### BREAKING ADVANCES

1041 Highlights from Recent Cancer Literature

### REVIEWS

1043 Concomitant Tumor Resistance: The Role of Tyrosine Isomers in the Mechanisms of Metastases Control
Raúl A. Ruggiero, Juan Bruzzo, Paula Chiarella, Oscar D. Bustuobad, Roberto P. Meiss, and Christiane D. Pasqualini

1051 Consistency Test of the Cell Cycle: Roles for p53 and EGR1
Yaara Zwang, Moshe Oren, and Yosef Yarden

### PERSPECTIVE

1055 Repurposing Approved and Abandoned Drugs for the Treatment and Prevention of Cancer through Public–Private Partnership
Scott J. Weir, Louis J. DeGennaro, and Christopher P. Austin

### PRIORITY REPORTS

1059 Human Th17 Immune Cells Specific for the Tumor Antigen MAGE-A3 Convert to IFN-γ-Secreting Cells as They Differentiate into Effector T Cells In Vivo
Ahmed Hamai, Pascale Pignon, Isabelle Raimbaud, Karine Duperrier-Amouriaux, Hélène Senellart, Sandrine Hiret, Jean-Yves Douillard, Jaafar Bennouma, Maha Ayyoub, and Danila Valmori

**Précis:** Naturally arising Th17 helper T cells that are specific for a common tumor antigen in cancer patients tend to convert into IFN-γ-secreting cells as they differentiate into effector T cells, a finding that encourages the development of methods to amplify them through immunotherapy.

1064 Ovarian Cancer Risk Associated with Inherited Inflammation-Related Variants

**Précis:** A large case–control study reveals that an inherited variant of the proinflammatory interleukin gene IL1A is associated with the risk of most types of ovarian cancer, offering powerful genetic support for a common role of inflammation in this disease.

### MICROENVIRONMENT AND IMMUNOLOGY

1070 Immunotype and Immunohistologic Characteristics of Tumor-Infiltrating Immune Cells Are Associated with Clinical Outcome in Metastatic Melanoma
Gulsun Erdag, Jochen T. Schafer, Mark E. Smolkin, Donna H. Deacon, Sofia M. Shea, Lynn T. Dengel, James W. Patterson, and Craig L. Slingluff Jr

**Précis:** The characteristics of immune infiltrates in metastases—an immunotype—may not only offer useful prognostic information but also the potential for personalized immunotherapy by tailoring strategies to manipulate the immunotype appropriately.

1081 Exploiting the Mutanome for Tumor Vaccination
John C. Castle, Sebastian Kreiter, Jan Diekmann, Martin Löwer, Niels van de Roemer, Jos de Graaf, Abderraouf Selmi, Mustafa Diken, Sebastian Boegel, Claudia Paret, Michael Koslowski, Andreas N. Kuhn, Cedrik M. Britten, Christoph Huber, Ozlem Tureci, and Ugur Sahin

**Précis:** This important study heralds strategies for personalized vaccinations of cancer patients, through the use of deep sequencing analysis, which shows that many nonsynonymous somatic mutations in a tumor are sufficient to confer antitumor activity to a peptide vaccine.
Tumor-Derived Chemokine CCL5 Enhances TGF-β–Mediated Killing of CD8+ T Cells in Colon Cancer by T-Regulatory Cells


Precis: This intriguing study tightens the emerging connections in cancer between inflammation, immune escape, and metastasis by showing how a chemokine implicated in inflammation and metastasis also drives immune escape by recruiting Treg cells that promote progression into tumors.

VEGF Receptor Inhibitors Block the Ability of Metronomically Dosed Cyclophosphamide to Activate Innate Immunity–Induced Tumor Regression

Joshua C. Doloff and David J. Waxman

Precis: Anti-VEGFR drugs can block beneficial antitumor immune responses that are triggered by periodic administration of cytotoxic chemotherapy, with implications for clinical trials that combine these drug classes.

