

## BREAKING ADVANCES

- 3193** Highlights from Recent Cancer Literature

## REVIEWS

- 3195** Galectin-Binding O-Glycosylations as Regulators of Malignancy  
Charles J. Dimitroff
- 3203** Mitochondrial DNA in Tumor Initiation, Progression, and Metastasis: Role of Horizontal mtDNA Transfer  
Michael V. Berridge, Lanfeng Dong, and Jiri Neuzil

## PRIORITY REPORT

- 3209** Interleukin-6 Prevents the Initiation but Enhances the Progression of Lung Cancer  
Zhaoxia Qu, Fan Sun, Jingjiao Zhou, Liwen Li, Steven D. Shapiro, and Gutian Xiao
- Précis:* These findings reveal complexity in the role of IL6 signaling at different stages of lung cancer development, improving pathophysiological understanding in this disease and rationalizing IL6/STAT3 targeting therapies there.

## CLINICAL STUDIES

- 3216** Tumor-Specific Effector CD8<sup>+</sup> T Cells That Can Establish Immunological Memory in Humans after Adoptive Transfer Are Marked by Expression of IL7 Receptor and *c-myc*  
Smita S. Chandran, Biman C. Paria, Abhishek K. Srivastava, Luke D. Rothermel, Daniel J. Stephens, and Udai S. Kammula
- Précis:* The discovery of two cell intrinsic biomarkers that can predict long-term host persistence of tumor-specific T cells that are adoptively transferred to cancer patients has direct and immediate implications for improving adoptive T-cell immunotherapies.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 3227** Discovery and Validation of Biomarkers That Distinguish Mucinous and Nonmucinous Pancreatic Cysts  
Jisook Park, Hwan Sic Yun, Kwang Hyuck Lee, Kyu Taek Lee, Jong Kyun Lee, and Soo-Youn Lee
- Précis:* This study illustrates the usefulness of MS-based comprehensive proteomics methodologies to identify candidate biomarkers that can distinguish mucinous cysts in the pancreas at a time when more successful therapeutic interventions may be possible.
- 3236** Investigation of Optical Coherence Microelastography as a Method to Visualize Cancers in Human Breast Tissue  
Brendan F. Kennedy, Robert A. McLaughlin, Kelsey M. Kennedy, Lixin Chin, Philip Wijesinghe, Andrea Curatolo, Alan Tien, Maxine Ronald, Bruce Latham, Christobel M. Saunders, and David D. Sampson
- Précis:* A novel noninvasive imaging technology may improve monitoring of human breast tissue microarchitecture for benign and malignant lesions, including for rapid, intraoperative assessment of tumor margins during surgery.
- 3246** An Autoimmune Response Signature Associated with the Development of Triple-Negative Breast Cancer Reflects Disease Pathogenesis  
Hiroyuki Katayama, Clayton Boldt, Jon J. Ladd, Melissa M. Johnson, Timothy Chao, Michela Capello, Jinfeng Suo, Jianning Mao, JoAnn E. Manson, Ross Prentice, Francisco Esteva, Hong Wang, Mary L. Disis, and Samir Hanash
- Précis:* Humoral responses to 'triple negative' breast cancers, which occur in patients themselves, are composed of a dynamic repertoire of autoimmune antigens, illustrating the nature of cancer pathogenesis as an abortive autoimmune response against altered-self.
- 3255** Endothelial Thermotolerance Impairs Nanoparticle Transport in Tumors  
Alexander F. Bagley, Ruth Scherz-Shouval, Peter A. Galie, Angela Q. Zhang, Jeffrey Wyckoff, Luke Whitesell, Christopher S. Chen, Susan Lindquist, and Sangeeta N. Bhatia
- Précis:* Nanomaterials that assist the delivery of therapeutics into solid tumors are desired, but molecular adaptations in the tumor endothelium may counteract these effects, with direct consequences for therapeutic efficacy.

# Table of Contents

## MICROENVIRONMENT AND IMMUNOLOGY

**3268** Tumors Escape CD4<sup>+</sup> T-cell–Mediated Immunosurveillance by Impairing the Ability of Infiltrating Macrophages to Indirectly Present Tumor Antigens

Anders Aune Tveita, Fredrik Schjesvold, Ole Audun Haabeth, Marte Fauskanger, and Bjarne Bogen

*Précis:* Tumors appear to escape immunity in part by indirectly blocking the ability of roving macrophages to present tumor antigens to the immune system, a finding that may be relevant to optimizing T-cell immunotherapies for cancer.

