# Contents

## Cancer Research

April 15, 2012 • Volume 72 • Number 8

### BREAKING ADVANCES

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<td>Highlights from Recent Cancer Literature</td>
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### REVIEWS

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<td>1909</td>
<td>Anti-VEGF/VEGFR Therapy for Cancer: Reassessing the Target</td>
<td>Basel Sitohy, Janice A. Nagy, and Harold F. Dvorak</td>
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<td>1915</td>
<td>Nodal Expression and Detection in Cancer: Experience and Challenges</td>
<td>Luigi Strizzi, Katharine M. Hardy, Dawn A. Kirschmann, Lars Ahrlund-Richter, and Mary J.C. Hendrix</td>
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### PRIORITY REPORTS

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<td>1921</td>
<td>Detection of Redundant Fusion Transcripts as Biomarkers or Disease-Specific Therapeutic Targets in Breast Cancer</td>
<td>Yan W. Asmann, Brian M. Necela, Krishna B. Kalari, Asif Hossain, Tiffany R. Baker, Jennifer M. Carr, Caroline Davis, Julie E. Getz, Galen Hostetter, Xing Li, Sarah A. McLaughlin, Derek C. Radisky, Gary P. Schroth, Heather E. Cunliffe, Edith A. Perez, and E. Aubrey Thompson</td>
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### INTEGRATED SYSTEMS AND TECHNOLOGIES

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<td>1935</td>
<td>Concordant Release of Glycolysis Proteins into the Plasma Preceding a Diagnosis of ER+ Breast Cancer</td>
<td>Lynn M. Amon, Sharon J. Pitteri, Christopher I. Li, Martin McIntosh, Jon J. Laid, Mary Disis, Peggy Porter, Chee Hong Wong, Qing Zhang, Paul Lampe, Ross L. Prentice, and Samir M. Hanash</td>
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**Précis:** Through a combination of mass spectrometry and gene set analysis, glycolysis pathway proteins are identified in the blood of breast cancer patients prior to diagnosis, suggesting that these proteins may serve as circulating biomarkers and potentially complement mammography in breast cancer screening.

### MICROENVIRONMENT AND IMMUNOLOGY

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**Précis:** Expression and structure of an extracellular proteoglycan that is altered widely in esophageal cancer is responsible for driving invasive cell migration, suggesting a novel targeting approach to attack this deadly cancer.

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<td>1953</td>
<td>Genetic Deficiency in Plasma Protein HRG Enhances Tumor Growth and Metastasis by Exacerbating Immune Escape and Vessel Abnormalization</td>
<td>Sónia Tuges, Satoshi Honjo, Christian König, Oriol Noguer, Marie Hedlund, Johan Botling, Solve Deschoomacker, Mathias Wenes, Charlotte Rolny, Wilhelm Jahnert-Dechent, Massimiliano Mazzone, and Lena Claesson-Welsh</td>
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**Précis:** Findings establish an important link between deficiency of a highly expressed plasma protein and tumor progression via activation of protumoral macrophages and immune suppression.
Densely Granulated Murine NK Cells Eradicate Large Solid Tumors
Rebecca B. Liu, Boris Engels, Ainhoa Arina, Karin Schreiber, Elizabeth Hyjek, Andrea Schietinger, David C. Binder, Eric Butz, Thomas Krausz, Donald A. Rowley, Bana Jabri, and Hans Schreiber

Precis: If present, high levels of a cytokine implicated in immune memory in the tumor microenvironment will promote the accumulation of densely granulated natural killer cells that are capable of eradicating large solid tumors.

Increased CD8⁺ T-cell Function following Castration and Immunization Is Counteracted by Parallel Expansion of Regulatory T Cells
Shuai Tang, Miranda L. Moore, Jason M. Grayson, and Purnima Dubey

Precis: Findings show that androgen ablation expands both the effector and inhibitory arms of the immune response to tumors, resulting in only a transient enhancement of immune function.

