

# Contents

### Highlights of This Issue 1485

#### SPECIAL FEATURES

#### CCR Translations

- 1487 **Imaging Tumor Sensitivity to a Bioreductive Prodrug: Two for the Price of One!**  
J. Martin Brown  
*See article p. 1684*
- 1490 **Two Sides of the Same Coin: EGFR Exon 19 Deletions and Insertions in Lung Cancer**  
Katerina Politi and Thomas J. Lynch  
*See article p. 1790*
- 1493 **Phospho-specific Flow: Fixating on the Target**  
Mark Levis  
*See article p. 1716*

#### CCR Perspectives in Drug Approval

- 1496 **Eribulin Mesylate for the Treatment of Patients with Refractory Metastatic Breast Cancer: Use of a "Physician's Choice" Control Arm in a Randomized Approval Trial**  
Martha Donoghue, Steven J. Lemery, Weishi Yuan, Kun He, Rajeshwari Sridhara, Stacy Shord, Hong Zhao, Anshu Marathe, Lori Kotch, Josephine Jee, Ying Wang, Liang Zhou, William M. Adams, Vaishali Jarral, Anne Pilaro, Richard Lostritto, Joseph E. Gootenberg, Patricia Keegan, and Richard Pazdur

#### Molecular Pathways

- 1506 **Molecular Pathways: Microsatellite Instability in Colorectal Cancer: Prognostic, Predictive, and Therapeutic Implications**  
Frank A. Sinicrope and Daniel J. Sargent

#### CCR Focus

- 1514 **Molecular Diagnostics: Are We There Yet?**  
Susan E. Bates

- 1515 **Leveling the Playing Field: Bringing Development of Biomarkers and Molecular Diagnostics up to the Standards for Drug Development**  
George Poste, David P. Carbone, David R. Parkinson, Jaap Verweij, Stephen M. Hewitt, and J. Milburn Jessup

- 1524 **Impact of Preanalytic Factors on the Design and Application of Integral Biomarkers for Directing Patient Therapy**  
Stephen M. Hewitt, Sunil S. Badve, and Lawrence D. True

- 1531 **Bridging the Gap: Moving Predictive and Prognostic Assays from Research to Clinical Use**  
P. Michael Williams, Tracy G. Lively, J. Milburn Jessup, and Barbara A. Conley

- 1540 **Development and Use of Integral Assays in Clinical Trials**  
Richard L. Schilsky, James H. Doroshow, Michael LeBlanc, and Barbara A. Conley

- 1547 **Lessons Learned from the Investigational Device Exemption Review of Children's Oncology Group Trial AAML1031**  
Soheil Meshinchi, Stephen P. Hunger, Richard Aplenc, Peter C. Adamson, and J. Milburn Jessup

- 1555 **Biomarker Discovery, Development, and Implementation in France: A Report from the French National Cancer Institute and Cooperative Groups**  
Fabrice Andre, Frederique Nowak, Monica Arnedos, Ludovic Lacroix, Patrice Viens, and Fabien Calvo

#### Review

- 1561 **The Fundamental Role of the p53 Pathway in Tumor Metabolism and Its Implication in Tumor Therapy**  
Lan Shen, Xiang Sun, Zhenhong Fu, Guodong Yang, Jianying Li, and Libo Yao

