

# Cancer Research Table of Contents

**AACR**  
American Association  
for Cancer Research

August 15, 2014 • Volume 74 • Number 16

## BREAKING ADVANCES

- 4209 **Highlights from Recent Cancer Literature**

## REVIEWS

- 4211 **Immunogenetic Studies of Chronic Lymphocytic Leukemia: Revelations and Speculations about Ontogeny and Clinical Evolution**  
Anna Vardi, Andreas Agathangelidis, Lesley-Ann Sutton, Paolo Ghia, Richard Rosenquist, and Kostas Stamatopoulos
- 4217 **Harnessing the Intestinal Microbiome for Optimal Therapeutic Immunomodulation**  
S. Viaud, R. Daillère, I.G. Boneca, P. Lepage, M.J. Pittet, F. Ghiringhelli, G. Trinchieri, R. Goldszmid, and L. Zitvogel

## PRIORITY REPORT

- 4222 **MYC Synergizes with Activated BRAF<sup>V600E</sup> in Mouse Lung Tumor Development by Suppressing Senescence**  
Vedrana Tabor, Matteo Bocci, Nyosha Alikhani, Raoul Kuiper, and Lars-Gunnar Larsson
- Précis:* This study suggests a route through which senescence can be defeated to blunt a fail-safe mechanism that can restrain the powerful oncogenic effects of deregulated MYC, which underpins the malignant development of most human tumors.

## CLINICAL STUDIES

- 4230 **Pentraxin 3: A Novel Biomarker for Predicting Progression from Prostatic Inflammation to Prostate Cancer**  
Giovanni Stallone, Luigi Cormio, Giuseppe Stefano Netti, Barbara Infante, Oscar Selvaggio, Giuseppe Di Fino, Elena Ranieri, Francesca Bruno, Clelia Prattichizzo, Francesca Sanguedolce, Simona Tortorella, Pantaleo Bufo, Giuseppe Grandaliano, and Giuseppe Carrieri
- Précis:* These findings encourage further evaluation of an innate immune regulator as a noninvasive biomarker that discriminates cancer from benign hyperplasia in the prostate, perhaps reducing the need for a biopsy to diagnose prostate cancer in the primary care setting.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 4239 **Capillary-Wall Collagen as a Biophysical Marker of Nanotherapeutic Permeability into the Tumor Microenvironment**  
Kenji Yokoi, Milos Kojic, Miljan Milosevic, Tomonori Tanei, Mauro Ferrari, and Arturas Ziemys
- Précis:* Determining the level of blood vessel collagen in different tumor types may help guide efforts to optimize the delivery routes for nanotherapeutics.
- 4247 **Hyperpolarized [<sup>1-13</sup>C] Glutamate: A Metabolic Imaging Biomarker of IDH1 Mutational Status in Glioma**  
Myriam M. Chaumeil, Peder E.Z. Larson, Sarah M. Woods, Larry Cai, Pia Eriksson, Aaron E. Robinson, Janine M. Lupo, Daniel B. Vigneron, Sarah J. Nelson, Russell O. Pieper, Joanna J. Phillips, and Sabrina M. Ronen
- Précis:* This study describes a novel noninvasive imaging method that can inform the status of metabolic reprogramming in tumors.


## MICROENVIRONMENT AND IMMUNOLOGY

- 4258 **Transient Ablation of Regulatory T cells Improves Antitumor Immunity in Colitis-Associated Colon Cancer**  
Eva Pastille, Katrin Bardini, Diana Fleissner, Alexandra Adamczyk, Annika Frede, Munisch Wadwa, Dorthé von Smolinski, Stefan Kasper, Tim Sparwasser, Achim D. Gruber, Martin Schuler, Shimon Sakaguchi, Axel Roers, Werner Müller, Wiebke Hansen, Jan Buer, and Astrid M. Westendorf
- Précis:* This study addresses the controversy concerning whether T-regulatory cells promote or retard the formation of colon cancers driven by chronic intestinal inflammation, with implications for how to use cancer immunotherapies that ablate T-regulatory cells in this setting.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 4270 **Cancer Affects microRNA Expression, Release, and Function in Cardiac and Skeletal Muscle**  
Daohong Chen, Chirayu P. Goswami, Riesa M. Burnett, Manjushree Anjanappa, Poornima Bhat-Nakshatri, William Muller, and Harikrishna Nakshatri
- Précis:* This study offers evidence that a circulating microRNA could serve as a surrogate of the effects of cancer on microRNA expression in distant organs.

