### 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**


**Précis:** Fusion transcripts generating cancer-specific chimeric molecules have been widely used in hematopoietic cancers for diagnosis, prognosis, and treatment, but these genomic features have not been exploited in solid tumors due to the lack of a technology that could readily define targets to exploit, as this important study now addresses.

**1929**

**The Mixed Lineage Leukemia (MLL) Fusion–Associated Gene AFI Promotes CD133 Transcription**

Anthony B. Mak, Allison M.L. Nixon, and Jason Moffat

**Précis:** Findings illuminate the regulation of a stem cell marker that functions in a variety of cancers, including the class of pediatric leukemias studied here.

### 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. Ladul, 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.

### MICROENVIRONMENT AND IMMUNOLOGY

**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 Belting, 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

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 Guo, 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.

PREVENTION AND EPIDEMIOLOGY

2028  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.

2036  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.
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, 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.

Type I and II IFNs Inhibit Merkel Cell Carcinoma via Modulation of the Merkel Cell Polyomavirus T Antigens
Christoph Willmes, Christian Adam, Miriam Alb, Lena Völker, 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.
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<td>2129</td>
<td>CDK8 Maintains Tumor Dedifferentiation and Embryonic Stem Cell Pluripotency</td>
<td>Adam S. Adler, Mark L. McCleland, Tom Truong, Shari Lau, Zora Modrusan, Tim M. Soukup, Merone Roose-Girma, Elizabeth M. Blackwood, and Ron Firestein</td>
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<td><strong>Précis:</strong> Therapeutic targeting of the cyclin-dependent kinase CDK8 may specifically blunt stem-like properties in cancer cells.</td>
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<td>2140</td>
<td>Expression of a Truncated Active Form of VDAC1 in Lung Cancer Associates with Hypoxic Cell Survival and Correlates with Progression to Chemotherapy Resistance</td>
<td>M. Christiane Brahimi-Horn, Danya Ben-Hail, Marius Ilie, Pierre Gounon, Matthieu Rouleau, Véronique Hofman, Jérôme Doyen, Bernard Mari, Varda Shoshan-Barmatz, Paul Hofman, Jacques Pouysségur, and Nathalie M. Mazure</td>
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<td><strong>Précis:</strong> Blockade of a mitochondria anion channel may improve response to lung cancer therapy by restoring apoptotic sensitivity and circumventing chemoresistance in hypoxic tumor cells.</td>
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<td>2151</td>
<td>Correction: Preclinical Profile of a Potent γ-Secretase Inhibitor Targeting Notch Signaling with In vivo Efficacy and Pharmacodynamic Properties</td>
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<td>2152</td>
<td>Correction: p53 Pre- and Postbinding Event Theories Revisited: Stresses Reveal Specific and Dynamic p53-Binding Patterns on the p21 Gene Promoter</td>
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**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.