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# Cancer Research

December 1, 2013 • Volume 73 • Number 23

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## REVIEWS

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Valbona Luga and Jeffrey L. Wrana
- 6848 | **The Role of Polo-like Kinase 1 in Carcinogenesis: Cause or Consequence?**  
Brian D. Cholewa, Xiaoqi Liu, and Nihal Ahmad

## PRIORITY REPORT

- 6856 | **D538G Mutation in Estrogen Receptor- $\alpha$ : A Novel Mechanism for Acquired Endocrine Resistance in Breast Cancer**  
Keren Merenbakh-Lamin, Noa Ben-Baruch, Adva Yehekel, Addie Dvir, Lior Soussan-Gutman, Rinath Jeselsohn, Roman Yelensky, Myles Brown, Vincent A. Miller, David Sarid, Shulamith Rizel, Baruch Klein, Tami Rubinek, and Ido Wolf
- Précis:* The identification of a novel mechanism of acquired endocrine resistance in metastatic breast cancer suggests a novel druggable target in this setting.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6865 | **Free Somatostatin Receptor Fraction Predicts the Antiproliferative Effect of Octreotide in a Neuroendocrine Tumor Model: Implications for Dose Optimization**  
Pedram Heidari, Eric Wehrenberg-Klee, Peiman Habibollahi, Daniel Yokell, Matthew Kulke, and Umar Mahmood
- Précis:* A novel noninvasive imaging method may be clinically useful to optimize the individualized dose of a drug used to treat neuroendocrine tumors, providing a basis for personalized, risk-tailored therapy.

- 6874 | **Senescent Fibroblasts in Melanoma Initiation and Progression: An Integrated Theoretical, Experimental, and Clinical Approach**  
Eunjung Kim, Vito Rebecca, Inna V. Fedorenko, Jane L. Messina, Rahel Mathew, Silvy S. Maria-Engler, David Basanta, Keiran S.M. Smalley, and Alexander R.A. Anderson

*Précis:* These findings developed by in silico modeling reinforce an alternative perspective on cancer, in which senescent fibroblasts create the core conditions required to license the ability of cancer cell mutations to promote malignancy, reinforcing a greater therapeutic focus on the tumor microenvironment as a cause of cancer.

## MICROENVIRONMENT AND IMMUNOLOGY

- 6886 | **A Novel Model of Dormancy for Bone Metastatic Breast Cancer Cells**  
Rebecca Marlow, Gabriella Honeth, Sara Lombardi, Massimiliano Cariati, Sonya Hessey, Aikaterini Pipili, Veronica Mariotti, Bharath Buchupalli, Katie Foster, Dominique Bonnet, Agamemnon Grigoriadis, Pranela Rameshwar, Anand Purushotham, Andrew Tutt, and Gabriela Dontu

*Précis:* This study presents novel experimental systems for investigating cancer cell dormancy, a phenomenon of high clinical relevance that is largely under-investigated due to lack of appropriate models.

- 6900 | **Therapeutic PD-1 Pathway Blockade Augments with Other Modalities of Immunotherapy T-Cell Function to Prevent Immune Decline in Ovarian Cancer**  
Jaikumar Duraiswamy, Gordon J. Freeman, and George Coukos

*Précis:* Immune escape, a core hallmark of advanced cancer, can be reversed by strategies that block a central pathway of T-cell exhaustion activated in the microenvironment of many solid tumors.

6913 **Low PIP4K2B Expression in Human Breast Tumors Correlates with Reduced Patient Survival: A Role for PIP4K2B in the Regulation of E-Cadherin Expression**  
Willem-Jan Keune, Andrew H. Sims, David R. Jones, Yvette Bultsma, James T. Lynch, Karin Jirstrom, Goran Landberg, and Nullin Divecha

*Précis:* An enzyme that regulates second messengers in lipid signaling impacts the survival of breast cancer patients by modifying a pivotal tumor suppressor function.

6926 **Skin Tumorigenesis Stimulated by Raf Inhibitors Relies Upon Raf Functions That Are Dependent and Independent of ERK**  
Eszter Doma, Christian Rupp, Andrea Varga, Florian Kern, Bettina Riegler, and Manuela Baccarini

*Précis:* Provocative preclinical results suggest that B-Raf inhibitors being used currently in the clinic to treat melanoma may not only trigger development of cutaneous skin tumors, a known side effect, but also gastric tumors, which are far less manageable.

