**Breaking Advances**

7149 Highlights from Recent Cancer Literature

**Point-Counterpoint Reviews**

7151 It Is Not Always Necessary to Do Axillary Dissection for T1 and T2 Breast Cancer—Point
Monica Morrow
See Counterpoint and Reply by Sabel, p. 7156 and 7155

7155 It Is Not Always Necessary to Do Axillary Dissection for T1 and T2 Breast Cancer—Reply to Point
Michael S. Sabel
See Point by Morrow, p. 7151

7156 The Need for Axillary Lymph Node Dissection in T1/T2 Breast Cancer Surgery—Counterpoint
Michael S. Sabel
See Point and Reply by Morrow, p. 7151 and p. 7161

7161 The Need for Axillary Lymph Node Dissection in T1/T2 Breast Cancer Surgery—Reply to Counterpoint
Monica Morrow
See Counterpoint by Sabel, p. 7156

**Priority Report**

7162 TERT Promoter Mutations Occur Early in Urothelial Neoplasia and Are Biomarkers of Early Disease and Disease Recurrence in Urine
Isaac Kinde, Enrico Munari, Sheila F. Faraj, Ralph H. Hruban, Mark Schoenberg, Trinity Bivalacqua, Mohammad Allaf, Simeon Springer, Yuxuan Wang, Luis A. Diaz, Jr., Kenneth W. Kinzler, Bert Vogelstein, Nicholas Papadopoulos, and George J. Netto

**Integrated Systems and Technologies**

7168 The Role of Cell Density and Intratumoral Heterogeneity in Multidrug Resistance
Orit Lavi, James M. Greene, Doron Levy, and Michael M. Gottesman

Précis: The new model suggested in this report might improve the design of treatment protocols and the analysis of patient responses to therapy.

7176 A Circadian Clock Transcription Model for the Personalization of Cancer Chronotherapy

Précis: A better understanding of a regulatory transcription loop that controls the molecular clock functions of normal cells might critically improve the tolerability of chemotherapy in patients.

**Microenvironment and Immunology**

7189 OX40 Is a Potent Immune-Stimulating Target in Late-Stage Cancer Patients
Brendan D. Curti, Magdalena Kovacsovics-Bankowski, Nicholas Morris, Edwin Walker, Lana Chisholm, Kevin Floyd, Joshua Walker, Iliana Gonzalez, Tanisha Meeusen, Bernard A. Fox, Tarsem Moudgil, William Miller, Daniel Haley, Todd Coffey, Brenda Fisher, Laurie Delaney-Miller, Nicole Rymarchuk, Tracy Kelly, Todd Crocenzi, Eric Bernstein, Rachel Sanborn, Walter J. Urba, and Andrew D. Weinberg

Précis: This study offers clinical validation of a cancer therapy composed of a monoclonal antibody that can agonize signaling by the OX40 coreceptor on T cells, acting to enhance their antitumor properties as a generalized immunotherapy.

7199 Gut Microbiota Protects against Gastrointestinal Tumorigenesis Caused by Epithelial Injury
Yu Zhan, Po-Ju Chen, William D. Sadler, Fuyuan Wang, Sara Poe, Gabriel Nüñez, Kathryn A. Eaton, and Grace Y. Chen

Précis: This study highlights the beneficial impact of commensal bacteria on limiting colon tumorigenesis and provides a model system that will enable us to identify bacteria that help reduce susceptibility to colon cancer.
TLR9 Signaling in the Tumor Microenvironment Initiates Cancer Recurrence after Radiotherapy

Chan Gao, Anna Kozlowska, Sergey Nechaev, Haiqing Li, Qifang Zhang, Dewan M.S. Hossain, Claudia M. Kowollik, Peiguo Chu, Piotr Swiderski, Don J. Diamond, Sumanta K. Pal, Andrew Rauhtsche, and Marcin Kortylewski

Précis: These findings suggest a rationale to improve the efficacy of cancer radiotherapy with inhibitors of the TLR9–STAT3 pathway, the activation of which appears to jump-start the regrowth of irradiated tumors.

MOLECULAR AND CELLULAR PATHOBIOLOGY

APOBEC3B Upregulation and Genomic Mutation Patterns in Serous Ovarian Carcinoma


Précis: Mutagenesis by APOBEC3B explains some of the genomic instability seen in ovarian cancer and represents a potential novel drug target for ovarian cancer treatment.

PREVENTION AND EPIDEMIOLOGY

Functional TLR5 Genetic Variants Affect Human Colorectal Cancer Survival


Précis: Genetic polymorphisms that alter the function of a Toll-like receptor and two of its effector molecules in colorectal cancer cells may exert an important impact on patient survival, with implications for biomarker and therapy development.

