

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, Mohamad Allaf, Simeon Springer, Yuxuan Wang, Luis A. Diaz, Jr. Kenneth W. Kinzler, Bert Vogelstein, Nickolas Papadopoulos, and George J. Netto
Précis: TERT promoter somatic mutations occur early in bladder cancer and are detectable in urine, providing an opportunity to develop highly accurate and inexpensive methods for early detection and monitoring of bladder cancer.

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**
Xiao-Mei Li, Ali Mohammad-Djafari, Mircea Dumitru, Sandrine Dulong, Elisabeth Filipski, Sandrine Siffroi-Fernandez, Ali Mteyrek, Francesco Scaglione, Catherine Guettier, Franck Delaunay, and Francis Lévi
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 Meeuwsen, Bernard A. Fox, Tarsem Moudgil, William Miller, Daniel Haley, Todd Coffey, Brenda Fisher, Laurie Delanty-Miller, Nicole Rymarchyk, 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 Núñez, 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.

7211

TLR9 Signaling in the Tumor Microenvironment Initiates Cancer Recurrence after Radiotherapy

Chan Gao, Anna Kozłowska, Sergey Nechaev, Haiqing Li, Qifang Zhang, Dewan M.S. Hossain, Claudia M. Kowolik, Peiguo Chu, Piotr Swiderski, Don J. Diamond, Sumanta K. Pal, Andrew Raubitschek, 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.

7243



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

Laura Fejerman, 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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

7222

APOBEC3B Upregulation and Genomic Mutation Patterns in Serous Ovarian Carcinoma

Brandon Leonard, Steven N. Hart, Michael B. Burns, Michael A. Carpenter, Nuri A. Temiz, Anurag Rathore, Rachel I. Vogel, Jason B. Nikas, Emily K. Law, William L. Brown, Ying Li, Yuji Zhang, Matthew J. Maurer, Ann L. Oberg, Julie M. Cunningham, Viji Shridhar, Debra A. Bell, Craig April, David Bentley, Marina Bibikova, R. Keira Cheetham, Jian-Bing Fan, Russell Grocock, Sean Humphray, Zoya Kingsbury, John Peden, Jeremy Chien, Elizabeth M. Swisher, Lynn C. Hartmann, Kimberly R. Kalli, Ellen L. Goode, Hugues Sicotte, Scott H. Kaufmann, and Reuben S. Harris

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

7232

Functional TLR5 Genetic Variants Affect Human Colorectal Cancer Survival

Sascha N. Klimosch, Asta Försti, Jana Eckert, Jelena Knežević, Melanie Bevier, Witigo von Schönfels, Nils Heits, Jessica Walter, Sebastian Hinz, Jesus Lascorz, Jochen Hampe, Dominik Hartl, Julia-Stefanie Frick, Kari Hemminki, Clemens Schafmayer, and Alexander N.R. Weber

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

7254

Lenalidomide Inhibits Lymphangiogenesis in Preclinical Models of Mantle Cell Lymphoma

Kai Song, Brett H. Herzog, Minjia Sheng, Jianxin 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.

7265

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.

7277

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.

7290

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 Jacquemier, Jeanne Thomassin-Piana, Guillaume Pinna, Aurélie Jalaguier, Eric Lambaudie, Gilles Houvenaeghel, Luc Xerri, Annick Harel-Bellan, Max Chaffanet, Patrice Viens, and Daniel Birnbaum

Précis: 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.

7301



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

Précis: 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

Précis: 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.

7324

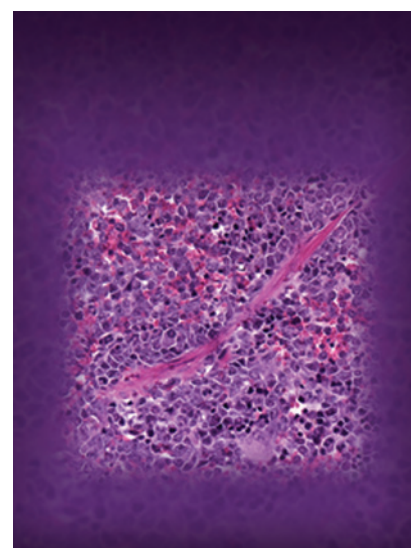
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ABOUT THE COVER

The antitumor effects of histone deacetylase inhibitors (HDACi) are repressed in immunocompromised mice. Rag-2 γ c^{-/-} mice transplanted with E μ -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, $\times 10$). 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.



Cancer Research

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