**HUMAN CANCER BIOLOGY**

- 1568 **Expression of Interleukin-4 Receptor Alpha in Human Pleural Mesothelioma Is Associated with Poor Survival and Promotion of Tumor Inflammation**  
Bryan M. Burt, Andrew Bader, Daniel Winter, Scott J. Rodig, Raphael Bueno, and David J. Sugarbaker
- 1578 **Integrated Analysis Reveals Critical Genomic Regions in Prostate Tumor Microenvironment Associated with Clinicopathologic Phenotypes**  
Shingo Ashida, Mohammed S. Orloff, Gurkan Bebek, Li Zhang, Pan Zheng, Donna M. Peehl, and Charis Eng
- 1588 **Mechanisms of *CHD5* Inactivation in Neuroblastomas**  
Hiroshi Koyama, Tiangang Zhuang, Jennifer E. Light, Venkatadri Kolla, Mayumi Higashi, Patrick W. McGrady, Wendy B. London, and Garrett M. Brodeur
- 1598 **Characterization of Gene Amplification-Driven *SKP2* Overexpression in Myxofibrosarcoma: Potential Implications in Tumor Progression and Therapeutics**  
Chien-Feng Li, Ju-Ming Wang, Hong-Yo Kang, Chiung-Kuei Huang, Jun-Wen Wang, Fu-Min Fang, Yu-Hui Wang, Wen-Ren Wu, Shau-Hsuan Li, Shih-Chen Yu, Jen-Chieh Lee, Jui Lan, Yow-Ling Shiue, Li-Ching Wu, and Hsuan-Ying Huang
- 1611 **Constitutive AP-1 Activity and EBV Infection Induce PD-L1 in Hodgkin Lymphomas and Posttransplant Lymphoproliferative Disorders: Implications for Targeted Therapy**  
Michael R. Green, Scott Rodig, Przemyslaw Juszczynski, Jing Ouyang, Papiya Sinha, Evan O'Donnell, Donna Neuberger, and Margaret A. Shipp
- 1619 **Genome-Wide miRNA Expression Profiling Identifies *miR-9-3* and *miR-193a* as Targets for DNA Methylation in Non-Small Cell Lung Cancers**  
Gerwin Heller, Marlene Weinzierl, Christian Noll, Valerie Babinsky, Barbara Ziegler, Corinna Altenberger, Christoph Minichsdorfer, György Lang, Balazs Döme, Adelheid End-Pfützenreuter, Britt-Madeleine Arns, Yuliya Grin, Walter Klepetko, Christoph C. Zielinski, and Sabine Zöchbauer-Müller

**CANCER THERAPY: PRECLINICAL**

- 1630 **Interleukin-27 Inhibits the Growth of Pediatric Acute Myeloid Leukemia in NOD/SCID/*Il2rg*<sup>-/-</sup> Mice**  
Alessia Zorzoli, Emma Di Carlo, Claudia Cocco, Emanuela Ognio, Domenico Ribatti, Elisa Ferretti, Carlo Dufour, Franco Locatelli, Daniela Montagna, and Irma Airolidi
- 1641 **Combined MEK and VEGFR Inhibition in Orthotopic Human Lung Cancer Models Results in Enhanced Inhibition of Tumor Angiogenesis, Growth, and Metastasis**  
Osamu Takahashi, Ritsuko Komaki, Paul D. Smith, Juliane M. Jürgensmeier, Anderson Ryan, B. Nebiyou Bekele, Ignacio I. Wistuba, Jörg J. Jacoby, Maria V. Korshunova, Anna Biernacka, Baruch Erez, Keiko Hosho, Roy S. Herbst, and Michael S. O'Reilly
- 1655 **Failure of Iniparib to Inhibit Poly(ADP-Ribose) Polymerase *In Vitro***  
Anand G. Patel, Silvana B. De Lorenzo, Karen S. Flatten, Guy G. Poirier, and Scott H. Kaufmann
- 1663 **Met Kinase Inhibitor E7050 Reverses Three Different Mechanisms of Hepatocyte Growth Factor-Induced Tyrosine Kinase Inhibitor Resistance in *EGFR* Mutant Lung Cancer**  
Wei Wang, Qi Li, Shinji Takeuchi, Tadaaki Yamada, Hitomi Koizumi, Takahiro Nakamura, Kunio Matsumoto, Naofumi Mukaida, Yasuhiko Nishioka, Saburo Sone, Takayuki Nakagawa, Toshimitsu Uenaka, and Seiji Yano
- 1672 **Local Delivery of Interleukin-12 Using T Cells Targeting VEGF Receptor-2 Eradicates Multiple Vascularized Tumors in Mice**  
Dhanalakshmi Chinnasamy, Zhiya Yu, Sid P. Kerker, Ling Zhang, Richard A. Morgan, Nicholas P. Restifo, and Steven A. Rosenberg