Genetic Ancestry and Risk of Mortality among U.S. Latinas with Breast Cancer

Laura Pejerman, Donglei Hu, Scott Huntsman, Esther M. John, Mariana C. Stern, Christopher A. Haiman, Eliseo J. Pérez-Stable, and Elad Ziv

Précis: Genetic factors and/or unmeasured differences in treatment or access to care should be further explored to understand and reduce ethnic disparities in breast cancer outcomes.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Lenalidomide Inhibits Lymphangiogenesis in Preclinical Models of Mantle Cell Lymphoma

Kai Song, Brett H. Herzog, Minjia Sheng, Jiuxin Fu, J. Michael McDaniel, Jia Ruan, and Lijun Xia

Précis: This is the first report on the novel therapeutic antilymphangiogenic mechanism of the immunomodulatory drug lenalidomide in lymphoma, which highlights the potential pathogenic role of lymphangiogenesis in lymphoma progression and dissemination.

An Intact Immune System Is Required for the Anticancer Activities of Histone Deacetylase Inhibitors

Alison C. West, Stephen R. Mattarollo, Jake Shortt, Leonie A. Cluse, Ailsa J. Christiansen, Mark J. Smyth, and Ricky W. Johnstone

Précis: These provocative findings suggest that HDAC inhibitors would be most effective if combined with immunotherapy in the clinic.

Combined Targeting of PDK1 and EGFR Triggers Regression of Glioblastoma by Reversing the Warburg Effect

Kiran Kumar Velpula, Arnima Bhasin, Swapna Asuthkar, and Andrew J. Tsung

Précis: This work suggests that PDK1 may serve as a novel therapeutic target in treating glioblastoma along with EGFR, and targeting this protein complex may open up further treatment avenues in the metabolic modulation of glioblastoma.
ALDH1-Positive Cancer Stem Cells Predict Engraftment of Primary Breast Tumors and Are Governed by a Common Stem Cell Program
Emmanuelle Charafe-Jauffret, Christophe Ginestier, François Bertucci, Olivier Cabaud, Julien Wicinski, Pascal Finetti, Emmanuelle Josselin, José Adelaide, Tien-Tuan Nguyen, Florence Monville, Jocelyne Jacquier, Jeanne Thomassin-Piana, Guillaume Pinna, Aurélie Jalaguier, Eric Lambaudie, Gilles Houvenaeghel, Luc Xerri, Annick Harel-Bellan, Max Chaffanet, Patrice Viens, and Daniel Birnbaum

Precis: This work offers a convincing proof for the functional relevance of CSCs in breast cancer, and it establishes the reliability of patient-derived xenografts for use in developing personalized CSC therapies for breast cancer patients in the clinic.

YEATS4 Is a Novel Oncogene Amplified in Non–Small Cell Lung Cancer That Regulates the p53 Pathway
Larissa A. Pikor, William W. Lockwood, Kelsie L. Thu, Emily A. Vucic, Raj Chari, Adi F. Gazdar, Stephen Lam, and Wan L. Lam

Precis: This study identifies a novel candidate oncogene that may be amplified in up to one fifth of non–small cell lung carcinomas, with implications for understanding etiology and drug resistance.

GLI1 Interferes with the DNA Mismatch Repair System in Pancreatic Cancer through BHLHE41-Mediated Suppression of MLH1
Shingo Inaguma, Miho Riku, Mitsuyoshi Hashimoto, Hideki Murakami, Shinsuke Saga, Hiroshi Ikeda, and Kenji Kasai

Precis: A pivotal transcription factor in the Hedgehog signaling pathway is found to regulate the DNA mismatch repair system in pancreatic carcinoma cells, with potential implications for understanding how these cancers arise and how they might be controlled by Hedgehog pathway inhibitors.

Acknowledgment to Reviewers

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ABOUT THE COVER

The antitumor effects of histone deacetylase inhibitors (HDACi) are repressed in immunocompromised mice. Rag-2γc−/− mice transplanted with Eμ-myc B-cell lymphomas and treated with HDACi succumb significantly earlier than wild-type tumor-bearing mice and die with high splenic tumor burden as shown in this image (magnification, ×10). HDACi are able to inhibit their target enzymes and mediate tumor cell apoptosis in immunocompromised mice, however, in the absence of a functional immune system, the therapeutic efficacy of HDACi is significantly diminished. These data demonstrate the importance of a host immune system for sustained antitumor responses mediated by HDACi and indicate that these agents could be combined with immunotherapy to enhance efficacy. For details, see article by West and colleagues on page 7265.