Highlights from Recent Cancer Literature

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

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

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.

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

The Mixed Lineage Leukemia (MLL) Fusion–Associated Gene API 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.

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 Lamp, 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.

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, Mof 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.

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.
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 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.

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.

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.

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.

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.
**AZD4547: An Orally Bioavailable, Potent, and Selective Inhibitor of the Fibroblast Growth Factor Receptor Tyrosine Kinase Family**

Paul R. Gavine, Lorraine Mooney, Elaine Kilgour, Andrew P. Thomas, Katherine Al-Kadhimi, Sarah Beck, Claire Rooney, Tanya Coleman, Dawn Baker, Martine J. Mellor, A. Nigel Brooks, and Teresa Kliowska

*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.

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**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.

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**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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**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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**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.

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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.

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**Deficiency in Mammalian Histone H2B Ubiquitin Ligase Brc1 (Rnf20/Rnf40) Leads to Replication Stress and Chromosomal Instability**

Sophia B. Chernikova, Olga V. Razorenova, John P. Higgins, Brock J. Sishch, Monica Nicola, Jennifer A. Dorth, Diana 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.

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**Type I and II IFNs Inhibit Merkel Cell Carcinoma via Modulation of the Merkel Cell Polyomavirus T Antigens**

Christoph Willmes, Christian Adam, Miriam Albi, 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

Adam S. Adler, Mark L. McCleland, Tom Truong, Shari Lau, Zora Modrusan, Tim M. Soukup, Merone Roose-Girma, Elizabeth M. Blackwood, and Ron Firestein

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

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

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.

## 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.