**IMAGING, DIAGNOSIS, PROGNOSIS**

- 1684 **The 2-Nitroimidazole EF5 Is a Biomarker for Oxidoreductases That Activate the Bioreductive Prodrug CEN-209 under Hypoxia**  
Jingli Wang, Annika Foehrenbacher, Jiechuang Su, Rita Patel, Michael P. Hay, Kevin O. Hicks, and William R. Wilson  
*See commentary p. 1487*

1696 **Relationship between <sup>18</sup>F-Fluorodeoxyglucose Accumulation and KRAS/BRAF Mutations in Colorectal Cancer**  
Kenji Kawada, Yuji Nakamoto, Mayumi Kawada, Koya Hida, Takuya Matsumoto, Teppei Murakami, Suguru Hasegawa, Kaori Togashi, and Yoshiharu Sakai

1704 **Search for a Gene Expression Signature of Breast Cancer Local Recurrence in Young Women**  
Nicolas Servant, Marc A. Bollet, Hans Halfwerk, Kevin Bleakley, Bas Kreike, Laurent Jacob, Daoud Sie, Ron M. Kerkhoven, Philippe Hupé, Rim Hadhri, Alain Fourquet, Harry Bartelink, Emmanuel Barillot, Brigitte Sigal-Zafrani, and Marc J. van de Vijver

1743 **Phase I Dose-Escalation Study of Intravenous Afibercept in Combination with Docetaxel in Patients with Advanced Solid Tumors**  
Nicolas Isambert, Gilles Freyer, Sylvie Zanetta, Benoît You, Pierre Fumoleau, Claire Falandry, Laure Favier, Sylvie Assadourian, Karen Soussan-Lazard, Samira Ziti-Ljajic, and Veronique Trillet-Lenoir

1751 **Randomized Study of Autologous Cytokine-Induced Killer Cell Immunotherapy in Metastatic Renal Carcinoma**  
Liang Liu, Weihong Zhang, Xiuying Qi, Hui Li, Jinpu Yu, Sheng Wei, Xishan Hao, and Xiubao Ren

## CANCER THERAPY: CLINICAL

1716 **Single-Cell Pharmacodynamic Monitoring of S6 Ribosomal Protein Phosphorylation in AML Blasts during a Clinical Trial Combining the mTOR Inhibitor Sirolimus and Intensive Chemotherapy**  
Alexander E. Perl, Margaret T. Kasner, Doris Shank, Selina M. Luger, and Martin Carroll  
*See commentary p. 1493*

1726 **A Phase I Study of Veliparib in Combination with Metronomic Cyclophosphamide in Adults with Refractory Solid Tumors and Lymphomas**  
Shivaani Kummar, Jiuping Ji, Robert Morgan, Heinz-Josef Lenz, Shannon L. Puhalla, Chandra P. Belani, David R. Gandara, Deborah Allen, Brian Kiesel, Jan H. Beumer, Edward M. Newman, Larry Rubinstein, Alice Chen, Yiping Zhang, Lihua Wang, Robert J. Kinders, Ralph E. Parchment, Joseph E. Tomaszewski, and James H. Doroshow

1735 **A Phase I Trial of Erlotinib and Concurrent Chemoradiotherapy for Stage III and IV (M0) Squamous Cell Carcinoma of the Head and Neck**  
Jill Gilbert, Michelle A. Rudek, Michaela J. Higgins, Ming Zhao, Sara Bienvenu, Nancy Tsottles, Richard Wahl, Arlene Forastiere, and Maura Gillison

## PREDICTIVE BIOMARKERS AND PERSONALIZED MEDICINE

1760 **High EGFR Gene Copy Number and Skin Rash as Predictive Markers for EGFR Tyrosine Kinase Inhibitors in Patients with Advanced Squamous Cell Lung Carcinoma**  
Youngjoo Lee, Hyo Sup Shim, Moo Suk Park, Joo-Hang Kim, Sang-Jun Ha, Se Hoon Kim, and Byoung Chul Cho

