

## BREAKING ADVANCES

- 813** Highlights from Recent Cancer Literature

## OBITUARY

- 815** Alfred G. Knudson Jr, MD, PhD: In Memoriam (1922–2016)  
Jonathan Chernoff

## REVIEWS

- 817** Intrinsic Resistance of Solid Tumors to Immune Checkpoint Blockade Therapy  
Xianda Zhao and Subbaya Subramanian
- 823** Temozolomide in the Era of Precision Medicine  
Anish Thomas, Mamoru Tanaka, Jane Trepel, William C. Reinhold, Vinodh N. Rajapakse, and Yves Pommier

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 827** Cell-Specific Computational Modeling of the PIM Pathway in Acute Myeloid Leukemia  
Dana Silverbush, Shaun Grosskurth, Dennis Wang, Francoise Powell, Berthold Gottgens, Jonathan Dry, and Jasmin Fisher
- Précis:* An AML executable signaling model with cell-specific context switches can enable personalized tailoring of drug combinations to increase sensitivity and overcome drug resistance.

## MICROENVIRONMENT AND IMMUNOLOGY

- 839** Suppression of Type I IFN Signaling in Tumors Mediates Resistance to Anti-PD-1 Treatment That Can Be Overcome by Radiotherapy  
Xiaohong Wang, Jonathan E. Schoenhals, Ailin Li, David R. Valdecanas, Huiping Ye, Fenglin Zang, Chad Tang, Ming Tang, Chang-Gong Liu, Xiuping Liu, Sunil Krishnan, James P. Allison, Padmanee Sharma, Patrick Hwu, Ritsuko Komaki, Willem W. Overwijk, Daniel R. Gomez, Joe Y. Chang, Stephen M. Hahn, Maria Angelica Cortez, and James W. Welsh
- Précis:* These findings suggest that the poor efficacy of anti-PD-1 as an immune checkpoint therapy for many patients could be accentuated greatly by adjuvant radiotherapy, thereby broadening its useful application against cancers, where robust but relatively infrequent responses have been documented.

- 851** Early Effector T Lymphocytes Coexpress Multiple Inhibitory Receptors in Primary Non–Small Cell Lung Cancer

Elena Tassi, Giulia Grazia, Claudia Vegetti, Ilaria Bersani, Giulia Bertolini, Alessandra Molla, Paola Baldassari, Francesca Andriani, Luca Roz, Gabriella Sozzi, Ugo Pastorino, Roberta Mortarini, and Andrea Anichini

*Précis:* Identification in lung tumors of a particular subset of T lymphocytes at their earliest phase of functional differentiation will provide a useful biomarker to monitor the earliest stages of development of adaptive tumor immunity.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 862** The SWI/SNF Complex Protein Snr1 Is a Tumor Suppressor in *Drosophila* Imaginal Tissues  
Gengqiang Xie, Hanqing Chen, Dongyu Jia, Zhiqiang Shu, William Hunt Palmer, Yi-Chun Huang, Xiankun Zeng, Steven X. Hou, Renjie Jiao, and Wu-Min Deng
- Précis:* These findings in a *Drosophila* model system illuminate a mechanism by which the human SMARB1/hSNF5 gene gives rise to malignant rhabdoid tumors during early childhood.
- 874** ESE3 Inhibits Pancreatic Cancer Metastasis by Upregulating E-Cadherin  
Tiansuo Zhao, Wenna Jiang, Xiuchao Wang, Hongwei Wang, Chen Zheng, Yang Li, Yan Sun, Chongbiao Huang, Zhi-bo Han, Shengyu Yang, Zhiliang Jia, Keping Xie, He Ren, and Jihui Hao
- Précis:* The ETS family transcription factor ESE3 binds and upregulates expression of the E-cadherin gene, a determinant of epithelial function and an inhibitor of invasion and metastasis in pancreatic cancer cells.

- 886** An Essential Role of Maspin in Embryogenesis and Tumor Suppression  
Sijana H. Dzinic, M. Margarida Bernardo, Xiaohua Li, Rodrigo Fernandez-Valdivia, Ye-Shih Ho, Qing-Sheng Mi, Sudeshna Bandyopadhyay, Fulvio Lonardo, Semir Vranic, Daniel S.M. Oliveira, R. Daniel Bonfil, Gregory Dyson, Kang Chen, Almasa Omerovic, Xiujie Sheng, Xiang Han, Dinghong Wu, Xinling Bi, Dzenana Cabaravdic, Una Jakupovic, Marian Wahba, Aaron Pang, Deanna Harajli, Wael A. Sakr, and Shijie Sheng
- Précis:* A new mouse knockout model for the tumor suppressor gene Maspin resolves questions surrounding its specific functions in cancer and its therapeutic potential for cancer diagnosis and treatment.