Effective Treatment of Metastatic Forms of Epstein-Barr Virus–Associated Nasopharyngeal Carcinoma with a Novel Adenovirus-Based Adoptive Immunotherapy

Corey Smith, Janice Tsang, Leone Beagley, Daniel Chua, Victor Lee, Vivian Li, Denis J. Moss, William Coman, Kwok H. Chan, John Nicholls, Dora Kwong, and Rajiv Khanna

Precis: Early clinical findings reported in this study support the ongoing development of an immunotherapy for progressed forms of the most common throat cancer in the Far East, an endemic disease associated with EBV infections in a manner analogous to the association of HPV infections in cervical cancer.

Upregulation of miR-196a and HOTAIR Drive Malignant Character in Gastrointestinal Stromal Tumors

Takeshi Niinuma, Hiromu Suzuki, Masanori Nojima, Katsuhiko Nosho, Hiroyuki Yamamoto, Hiroaki Takamaru, Eiichiro Yamamoto, Reo Maruyama, Takayuki Nishida, Yasuaki Miyazaki, Toshiro Nishida, Takeo Bamba, Tatsuo Kanda, Yoichi Ajikawa, Takahiro Taguchi, Satoshi Okahara, Hiroaki Takahashi, Yasunori Nishida, Masao Hosokawa, Tadashi Hasagawa, Takashi Tokino, Koichi Hirata, Kohzhoh Imai, Minoru Toyota, and Yasuhsa Shinomura

Precis: This study is among the first to reveal an important role in human cancer for HOTAIR, a member of an as yet little studied new category of long noncoding RNAs that may have broad applications as biomarkers or therapeutic targets in oncology.

KR-POK Interacts with p53 and Represses Its Ability to Activate Transcription of p21WAF1/CDKN1A

Bu-Nam Jeon, Min-Kyeong Kim, Won-Il Choi, Dong-In Koh, Sung-Yi Hong, Kyung-Sup Kim, Minjung Kim, Chae-Ok Yun, Ju young Yoon, Kang-Yell Choi, Kyung-Ryul Lee, Kenneth P. Nepherw, and Man-Wook Hur

Precis: Findings provide important novel insights into how the transcriptional activation function of p53 is repressed in cells, with implications for understanding a new oncogenic pathway in kidney cancers.

ATR–ATRIP Kinase Complex Triggers Activation of the Fanconi Anemia DNA Repair Pathway

Tomoko Shigechi, Junya Tomida, Koichi Sato, Masahiko Kobayashi, John K. Eykelenboom, Fabio Pessina, Yanbin Zhang, Emi Uchida, Masamichi Ishii, Noel F. Lowndes, Kenichi Yamamoto, Hitoshi Kurumizaka, Yoshikiko Maehara, and Minoru Takata