# Table of Contents

- 4282 Germline Mutations in BAP1 Impair Its Function in DNA Double-Strand Break Repair**  
Ismail Hassan Ismail, Riley Davidson, Jean-Philippe Gagné, Zhi Zhong Xu, Guy G. Poirier, and Michael J. Hendzel  
*Précis:* This study provides a missing link in the DNA damage response and provides a mechanistic explanation for how BAP1 functions as a tumor suppressor gene.
- 4295 PME-1 Modulates Protein Phosphatase 2A Activity to Promote the Malignant Phenotype of Endometrial Cancer Cells**  
Ewa Wandzioch, Michelle Pusey, Amy Werda, Sophie Bail, Aishwarya Bhaskar, Mariya Nestor, Jing-Jing Yang, and Lyndi M. Rice  
*Précis:* These findings identify a methyltransferase for the protein phosphatase PP2A as a modifier of cancer development and a therapeutic target in endometrial tumors.
- 4306 AR-Regulated TWEAK-FN14 Pathway Promotes Prostate Cancer Bone Metastasis**  
 JuanJuan Yin, Yen-Nien Liu, Heather Tillman, Ben Barrett, Stephen Hewitt, Kris Ylaya, Lei Fang, Ross Lake, Eva Corey, Colm Morrissey, Robert Vessella, and Kathleen Kelly  
*Précis:* These findings identify a TNF receptor family member as a candidate therapeutic agent and imaging target in castrate-resistant prostate cancer.
- 4318 B-cell Expansion and Lymphomagenesis Induced by Chronic CD40 Signaling Is Strictly Dependent on CD19**  
Caroline Hojer, Samantha Frankenberger, Lothar J. Strobl, Samantha Feicht, Kristina Djermanovic, Franziska Jagdhuber, Cornelia Hömig-Hölzel, Uta Ferch, Jürgen Ruland, Klaus Rajewsky, and Ursula Zimmer-Strobl  
*Précis:* CD19 acts as a coreceptor not only for the B-cell receptor but also for CD40, mediating critical survival and proliferation signals in B-cell tumors.
- 4329 IL4 Receptor ILR4 $\alpha$  Regulates Metastatic Colonization by Mammary Tumors through Multiple Signaling Pathways**  
Katherine T. Venmar, Kathy J. Carter, Daniel G. Hwang, E. Ashley Dozier, and Barbara Fingleton  
*Précis:* Although the IL4 receptor is usually associated with immune cells, it has a significant role in controlling the metastatic capabilities of breast tumor cells, with immediate implications for targeting this receptor as a strategy to treat advanced breast cancer.
- 4341 miR-21 Induces Myofibroblast Differentiation and Promotes the Malignant Progression of Breast Phyllodes Tumors**  
Chang Gong, Yan Nie, Shaohua Qu, Jian-You Liao, Xiuying Cui, Herui Yao, Yunjie Zeng, Fengxi Su, Erwei Song, and Qiang Liu  
*Précis:* The perspective afforded by this study confirms the suspicion that prospects for effective immunotherapy are far more likely to emerge from targeting multiple tumor antigens than single tumor antigens.
- 4353 Snail Recruits Ring1B to Mediate Transcriptional Repression and Cell Migration in Pancreatic Cancer Cells**  
Jiangzhi Chen, Hong Xu, Xiuqun Zou, Jiamin Wang, Yi Zhu, Hao Chen, Baiyong Shen, Xiaying Deng, Aiwu Zhou, Y. Eugene Chin, Frank J. Rauscher, III, Chenghong Peng, and Zhaoyuan Hou  
*Précis:* This study unravels an epigenetic mechanism underlying transcriptional repression by a core regulator of EMT in pancreatic cancer, suggesting new candidate therapeutic targets in this disease.
- 4364 AEG-1 Regulates Retinoid X Receptor and Inhibits Retinoid Signaling**  
Jyoti Srivastava, Chadia L. Robertson, Devaraja Rajasekaran, Rachel Gredler, Ayesha Siddiq, Luni Emdad, Nitai D. Mukhopadhyay, Shobha Ghosh, Phillip B. Hylemon, Gregorio Gil, Khalid Shah, Deepak Bhare, Mark A. Subler, Jolene J. Windle, Paul B. Fisher, and Devanand Sarkar  
*Précis:* This article presents evidence of a functional biomarker in cancer cell responses to retinoic acids used for therapy, with implications for screening procedures before these agents are prescribed for patients.
- 4378 In Vivo Regulation of Human Glutathione Transferase GSTP by Chemopreventive Agents**  
Colin J. Henderson, Aileen W. McLaren, and C. Roland Wolf  
*Précis:* These findings suggest how dietary components modulate an enzyme that is critical for determining cancer susceptibility and the outcome of chemotherapy treatments.