6938 **TRAF4 Is a Critical Molecule for Akt Activation in Lung Cancer**  
Wei Li, Cong Peng, Mee-Hyun Lee, DoYoung Lim, Feng Zhu, Yang Fu, Ge Yang, Yuqiao Sheng, Lanbo Xiao, Xin Dong, WeiYa Ma, Ann M. Bode, Ya Cao, and Zigang Dong

*Précis:* These findings reveal a pivotal role for a ubiquitylation enzyme in Akt control and lung cancer pathophysiology, suggesting its role as a candidate molecular target for lung cancer prevention and therapy.

6951 **SHON Is a Novel Estrogen-Regulated Oncogene in Mammary Carcinoma That Predicts Patient Response to Endocrine Therapy**  
Yewon Jung, Tarek M.A. Abdel-Fatah, Stephen Y.T. Chan, Christopher C. Nolan, Andrew R. Green, Ian O. Ellis, Lili Li, Baiqu Huang, Jun Lu, Bing Xu, Longxin Chen, Runlin Z. Ma, Min Zhang, Jingru Wang, ZhengSheng Wu, Tao Zhu, Jo K. Perry, Peter E. Lobie, and Dong-Xu Liu

*Précis:* These findings identify a human oncogene that may serve as a simple biomarker to predict the therapeutic efficacy of antiestrogen therapy in ER<sup>+</sup> breast tumors.

6963 **Androgen Glucuronidation: An Unexpected Target for Androgen Deprivation Therapy, with Prognosis and Diagnostic Implications**  
Laurent Grosse, Sophie Pâquet, Patrick Caron, Ladan Fazli, Paul S. Rennie, Alain Bélanger, and Olivier Barbier

*Précis:* These findings reveal a local pathway of androgen metabolism in prostate cells that can antagonize the effects of androgen deprivation therapy in prostate cancer

6972 **miRNA-95 Mediates Radioresistance in Tumors by Targeting the Sphingolipid Phosphatase SGPP1**  
Xiaoyong Huang, Samira Taeb, Sahar Jahangiri, Urban Emmenegger, Elisa Tran, Jeff Bruce, Aruz Mesci, Elina Korpela, Danny Vesprini, C. Shun Wong, Robert G. Bristow, Fei-Fei Liu, and Stanley K. Liu

*Précis:* This seminal report identifies a little-studied microRNA as a major mediator of radiation resistance in tumors, also showing how resistance can be reversed with a clinically approved inhibitor of sphingosine-1-phosphate signaling.

THERAPEUTICS, TARGETS, AND  
CHEMICAL BIOLOGY

6987 **Supramolecular Nanoparticles That Target Phosphoinositide-3-Kinase Overcome Insulin Resistance and Exert Pronounced Antitumor Efficacy**  
Ashish A. Kulkarni, Bhaskar Roy, Poornima S. Rao, Gregory A. Wyant, Ayaat Mahmoud, Madhumitha Ramachandran, Poulomi Sengupta, Aaron Goldman, Venkata Ramana Kotamraju, Sudipta Basu, Raghunath A. Mashelkar, Erkki Ruoslahti, Daniela M. Dinulescu, and Shiladitya Sengupta

*Précis:* This study provides a preclinical foundation for the use of supramolecular nanochemistry to overcome current challenges associated with PI3K inhibitors and also offers a more general paradigm for the development of molecular targeted therapeutics for cancer treatment.

6998 **Contribution of Bcl-2 Phosphorylation to Bak Binding and Drug Resistance**  
Haiming Dai, Husheng Ding, X. Wei Meng, Sun-Hee Lee, Paula A. Schneider, and Scott H. Kaufmann

*Précis:* These findings offer a mechanistic basis to understand the enhanced antiapoptotic activity of phosphorylated Bcl-2, along with the ability of BH3 mimetics to enhance cancer cell sensitivity to taxanes.

7009

**Carbon Monoxide Expedites Metabolic Exhaustion to Inhibit Tumor Growth**

Barbara Wegiel, David Gallo, Eva Csizmadia, Clair Harris, John Belcher, Gregory M. Vercellotti, Nuno Penacho, Pankaj Seth, Vikas Sukhatme, Asif Ahmed, Pier Paolo Pandolfi, Leszek Helczynski, Anders Bjartell, Jenny Liao Persson, and Leo E. Otterbein

*Précis:* Clinical trials of carbon monoxide that are being conducted as a strategy for chemosensitization may benefit from mechanistic insights into CO-induced cancer cell death provided in this study.

