

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 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 Øvrebø, 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 Reyat, 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.*

4954 **Frequent *PVT1* Rearrangement and Novel Chimeric Genes *PVT1-NBEA* and *PVT1-WWOX* Occur in Multiple Myeloma with 8q24 Abnormality**

Hisao Nagoshi, Tomohiko Taki, Ichiro Hanamura, Masakazu Nitta, Takemi Otsuki, Kazuhiro Nishida, Keiko Okuda, Natsumi Sakamoto, Satoru Kobayashi, Mio Yamamoto-Sugitani, Yasuhiko Tsutsumi, Tsutomu Kobayashi, Yosuke Matsumoto, Shigeo Horiike, Junya Kuroda, and Masafumi Taniwaki

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.

4963 **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.

4974 **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.

4984 **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

4993 **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.

5004 **Biomarkers of HPV in Head and Neck Squamous Cell Carcinoma**

Caihua Liang, Carmen J. Marsit, Michael D. McClean, Heather H. Nelson, Brock C. Christensen, Robert I. Haddad, John R. Clark, Richard O. Wein, Gregory A. Grillone, E. Andres Houseman, Gordana Halec, Tim Waterboer, Michael Pawlita, Jeffrey F. Krane, and Karl T. Kelsey

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

5014 **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.

5025 **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 Pireddu, Ying Sun, Nan Sun, Mathew P. Martin, Ernst Schönbrunn, 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.

5035

Inactivation of the HIF-1 α /PDK3 Signaling Axis Drives Melanoma toward Mitochondrial Oxidative Metabolism and Potentiates the Therapeutic Activity of Pro-Oxidants

Jérôme Kluza, Paola Corazao-Rozas, Yasmine Touil, Manel Jendoubi, Cyril Maire, Pierre Guerreschi, Aurélie Jonneaux, Caroline Ballot, Stéphane Balayssac, Samuel Valable, Aurélien Corroyer-Dulmont, Myriam Bernaudin, Myriam Malet-Martino, Elisabeth Martin de Lassalle, Patrice Maboudou, Pierre Formstecher, Renata Polakowska, Laurent Mortier, and Philippe Marchetti

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

5048

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

Bhuvanewari 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.

5060

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 Jeyabalan, Anita A.C. Reed, Brian Harding, Damian J. Tyler, Daniel J. Stuckey, Sian Piret, Paul T. Christie, Olaf Ansorge, Kieran Clarke, Len Seymour, and Rajesh V. Thakker

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.

5069

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.

TUMOR AND STEM CELL BIOLOGY

5080

RAP80 Is Critical in Maintaining Genomic Stability and Suppressing Tumor Development

Zhengyu Yin, Daniel Menendez, Michael A. Resnick, John E. French, Kyathanahalli S. Janardhan, and Anton M. Jetten

Précis: A protein that binds ubiquitinated histones and recruits BRCA1 and other DNA repair proteins to chromatin is found to exert an important function in tumor suppression.

5091

Transition from Colitis to Cancer: High Wnt Activity Sustains the Tumor-Initiating Potential of Colon Cancer Stem Cell Precursors

Anitha K. Shenoy, Robert C. Fisher, Elizabeth A. Butterworth, Liya Pi, Lung-Ji Chang, Henry D. Appelman, Myron Chang, Edward W. Scott, and Emina H. Huang

Précis: These findings link activation of the Wnt signaling pathway to colitis-associated cancer, suggesting both a promising diagnostic marker and a therapeutic target to prevent the transition from inflammatory colitis to colon cancer.

5101

Induction of the Stem-like Cell Regulator CD44 by Rho Kinase Inhibition Contributes to the Maintenance of Colon Cancer-Initiating Cells

Hirokazu Ohata, Tatsuya Ishiguro, Yuki Aihara, Ai Sato, Hiroaki Sakai, Shigeki Sekine, Hirokazu Taniguchi, Takayuki Akasu, Shin Fujita, Hitoshi Nakagama, and Koji Okamoto

Précis: This study offers a potentially seminal mechanistic insight into how cancer stem-like cells maintain their tumor-initiating characteristics, with immediate implications for how to therapeutically target these cells for eradication.

5111

CD133⁺ Melanoma Subpopulations Contribute to Perivascular Niche Morphogenesis and Tumorigenicity through Vasculogenic Mimicry

Chiou-Yan Lai, Brian E. Schwartz, and Mei-Yu Hsu

Précis: This important study broadens the concept of how cancer stem-like cells drive tumor formation and progression by revealing that they can enable vascular mimicry—the formation of unique perivascular structures that can promote blood supply.

5119

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.

5130

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.

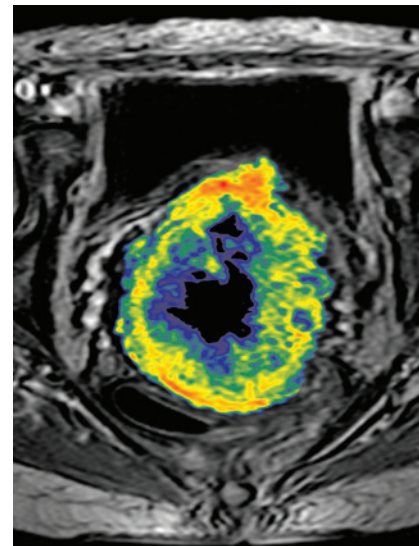
CORRECTION

5141

Correction: Small-Molecule Anticancer Compounds Selectively Target the Hemopexin Domain of Matrix Metalloproteinase-9

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.



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