1769 **KRAS and BRAF Mutations Predict Primary Resistance to Imatinib in Gastrointestinal Stromal Tumors**  
Claudia Miranda, Martina Nucifora, Francesca Molinari, Elena Conca, Maria Chiara Anania, Andrea Bordoni, Piercarlo Saletti, Luca Mazzucchelli, Silvana Pilotti, Marco A. Pierotti, Elena Tamborini, Angela Greco, and Milo Frattini

1777 **PIK3CA/PTEN Mutations and Akt Activation As Markers of Sensitivity to Allosteric mTOR Inhibitors**  
Funda Meric-Bernstam, Argun Akcakanat, Huiqin Chen, Kim-Anh Do, Takafumi Sangai, Farrell Adkins, Ana Maria Gonzalez-Angulo, Asif Rashid, Katherine Crosby, Mei Dong, Alexandria T. Phan, Robert A. Wolff, Sanjay Gupta, Gordon B. Mills, and James Yao

1790 **EGFR Exon 19 Insertions: A New Family of Sensitizing EGFR Mutations in Lung Adenocarcinoma**  
Mai He, Marzia Capelletti, Khedoudja Nafa, Cai-Hong Yun, Maria E. Arcila, Vincent A. Miller, Michelle S. Ginsberg, Binsheng Zhao, Mark G. Kris, Michael J. Eck, Pasi A. Jänne, Marc Ladanyi, and Geoffrey R. Oxnard  
*See commentary p. 1490*

1798

**Prognostic and Predictive Significance of Plasma HGF and IL-8 in a Phase III Trial of Chemoradiation with or without Tirapazamine in Locoregionally Advanced Head and Neck Cancer**

Quynh-Thu Le, Richard Fisher, Kelly S. Oliner, Richard J. Young, Hongbin Cao, Christina Kong, Edward Graves, Rodney J. Hicks, Grant A. McArthur, Lester Peters, Brian O'Sullivan, Amato Giaccia, and Danny Rischin

1808

**IGFBP Ratio Confers Resistance to IGF Targeting and Correlates with Increased Invasion and Poor Outcome in Breast Tumors**

Marc A. Becker, Xiaonan Hou, Sean C. Harrington, S. John Weroha, Sergio E. Gonzalez, Kristina A. Jacob, Joan M. Carboni, Marco M. Gottardis, and Paul Haluska

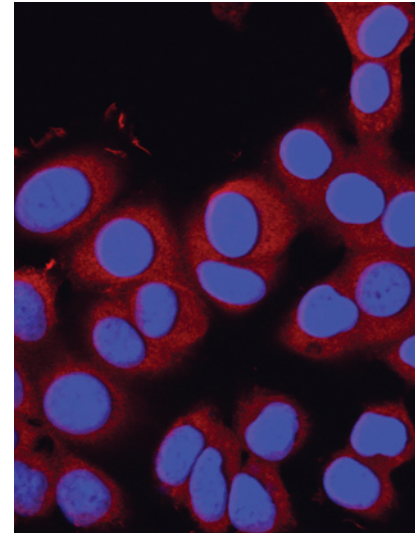
**RETRACTION**

1818

**Retraction: Characterizing the Clinical Relevance of an Embryonic Stem Cell Phenotype in Lung Adenocarcinoma**

**ABOUT THE COVER**

IGFBP-5 may be an important regulator of IGF signaling in breast cancer cells. Distribution of IGFBP-5 in MCF-7 cells is shown by immunofluorescence analysis using confocal microscopy. IGFBP-5 is shown in red and nuclei are shown in blue (DAPI). For details, see the article by Becker and colleagues on page 1808 of this issue.



# Clinical Cancer Research

**18 (6)**

*Clin Cancer Res* 2012;18:1485-1818.

**Updated version** Access the most recent version of this article at:  
<http://clincancerres.aacrjournals.org/content/18/6>

**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://clincancerres.aacrjournals.org/content/18/6>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.