7022

**The HSP90 Inhibitor Ganetespib Synergizes with the MET Kinase Inhibitor Crizotinib in both Crizotinib-Sensitive and -Resistant MET-Driven Tumor Models**

Naoto Miyajima, Shinji Tsutsumi, Carole Sourbier, Kristin Beebe, Mehdi Mollapour, Candy Rivas, Soichiro Yoshida, Jane B. Trepel, Ying Huang, Manabu Tatokoro, Nobuo Shinohara, Katsuya Nonomura, and Len Neckers

*Précis:* Hsp90 inhibition synergizes with MET tyrosine kinase inhibition and restores sensitivity to drug-resistant MET mutants.

7034

**PTEN Loss Mitigates the Response of Medulloblastoma to Hedgehog Pathway Inhibition**

Ciara Metcalfe, Bruno Aliche, Ailey Crow, Marlea Lamoureux, Gerrit J.P. Dijkgraaf, Franklin Peale, Stephen E. Gould, and Frederic J. de Sauvage

*Précis:* This study offers new insights into the potential efficacy of Hedgehog pathway inhibitors being tested clinically against a common pediatric cancer.

7043

**Antitumor Activity of the Selective Pan-RAF Inhibitor TAK-632 in BRAF Inhibitor-Resistant Melanoma**

Akito Nakamura, Takeo Arita, Shuntarou Tsuchiya, Jill Donelan, Jouhara Chouitar, Elizabeth Carideo, Katherine Galvin, Masanori Okaniwa, Tomoyasu Ishikawa, and Sei Yoshida

*Précis:* This pan-RAF inhibitor may offer needed therapeutic options for patients with NRAS- or BRAF-driven melanomas that are refractory to BRAF inhibitor treatment.

**TUMOR AND STEM CELL BIOLOGY**

7056

**A Novel EGFR Isoform Confers Increased Invasiveness to Cancer Cells**

Min Zhou, Hai Wang, Keke Zhou, Xiaoying Luo, Xiaorong Pan, Bizhi Shi, Hua Jiang, Jiqin Zhang, Kesang Li, Hua-Mao Wang, Huiping Gao, Shun Lu, Ming Yao, Ying Mao, Hong-Yang Wang, Shengli Yang, Jianren Gu, Chuanyuan Li, and Zonghai Li

*Précis:* These findings reveal a novel mechanism through which dysregulated EGFR signaling drives cancer cell invasion and poor prognosis, in glioma and other cancers, with implications for new prognosis and treatment paradigms involving this core pathway in cancer.

7068

**Silencing of the miR-17~92 Cluster Family Inhibits Medulloblastoma Progression**

Brian L. Murphy, Susanna Obad, Laure Bihannic, Olivier Ayrault, Frederique Zindy, Sakari Kauppinen, and Martine F. Roussel

*Précis:* This study highlights the therapeutic utility achieved by systemic delivery of a drug-like antisense molecule directed against microRNAs, termed tiny LNAs, to suppress tumor progression.

7079

**Glioblastoma Stem Cells Are Regulated by Interleukin-8 Signaling in a Tumoral Perivascular Niche**

David W. Infanger, YouJin Cho, Brina S. Lopez, Sunish Mohanan, S. Chris Liu, Demirkan Gursel, John A. Boockvar, and Claudia Fischbach

*Précis:* This study demonstrates the impact that a 3D tumor environment exerts on chemokine-mediated signals needed to maintain cancer stem-like cells, with broader implications for illustrating the important role of 3D culture models in gaining a better understanding of cancer pathogenesis.

7090

**Generation of Prostate Tumor-Initiating Cells Is Associated with Elevation of Reactive Oxygen Species and IL-6/STAT3 Signaling**

Yi Qu, Anne Margrete Oyan, Runhui Liu, Yaping Hua, Jigang Zhang, Randi Hovland, Mihaela Popa, Xiaojun Liu, Karl A. Brokstad, Ronald Simon, Anders Molven, Biaoyang Lin, Wei-dong Zhang, Emmet McCormack, Karl-Henning Kalland, and Xi-Song Ke

*Précis:* A novel stepwise-generated model of human prostate carcinogenesis reveals an intrinsic association of ROS and IL-6/STAT3 signaling, illuminating this relationship and defining therapeutic targets in this setting.

7101 **In Vivo MAPK Reporting Reveals the Heterogeneity in Tumoral Selection of Resistance to RAF Inhibitors**

Kevin J. Basile, Ethan V. Abel, Neda Dadpey, Edward J. Hartsough, Paolo Fortina, and Andrew E. Aplin

*Précis:* This article describes a novel in vivo system for noninvasive evaluation of a kinase-mediated mechanism of acquired resistance to BRAF-targeting drugs, an area of present clinical challenge for treating metastatic melanoma.

