essential for tumorigenesis.

**2370** Single-Cell Transcriptome Analyses Reveal Endothelial Cell Heterogeneity in Tumors and Changes following Antiangiogenic Treatment



Qi Zhao, Alexandra Eichten, Asma Parveen, Christina Adler, Ying Huang, Wei Wang, Yueming Ding, Alexander Adler, Thomas Nevins, Min Ni, Yi Wei, and Gavin Thurston

*Significance:* These findings provide a framework for defining subpopulations of endothelial cells and tumor-associated fibroblasts and their rapid changes in gene expression following antiangiogenic treatment.

## TRANSLATIONAL SCIENCE

**2383** Cross-talk Signaling between HER3 and HPV16 E6 and E7 Mediates Resistance to PI3K Inhibitors in Head and Neck Cancer

Toni M. Brand, Stefan Hartmann, Neil E. Bhola, Hua Li, Yan Zeng, Rachel A. O'Keefe, Max V. Ranall, Sourav Bandyopadhyay, Margaret Soucheray, Nevan J. Krogan, Carolyn Kemp, Umamaheswar Duvvuri, Theresa LaVallee, Daniel E. Johnson, Michelle A. Ozbun, Julie E. Bauman, and Jennifer R. Grandis

*Significance:* These findings suggest a new therapeutic combination that may improve outcomes in HPV(+) head and neck cancer patients.

**2396** The FACT inhibitor CBL0137 Synergizes with Cisplatin in Small-Cell Lung Cancer by Increasing NOTCH1 Expression and Targeting Tumor-Initiating Cells



Sarmishtha De, Daniel J. Lindner, Claire J. Coleman, Gary Wildey, Afshin Dowlati, and George R. Stark

*Significance:* These findings reveal a novel therapeutic regimen for SCLC, combining cisplatin with an inhibitor that preferentially targets tumor-initiating cells.

**2407** Patient-Customized Drug Combination Prediction and Testing for T-cell Prolymphocytic Leukemia Patients



Liye He, Jing Tang, Emma I. Andersson, Sanna Timonen, Steffen Koschmieder, Krister Wennerberg, Satu Mustjoki, and Tero Aittokallio

*Significance:* An integrated use of functional drug screening combined with genomic and molecular profiling enables patient-customized prediction and testing of drug combination synergies for T-PLL patients.

## CONVERGENCE AND TECHNOLOGIES

**2419** Combination Therapy and the Evolution of Resistance: The Theoretical Merits of Synergism and Antagonism in Cancer

Elysia C. Saputra, Lu Huang, Yihui Chen, and Lisa Tucker-Kellogg

*Significance:* Computational simulations show that if different combination therapies have similar initial efficacy in cancers, then nonsynergistic drug combinations are more likely than synergistic drug combinations to provide a long-term defense against the evolution of therapeutic resistance.

## POPULATION AND PREVENTION SCIENCE

**2432** Genetic Hitchhiking and Population Bottlenecks Contribute to Prostate Cancer Disparities in Men of African Descent

Joseph Lachance, Ali J. Berens, Matthew E.B. Hansen, Andrew K. Teng, Sarah A. Tishkoff, and Timothy R. Rebbeck

*Significance:* A small number of genetic variants cause an elevated risk of prostate cancer in men of West African descent.

## CORRECTIONS

**2444** Correction: Ormeloxifene Suppresses Desmoplasia and Enhances Sensitivity of Gemcitabine in Pancreatic Cancer

**2445** Correction: SlicerDMRI: Open Source Diffusion MRI Software for Brain Cancer Research

**2446** Correction: Comparative Cistromics Reveals Genomic Cross-talk between FOXA1 and ER $\alpha$  in Tamoxifen-Associated Endometrial Carcinomas

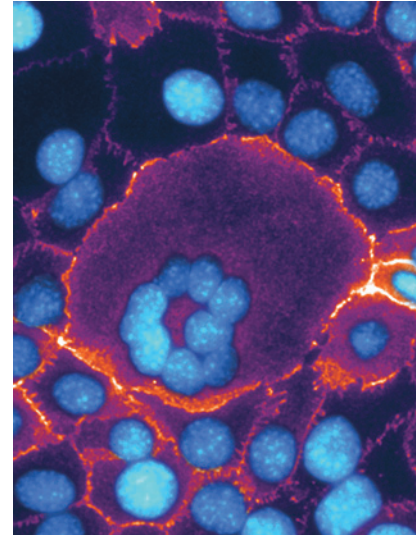
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## ABOUT THE COVER

Multinucleation is found in more than one third of tumors and is linked to increased tolerance for mutation, resistance to chemotherapy, and invasive potential. Tissue stiffening during tumorigenesis induces multinucleation in mammary epithelial cells. This phenomenon is exacerbated by increased levels of EMT-promoting transcription factor Snail, which causes midbody persistence and abscission failure. For details, see article by Simi and colleagues on page 2277.



# Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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