



**BREAKING ADVANCES**

- 1243** Highlights from Recent Cancer Literature



**REVIEWS**

- 1245**  **Interplay between Immune Checkpoint Proteins and Cellular Metabolism**  
Sangbin Lim, Joshua B. Phillips, Luciana Madeira da Silva, Ming Zhou, Oystein Fodstad, Laurie B. Owen, and Ming Tan
- 1250**  **Recommended Guidelines for Validation, Quality Control, and Reporting of *TP53* Variants in Clinical Practice**  
Bernard Leroy, Mandy L. Ballinger, Fanny Baran-Marszak, Gareth L. Bond, Antony Braithwaite, Nicole Concin, Lawrence A. Donehower, Wafik S. El-Deiry, Pierre Fenaux, Gianluca Gaidano, Anita Langerød, Eva Hellstrom-Lindberg, Richard Iggo, Jacqueline Lehmann-Che, Phuong L. Mai, David Malkin, Ute M. Moll, Jeffrey N. Myers, Kim E. Nichols, Sarka Pospisilova, Patricia Ashton-Prolla, Davide Rossi, Sharon A. Savage, Louise C. Strong, Patricia N. Tonin, Robert Zeillinger, Thorsten Zenz, Joseph F. Fraumeni Jr, Peter E.M. Taschner, Pierre Hainaut, and Thierry Soussi
- 1261** **Advances in the Classification and Treatment of Mastocytosis: Current Status and Outlook toward the Future**  
Peter Valent, Cem Akin, Karin Hartmann, Gunnar Nilsson, Andreas Reiter, Olivier Hermine, Karl Sotlar, Wolfgang R. Sperr, Luis Escribano, Tracy I. George, Hanneke C. Kluin-Nelemans, Celalettin Ustun, Massimo Triggiani, Knut Brockow, Jason Gotlib, Alberto Orfao, Lawrence B. Schwartz, Sigurd Broesby-Olsen, Carsten Bindslev-Jensen, Petri T. Kovanen, Stephen J. Galli, K. Frank Austen, Daniel A. Arber, Hans-Peter Horny, Michel Arock, and Dean D. Metcalfe

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

- 1271** **Systematic Pan-Cancer Analysis Reveals Immune Cell Interactions in the Tumor Microenvironment**  
Frederick S. Varn, Yue Wang, David W. Mullins, Steven Fiering, and Chao Cheng  
*Précis:* This study uses genomic data to deepen our understanding of the interplay between immune cells within the tumor microenvironment, with a specific focus on myeloid cell-driven modulation of CD8<sup>+</sup> T cells and their role in patient survival.

**MICROENVIRONMENT AND IMMUNOLOGY**

- 1283** **Bone Pain Induced by Multiple Myeloma Is Reduced by Targeting V-ATPase and ASIC3**  
Masahiro Hiasa, Tatsuo Okui, Yohance M. Allette, Matthew S. Ripsch, Ge-Hong Sun-Wada, Hiroki Wakabayashi, G. David Roodman, Fletcher A. White, and Toshiyuki Yoneda  
*Précis:* These findings present a mechanistic rationale to relieve the severe bone pain experienced by multiple myeloma patients, with immediate clinical implications for treatment.
- 1296**  **A Multifunctional Role for Adjuvant Anti-4-1BB Therapy in Augmenting Antitumor Response by Chimeric Antigen Receptor T Cells**  
Sherly Mardiana, Liza B. John, Melissa A. Henderson, Clare Y. Slaney, Bianca von Scheidt, Lauren Giuffrida, Alexander J. Davenport, Joseph A. Trapani, Paul J. Neeson, Sherene Loi, Nicole M. Haynes, Michael H. Kershaw, Paul A. Beavis, and Phillip K. Darcy  
*Précis:* Combination therapy using an agonistic antibody can significantly enhance CAR T-cell response, concomitant with reduced numbers of immunosuppressive cell types, suggesting a potentially powerful approach to treat solid cancers with adoptive immunotherapy.
- 1310** **Radiation-Induced Enhancement of Antitumor T-cell Immunity by VEGF-Targeted 4-1BB Costimulation**  
Brett Schrand, Bhavna Verma, Agata Levay, Shradha Patel, Iris Castro, Ana Paula Benaduce, Randall Brenneman, Oliver Umland, Hideo Yagita, Eli Gilboa, and Adrian Ishkanian  
*Précis:* Immunomodulatory aptamers can be targeted directly to tumors by binding to radiation-induced tumor stress products, increasing therapeutic index.
- 1322**  **Immune Toxicities Elicited by CTLA-4 Blockade in Cancer Patients Are Associated with Early Diversification of the T-cell Repertoire**  
David Y. Oh, Jason Cham, Li Zhang, Grant Fong, Serena S. Kwek, Mark Klinger, Malek Faham, and Lawrence Fong  
*Précis:* Autoimmune side effects often seen with immune checkpoint inhibitors are associated with rapid increases in the diversity of the circulating T-cell pool.

