

Highlights of This Issue 2069

SPECIAL FEATURES

CCR Translations

- 2071 **Targeting the Hedgehog Pathway in Cancer: Can the Spines Be Smoothened?**
Laurie Ailles and Lillian L. Siu
See articles p. 2502 and 2512

Molecular Pathways

- 2074 **CXCL12 (SDF1 α)-CXCR4/CXCR7 Pathway Inhibition: An Emerging Sensitizer for Anticancer Therapies?**
Dan G. Duda, Sergey V. Kozin, Nathaniel D. Kirkpatrick, Lei Xu, Dai Fukumura, and Rakesh K. Jain
- 2081 **Targeting Anaplastic Lymphoma Kinase in Lung Cancer**
Alice T. Shaw and Benjamin Solomon

Review

- 2087 **Therapeutic Implications of the Emerging Molecular Biology of Uveal Melanoma**
Mrinali Patel, Elizabeth Smyth, Paul B. Chapman, Jedd D. Wolchok, Gary K. Schwartz, David H. Abramson, and Richard D. Carvajal

HUMAN CANCER BIOLOGY

- 2101 **Identification of Loss of p16 Expression and Upregulation of MDR-1 as Genetic Events Resulting from Two Novel Chromosomal Translocations Found in a Plasmablastic Lymphoma of the Uterus**
Eri Matsuki, Yoshitaka Miyakawa, Shuichi Asakawa, Yuiko Tsukada, Taketo Yamada, Kenji Yokoyama, Jun Kudoh, Yasuo Ikeda, and Shinichiro Okamoto

- 2110 **Tumor-Infiltrating Macrophages Are Associated with Metastasis Suppression in High-Grade Osteosarcoma: A Rationale for Treatment with Macrophage Activating Agents**
Emilie P. Buddingh, Marieke L. Kuijjer, Ronald A.J. Duim, Horst Bürger, Konstantin Agelopoulos, Ola Myklebost, Massimo Serra, Fredrik Mertens, Pancras C.W. Hogendoorn, Arjan C. Lankester, and Anne-Marie Cleton-Jansen

- 2120 **Aberrant Methylation of the X-Linked Ribosomal S6 Kinase *RPS6KA6* (*RSK4*) in Endometrial Cancers**
Summer B. Dewdney, BJ Rimel, Premal H. Thaker, Dominic M. Thompson Jr., Amy Schmidt, Phyllis Huettner, David G. Mutch, Feng Gao, and Paul J. Goodfellow

- 2130 **Yes-Associated Protein 1 Exhibits Oncogenic Property in Gastric Cancer and Its Nuclear Accumulation Associates with Poor Prognosis**
Wei Kang, Joanna H.M. Tong, Anthony W.H. Chan, Tin-Lap Lee, Raymond W.M. Lung, Patrick P.S. Leung, Ken K.Y. So, Kaichun Wu, Daiming Fan, Jun Yu, Joseph J.Y. Sung, and Ka-Fai To

- 2140 **Role of ERK-BIM and STAT3-Survivin Signaling Pathways in ALK Inhibitor-Induced Apoptosis in EML4-ALK-Positive Lung Cancer**
Ken Takezawa, Isamu Okamoto, Kazuto Nishio, Pasi A. Jänne, and Kazuhiko Nakagawa

- 2149 ***EGFR* L858R Mutation and Polymorphisms of Genes Related to Estrogen Biosynthesis and Metabolism in Never-Smoking Female Lung Adenocarcinoma Patients**
Shi-Yi Yang, Tsung-Ying Yang, Kun-Chieh Chen, Yao-Jen Li, Kuo-Hsuan Hsu, Chi-Rne Tsai, Chih-Yi Chen, Chung-Ping Hsu, Jiun-Yi Hsia, Cheng-Yen Chuang, Ying-Huang Tsai, Kuan-Yu Chen, Ming-Shyan Huang, Wu-Chou Su, Yuh-Min Chen, Chao A. Hsiung, Chen-Yang Shen, Gee-Chen Chang, Pan-Chyr Yang, and Chien-Jen Chen