7111 **Neuropilin-2 Is Upregulated in Lung Cancer Cells during TGF- $\beta$ 1-Induced Epithelial-Mesenchymal Transition**

Patrick Nasarre, Robert M. Gemmill, Vincent A. Potiron, Joëlle Roche, Xian Lu, Anna E. Barón, Christopher Korch, Elizabeth Garrett-Mayer, Alessandro Lagana, Philip H. Howe, and Harry A. Drabkin

*Précis:* These findings provide insights into how TGF- $\beta$ 1 mediates invasion and tumorigenesis and identify a novel therapeutic target that may prevent or reverse EMT associated with metastatic progression.

7122 **BCCIP Suppresses Tumor Initiation but Is Required for Tumor Progression**

Yi-Yuan Huang, Li Dai, Dakim Gaines, Roberto Droz-Rosario, Huimei Lu, Jingmei Liu, and Zhiyuan Shen

*Précis:* This study describes a paradoxical tumor suppressor that can also promote cancer progression, serving as a prototype for a class of suppressors that does not need to be permanently inactivated to trigger tumorigenesis.

7134 **Molecular Profiling of Tumor Cells in Cerebrospinal Fluid and Matched Primary Tumors from Metastatic Breast Cancer Patients with Leptomeningeal Carcinomatosis**

Mark Jesus M. Magbanua, Michelle Melisko, Ritu Roy, Eduardo V. Sosa, Louai Hauranieh, Andrea Kablanian, Lauren E. Eisenbud, Artem Ryazantsev, Alfred Au, Janet H. Scott, and John W. Park

*Précis:* This study describes a method for molecular analysis of tumor cells isolated from cerebrospinal fluid, shedding light on their molecular characteristics and suggesting candidate biomarkers and therapeutic targets relevant to metastatic spread in the central nervous system.

## LETTERS TO THE EDITOR

7144 **Benefits of Vascular Normalization Are Dose and Time Dependent—Letter**

Yuhui Huang, Triantafyllos Stylianopoulos, Dan G. Duda, Dai Fukumura, and Rakesh K. Jain

7147 **Bevacizumab-Induced Vessel Normalization Hampers Tumor Uptake of Antibodies—Response**

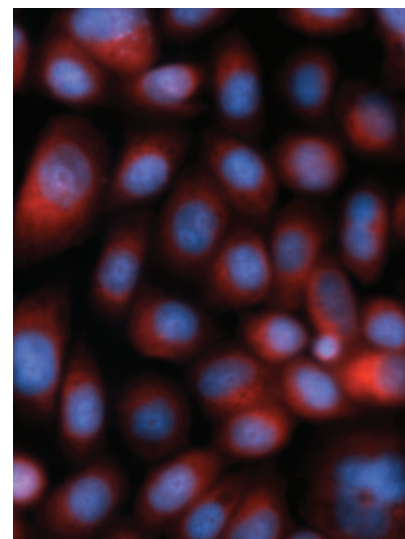
Marlous Arjaans, Sjoukje F. Oosting, Carolina P. Schröder, and Elisabeth G.E. de Vries

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## ABOUT THE COVER

Carbon monoxide (CO) at therapeutic concentrations induces growth arrest of lung and prostate cancer cell lines and tumors. CO is generated endogenously as a bioactive signaling molecule by the cytoprotective gene heme oxygenase-1 (HO-1). In cancer cells, HO-1 activity, and thus endogenous CO levels, is decreased and can be rescued by delivery of exogenous CO. Astonishingly, CO sensitizes cancer cells to chemotherapeutic agents while simultaneously protecting normal cells from genotoxin-induced cell death. The mechanism of CO involves its propensity to bind to heme-containing oxidases in mitochondria. Shown here are prostate cancer cells (PC3) exposed to CO in the presence of the genotoxin doxorubicin, which resulted in a dramatic shift in mitochondrial membrane potential and metabolic collapse driven by an anti-Warburg effect. Using MitoTracker Red CMXRos staining (red), which fluoresces when a cell is actively respiring, Wegiel and colleagues observed that CO decreased respiration and mitochondrial membrane potential, indicative of mitochondrial failure. Nuclei were stained with Hoechst (blue). For details, see article by Wegiel and colleagues on page 7009.



# Cancer Research

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

## 73 (23)

*Cancer Res* 2013;73:6841-7148.

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