## BREAKING ADVANCES

4873  | Highlights from Recent Cancer Literature

## REVIEWS

4875  | Intratumor Heterogeneity: Evolution through Space and Time  
Charles Swanton

4883  | Microenvironmental Regulation of Epithelial–Mesenchymal Transitions in Cancer  
Dingcheng Gao, Linda T. Vahdat, Stephen Wong, Jenny C. Chang, and Vivek Mittal

4890  | The Growing Arsenal of ATP-Competitive and Allosteric Inhibitors of BCR–ABL  
Oliver Hantschel, Florian Grebien, and Giulio Superti-Furga

## COMMENTARY

4896  | Biomarkers of HPV Infection in Oropharyngeal Carcinomas: Can We Find Simplicity in the Puzzle of Complexity?  
Eduardo M. Méndez

## INTEGRATED SYSTEMS AND TECHNOLOGIES

4899  | Interstitial Fluid Pressure and Associated Lymph Node Metastasis Revealed in Tumors by Dynamic Contrast-Enhanced MRI  
Tord Hompland, Christine Ellingsen, Kirsti Marie Øvrebo, and Einar K. Rofstad

**Précis:** Seminal findings describe a new noninvasive tool to image the internal fluid pressure in tumors, revealing a metric that might be used to predict the metastatic potential of any solid tumor.

## MICROENVIRONMENT AND IMMUNOLOGY

4909  | Roles for Endothelin Receptor B and BCL2A1 in Spontaneous CNS Metastasis of Melanoma  
William Cruz-Muñoz, Maria L. Jaramillo, Shan Man, Ping Xu, Myriam Banville, Catherine Collins, Andre Nantel, Giulio Francia, Sherif S. Morgan, Lee D. Cranmer, Maureen D. O’Connor-McCourt, and Robert S. Kerbel

**Précis:** A model to evaluate genes relevant to brain metastasis by malignant melanoma provides important new insights into this little-understood process.

4920  | Rab27a Supports Exosome-Dependent and -Independent Mechanisms That Modify the Tumor Microenvironment and Can Promote Tumor Progression  
Angélique Bobrie, Sophie Krumeich, Fabien Reyal, Chiara Recchi, Luis F. Moita, Miguel C. Seabra, Matias Ostrowski, and Clotilde Théry

**Précis:** This important study offers what may be the first evidence of a role for in vivo secreted cancer cell-exosomes in primary tumor growth and metastasis.

4931  | Soluble CD200 Is Critical to Engraft Chronic Lymphocytic Leukemia Cells in Immunocompromised Mice  
Karrie K. Wong, Fred Brenneman, Alden Chesney, David E. Spaner, and Reginald M. Gorczynski

**Précis:** This study characterizes a novel soluble isoform of the immunosuppressive molecule CD200, which, when overexpressed on cancer cells, may mediate immune escape.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

4944  | Functional Genomics Identifies Drivers of Medulloblastoma Dissemination  
Michael Mumert, Adrian Dubuc, Xiaochong Wu, Paul A. Northcott, Steven S. Chin, Carolyn A. Pedone, Michael D. Taylor, and Daniel W. Fults

**Précis:** An understanding of the genetic determinants of metastatic dissemination of medulloblastoma will make it possible to eliminate highly neurotoxic treatments, such as craniospinal radiation, which are currently indispensable for long-term survival.
Frequent PVT1 Rearrangement and Novel Chimeric Genes PVT1-NBEA and PVT1-WWOX Occur in Multiple Myeloma with 8q24 Abnormality

Précis: Not only MYC but also PVT1 has a pivotal role in the pathophysiology of multiple myeloma and possibly in other tumors with 8q24 abnormalities where MYC resides.

Chemotherapeutic Sensitivity of Testicular Germ Cell Tumors Under Hypoxic Conditions Is Negatively Regulated by SENP1-Controlled Sumoylation of OCT4
Yu-Chih Wu, Thai-Yen Ling, Shing-Hwa Lu, Hung-Chih Kuo, Hong-Nerng Ho, Shauh-Der Yeh, Chia-Ning Shen, and Yen-Hua Huang

Précis: This study reveals a rational strategy to degrade the chemoresistance of testicular tumors that have a poor prognosis.

RNF8 Regulates Assembly of RAD51 at DNA Double-Strand Breaks in the Absence of BRCA1 and 53BP1
Shinichiro Nakada, Rikako Miyamoto Yonamine, and Koichi Matsuo

Précis: By defining a major new component of DNA repair through homologous recombination, this study also suggests a new strategy to attack BRCA1-deficient breast cancers that are resistant to traditional chemotherapy as well as to experimental PARP1 inhibitors.

Cardiac Inflammation after Local Irradiation Is Influenced by the Kallikrein-Kinin System
Vijayalakshmi Sridharan, Preeti Tripathi, Sunil K. Sharma, Eduardo G. Moros, Peter M. Corry, Benjamin J. Lieblong, Elena Kaschina, Thomas Unger, Christa Thöne-Reineke, Martin Hauer-Jensen, and Marjan Boerma

Précis: These results enhance understanding of the causes of radiation-induced heart disease, a severe side effect that can occur with certain forms of radiotherapy of chest tumors, with possible implications for its prevention or management.

Prevention and Epidemiology

Viral RNA Patterns and High Viral Load Reliably Define Oropharynx Carcinomas with Active HPV16 Involvement
Dana Holzinger, Markus Schmitt, Gerhard Dyckhoff, Axel Benner, Michael Pawlita, and Franz X. Bosch

Précis: Identifying biomarkers that define the subset of oropharyngeal cancers driven by an increasing incidence of HPV16 infection could help improve treatment and clinical outcomes.

