# Cancer Research

## January 1, 2011 • Volume 71 • Number 1

### BreakinG Advances

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### Reviews

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<td>Long Intergenic Noncoding RNAs: New Links in Cancer Progression</td>
<td>Miao-Chih Tsai, Robert C. Spitale, and Howard Y. Chang</td>
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<td>Fetal Cell Microchimerism and Cancer: A Nexus of Reproduction, Immunology, and Tumor Biology</td>
<td>Lisa R. Kallenbach, Kirby L. Johnson, and Diana W. Bianchi</td>
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### Priority Report

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<td>Lactate Dehydrogenase B Is Critical for Hyperactive mTOR-Mediated Tumorigenesis</td>
<td>Xiaojun Zha, Fang Wang, Ying Wang, Shaoyong He, Yanling Jing, Xueyan Wu, and Hongbing Zhang</td>
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**Précis:** Findings offer preclinical proof-of-concept for targeting a key glycolytic enzyme as a therapeutic strategy to attack cancers driven by mTOR signaling.

### Clinical Studies

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<td>Glioblastoma Recurrence after Cediranib Therapy in Patients: Lack of “Rebound” Revascularization as Mode of Escape</td>
<td>Emmanuelle di Tomaso, Matija Snuderl, Walid S. Kamoun, Dan G. Duda, Pavan K. Auluck, Ladan Fazlollahi, Ovidiu C. Andronesi, Matthew P. Frosch, Patrick Y. Wen, Scott R. Plotkin, E. Tessa Hedley-Whyte, A. Gregory Sorensen, Tracy T. Batchelor, and Rakesh K. Jain</td>
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**Précis:** Glioblastomas switch their growth pattern after anti-VEGF therapy in the absence of a second wave of angiogenesis.

### Integrated Systems and Technologies

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<td>Genetic and Structural Variation in the Gastric Cancer Kinome Revealed through Targeted Deep Sequencing</td>
<td>Zhi Jiang Zang, Chohe Kiat Ong, Joana Cutcutache, Willie Yu, Shen Li Zhang, Dachuan Huang, Lian Dee Lee, Karl Dykema, Anna Gan, Jiong Tao, Siyu Lim, Yujing Liu, P. Andrew Futreal, Heike Grabsch, Kyle A. Forge, Lang Kee Goh, Steve Rozen, Bin Tean Teh, and Patrick Tan</td>
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**Précis:** Deep sequencing of the gastric cancer cell genome identifies hundreds of new kinase variants, revealing new extremes of genetic complexity in cancer development and progression.

### Microenvironment and Immunology

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<td>40</td>
<td>Endothelial Cell-Specific Deletion of Transcription Factor FoxM1 Increases Urethane-Induced Lung Carcinogenesis</td>
<td>David Balli, Yufang Zhang, Jonathan Snyder, Vladimir V. Kalinichenko, and Tanya V. Kalin</td>
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**Précis:** A known oncogene in lung tumorigenesis functions in an opposing manner as a tumor suppressor in endothelial cells, acting to restrict pulmonary inflammation and canonical Wnt signaling.

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<td>51</td>
<td>Tamoxifen, Flaxseed, and the Lignan Enterolactone Increase Stroma- and Cancer Cell–Derived IL-1Ra and Decrease Tumor Angiogenesis in Estrogen-Dependent Breast Cancer</td>
<td>Gabriel Lindahl, Niina Saarinen, Annelie Abrahamsson, and Charlotta Dabrosin</td>
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**Précis:** Antiestrogen therapies may act in part by depriving an inflammatory signal that supports angiogenesis, through a mechanism that might also be targeted by the IL-1 receptor antagonist anakinra, a clinically approved agent.

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<td>61</td>
<td>In Vivo Antitumor Activity of a Recombinant IL-7/HGFβ Hybrid Cytokine in Mice</td>
<td>Lajun Lai, Jingjun Jin, and Irving Goldscheider</td>
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**Précis:** Findings offer preclinical proof-of-concept for use of a naturally occurring cytokine heterodimer as a potentially universal biological therapy in cancer treatment.
MOLECULAR AND CELLULAR PATHOBIOLOGY

68  BRCA2 and Nucleophosmin Coregulate Centrosome Amplification and Form a Complex with the Rho Effector Kinase ROCK2
Hui-Feng Wang, Katsuya Takenaka, Akira Nakanishi, and Yoshio Miki

Précis: Findings suggest that interactions between BRCA2 and NPM mediate suppression of hereditary breast and ovarian cancer.

78  Identification of New MicroRNAs in Paired Normal and Tumor Breast Tissue Suggests a Dual Role for the ERBB2/Her2 Gene
Helena Persson, Anders Kvist, Natalia Rego, Johan Staal, Johan Vallon-Christersson, Lena Luts, Niklas Loman, Goran Jonsson, Hugo Naya, Mattias Hoglund, Ake Borg, and Carlos Rovira

Précis: Characterization of known and new microRNAs leads to the discovery of a new gene within the human ERBB2 oncogene.