A Potent Vaccination Strategy That Circumvents Lymphodepletion for Effective Antitumor Adoptive T-cell Therapy
Hyun-Il Cho, Eduardo Reyes-Vargas, Julio C. Delgado, and Esteban Celis

Precis: Findings suggest a simple, effective strategy to improve adoptive T-cell therapy for melanoma treatment that avoids complications associated with lymphodepletion and high-dose interleukin-2 treatment.

p53/HMGB1 Complexes Regulate Autophagy and Apoptosis

Precis: These insights provide a novel link between a chromatin-binding factor and p53 in the cross-regulation of apoptosis and autophagy during cell stress, providing insights into carcinogenesis during stress-associated tumor development.

FGFR2 Isoforms Support Epithelial–Stromal Interactions in Thyroid Cancer Progression
Miao Gao, Wei Liu, Stefano Serra, Sylvia L. Asa, and Shereen Ezzat

Precis: This study highlights the importance of the context in the tumor of the regulatory properties of different growth factor receptor isoforms by illustrating how alternative splicing can confer different functions depending on whether the receptor is expressed in tumor versus tumor stromal cells.

Effect of Depo-Medroxyprogesterone Acetate on Breast Cancer Risk among Women 20 to 44 Years of Age
Christopher I. Li, Elisabeth F. Beaber, Mei Tzu Chen Tang, Peggy L. Porter, Janet R. Daling, and Kathleen E. Malone

Precis: The most common injectable contraceptive may increase breast cancer risk among young women who use it.

Characterization of Gene–Environment Interactions for Colorectal Cancer Susceptibility Loci

Precis: This study reveals a colon cancer risk locus variant that appears to be modified by vegetable consumption, motivating further work to elucidate environmental influences on cancer susceptibility genes.

INT6/EIF3E Interacts with ATM and Is Required for Proper Execution of the DNA Damage Response in Human Cells
Christelle Morris, Nozomi Tomimatsu, Derek J. Richard, David Cluet, Sandeep Burma, Kum Kum Khanna, and Pierre Jalinot

Precis: Findings reveal a novel and important function in DNA repair that may be closely involved in the onset of breast cancers initiated by defects in the DNA damage response.
AZD4547: An Orally Bioavailable, Potent, and Selective Inhibitor of the Fibroblast Growth Factor Receptor Tyrosine Kinase Family

Précis: A potent and highly selective small-molecule inhibitor may offer a broad-based approach for treatment of many kinds of tumors that involve activation of the fibroblast growth factor receptor.

Intratracheal Administration of a Nanoparticle-Based Therapy with the Angiotensin II Type 2 Receptor Gene Attenuates Lung Cancer Growth
Atsushi Kawabata, Abdulgader Baoum, Naomi Ohta, Stephanie Jacquez, Cory Berkland, and Masaaki Tamura

Précis: Findings offer a preclinical validation for a nontoxic cationic, peptide-based nanoparticle vector that can deliver genes via the trachea for effective treatment of lung cancers.

Common Variation at BARD1 Results in the Expression of an Oncogenic Isoform That Influences Neuroblastoma Susceptibility and Oncogenicity

Précis: Genetic predisposition studies not only can identify mechanisms of cancer susceptibility but also can reveal therapeutically relevant oncogenic vulnerabilities that may be exploitable clinically.

Tumor Vascular Microenvironment Determines Responsiveness to Photodynamic Therapy
Amanda L. Maas, Shirron L. Carter, E. Paul Wileyto, Joann Miller, Min Yuan, Guoqiang Yu, Amy C. Durham, and Theresa M. Busch

Précis: Collagen in the basement membrane of vascular cells is a site of drug localization and treatment effect in photodynamic therapy, with implications that may help to improve the effectiveness of these treatments for cancer.