Biomarkers of HPV in Head and Neck Squamous Cell Carcinoma

Précis: Determining only the HPV16 DNA status or p16 immunostaining is not an effective prognostic biomarker for head and neck cancers on the rise, but combining these markers with E6/E7 antibody status has high predictive clinical value.

Therapeutics, Targets, and Chemical Biology

FLT-PET Is Superior to FDG-PET for Very Early Response Prediction in NPM-ALK-Positive Lymphoma Treated with Targeted Therapy
Zhoulei Li, Nicolas Graf, Ken Herrmann, Alexandra Jünger, Michaela Aichler, Annette Feuchtinger, Anja Baumgart, Axel Walch, Christian Peschel, Markus Schwaiger, Andreas Buck, Ulrich Keller, and Tobias Dechow

Précis: A novel method of PET imaging can predict responses to treatment with a targeted inhibitor early enough in the course of treatment that it may be possible to generate faster predictions of treatment efficacy, thereby determining whether or not a patient should remain on the treatment.

RKI-1447 Is a Potent Inhibitor of the Rho-Associated ROCK Kinases with Anti-Invasive and Antitumor Activities in Breast Cancer
Ronil A. Patel, Kara D. Forinash, Roberta Pirreddu, Ying Sun, Nan Sun, Mathew P. Martin, Ernst Schonbrunn, Nicholas J. Lawrence, and Saïd M. Sebti

Précis: ROCK kinases are intimately involved in tumor migration and invasion, and the discovery of a drug-like ROCK inhibitor offers significant potential as a novel anti-invasive and antitumor agent.
Inactivation of the HIF-1α/PDK3 Signaling Axis Drives Melanoma toward Mitochondrial Oxidative Metabolism and Potentiates the Therapeutic Activity of Pro-Oxidants


Précis: These findings offer preclinical validation of a bioenergetic pathway that can be exploited immediately to improve therapeutic intervention in metastatic melanoma.

Hedgehog Signaling Is a Novel Therapeutic Target in Tamoxifen-Resistant Breast Cancer Aberrantly Activated by PI3K/AKT Pathway

Bhuvaneswari Ramaswamy, Yuanzhi Lu, Kun-yu Teng, Gerard Nuovo, Xiaobai Li, Charles L. Shapiro, and Sarmila Majumder

Précis: Pharmacologic blockade of Hedgehog signaling may offer a general strategy to target breast cancer cells that have become resistant to hormone ablative therapy.

MEN1 Gene Replacement Therapy Reduces Proliferation Rates in a Mouse Model of Pituitary Adenomas

Gerard V. Walls, Manuel C. Lemos, Mahsa Javid, Miriam Bazan-Peregrino, Jeshmi Jeyabalanan, Anita A.C. Reed, Brian Harding, Damian J. Tyler, Daniel J. Stuckey, Ryan Piret, John E. French, Kyathanahalli S. Janardhan, and Anton M. Jetten

Précis: These findings offer a preclinical proof-of-concept for gene replacement therapy of pituitary adenomas with a relevant tumor-suppressor gene that is often mutated in this setting.

Intravesical Delivery of Small Activating RNA Formulated into Lipid Nanoparticles Inhibits Orthotopic Bladder Tumor Growth

Moo Rim Kang, Glen Yang, Robert F. Place, Klaus Charisse, Hila Epstein-Barash, Muthiah Manoharan, and Long-Cheng Li

Précis: This article offers a preclinical proof-of-concept for cancer treatment by RNA activation (RNAa), an RNA interference-related technology that uses small dsRNAs formulated into lipid nanoparticles to stimulate the expression of endogenous tumor-suppressor genes.
Adenylate Kinase-4 Is a Marker of Poor Clinical Outcomes That Promotes Metastasis of Lung Cancer by Downregulating the Transcription Factor ATF3

Yi-Hua Jan, Hong-Yuan Tsai, Chih-Jen Yang, Ming-Shyan Huang, Yi-Fang Yang, Tsung-Ching Lai, Chien-Hsin Lee, Yung-Ming Jeng, Chi-Ying Huang, Jen-Liang Su, Yung-Jen Chuang, and Michael Hsiao

Précis: These findings identify an adenylate kinase gene as a lung cancer progression marker that enhances the invasion ability of lung cancer and may represent a biomarker of metastasis.

Reciprocal Metabolic Reprogramming through Lactate Shuttle Coordinately Influences Tumor-Stroma Interplay

Tania Fiaschi, Alberto Marini, Elisa Giannoni, Maria Letizia Taddei, Paolo Gandellini, Alina De Donatis, Michele Lanciotti, Sergio Serni, Paolo Cirri, and Paola Chiarugi

Précis: This study furthers understanding of how cancer cells and cancer-associated fibroblasts support each other through coordinate control and exploitation of metabolic activity to survive nutrient-deprived conditions and license progress to more advanced stages of disease.

ABOUT THE COVER

Squamous cell carcinomas of the uterine cervix were subjected to dynamic contrast-enhanced magnetic resonance imaging by using gadolinium diethylene-triamine penta-acetic acid (Gd-DTPA) as contrast agent and an axial $T_1$-weighted spoiled gradient recalled sequence for imaging. The $T_1$-weighted images showed a high-signal intensity rim in the tumor periphery immediately after the contrast administration, and this rim moved outwards with time. The velocity of the rim movement at the tumor surface was associated with tumor interstitial fluid pressure and incidence of lymph node metastases, and may serve as a novel general biomarker of interstitial hypertension-induced tumor aggressiveness. For details, see article by Hompland and colleagues on page 4899.