- 2159 **Human Prostate Cancer Harbors the Stem Cell Properties of Bone Marrow Mesenchymal Stem Cells**
Haiyen E. Zhau, Hui He, Christopher Y. Wang, Majd Zayzafoon, Colm Morrissey, Robert L. Vessella, Fray F. Marshall, Leland W. K. Chung, and Ruoxiang Wang

2170 **Coordinated Cancer Germline Antigen Promoter and Global DNA Hypomethylation in Ovarian Cancer: Association with the *BORIS/CTCF* Expression Ratio and Advanced Stage**
Anna Woloszynska-Read, Wa Zhang, Jihneeh Yu, Petra A. Link, Paulette Mhaweche-Fauceglia, Golda Collamat, Stacey N. Akers, Kelly R. Ostler, Lucy A. Godley, Kunle Odunsi, and Adam R. Karpf

2181 **The Biphasic Role of NF- κ B in Progression and Chemoresistance of Ovarian Cancer**
Gong Yang, Xue Xiao, Daniel G. Rosen, Xi Cheng, Xiaohua Wu, Bin Chang, Guangzhi Liu, Fengxia Xue, Imelda Mercado-Uribe, Paul Chiao, Xiang Du, and Jinsong Liu

CANCER THERAPY: PRECLINICAL

2195 **Humanized Bone Marrow Mouse Model as a Preclinical Tool to Assess Therapy-Mediated Hematotoxicity**
Shanbao Cai, Haiyan Wang, Barbara Bailey, Aaron Ernstberger, Beth E. Juliar, Anthony L. Sinn, Rebecca J. Chan, David R. Jones, Lindsey D. Mayo, Arthur R. Baluyut, W. Scott Goebel, and Karen E. Pollok

2207 **Imaging and Therapy with Rituximab Anti-CD20 Immunotherapy in an Animal Model of Central Nervous System Lymphoma**
Leslie L. Muldoon, Seth J. Lewin, Edit Dósa, Dale F. Kraemer, Michael A. Pagel, Nancy D. Doolittle, and Edward A. Neuwelt

2216 **Oncogenic B-RAF Signaling in Melanoma Impairs the Therapeutic Advantage of Autophagy Inhibition**
Jane L. Armstrong, Marco Corazzari, Shaun Martin, Vittoria Pagliarini, Laura Falasca, David S. Hill, Nicola Ellis, Salim Al Sabah, Christopher P.F. Redfern, Gian Maria Fimia, Mauro Piacentini, and Penny E. Lovat

2227 **DNA Damage Persistence as Determinant of Tumor Sensitivity to the Combination of Topo I Inhibitors and Telomere-Targeting Agents**
Annamaria Biroccio, Manuela Porru, Angela Rizzo, Erica Salvati, Carmen D'Angelo, Augusto Orlandi, Daniela Passeri, Marco Franceschin, Malcolm F.G. Stevens, Eric Gilson, Giovanni Beretta, Gabriella Zupi, Claudio Pisano, Franco Zunino, and Carlo Leonetti

2237 **Heat Shock Protein 90-Sheltered Overexpression of Insulin-Like Growth Factor 1 Receptor Contributes to Malignancy of Thymic Epithelial Tumors**
Marco Breinig, Philipp Mayer, Andreas Harjung, Benjamin Goeppert, Mona Malz, Roland Penzel, Olaf Neumann, Arndt Hartmann, Hendrik Dienemann, Giuseppe Giaccone, Peter Schirmacher, Michael André Kern, Gabriela Chiosis, and Ralf Joachim Rieker

2250 **Therapeutic Targeting of PELP1 Prevents Ovarian Cancer Growth and Metastasis**
Dimple Chakravarty, Sudipa Saha Roy, Challa Ram Babu, Rajasekhar Dandamudi, Tyler J. Curiel, Pablo Vivas-Mejia, Gabriel Lopez-Berestein, Anil K. Sood, and Ratna K. Vadlamudi

2260 **Transient PI3K Inhibition Induces Apoptosis and Overcomes HGF-Mediated Resistance to EGFR-TKIs in *EGFR* Mutant Lung Cancer**
Ivan S. Donev, Wei Wang, Tadaaki Yamada, Qi Li, Shinji Takeuchi, Kunio Matsumoto, Takao Yamori, Yasuhiko Nishioka, Saburo Sone, and Seiji Yano