# Table of Contents

**4388** **Germline Mutation of *Bap1* Accelerates Development of Asbestos-Induced Malignant Mesothelioma**



Jinfei Xu, Yuwaraj Kadariya, Mitchell Cheung, Jianming Pei, Jacqueline Talarchek, Eleonora Sementino, Yinfei Tan, Craig W. Menges, Kathy Q. Cai, Samuel Litwin, Hongzhuang Peng, Jayashree Karar, Frank J. Rauscher, and Joseph R. Testa

**Précis:** *Unbiased genetic findings demonstrate that BAP1 mutation carriers are predisposed to asbestos-induced mesothelioma, a hazard of certain domiciles and workplaces, where asbestos exposure would greatly synergize with inherited mutations of BAP1 in elevating risk.*

## PREVENTION AND EPIDEMIOLOGY

**4398** **Increased Dietary Vitamin D Suppresses MAPK Signaling, Colitis, and Colon Cancer**

Stacey Meeker, Audrey Seamons, Jisun Paik, Piper M. Treuting, Thea Brabb, William M. Grady, and Lillian Maggjo-Price

**Précis:** *In a mouse model of colitis and colon cancer, increasing dietary vitamin D prevented inflammatory responses involved in early stages of carcinogenesis, with potential clinical implications for chemoprevention by vitamin D.*

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**4409** **Inhibition of miR17 and miR20a by Oridonin Triggers Apoptosis and Reverses**



**Chemoresistance by Derepressing BIM-S**  
Hengyou Weng, Huilin Huang, Bowen Dong, Panpan Zhao, Hui Zhou, and Lianghu Qu

**Précis:** *These results suggest the combined use of chemotherapy drugs with a natural microRNA-targeting agent to reverse cancer chemoresistance.*

**4420** **ASC-J9 Suppresses Renal Cell Carcinoma Progression by Targeting an Androgen Receptor-Dependent HIF2 $\alpha$ /VEGF Signaling Pathway**

Dalin He, Lei Li, Guodong Zhu, Liang Liang, Zhenfeng Guan, Luke Chang, Yuan Chen, Shuyuan Yeh, and Chawnschang Chang

**Précis:** *These findings may explain why men have a higher incidence of kidney cancer than women, by revealing contributions of the androgen receptor that offers a new candidate target in this disease.*

**4431** **Afatinib Enhances the Efficacy of Conventional Chemotherapeutic Agents by Eradicating Cancer Stem-like Cells**