Mitigating Age-Related Immune Dysfunction Heightens the Efficacy of Tumor Immunotherapy in Aged Mice

Précis: The ability of the immune system to control cancer is increasingly compromised with a patient's age, but emerging strategies to reprogram immunity in the elderly may heighten these patients' ability to respond efficiently to cancer immunotherapy.

"OA02" Peptide Facilitates the Precise Targeting of Paclitaxel-Loaded Micellar Nanoparticles to Ovarian Cancer In Vivo
Kai Xiao, Yuanpei Li, Joyce S. Lee, Abby M. Genik, Tiffany Dong, Gabriel Fung, Eduardo Sanchez, Li Xing, Holland R. Cheng, Juntao Luo, and Kit S. Lam

Précis: Findings offer preclinical proof-of-concept for a peptidyl nanoformulation with significant potential to improve treatment of patients with ovarian cancer.

Deficiency in Mammalian Histone H2B Ubiquitin Ligase Bre1 (Rnf20/Rnf40) Leads to Replication Stress and Chromosomal Instability
Sophia B. Chernikova, Olga V. Razorenova, John P. Higgins, Brock J. Sishc, Monica Nicolau, Jennifer A. Dorth, Dina A. Chernikova, Shirley Kwok, James D. Brooks, Susan M. Bailey, John C. Game, and J. Martin Brown

Précis: Genomic instability caused by deficiency in a histone ubiquitin ligase may be an important initial step in acquisition of an invasive phenotype by an early-stage noninvasive tumor.

Type I and II IFNs Inhibit Merkel Cell Carcinoma via Modulation of the Merkel Cell Polyomavirus T Antigens
Christoph Willmes, Christian Adam, Miriam Alth, Lena Völkert, Roland Houben, Jürgen C. Becker, and David Schrama

Précis: Merkel cell carcinoma, a rare but highly aggressive skin cancer driven by a polyomavirus tumor antigen, may be susceptible to IFN therapies found to modulate the antigen's expression.
CDK8 Maintains Tumor Dedifferentiation and Embryonic Stem Cell Pluripotency

Précis: Therapeutic targeting of the cyclin-dependent kinase CDK8 may specifically blunt stem-like properties in cancer cells.

Expression of a Truncated Active Form of VDAC1 in Lung Cancer Associates with Hypoxic Cell Survival and Correlates with Progression to Chemotherapy Resistance

Précis: Blockade of a mitochondria anion channel may improve response to lung cancer therapy by restoring apoptotic sensitivity and circumventing chemoresistance in hypoxic tumor cells.

Correction: Preclinical Profile of a Potent γ-Secretase Inhibitor Targeting Notch Signaling with In vivo Efficacy and Pharmacodynamic Properties

Correction: p53 Pre- and Postbinding Event Theories Revisited: Stresses Reveal Specific and Dynamic p53-Binding Patterns on the p21 Gene Promoter

Correction: Potentiation of the Novel Topoisomerase I Inhibitor Indenoisoquinoline LMP-400 by the Cell Checkpoint and Chk1-Chk2 Inhibitor, AZD7762

OBITUARY

Ricardo Renzo Brentani: In Memoriam (1937–2011)

Luisa L. Villa and Eduardo L. Franco

ABOUT THE COVER

The HIV-1 TAT peptide was dimerized and used to formulate a nanoparticle vector (dTAT NP) to leverage efficient tumor-targeted gene delivery following intratracheal administration. In vitro expression efficiency for dTAT NP–encapsulated luciferase or angiotensin II type 2 receptor (AT2R) plasmid DNA (pDNA) revealed effective pDNA transfection with negligible cytotoxicity. In orthotopic tumor grafts, immunohistochemical analysis confirmed that dTAT NP successfully delivered pDNA to the tumor, and gene expression in tumor tissues persisted at least 14 days after intratracheal administration. Bolus administration of dTAT NP–encapsulated AT2R or TRAIL pDNA, both endogenous apoptosis inducers, markedly attenuated tumor growth. For details, see article by Kawabata and colleagues on page 2057.