2270 **Local Activation of CD8 T Cells and Systemic Tumor Eradication without Toxicity via Slow Release and Local Delivery of Agonistic CD40 Antibody**
Marieke F. Fransen, Marjolein Sluijter, Hans Morreau, Ramon Arens, and Cornelis J.M. Melief

2281 **Targeted Therapy of VEGFR2 and EGFR Significantly Inhibits Growth of Anaplastic Thyroid Cancer in an Orthotopic Murine Model**
Maria K. Gule, Yunyun Chen, Daisuke Sano, Mitchell J. Frederick, Ge Zhou, Mei Zhao, Zvonimir L. Milas, Chad E. Galer, Ying C. Henderson, Samar A. Jasser, David L. Schwartz, James A. Bankson, Jeffrey N. Myers, and Stephen Y. Lai

2292 **Bortezomib Enhances the Efficacy of Fulvestrant by Amplifying the Aggregation of the Estrogen Receptor, which Leads to a Proapoptotic Unfolded Protein Response**
Yuki Ishii, Luena Papa, Urvashi Bahadur, Zhenyu Yue, Julio Aguirre-ghiso, Toshi Shioda, Samuel Waxman, and Doris Germain

2301	<p>A Novel HSP90 Inhibitor Delays Castrate-Resistant Prostate Cancer without Altering Serum PSA Levels and Inhibits Osteoclastogenesis Francois Lamoureux, Christian Thomas, Min-Jean Yin, Hidetoshi Kuruma, Ladan Fazli, Martin E. Gleave, and Amina Zoubeidi</p>	2385	<p>A High-Throughput Proteomic Approach Provides Distinct Signatures for Thyroid Cancer Behavior Sonia Cheng, Stefano Serra, Moises Mercado, Shereen Ezzat, and Sylvia L. Asa</p>
2314	<p>High IGF-IR Activity in Triple-Negative Breast Cancer Cell Lines and Tumorgrafts Correlates with Sensitivity to Anti-IGF-IR Therapy Beate C. Litzzenburger, Chad J. Creighton, Anna Tsimelzon, Bonita T. Chan, Susan G. Hilsenbeck, Tao Wang, Joan M. Carboni, Marco M. Gottardis, Fei Huang, Jenny C. Chang, Michael T. Lewis, Mothaffar F. Rimawi, and Adrian V. Lee</p>	2395	<p>Pentraxin-3 Is a Novel Biomarker of Lung Carcinoma Eleftherios P. Diamandis, Lee Goodglick, Chris Planque, and Mark D. Thornquist</p>
2328	<p>Inhibition of Prostate Cancer Osteoblastic Progression with VEGF₁₂₁/rGel, a Single Agent Targeting Osteoblasts, Osteoclasts, and Tumor Neovasculature Khalid A. Mohamedali, Zhi Gang Li, Michael W. Starbuck, Xinhai Wan, Jun Yang, Sehoon Kim, Wendy Zhang, Michael G. Rosenblum, and Nora M. Navone</p>	2400	<p>PET Tumor Metabolism in Locally Advanced Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy: Value of Static versus Kinetic Measures of Fluorodeoxyglucose Uptake Lisa K. Dunnwald, Robert K. Doot, Jennifer M. Specht, Julie R. Gralow, Georgiana K. Ellis, Robert B. Livingston, Hannah M. Linden, Vijayakrishna K. Gadi, Brenda F. Kurland, Erin K. Schubert, Mark Muzi, and David A. Mankoff</p>