87  Molecular Pathobiology of Human Cervical High-Grade Lesions: Paracrine STAT3 Activation in Tumor-Instructed Myeloid Cells Drives Local MMP-9 Expression
Nadine Schroer, Jennifer Pahe, Barbara Walch, Claudia Wickenhauser, and Sigrun Smola

Précis: Findings define a molecular cascade that mechanistically rationalizes the design of new adjuvant therapies to treat cervical precancerous lesions and prevent their malignant progression.

98  Appearance of the Novel Activating F1174S ALK Mutation in Neuroblastoma Correlates with Aggressive Tumor Progression and Unresponsiveness to Therapy
Tommy Martinsson, Therese Eriksson, Jonas Abrahamsson, Helena Caren, Magnus Hansson, Per Kogner, Sattu Kamaraj, Christina Schönher, Joel Weimann, Kristina Rauth, Ruth H. Palmer, and Bengt Hallberg

Précis: Mutation of a critical kinase in neuroblastoma progression may be missed in the initial tumor biopsy, requiring testing later at progression.

Dose-Dependent Effects of Focal Fractionated Irradiation on Secondary Malignant Neoplasms in Nf1 Mutant Mice
Jean L. Nakamura, Connie Phong, Emile Pinarbasi, Scott C. Kogan, Scott Vandenberg, Andrew E. Horvai, Bruce A. Faddagov, Dorothea Fiedler, Kevan Shokat, Benjamin T. Housman, Richard Chao, Russell O. Pieper, and Kevin Shannon

Précis: Findings offer the first validated mouse model to study secondary malignancies, an increasingly common complication of cancer therapy in survivors that has yet to be systematically analyzed.

PREVENTION AND EPIDEMIOLOGY

106  Risk of Infection-Related Cancers after the Loss of a Child: A Follow-up Study in Sweden
Fang Fang, Katja Fall, Pär Sparén, Hans-Olov Adami, Heiddis B. Valdimarsdóttir, Mats Lambe, and Unnur Valdimarsdóttir

Précis: Loss of a child associates with a higher risk of several cancers, chiefly ones that are associated with HPV infections.

123  A Randomized Trial of Dietary Intervention for Breast Cancer Prevention
Lisa J. Martin, Qing Li, Olga Melnichouk, Cary Greenberg, Salomon Minkin, Greg Hislop, and Norman F. Boyd

Précis: A sustained reduction in dietary fat intake did not reduce risk of breast cancer in women with extensive mammographic density.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

134  Carminomycin I Is an Apoptosis Inducer That Targets the Golgi Complex in Clear Cell Renal Carcinoma Cells
Girma M. Woldemichael, Thomas J. Turbyville, W. Marston Linehan, and James B. McMahon

Précis: Use of a natural products-based small molecule screening approach reveals a novel targeting strategy to attack clear cell renal cell carcinoma.
VEGF-PET Imaging Is a Noninvasive Biomarker Showing Differential Changes in the Tumor during Sunitinib Treatment

Wouter B. Nagengast, Marjolijn N. Lub-de Hooge, Sjouke F. Osting, Wilfred F.A. den Dunnen, Frank-Jan Warners, Adrienne H. Brouwers, Johan R. de Jong, Patricia M. Price, Harry Hollema, Geke A.P. Hospers, Philip H. Elsinga, Jan Willem Hesselink, Jourik A. Gietema, and Elisabeth G.E. de Vries

Précis: A PET imageable marker for tumor angiogenesis could enable noninvasive monitoring of dynamic changes in patients, helping guide treatment strategies, optimal dose finding, and drug combination studies.

A Dual PI3K/mTOR Inhibitor, PI-103, Cooperates with Stem Cell–Delivered TRAIL in Experimental Glioma Models

Tugba Bagci-Onder, Hiroaki Wakimoto, Maarten Anderegg, Cody Cameron, and Khalid Shah

Précis: Findings offer preclinical proof-of-concept for an effective combination of proapoptotic therapies that can eradicate malignant glioma cells in vitro and in vivo.

PDGF Signaling Blockade in Marrow Stroma Impairs Lung Cancer Bone Metastasis

Raúl Catena, Diego Luis-Ravelo, Iker Antón, Carolina Zandueta, Pablo Salazar-Colocho, Leyre Larzábal, Alfonso Calvo, and Fernando Lecanda

Précis: Findings support the important concept that concomitant targeting of the tumor and tumor stroma can confer a far more effective approach to block bone metastasis in cancer.

TGF-β-RI Kinase Inhibitor SD-208 Reduces the Development and Progression of Melanoma Bone Metastases

Khalid S. Mohammad, Delphine Javelaud, Pierrick G. J. Fournier, Maria Niewolna, C. Ryan McKenna, Xiang H. Peng, Vu Duong, Lauren K. Dunn, Alain Mauryel, and Theresa A. Guise

Précis: Preclinical proof-of-concept rationalizes application of small molecule inhibitors of TGF-β receptor signaling to prevent and treat osteolytic bone metastases in melanoma.