Xiao-kun Wang, Jie-hua He, Jing-hong Xu, Sheng Ye, Fang Wang, Hui Zhang, Zhen-cong Huang, Kenneth Kin Wah To, and Li-wu Fu

**Précis:** *These findings suggest use of an approved tyrosine kinase inhibitor to improve the efficacy of conventional chemotherapeutic drugs by improving eradication of cancer stem-like cells, with immediate clinical implications.*

**4446** **NSAID Use Reduces Breast Cancer Recurrence in Overweight and Obese Women: Role of Prostaglandin-Aromatase Interactions**

Laura W. Bowers, Ilane X.F. Maximo, Andrew J. Brenner, Muralidhar Beeram, Stephen D. Hursting, Ramona S. Price, Rajeshwar R. Tekmal, Christopher A. Jolly, and Linda A. deGraffenried

**Précis:** *This study deepens the potential connections between obesity-associated inflammation and breast cancer, with implications for a straightforward treatment and prevention strategy in estrogen-positive cancers, which are the most common clinically.*

**4458** **Selective and Potent Akt Inhibition Triggers Anti-Myeloma Activities and Enhances Fatal Endoplasmic Reticulum Stress Induced by Proteasome Inhibition**

Naoya Mimura, Teru Hideshima, Toshiyasu Shimomura, Rikio Suzuki, Hiroto Ohguchi, Ola Rizq, Shohei Kikuchi, Yasuhiro Yoshida, Francesca Cottini, Jana Jakubikova, Diana Cirstea, Gullu Gorgun, Jiro Minami, Yu-Tzu Tai, Paul G. Richardson, Teruhiro Utsugi, Atsushi Iwama, and Kenneth C. Anderson

**Précis:** *These results offer a preclinical proof of concept for the use of a novel Akt inhibitor in treating multiple myeloma, alone or in combination with proteasome inhibitors that are currently approved for this use.*

# Table of Contents

**4470 Targeting EphA3 Inhibits Cancer Growth by Disrupting the Tumor Stromal Microenvironment**



Mary E. Vail, Carmel Murone, April Tan, Linda Hii, Degu Abebe, Peter W. Janes, Fook-Thean Lee, Mark Baer, Varghese Palath, Christopher Bebbington, Geoffrey Yarranton, Carmen Llerena, Slavisa Garic, David Abramson, Glenn Cartwright, Andrew M. Scott, and Martin Lackmann

**Précis:** *Eph tyrosine kinases controlling cell attraction and repulsion forces involved in migration have been challenging to position for therapeutic invention, but this article suggests an approach to effectively target EphA3 in solid tumors as a novel type of generalized therapy for malignant tumors.*

## TUMOR AND STEM CELL BIOLOGY

**4482 Crosstalk between Glioma-Initiating Cells and Endothelial Cells Drives Tumor Progression**

Hye-Min Jeon, Sung-Hak Kim, Xun Jin, Jong Bae Park, Se Hoon Kim, Kaushal Joshi, Ichiro Nakano, and Hyunggee Kim

**Précis:** *Targeting NOTCH and PDGF signaling mechanisms identified in this study in the perivascular microenvironment may offer a more efficacious approach to treat aggressive brain cancers.*

**4493 YAP-Induced Resistance of Cancer Cells to Antitubulin Drugs Is Modulated by a Hippo-Independent Pathway**

Yulei Zhao, Prem Khanal, Paul Savage, Yi-Min She, Terry D. Cyr, and Xiaolong Yang

**Précis:** *Hippo signaling component YAP is a novel mediator of antitubulin drug-induced cancer cell death and may be a biomarker for predicting antitubulin drug sensitivity in cancers.*

**4504 Heparanase Cooperates with Ras to Drive Breast and Skin Tumorigenesis**

Ilanit Boyango, Uri Barash, Inna Naroditsky, Jin-Ping Li, Edward Hammond, Neta Ilan, and Israel Vlodavsky

**Précis:** *Overexpression of an enzyme that degrades cell surface heparan sulfate is associated with malignant progression, but this study shows that it is also important at early stages of tumor development, reinforcing its candidacy as a therapeutic target.*