Precis: Findings advance pathophysiologic understanding of a cancer-disposing disorder, Fanconi anemia, and reveal key insights into fundamental control pathways for S-phase DNA repair and cell-cycle checkpoint defective in cancer.
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<td><strong>Kaposi Sarcoma Herpesvirus Promotes Endothelial-to-Mesenchymal Transition through Notch-Dependent Signaling</strong>&lt;br&gt;Paola Gasperini, Georgina Espigol-Frigole, Peter J. McCormick, Ombretta Salvucci, Dragan Maric, Thomas S. Uldrick, Mark N. Polizzotto, Robert Yarchoon, and Giovanna Tosato&lt;br&gt;&lt;br&gt;<em>Précis: This study identifies a basis to understand the aggressiveness of a mesenchymal cancer that occurs commonly in AIDS patients, with implications for its better treatment with Notch pathway inhibitors currently being explored in clinical trials.</em></td>
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<td><strong>DNA Methylation Does Not Stably Lock Gene Expression but Instead Serves as a Molecular Mark for Gene Silencing Memory</strong>&lt;br&gt;Noël J.-M. Raynal, Jiali Si, Rodolphe F. Taby, Vazganush Gharibyan, Saira Ahmed, Jaroslav Jelinek, Marcos R.H. Estécio, and Jean-Pierre J. Issa&lt;br&gt;&lt;br&gt;<em>Précis: Chromatin is a target for epigenetic cancer therapies that reactivate gene expression, but removal of DNA methylation signals is required first to achieve durable long-term effects.</em></td>
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<td><strong>Impact of Circulating Vitamin D Binding Protein Levels on the Association between 25-Hydroxyvitamin D and Pancreatic Cancer Risk: A Nested Case-Control Study</strong>&lt;br&gt;Stephanie J. Weinstein, Rachael Z. Stolzenberg-Solomon, William Kopp, Helen Rager, Jarmo Virtamo, and Demetrius Albanes&lt;br&gt;&lt;br&gt;<em>Précis: Findings suggest an explanation for the adverse influence of vitamin D on risk of pancreatic cancer, which contrasts with some other solid tumors, with implications for how future risk association studies of vitamin D may be designed.</em></td>
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<td><strong>Cathepsin B Inhibition Limits Bone Metastasis in Breast Cancer</strong>&lt;br&gt;Nimani P. Withana, Gahia Blum, Mansoureh Sameni, Clare Slaney, Arulselvi Anbalagan, Mary B. Olive, Bradley N. Bidwell, Laura Edgington, Ling Wang, Kamiar Moin, Bonnie F. Sloane, Robin L. Anderson, Matthew S. Bogyo, and Belinda S. Parker&lt;br&gt;&lt;br&gt;<em>Précis: Important findings suggest a new strategy to block metastasis of breast cancer cells to bone, a common feature of malignant progression in breast cancer patients with few effective treatment options at present.</em></td>
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<td><strong>DNA Methylation Does Not Stably Lock Gene Expression but Instead Serves as a Molecular Mark for Gene Silencing Memory</strong>&lt;br&gt;Noël J.-M. Raynal, Jiali Si, Rodolphe F. Taby, Vazganush Gharibyan, Saira Ahmed, Jaroslav Jelinek, Marcos R.H. Estécio, and Jean-Pierre J. Issa&lt;br&gt;&lt;br&gt;<em>Précis: Chromatin is a target for epigenetic cancer therapies that reactivate gene expression, but removal of DNA methylation signals is required first to achieve durable long-term effects.</em></td>
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<td><strong>RNAi-Mediated Targeting of Noncoding and Coding Sequences in DNA Repair Gene Messages Efficiently Radiosensitizes Human Tumor Cells</strong>&lt;br&gt;Zhiming Zheng, Wooi Loon Ng, Xiangning Zhang, Jeffrey J. Olson, Chunhui Hao, Walter J. Curran, and Ya Wang&lt;br&gt;&lt;br&gt;<em>Précis: This study defines a generalized approach for highly efficient RNAi-based gene silencing, using a combinatorial targeting strategy to illustrate how knockdown of DNA repair genes can effectively radiosensitize tumor cells.</em></td>
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<td><strong>LRIG1 Modulates Cancer Cell Sensitivity to Smac Mimetics by Regulating TNFα Expression and Receptor Tyrosine Kinase Signaling</strong>&lt;br&gt;Longchuan Bai, Donna McEachern, Chao-Yie Yang, Jianfeng Lu, Haiying Sun, and Shaomeng Wang&lt;br&gt;&lt;br&gt;<em>Précis: This study provides key insights into the basis for resistance to IAP inhibitors, possibly critical to the successful clinical development of this new class of cancer drugs.</em></td>
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Adoptive Cell Therapy for Lymphoma with CD4 T Cells Depleted of CD137-Expressing Regulatory T Cells
Matthew J. Goldstein, Holbrook E. Kohrt, Roch Houot, Bindu Varghese, Jack T. Lin, Erica Swanson, and Ronald Levy

Précis: This important study provides knowledge that can immediately be translated into the clinical setting to optimize cell-based cancer immunotherapies based on adoptive transfer of CD4+ T lymphocytes.

TUMOR AND STEM CELL BIOLOGY

Targeting Pioneering Factor and Hormone Receptor Cooperative Pathways to Suppress Tumor Progression
Supriya Shah, Shikha Prasad, and Karen E. Knudsen

Précis: Findings reveal that the turmeric spice component curcumin can act in a combinatorial manner to disrupt histone modification and androgen receptor signaling to control prostate cancer growth.