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## MOLECULAR AND CELLULAR PATHOBIOLOGY

**1331** Bone Metastasis of Prostate Cancer Can Be Therapeutically Targeted at the TBX2–WNT Signaling Axis



Srinivas Nandana, Manisha Tripathi, Peng Duan, Chia-Yi Chu, Rajeev Mishra, Chunyan Liu, Renjie Jin, Hironobu Yamashita, Majd Zayzafoon, Neil A. Bhowmick, Haiyen E. Zhau, Robert J. Matusik, and Leland W.K. Chung

*Précis:* These findings provide a mechanism-based targeting rationale to inhibit bone metastasis in advanced prostate cancer, a common feature of late stage disease.

**1345** RelB Expression Determines the Differential Effects of Ascorbic Acid in Normal and Cancer Cells

Xiaowei Wei, Yong Xu, Fang Fang Xu, Luksana Chaiswing, David Schnell, Teresa Noel, Chi Wang, Jinfei Chen, Daret K. St. Clair, and William H. St. Clair

*Précis:* Changing ROS levels affects levels of the NF- $\kappa$ B transcription factor RelB, thereby affecting the capability of *i.v.* ascorbic acid to differentially and usefully influence the radiosensitivity of normal and cancer tissues.

**1357** A Transposon-based Analysis Reveals RASA1 Is Involved in Triple-Negative Breast Cancer

Cristian Suárez-Cabrera, Rita M. Quintana, Ana Bravo, M. Llanos Casanova, Angustias Page, Josefa P. Alameda, Jesús M. Paramio, Alicia Maroto, Javier Salamanca, Adam J. Dupuy, Angel Ramírez, and Manuel Navarro

*Précis:* Allelic loss of *Rasa1*, a gene controlling the *Ras* pathway, is a frequent occurrence in triple-negative breast cancer.

**1369** Long Noncoding RNA LINC00092 Acts in Cancer-Associated Fibroblasts to Drive Glycolysis and Progression of Ovarian Cancer

Linjie Zhao, Gaili Ji, Xiaobing Le, Chenlu Wang, Lian Xu, Min Feng, Yaguang Zhang, Huiliang Yang, Yu Xuan, Yanfei Yang, Lingzi Lei, Qilian Yang, Wayne Bond Lau, Bonnie Lau, Yi Chen, Xiangbing Deng, Shaohua Yao, Tao Yi, Xia Zhao, Yuquan Wei, and Shengtao Zhou

*Précis:* This study uncovers a positive feedback loop in the metabolism of cancer-associated fibroblasts and epithelial ovarian cancer cells critical for their metastatic progression.

**1383** Aberrant Phosphorylation of SMAD4 Thr277-Mediated USP9x–SMAD4 Interaction by Free Fatty Acids Promotes Breast Cancer Metastasis



Yong Wu, Xiaoting Yu, Xianghua Yi, Ke Wu, Sami Dwabe, Mohammad Atefi, Yahya Elshimali, Kevin T. Kemp II, Kruttika Bhat, Jesse Haro, Marianna Sarkissyan, and Jaydutt V. Vadgama

*Précis:* These findings highlight the mechanism behind the increased risk of distant metastatic recurrence in overweight and obese breast cancer patients.

**1395** Tumor-Associated Neutrophils and Macrophages Promote Gender Disparity in Hepatocellular Carcinoma in Zebrafish

Chuan Yan, Qiqi Yang, and Zhiyuan Gong

*Précis:* Increased production of the chronic inflammation factor cortisol contributes to the predominance of liver cancer development in males versus females.

## PREVENTION AND EPIDEMIOLOGY

**1408** Biomarker Dynamics in B-cell Lymphoma: A Longitudinal Prospective Study of Plasma Samples Up to 25 Years before Diagnosis



Florentin Späth, Carl Wibom, Esmeralda J.M. Krop, Ann-Sofie Johansson, Ingvar A. Bergdahl, Roel Vermeulen, and Beatrice Melin

*Précis:* Sustained B-cell activation is a dynamic process during lymphomagenesis that may be indicative of occult disease or disease progression in monitoring patients with indolent lymphomas.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**1416** Reprogramming Medulloblastoma-Propagating Cells by a Combined Antagonism of Sonic Hedgehog and CXCR4



Stacey A. Ward, Nicole M. Warrington, Sara Taylor, Najla Kfoury, Jingjin Luo, and Joshua B. Rubin

*Précis:* These findings suggest a mechanism-based approach to eradicate the most recalcitrant cells in one common type of pediatric brain cancer.

**1427** Two-Pore Channel Function Is Crucial for the Migration of Invasive Cancer Cells

Ong Nam Phuong Nguyen, Christian Grimm, Lina S. Schneider, Yu-Kai Chao, Carina Atzberger, Karin Bartel, Anna Watermann, Melanie Ullrich, Doris Mayr, Christian Wahl-Schott, Martin Biel, and Angelika M. Vollmar

*Précis:* These findings reveal a role for endolysosomal two-pore channels in leading edge formation in cancer cells, suggesting their novelty as targets for treatment of invasive tumors.