Autophagic Survival in Resistance to Histone Deacetylase Inhibitors: Novel Strategies to Treat Malignant Peripheral Nerve Sheath Tumors

Gonzalo Lopez, Keila Torres, Juehui Liu, Belinda Hernandez, Eric Young, Roman Belousov, Svetlana Bolsmakov, Alexander J. Lazar, John M. Slopis, Ian E. McCutcheon, David McConkey, and Dina Lev

Précis: Findings identify a potentially important resistance mechanism to histone deacetylase inhibitors, the abrogation of which could in particular enhance their anticancer activity against an aggressive neurological tumor that is poorly managed in the clinic.

Novel Synthetic Antagonists of Canonical Wnt Signaling Inhibit Colorectal Cancer Cell Growth

Jo Waaler, Ondrej Machon, Jens Peter von Kries, Steven Ray Wilson, Elsa Lundenes, Doris Wedlich, Dietmar Gradl, Ian Erik Paulsen, Olga Machonova, Jennifer L. Dembinski, Huyen Dinh, and Stefan Krauss

Précis: New small molecule inhibitors of the canonical Wnt pathway are described that potently block the growth of colorectal cancers.

Activation and Involvement of Ral GTPases in Colorectal Cancer

Timothy D. Martin, Jonathan C. Samuel, Elizabeth D. Routh, Channing J. Der, and Jen Jen Yeh

Précis: Findings validate the significance of a lesser studied Ras effector pathway for therapeutic inhibition of mutant KRAS in colorectal cancer.

Biological Activity of 4-Substituted Methoxybenzoyl-Aryl-Thiazole: An Active Microtubule Inhibitor

Chien-Ming Li, Zhao Wang, Yan Lu, Sunjoo Ahn, Ramesh Narayanan, Jeffrey D. Kearbey, Deanna N. Parke, Wei Li, Duane D. Miller, and James T. Dalton

Précis: SMART compounds are as efficacious as currently approved antitubulin drugs for cancer treatment, but unlike these drugs they can circumvent P-glycoprotein–mediated drug resistance.

MiR-26a Inhibits Cell Growth and Tumorigenesis of Nasopharyngeal Carcinoma through Repression of EZH2

Juan Lu, Ming-Liang He, Lu Wang, Ying Chen, Xiong Liu, Qi Dong, Yang-Chao Chen, Ying Peng, Kai-Tai Yao, Hsiang-Fu Kung, and Xiang-Ping Li

Précis: This study contributes significant new information concerning the molecular pathogenesis of nasopharyngeal carcinoma, a major cancer in China where it is associated with Epstein-Barr virus infection.
Phosphatase PRL-3 Is a Direct Regulatory Target of TGFβ in Colon Cancer Metastasis
Yanjun Jiang, Xiao-Qiong Liu, Ashwani Rajput, Liying Geng, Melanie Ongchin, Qi Zeng, Gregory S. Taylor, and Jing Wang

Précis: Findings link TGFβ signaling in cancer progression to upregulation of a survival pathway that could be a determinant of metastasis, with implications for its therapeutic attack.

Snail2 is an Essential Mediator of Twist1-Induced Epithelial Mesenchymal Transition and Metastasis
Esmeralda Casas, Jihoon Kim, Andrés Bendesky, Lucila Ohno-Machado, Cecily J. Wolfe, and Jing Yang

Précis: Findings identify an essential regulatory relationship between two key factors that control the EMT program to promote metastasis.

Higher miRNA Tolerance in Immortal Li-Fraumeni Fibroblasts with Abrogated Interferon Signaling Pathway
Qunfang Li and Michael A. Tainsky

Précis: Results reveal the first solid evidence that disruption of IFN signaling is a checkpoint tolerizing cells to deregulation of miRNA expression, providing new insight into how certain transcription factors in innate immunity can promote cellular immortalization.

hTERT Overexpression Alleviates Intracellular ROS Production, Improves Mitochondrial Function, and Inhibits ROS-Mediated Apoptosis in Cancer Cells
Inthirani R. Indran, Manoor P. Hande, and Shazib Pervaiz

Précis: Findings define a novel function for TERT in alleviating cellular ROS levels, endowing cancer cells with an additional mechanism to evade cell death stimuli.

Plasminogen Activator uPA is a Direct Transcriptional Target of the JAG1-Notch Receptor Signaling Pathway in Breast Cancer
Mamiko Shimizu, Brenda Cohen, Pavel Goldvasser, Hal Berman, Carl Virtanen, and Michael Reedijk

Précis: Important new mechanistic findings link two pathways of poor prognosis in breast cancer.

Fish Oil Exacerbates Colitis in SMAD3 Mice
Lesley M. Butler and Mimi C. Yu

Correction: F3-Targeted Cisplatin-Hydrogel Nanoparticles as an Effective Therapeutic that Targets Both Murine and Human Ovarian Tumor Endothelial Cells In vivo

Correction: Induction of Human Epithelial Stem/Progenitor Expansion by FOXM1

Double immunofluorescence for nestin (pink) and the endothelial marker CD34 (green) with EGFR fluorescence in situ hybridization (red) confirms expression of nestin in endothelial cells and in GBM cells of patients treated with cediranib. For details, see the article by di Tomaso et al. on page 19 of this issue.
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