**BREAKING ADVANCES**

1907  
**Highlights from Recent Cancer Literature**

**REVIEWS**

1909  
**Anti-VEGF/VEGFR Therapy for Cancer: Reassessing the Target**  
Basel Sitohy, Janice A. Nagy, and Harold F. Dvorak

1915  
**Nodal Expression and Detection in Cancer: Experience and Challenges**  
Luigi Strizzi, Katharine M. Hardy, Dawn A. Kirschmann, Lars Ahrlund-Richter, and Mary J.C. Hendrix

**PRIORITY REPORTS**

1921  
**Detection of Redundant Fusion Transcripts as Biomarkers or Disease-Specific Therapeutic Targets in Breast Cancer**  

**MICROENVIRONMENT AND IMMUNOLOGY**

1929  
**The Mixed Lineage Leukemia (MLL) Fusion–Associated Gene API Promotes CD133 Transcription**  
Anthony R. Mak, Allison M.L. Nixon, and Jason Moffat

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

1935  
**Concordant Release of Glycolysis Proteins into the Plasma Preceding a Diagnosis of ER Breast Cancer**  
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

**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.

1943  
**Dermatan Sulfate Is Involved in the Tumorigenic Properties of Esophageal Squamous Cell Carcinoma**  
Martin A. Thelin, Katrin J. Svensson, Xiaofeng Shi, Mariam Bagher, Jakob Axelsson, Anna Isinger-Ekstrand, Toin H. van Kuppevelt, Jan Johansson, Mef Nilbert, Joseph Zaia, Mattias Beltling, Marco Maccarana, and Anders Malmström

**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.

1953  
**Genetic Deficiency in Plasma Protein HRG Enhances Tumor Growth and Metastasis by Exacerbating Immune Escape and Vessel Abnormalization**  

**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.
1964  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.

1975  Increased CD8⁺ T-cell Function following Castration and Immunization Is Countered 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.

1986  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.

1996  p53/HMGB1 Complexes Regulate Autophagy and Apoptosis  
Kristen M. Livesey, Rui Kang, Philip Vernon, William Buchser, Patricia Loughran, 
Simon C. Watkins, Lin Zhang, James J. Manfredi, 
Herbert J. Zeh III, Luyuan Li, Michael T. Lotze, and Daolin Tang

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.

2006  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.

2017  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.

2018  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.

2028  Characterization of Gene–Environment Interactions for Colorectal Cancer Susceptibility Loci  
Carolyn M. Hutter, Jenny Chang-Claude, Martha L. Slattery, Bethann M. Pflueger, Yi Lin, 
David Duggan, Hongmei Nan, Mathieu Lemire, 
Jagadish Rangrej, Jane C. Figueiredo, Shuo Jiao, 
Tabitha A. Harrison, Yan Liu, Lin S. Chen, 
Deanna L. Stelling, Greg S. Warnick, 
Michael Hoffmeister, Sébastien Küry, 
Charles S. Fuchs, Edward Giovannucci, 
Aditi Hazra, Peter Kraft, David J. Hunter, 
Steven Gallinger, Brent W. Zanke, 
Herrmann Brenner, Bernd Frank, Jing Ma, 
Cornelia M. Ulrich, Emily White, 
Polly A. Newcomb, Charles Kooperberg, 
Andrew Z. LaCroix, Ross L. Prentice, 
Rebecca D. Jackson, Robert E. Schoen, 
Stephen J. Chan, Sonja I. Berndt, 
John D. Potter, Li Hsu, Stéphane Récaux, Andrew T. Chan, 
Thomas J. Hudson, and Ulrike Peters

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.
<table>
<thead>
<tr>
<th>THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY</th>
<th>2045</th>
<th>Mitigating Age-Related Immune Dysfunction Heightens the Efficacy of Tumor Immunotherapy in Aged Mice</th>
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<td>AZD4547: An Orally Bioavailable, Potent, and Selective Inhibitor of the Fibroblast Growth Factor Receptor Tyrosine Kinase Family</td>
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<td><strong>Précis:</strong> 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.</td>
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| Intrapulmonary 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, Gwi-Moon Seo, 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. |

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<tr>
<th>TUMOR AND STEM CELL BIOLOGY</th>
<th>2089</th>
<th>Type I and II IFNs Inhibit Merkel Cell Carcinoma via Modulation of the Merkel Cell Polyomavirus T Antigens</th>
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<td>Deficiency in Mammalian Histone H2B Ubiquitin Ligase Brc1 (Rnf20/Rnf40) Leads to Replication Stress and Chromosomal Instability</td>
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<td>Sophia B. Chernikova, Olga V. Razorenova, John P. Higgins, Brock J. Sishrc, Monica Nicolaus, Jennifer A. Dorth, Diana A. Chernikova, Shirley Kwok, James D. Brooks, Susan M. Bailey, John C. Game, and Martin Brown</td>
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<td><strong>Précis:</strong> 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.</td>
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| "OA02" Peptide Facilitates the Precise Targeting of Paclitaxel-Loaded Micellar Nanoparticles to Ovarian Cancer In Vivo |
| Kai Xiao, Yuanpei Li, Joyce S. Lee, Abhy 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. |

| 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. |

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A Journal of the American Association for Cancer Research

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CDK8 Maintains Tumor Dedifferentiation and Embryonic Stem Cell Pluripotency

Precis: 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

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

Corrections

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 I. 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.