**4515  $\beta$ -Catenin Activation in a Novel Liver Progenitor Cell Type Is Sufficient to Cause Hepatocellular Carcinoma and Hepatoblastoma**

Sharada Mokkalapati, Katharina Niopek, Le Huang, Kegan J. Cunniff, E. Cristy Ruteshouser, Mark deCaestecker, Milton J. Finegold, and Vicki Huff

**Précis:** *This study offers a new perspective on the etiology of liver cancer along with a valuable new tool to deepen understanding of its pathobiology and treatment.*

**4526 EWS-WT1 Oncoprotein Activates Neuronal Reprogramming Factor ASCL1 and Promotes Neural Differentiation**

Hong-Jun Kang, Jun Hong Park, WeiPing Chen, Soo Im Kang, Krzysztof Moroz, Marc Ladanyi, and Sean Bong Lee

**Précis:** *The findings of this study suggest that biologic or chemical agents that promote neural differentiation might offer a novel therapeutic approach to treat a rare but highly aggressive type of soft tissue sarcoma.*

**4536 Human *Brat* Ortholog *TRIM3* Is a Tumor Suppressor That Regulates Asymmetric Cell Division in Glioblastoma**

Gang Chen, Jun Kong, Carol Tucker-Burden, Monika Anand, Yuan Rong, Fahmia Rahman, Carlos S. Moreno, Erwin G. Van Meir, Constantinos G. Hadjipanayis, and Daniel J. Brat

**Précis:** *This study demonstrates that the regulation of tumor stem cell division as symmetric or asymmetric has a dramatic impact on growth properties.*

**4549 Hypoxia Promotes Nuclear Translocation and Transcriptional Function in the Oncogenic Tyrosine Kinase RON**



Hong-Yi Chang, Hsiao-Sheng Liu, Ming-Derg Lai, Yuh-Shyan Tsai, Tzong-Shin Tzai, Hong-Ling Cheng, and Nan-Haw Chow

**Précis:** *This article reports the discovery of a transcriptional function for a cell surface tyrosine kinase in the adaptation response of cancer cells to hypoxia, apparently acting to supercharge their ability to evolve more aggressive features of metastatic progression.*

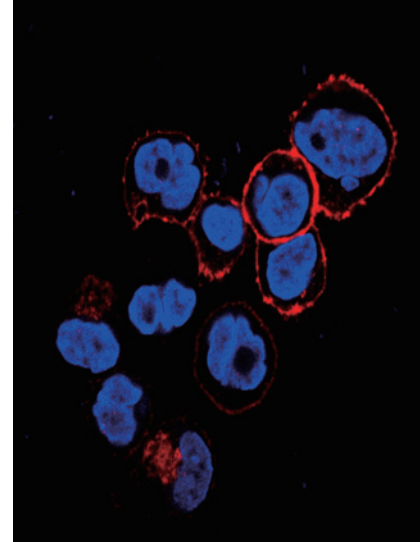
AC icon indicates Author Choice

For more information please visit [www.aacrjournals.org](http://www.aacrjournals.org)

# Table of Contents

## ABOUT THE COVER

Expression of the multidrug resistance protein ABCG2 confers chemoresistance to CSC where it serves as a potential biomarker and therapeutic target. Afatinib, a small molecule inhibitor of the tyrosine kinases EGFR, HER2, and HER4, can enhance the antitumor effect of the DNA damaging drug topotecan *in vitro* and *in vivo*. Immunofluorescence microscopic analysis showed that afatinib significantly decreased the cell surface expression of ABCG2 in a concentration-dependent manner. For details, see article by X.-K. Wang and colleagues on page 4431.





# Cancer Research

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

## 74 (16)

*Cancer Res* 2014;74:4209-4562.

**Updated version** Access the most recent version of this article at:  
<http://cancerres.aacrjournals.org/content/74/16>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/74/16>.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.