BREAKING ADVANCES

Highlights from Recent Cancer Literature

7149

INTEGRATED SYSTEMS AND TECHNOLOGIES

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.

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

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 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.

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.

PRIORITY REPORT

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 Allah, Simeon Springer, Yuxuan Wang, Luis A. Diaz, Jr., Kenneth W. Kinzler, Bert Vogelstein, Nicholas 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.

POINT-COUNTERPOINT REVIEWS

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

7151

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

7155

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

7156

The Need for Axillary Lymph Node Dissection in T1/T2 Breast Cancer Surgery—Reply to Counterpoint
Monica Morrow

 See Counterpoint by Sabel, p. 7156

7161

INTEGRATED SYSTEMS AND TECHNOLOGIES

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.

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

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 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.

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.

PRIORITY REPORT

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 Allah, Simeon Springer, Yuxuan Wang, Luis A. Diaz, Jr., Kenneth W. Kinzler, Bert Vogelstein, Nicholas 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.
### MOLECULAR AND CELLULAR PATHOBIOLOGY

**7243**

*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. Kowolik, Peiguo Chu, Piotr Swiderski, Don J. Diamond, Sumanta K. Pal, Andrew Rauhut's, 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.*

**7254**

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

Laura Peijerman, 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

**7243**

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

Laura Peijerman, 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.*

**7254**

*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.*

### PREVENTION AND EPIDEMIOLOGY

**7222**

*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.*

**7265**

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

Alison C. West, Stephen R. Mattarrollo, 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.*
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 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

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.

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.

Acknowledgment to Reviewers

AC icon indicates Author Choice

For more information please visit www.aacrjournals.org

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.