**1439** Constitutive NOTCH3 Signaling Promotes the Growth of Basal Breast Cancers



Lisa Choy, Thijs J. Hagenbeek, Margaret Solon, Dorothy French, David Finkle, Amy Shelton, Rayna Venook, Matthew J. Brauer, and Christian W. Siebel

*Précis:* An antibody that can directly assess receptor signaling distinguishes constitutive and ligand-independent activity of the oncogenic Notch pathway in enabling the malignant growth of basal breast cancers.

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**1453** Bone Marrow Adipocytes Facilitate Fatty Acid Oxidation Activating AMPK and a Transcriptional Network Supporting Survival of Acute Monocytic Leukemia Cells

Yoko Tabe, Shinichi Yamamoto, Kaori Saitoh, Kazumasa Sekihara, Norikazu Monma, Kazuho Ikeo, Kaoru Mogushi, Masato Shikami, Vivian Ruvolo, Jo Ishizawa, Numsen Hail Jr, Saiko Kazuno, Mamoru Igarashi, Hiromichi Matsushita, Yasunari Yamanaka, Hajime Arai, Isao Nagaoka, Takashi Miida, Yoshihide Hayashizaki, Marina Konopleva, and Michael Andreuff

*Précis:* These findings suggest that targeting metabolic abnormalities in leukemia cells located in the bone marrow is potentially promising and innovative therapeutic approach.

**1465** Fibrinolytic Enzyme Cotherapy Improves Tumor Perfusion and Therapeutic Efficacy of Anticancer Nanomedicine

Ameya R. Kirtane, Tanmoy Sadhukha, Hyunjoon Kim, Vidhi Khanna, Brenda Koniari, and Jayanth Panyam

*Précis:* These findings suggest that cotherapy with a fibrinolytic enzyme could be used to improve diffusion, intratumoral distribution, and overall effectiveness of anticancer nanomedicine.

**1476** [<sup>18</sup>F](2*S*,4*R*)4-Fluoroglutamine PET Detects Glutamine Pool Size Changes in Triple-Negative Breast Cancer in Response to Glutaminase Inhibition

Rong Zhou, Austin R. Pantel, Shihong Li, Brian P. Lieberman, Karl Ploessl, Hoon Choi, Eric Blankemeyer, Hsiaoju Lee, Hank F. Kung, Robert H. Mach, and David A. Mankoff

*Précis:* These findings reveal the utility of a noninvasive PET imaging method to monitor pharmacodynamic responses to cancer drugs that target glutamine breakdown.

**1485** Prostate Cancer Patients with Late Radiation Toxicity Exhibit Reduced Expression of Genes Involved in DNA Double-Strand Break Repair and Homologous Recombination

Bregje van Oorschot, Lon Uitterhoeve, Ilja Oomen, Rosemarie ten Cate, Jan Paul Medema, Harry Vrieling, Lukas J.A. Stalpers, Perry D. Moerland, and Nicolaas A.P. Franken

*Précis:* Patients who are inherently less efficient at DNA double-strand break repair may be at risk for severe late radiation toxicity.

**1492** Aberrant SYK Kinase Signaling Is Essential for Tumorigenesis Induced by TSC2 Inactivation

Ye Cui, Wendy K. Steagall, Anthony M. Lamattina, Gustavo Pacheco-Rodriguez, Mario Stylianou, Pranav Kidambi, Benjamin Stump, Fernanda Golzarri, Ivan O. Rosas, Carmen Priolo, Elizabeth P. Henske, Joel Moss, and Souheil El-Chemaly

*Précis:* These results illuminate how mutations in the tumor suppressor gene TSC2 lead to formation of a variety of organ lesions.

## CORRECTIONS

**1503** Correction: Long Noncoding RNA GCASPC, a Target of miR-17-3p, Negatively Regulates Pyruvate Carboxylase-Dependent Cell Proliferation in Gallbladder Cancer

**1504** Correction: Cdk5 Directly Targets Nuclear p21<sup>CIP1</sup> and Promotes Cancer Cell Growth

**1505** Correction: Differential Regulation of the Melanoma Proteome by eIF4A1 and eIF4E

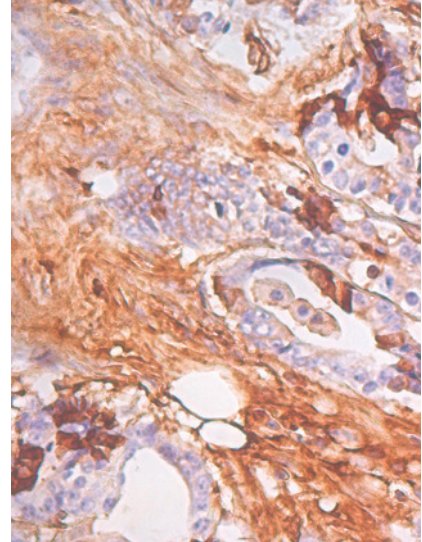
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## ABOUT THE COVER

Many human tumors are characterized by extensive fibrin deposition in their extracellular matrix. Shown here is a representative image of a human colon tumor section stained for fibrin. For details, see article by Kirtane and colleagues on page 1465.



# Cancer Research

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