2339	<p>Vorinostat Increases Expression of Functional Norepinephrine Transporter in Neuroblastoma <i>In Vitro</i> and <i>In Vivo</i> Model Systems Swati S. More, Melissa Itsara, Xiaodong Yang, Ethan G. Geier, Michelle K. Tadano, Youngho Seo, Henry F. VanBrocklin, William A. Weiss, Sabine Mueller, Daphne A. Haas-Kogan, Steven G. DuBois, Katherine K. Matthay, and Kathleen M. Giacomini</p>	2410	<p>Multiple Genetic Loci Modulate Lung Adenocarcinoma Clinical Staging Elisa Frullanti, Antonella Galvan, Felicia S. Falvella, Giacomo Manenti, Francesca Colombo, Alberto Vannelli, Matteo Incarbone, Marco Alloisio, Mario Nosotti, Luigi Santambrogio, Anna Gonzalez-Neira, Ugo Pastorino, and Tommaso A. Dragani</p>
2350	<p>Acquisition of Chemoresistance and EMT Phenotype Is Linked with Activation of the Endothelin A Receptor Pathway in Ovarian Carcinoma Cells Laura Rosanò, Roberta Cianfrocca, Francesca Spinella, Valeriana Di Castro, Maria Rita Nicotra, Alessandro Lucidi, Gabriella Ferrandina, Pier Giorgio Natali, and Anna Bagnato</p>	2417	<p>Plasma Markers for Identifying Patients with Metastatic Melanoma Harriet M. Kluger, Kathleen Hoyt, Antonella Bacchiocchi, Tina Mayer, Jonathan Kirsch, Yuval Kluger, Mario Sznol, Stephan Ariyan, Annette Molinaro, and Ruth Halaban</p>
2361	<p>Smac Modulates Chemosensitivity in Head and Neck Cancer Cells through the Mitochondrial Apoptotic Pathway Quanhong Sun, Xingnan Zheng, Lin Zhang, and Jian Yu</p>	2426	<p>Stromal LRP1 in Lung Adenocarcinoma Predicts Clinical Outcome He Meng, Guoan Chen, Xiaojie Zhang, Zhuwen Wang, Dafydd G. Thomas, Thomas J. Giordano, David G. Beer, and Michael M. Wang</p>
2373	<p>Dual Targeting of Phosphoinositide 3-Kinase and Mammalian Target of Rapamycin Using NVP-BEZ235 as a Novel Therapeutic Approach in Human Ovarian Carcinoma Chintda Santiskulvong, Gottfried E. Konecny, Mirela Fekete, Kuang-Yui Michael Chen, Amer Karam, David Mulholland, Carol Eng, Hong Wu, Min Song, and Oliver Dorigo</p>	2434	<p>Abnormalities of the <i>TTF-1</i> Lineage-Specific Oncogene in NSCLC: Implications in Lung Cancer Pathogenesis and Prognosis Ximing Tang, Humam Kadara, Carmen Behrens, Diane D. Liu, Yun Xiao, David Rice, Adi F. Gazdar, Junya Fujimoto, Cesar Moran, Marileila Varela-Garcia, J. Jack Lee, Waun Ki Hong, and Ignacio I. Wistuba</p>