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- 897** **Modeling Alveolar Soft Part Sarcoma Unveils Novel Mechanisms of Metastasis**  
Miwa Tanaka, Mizuki Homme, Yukari Yamazaki, Rikuka Shimizu, Yutaka Takazawa, and Takuro Nakamura  
*Précis:* A novel mouse model for alveolar soft part sarcoma (ASPS) demonstrates induction of hemangiopericytes by ASPS cells as well as intravasation of tumor cells mediated by GPNMB, providing novel mechanisms of ASPS development, angiogenesis, and hematogenous metastasis.

- 908** **A Novel Mouse Model to Study Image-Guided, Radiation-Induced Intestinal Injury and Preclinical Screening of Radioprotectors**  
Ioannis I. Verginadis, Rahul Kanade, Brett Bell, Sravya Koduri, Edgar Ben-Josef, and Constantinos Koumenis  
*Précis:* The new mouse model reported in this study will accelerate research on radiotherapy for gastrointestinal malignancies and speed drug development to protect normal tissues in this setting.

## PREVENTION AND EPIDEMIOLOGY

- 918** **Association of Estrogen Metabolism with Breast Cancer Risk in Different Cohorts of Postmenopausal Women**  
Joshua N. Sampson, Roni T. Falk, Catherine Schairer, Steven C. Moore, Barbara J. Fuhrman, Cher M. Dallal, Douglas C. Bauer, Joanne F. Dorgan, Xiao-Ou Shu, Wei Zheng, Louise A. Brinton, Mitchell H. Gail, Regina G. Ziegler, Xia Xu, Robert N. Hoover, and Gretchen L. Gierach  
*Précis:* These findings support the hypothesis that estrogen carcinogenicity relates mainly to the mitogenicity of a specific pathway of estrogen metabolism (16-pathway metabolites).

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 926** **The Natural Diterpenoid Isoforretin A Inhibits Thioredoxin-1 and Triggers Potent ROS-Mediated Antitumor Effects**  
Xiaoyan Sun, Weiguang Wang, Jiao Chen, Xueting Cai, Jie Yang, Yang Yang, Huaijiang Yan, Xiaolan Cheng, Juan Ye, Wuguang Lu, Chunping Hu, Handong Sun, Jianxin Pu, and Peng Cao  
*Précis:* These findings highlight a recently discovered natural product as a potent bioactive inhibitor of thioredoxin-1, a critical regulator of thiol homeostasis in cancer cells, and a candidate anticancer modality with potentially broad use in many types of cancer.

- 937** **Crystal Structure of the Emerging Cancer Target MTHFD2 in Complex with a Substrate-Based Inhibitor**  
Robert Gustafsson, Ann-Sofie Jemth, Nina M.S. Gustafsson, Katarina Färnegårdh, Olga Loseva, Elisée Wiita, Nadilly Bonagas, Leif Dahllund, Sabin Llona-Minguez, Maria Häggblad, Martin Henriksson, Yasmin Andersson, Evert Homan, Thomas Helleday, and Pål Stenmark  
*Précis:* These findings provide a rationale for continued development of a structural framework for the generation of potent and selective MTHFD2 inhibitors for cancer treatment.

- 949** **mda-7/IL-24 Mediates Cancer Cell-Specific Death via Regulation of miR-221 and the Beclin-1 Axis**  
Anjan K. Pradhan, Sarmistha Talukdar, Praveen Bhoopathi, Xue-Ning Shen, Luni Emdad, Swadesh K. Das, Devanand Sarkar, and Paul B. Fisher  
*Précis:* These findings reveal that the therapeutic efficacy of mda-7/IL-24 treatment in multiple cancer types is dependent upon downregulation of miR-221.

- 960** **Glioblastoma Therapy Can Be Augmented by Targeting IDH1-Mediated NADPH Biosynthesis**  
Daniel R. Wahl, Joseph Dresser, Kari Wilder-Romans, Joshua D. Parsels, Shuang G. Zhao, Mary Davis, Lili Zhao, Maureen Kachman, Stefanie Wernisch, Charles F. Burant, Meredith A. Morgan, Felix Y. Feng, Corey Speers, Costas A. Lyssiotis, and Theodore S. Lawrence  
*Précis:* Glioblastomas upregulate the isocitrate dehydrogenase IDH1 to help meet their demands for the reductant NADPH and this study shows how inhibiting this metabolic adaptation can improve the efficacy of radiotherapy in this disease.

## TUMOR AND STEM CELL BIOLOGY

- 971** **A Myc Activity Signature Predicts Poor Clinical Outcomes in Myc-Associated Cancers**  
MoonSun Jung, Amanda J. Russell, Bing Liu, Joshy George, Pei Yan Liu, Tao Liu, Anna DeFazio, David D.L. Bowtell, André Oberthuer, Wendy B. London, Jamie I. Fletcher, Michelle Haber, Murray D. Norris, and Michelle J. Henderson  
*Précis:* These findings define an 18-gene signature with prognostic utility in several cancers, where Myc activation occurs commonly, even in the absence of Myc gene amplification.

