**BREAKING ADVANCES**

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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. 7155

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**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

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**The Need for Axillary Lymph Node Dissection in T1/T2 Breast Cancer Surgery—Counterpoint**  
Michael S. Sabel  
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**The Need for Axillary Lymph Node Dissection in T1/T2 Breast Cancer Surgery—Reply to Counterpoint**  
Monica Morrow  
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**PRIORITIZED REPORT**

7162  
**TERT Promoter Mutations Occur Early in Urothelial Neoplasia and Are Biomarkers of Early Disease and Disease Recurrence in Urine**  

**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. Gottlieb

**Precis:** 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  

**Precis:** 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, Ilana Gonzalez, Tanisha Meeuwsen, Bernard A. Fox, Tarsem Moudgil, William Miller, Daniel Haley, Todd Coffey, Brenda Fisher, Laurie Delanty-Miller, Nicole Rymarchuk, Tracy Kelly, Todd Crocezni, Eric Bernstein, Rachel Sanborn, Walter J. Urba, and Andrew D. Weinberg

**Precis:** 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 Núñez, Kathryn A. Eaton, and Grace Y. Chen

**Precis:** 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 Rautitschek, and Marcin Kortylewski

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.

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.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Lenalidomide Inhibits Lymphangiogenesis in Preclinical Models of Mantle Cell Lymphoma
Kai Song, Brett H. Herzog, Minjia Sheng, Jiachun 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 Rippy 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.

Genetic Ancestry and Risk of Mortality among U.S. Latinas with Breast Cancer
Laura Feyerman, 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.
TUMOR AND STEM CELL BIOLOGY

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 Cabaudo, Julien Wicinski, Pascal Finetti, Emmanuelle Josselein, José Adelaide, Tien-Tuan Nguyen, Florence Monville, Jocelyne Jacquemier, Jeanne Thomassin-Piana, Guillaume Pinna, Aurélie Jalaguier, Eric Lambaudie, Gilles Houvenaeghel, Luc Xerri, Annick Harel-Bellan, Max Chaffanet, Patrice Viens, and Daniel Birnbaum

YETS4 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

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

Acknowledgment to Reviewers

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.