- 2444 **Clinical Significance of Osteoprotegerin Expression in Human Colorectal Cancer**
Shunsuke Tsukamoto, Toshiaki Ishikawa, Satoru Iida, Megumi Ishiguro, Kaoru Mogushi, Hiroshi Mizushima, Hiroyuki Uetake, Hiroshi Tanaka, and Kenichi Sugihara
- 2451 **Polymorphisms in the Endothelin-1 and Endothelin A Receptor Genes and Survival in Patients with Locoregionally Advanced Nasopharyngeal Carcinoma**
Yue-Feng Wen, Bin Qi, Huai Liu, Hao-Yuan Mo, Qiu-Yan Chen, Juan Li, Pei-Yu Huang, Yan-Fang Ye, Ying Zhang, Man-Quan Deng, Xiang Guo, Ming-Huang Hong, Ka-Jia Cao, and Hai-Qiang Mai
- 2459 **Combined Promoter Methylation Analysis of CADMI and MAL: An Objective Triage Tool for High-Risk Human Papillomavirus DNA-Positive Women**
Albertus T. Hesselink, Daniëlle A.M. Heideman, Renske D.M. Steenbergen, Veerle M.H. Coupé, Renee M. Overmeer, Dorien Rijkaart, Johannes Berkhof, Chris J.L.M. Meijer, and Peter J.F. Snijders
- 2466 **Can a Metastatic Gene Expression Profile Outperform Tumor Size as a Predictor of Occult Lymph Node Metastasis in Oral Cancer Patients?**
Eduardo Méndez, Pawadee Lohavanichbutr, Wenhong Fan, John R. Houck, Tessa C. Rue, David R. Doody, Neal D. Futran, Melissa P. Upton, Bevan Yueh, Lue Ping Zhao, Stephen M. Schwartz, and Chu Chen
- 2493 **Phase I Trial of Weekly and Twice-Weekly Bortezomib with Rituximab, Cyclophosphamide, and Prednisone in Relapsed or Refractory Non-Hodgkin Lymphoma**
John Gerecitano, Carol Portlock, Paul Hamlin, Craig H. Moskowitz, Ariela Noy, David Straus, Philip Schulman, Otilia Dumitrescu, Debra Sarasohn, Jennifer Pappanicholaou, Alexia Iasonos, Zhigang Zhang, Qianxing Mo, Endri Horanlli, Celeste N. Rojas, Andrew D. Zelenetz, and Owen A. O'Connor
- 2502 **Phase I Trial of Hedgehog Pathway Inhibitor Vismodegib (GDC-0449) in Patients with Refractory, Locally Advanced or Metastatic Solid Tumors**
Patricia M. LoRusso, Charles M. Rudin, Josina C. Reddy, Raoul Tibes, Glen J. Weiss, Mitesh J. Borad, Christine L. Hann, Julie R. Brahmer, Ilsung Chang, Walter C. Darbonne, Richard A. Graham, Kenn L. Zerivitz, Jennifer A. Low, and Daniel D. Von Hoff
See commentary p. 2071
- 2512 **Pharmacokinetics of Hedgehog Pathway Inhibitor Vismodegib (GDC-0449) in Patients with Locally Advanced or Metastatic Solid Tumors: the Role of Alpha-1-Acid Glycoprotein Binding**
Richard A. Graham, Bert L. Lum, Sravanthi Cheeti, Jin Yan Jin, Karin Jorga, Daniel D. Von Hoff, Charles M. Rudin, Josina C. Reddy, Jennifer A. Low, and Patricia M. LoRusso
See commentary p. 2071
- 2521 **Phase I/II Trial of Cetuximab and Erlotinib in Patients with Lung Adenocarcinoma and Acquired Resistance to Erlotinib**
Yelena Y. Janjigian, Christopher G. Azzoli, Lee M. Krug, Leanne K. Pereira, Naiyer A. Rizvi, M. Catherine Pietanza, Mark G. Kris, Michelle S. Ginsberg, William Pao, Vincent A. Miller, and Gregory J. Riely
- 2528 **Phase I Dose-Escalation Study and Biomarker Analysis of E7080 in Patients with Advanced Solid Tumors**
Kazuhiko Yamada, Noboru Yamamoto, Yasuhide Yamada, Hiroshi Nokihara, Yutaka Fujiwara, Taizo Hirata, Fumiaki Koizumi, Kazuto Nishio, Noriyuki Koyama, and Tomohide Tamura

CANCER THERAPY: CLINICAL

- 2474 **Heat-Shock Induction of Tumor-Derived Danger Signals Mediate Rapid Monocyte Differentiation into Clinically Effective Dendritic Cells**
Raquel Aguilera, Carlos Saffie, Andrés Tittarelli, Fermín E. González, Marcos Ramírez, Diego Reyes, Cristián Pereda, Daniel Hevia, Tamara García, Lorena Salazar, Arturo Ferreira, Marcela Hermoso, Ariadna Mendoza-Naranjo, Carlos Ferrada, Paola Garrido, Mercedes N. López, and Flavio Salazar-Onfray
- 2484 **A Phase I Clinical Trial of Safingol in Combination with Cisplatin in Advanced Solid Tumors**
Mark A. Dickson, Richard D. Carvajal, Alfred H. Merrill, Jr., Mithat Gonen, Lauren M. Cane, and Gary K. Schwartz