PRAS40 Is a Functionally Critical Target for EWS Repression in Ewing Sarcoma
Lin Huang, Yuji Nakai, Iku Kuwahara, and Ken Matsumoto

Précis: An Akt substrate is identified as a critical oncogenic mediator in an aggressive type of pediatric cancer that has had an elusive molecular pathobiology.

p53 Inhibits Angiogenesis by Inducing the Production of Arresten
Sarah Assaadian, Wissal El-Assaad, Xue Q.D. Wang, Phillipe O. Gannon, Véronique Barrès, Mathieu Latour, Anne-Marie Mes-Masson, Fred Saad, Yoshikazu Sado, Josée Dostie, and Jose G. Teodoro

Précis: In addition to its well studied effects on tumor cell growth, senescence, and survival, p53 also acts in many ways to modify the cellular microenvironment, including through regulation of antiangiogenic factors.

Pocket Proteins Suppress Head and Neck Cancer
Myeong-Kyun Shin, Henry C. Pitot, and Paul F. Lambert

Précis: Genetic inactivation of the tumor suppressor protein Rb, and its relative p107, is sufficient to phenocopy the oncogenic activity of the human papillomavirus E7 oncoprotein in stimulating formation of head and neck cancer in mice, thereby establishing the importance of Rb/p107 functions in virally associated forms of this cancer which are rising rapidly in incidence.

Epithelial–Mesenchymal Transition Induced by TNF-α Requires NF-κB-Mediated Transcriptional Upregulation of Twist1
Chia-Wei Li, Weiya Xia, Longlei Huo, Seung-Oe Lim, Yun Wu, Jennifer L. Hsu, Chi-Hong Chao, Hirohito Yamaguchi, Neng-Kai Yang, Qingqing Ding, Yan Wang, Yun-Ju Lai, Adam M. LaRuffa, Ting-Jung Wu, Been-Hen Lin, Muh-Hwa Yang, Gabriel N. Hortobagyi, and Mien-Chie Hung

Précis: Results offer key mechanistic insights into how a major proinflammatory driver in the tumor microenvironment promotes epithelial-to-mesenchymal transition and stemness properties in breast cancer cells, with implications into how to therapeutically reverse these features of aggressive progression.

Oncogenicity of the Developmental Transcription Factor Sox9
Ander Matheu, Manuel Collado, Clare Wise, Lorea Manterola, Lina Cekaite, Angela J. Tye, Marta Canamero, Luis Bujanda, Andreas Schell, Kathryn S.E. Cheah, Rolf I. Skotheim, Ragnhild A. Lothe, Adolfo López de Munain, James Briscoe, Manuel Serrano, and Robin Lovell-Badge

Précis: Sox9, a gene active during embryogenesis and in adult stem cells, is found to be widely upregulated in various cancers where its expression is associated with unrestrained cell proliferation, immortalization, and tumorigenesis.

CORRECTIONS

Correction: Increased Survival of Glioblastoma Patients Who Respond to Antiangiogenic Therapy with Elevated Blood Perfusion

Correction: Regulation of Matrix Metalloproteinase Genes by E2F Transcription Factors: Rb–Raf-1 Interaction as a Novel Target for Metastatic Disease
ABOUT THE COVER

A number of cathepsin proteases have been documented to promote tumor invasion and metastasis. However, the role of specific proteases in breast cancer metastasis and the therapeutic potential of their selective inhibition in clinically relevant models are not clear. Using 3D and in vivo models, Withana and colleagues have shown that the cysteine protease cathepsin B has important roles in breast cancer metastasis and that therapeutic inhibition of this protease using small-molecule inhibitors dramatically decreases metastasis to lung and bone. The cover image was produced with fluorescent whole-body imaging using a cysteine cathepsin activity–based fluorescent probe (GB123) and the fluorescent diphosphonate probe Osteosense 750, which detects bone remodeling. The image shows cysteine cathepsin activity along the spine of mice bearing bone metastatic tumors. This activity is reduced in mice treated with the cathepsin B selective small-molecule inhibitor CA-074. For details, see the article by Withana and colleagues on page 1199 of this issue.