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- 982** **RB Loss Promotes Prostate Cancer Metastasis**  
Chellappagounder Thangavel, Ettickan Boopathi, Yi Liu, Alex Haber, Adam Ertel, Anshul Bhardwaj, Sankar Addya, Noelle Williams, Stephen J. Ciment, Paolo Cotzia, Jeffrey L. Dean, Adam Snook, Chris McNair, Matt Price, James R. Hernandez, Shuang G. Zhao, Ruth Birbe, James B. McCarthy, Eva A. Turley, Kenneth J. Pienta, Felix Y. Feng, Adam P. Dicker, Karen E. Knudsen, and Robert B. Den

*Précis:* Extending the functional impact of RB loss in cancer, this study shows how this event promotes metastasis via expression of the cell migration receptor RHAMM, with potential implications for a broadly applicable therapeutic strategy in advanced cancers.

- 996** **Wnt5a Drives an Invasive Phenotype in Human Glioblastoma Stem-like Cells**



Elena Binda, Alberto Visioli, Fabrizio Giani, Nadia Trivieri, Orazio Palumbo, Silvia Restelli, Fabio Dezi, Tommaso Mazza, Caterina Fusilli, Federico Legnani, Massimo Carella, Francesco Di Meco, Rohit Duggal, and Angelo L. Vescovi

*Précis:* This milestone study establishes the noncanonical WNT family member Wnt5a as a master regulator of brain invasion in glioblastoma and offers a rationale for its therapeutic targeting in glioblastoma patients.

- 1008** **Sunitinib Treatment Enhances Metastasis of Innately Drug-Resistant Breast Tumors**

Joseph W. Wragg, Victoria L. Heath, and Roy Bicknell

*Précis:* These findings suggest candidate diagnostic markers of innate or acquired resistance to antiangiogenic resistance, with implications for personalized care with antiangiogenic tyrosine kinase inhibitors.

- 1021** **MicroRNA-194 Promotes Prostate Cancer Metastasis by Inhibiting SOCS2**

Rajdeep Das, Philip A. Gregory, Rayzel C. Fernandes, Iza Denis, Qingqing Wang, Scott L. Townley, Shuang G. Zhao, Adrienne R. Hanson, Marie A. Pickering, Heather K. Armstrong, Noor A. Lokman, Esmail Ebrahimie, Elai Davicioni, Robert B. Jenkins, R. Jeffrey Karnes, Ashley E. Ross, Robert B. Den, Eric A. Klein, Kim N. Chi, Hayley S. Ramshaw, Elizabeth D. Williams, Amina Zoubeydi, Gregory J. Goodall, Felix Y. Feng, Lisa M. Butler, Wayne D. Tilley, and Luke A. Selth

*Précis:* A newly identified miRNA-regulated pathway influences prostate cancer metastasis and serves as a potential therapeutic target.

- 1035** **ARF Confers a Context-Dependent Response to Chemotherapy in Muscle-Invasive Bladder Cancer**

Tomasz B. Owczarek, Takashi Kobayashi, Ricardo Ramirez, Lijie Rong, Anna M. Puzio-Kuter, Gopa Iyer, Min Yuen Teo, Francisco Sánchez-Vega, Jingqiang Wang, Nikolaus Schultz, Tian Zheng, David B. Solit, Hikmat A. Al-Ahmadie, and Cory Abate-Shen

*Précis:* These findings uncover a link between nucleolar ARF expression and adverse drug response, suggesting that patients with upregulated ARF may benefit from a combination of chemotherapy and modulator of protein translation.

## CORRECTION

- 1047** **Correction: YAP/TEAD-Mediated Transcription Controls Cellular Senescence**

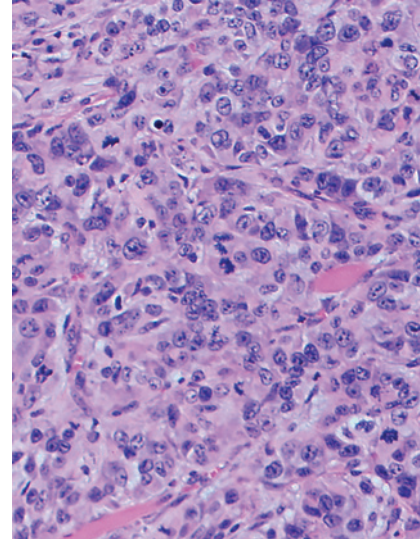
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## ABOUT THE COVER

Although PD-1/PD-L1 immune checkpoint blocking antibodies have demonstrated durable clinical responses in some patients, the majority of patients fail to respond to such a treatment. Histological staining of anti-PD-1-resistant tumors from a mouse model for lung cancer showed that the resistant tumor had significantly increased mitosis, more nuclear pleomorphism, and less immune cell infiltration than did the anti-PD-1 responsive tumor. For details, see article by Wang and colleagues on page 839.



# Cancer Research

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

**77 (4)**

*Cancer Res* 2017;77:813-1047.

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