2538 **IL6-STAT3-HIF Signaling and Therapeutic Response to the Angiogenesis Inhibitor Sunitinib in Ovarian Clear Cell Cancer**
Michael S. Anglesio, Joshy George, Hagen Kulbe, Michael Friedlander, Danny Rischin, Charlotte Lemech, Jeremy Power, Jermaine Coward, Prue A. Cowin, Colin M. House, Probir Chakravarty, Kylie L. Gorringer, Ian G. Campbell, Australian Ovarian Cancer Study Group, Aikou Okamoto, Michael J. Birrer, David G. Huntsman, Anna de Fazio, Steve E. Kalloger, Frances Balkwill, C. Blake Gilks, and David D. Bowtell

2570 **Overexpression of HMGA2 Promotes Metastasis and Impacts Survival of Colorectal Cancers**
Xiaochen Wang, Xiyong Liu, Angela Ying-Jian Li, Lirong Chen, Lily Lai, Her Helen Lin, Shuya Hu, Lifang Yao, Jiaping Peng, Sofia Loera, Lijun Xue, Bingsen Zhou, Lun Zhou, Shu Zheng, Peiguo Chu, Suzhan Zhang, David Kong Ann, and Yun Yen

2581 **Thymidylate Synthase and Excision Repair Cross-Complementing Group 1 as Predictors of Responsiveness in Mesothelioma Patients Treated with Pemetrexed/Carboplatin**
Paolo Andrea Zucali, Elisa Giovannetti, Annarita Destro, Manlio Mencoboni, Giovanni Luca Ceresoli, Letizia Gianoncelli, Elena Lorenzi, Fabio De Vincenzo, Matteo Simonelli, Matteo Perrino, Andrea Bruzzzone, Erik Thunnissen, Gianni Tunesi, Laura Giordano, Massimo Roncalli, Godefridus J Peters, and Armando Santoro

2591 **Distinct p53 Gene Signatures Are Needed to Predict Prognosis and Response to Chemotherapy in ER-Positive and ER-Negative Breast Cancers**
Charles Coutant, Roman Rouzier, Yuan Qi, Jacqueline Lehmann-Che, Giampaolo Bianchini, Takayuki Iwamoto, Gabriel N. Hortobagyi, W. Fraser Symmans, Serge Uzan, Fabrice Andre, Hugues de Thé, and Lajos Pusztai

PREDICTIVE BIOMARKERS AND PERSONALIZED MEDICINE

2549 **Comparison of Genomics and Functional Imaging from Canine Sarcomas Treated with Thermoradiotherapy Predicts Therapeutic Response and Identifies Combination Therapeutics**
Jen-Tsan Chi, Donald E. Thrall, Chen Jiang, Stacey Snyder, Diane Fels, Chelsea Landon, Linda McCall, Lan Lan, Marlene Hauck, James R. MacFall, Benjamin L. Viglianti, and Mark W. Dewhirst

2561 **Excision Repair Cross-Complementing Group 1 May Predict the Efficacy of Chemoradiation Therapy for Muscle-Invasive Bladder Cancer**
Atsunari Kawashima, Masashi Nakayama, Yoichi Kakuta, Toyofumi Abe, Koji Hatano, Masatoshi Mukai, Akira Nagahara, Yasutomo Nakai, Daizo Oka, Hitoshi Takayama, Toshiaki Yoshioka, Yoshihiko Hoshida, Hiroaki Itatani, Kazuo Nishimura, and Norio Nonomura

CORRECTION

2602 **Correction: Tumor Survivin Is Downregulated by the Antisense Oligonucleotide LY2181308: A Proof-of-Concept, First-in-Human Dose Study**

ABOUT THE COVER

In this issue, Meng and coworkers show that the multi-functional protein LDL receptor-related protein-1 (LRP1) predicts favorable outcomes in patients with lung adenocarcinoma. LRP1 is expressed predominantly in stromal cells of both lung squamous cell carcinomas (shown in the cover image) and adenocarcinomas. The investigators show that transcellular actions of LRP1 inhibit cancer cell growth, suggesting that stromal cells expressing LRP1 improve clinical outcomes. For further details, please see Meng and colleagues on page 2426 in this issue.