**3279** Rapamycin Impairs Antitumor CD8<sup>+</sup> T-cell Responses and Vaccine-Induced Tumor Eradication

Nada Chaoul, Catherine Fayolle, Belinda Desrues, Marine Oberkampff, Alexandre Tang, Daniel Ladant, and Claude Leclerc

*Précis:* The essential role of mTOR for antitumor T-cell functions implicated in immunotherapy and the immune-stimulating effects of radiotherapy and chemotherapy needed for effective therapeutic responses point to a fatal flaw in the rationale to develop mTOR inhibitors as cancer therapy.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

**3292** Activation-Induced Cytidine Deaminase Contributes to Pancreatic Tumorigenesis by Inducing Tumor-Related Gene Mutations

Yugo Sawai, Yuzo Kodama, Takahiro Shimizu, Yuji Ota, Takahisa Maruno, Yuji Eso, Akira Kurita, Masahiro Shiokawa, Yoshihisa Tsuji, Norimitsu Uza, Yuko Matsumoto, Toshihiko Masui, Shinji Uemoto, Hiroyuki Marusawa, and Tsutomu Chiba

*Précis:* Transgenic mice that express the cytosine deaminase AID develop precancerous pancreatic lesions without the apparent involvement of oncogenes, offering a unique mouse model of pancreatic cancer to analyze mutations involved in later stages of pancreatic carcinogenesis.

**3302** ITGBL1 Is a Runx2 Transcriptional Target and Promotes Breast Cancer Bone Metastasis by Activating the TGF $\beta$  Signaling Pathway

Xiao-Qing Li, Xin Du, Dong-Mei Li, Peng-Zhou Kong, Yan Sun, Pei-Fang Liu, Qing-Shan Wang, and Yu-Mei Feng

*Précis:* This study identifies a critical function for a little studied integrin  $\beta$ -like molecule in bone metastasis of breast cancer, a dismal feature of advanced disease that is presently untreatable, with implications for clinical biomarker and therapeutic targeting studies.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**3314** Pharmacological Ascorbate Radiosensitizes Pancreatic Cancer

Juan Du, John A. Cieslak III, Jessemae L. Welsh, Zita A. Sibenaller, Bryan G. Allen, Brett A. Wagner, Amanda L. Kalen, Claire M. Doskey, Robert K. Strother, Anna M. Button, Sarah L. Mott, Brian Smith, Susan Tsai, James Mezhir, Prabhat C. Goswami, Douglas R. Spitz, Garry R. Buettner, and Joseph J. Cullen

*Précis:* These striking findings offer a preclinical proof of concept for the parenteral delivery of pharmacological ascorbate (high levels of vitamin C) as a simple, safe, and effective radiosensitizer for pancreatic cancer treatment, with immediate implications for clinical evaluation.

**3327** Proteolysis of EphA2 Converts It from a Tumor Suppressor to an Oncoprotein

Naohiko Koshikawa, Daisuke Hoshino, Hiroaki Taniguchi, Tomoko Minegishi, Taizo Tomari, Sung-Ouk Nam, Mikiko Aoki, Takayuki Sueta, Takashi Nakagawa, Shingo Miyamoto, Kazuki Nabeshima, Alissa M. Weaver, and Motoharu Seiki

*Précis:* This important study sheds light on long-standing questions about the basis for the paradoxical actions of EphA2 in tumor progression.

**3340** Naturally Occurring Mutations in the MPS1 Gene Predispose Cells to Kinase Inhibitor Drug Resistance

Mark D. Gurden, Isaac M. Westwood, Amir Faisal, Sébastien Naud, Kwai-Ming J. Cheung, Craig McAndrew, Amy Wood, Jessica Schmitt, Kathy Boxall, Grace Mak, Paul Workman, Rosemary Burke, Swen Hoelder, Julian Blagg, Rob L.M. Van Montfort, and Spiros Linardopoulos


*Précis:* This study defines resistance mechanisms that may arise to a new class of cell-cycle checkpoint inhibitors being developed as cancer therapy—important during the early stages of drug development for several reasons—but it also reports an unexpected finding that many drug resistance mutations might be found in some normal and malignant cells even before drug treatment has started.

**3355** Therapeutic Targeting of the Warburg Effect in Pancreatic Cancer Relies on an Absence of p53 Function

N.V. Rajeshkumar, Prasanta Dutta, Shinichi Yabuuchi, Roeland F. de Wilde, Gary V. Martinez, Anne Le, Jurre J. Kamphorst, Joshua D. Rabinowitz, Sanjay K. Jain, Manuel Hidalgo, Chi V. Dang, Robert J. Gillies, and Anirban Maitra


*Précis:* The p53 status of a tumor may be a major factor in determining an efficacious response to inhibitors of lactate dehydrogenase, as a strategy to target the Warburg effect in solid tumors.

# Table of Contents

- 3365** **A Polymer-Based Antibody–Vinca Drug Conjugate Platform: Characterization and Preclinical Efficacy**  
 Alexander V. Yurkovetskiy, Mao Yin, Natalya Bodyak, Cheri A. Stevenson, Joshua D. Thomas, Charles E. Hammond, LiuLiang Qin, Bangmin Zhu, Dmitry R. Gumerov, Elena Ter-Ovanesyan, Alex Uttard, and Timothy B. Lowinger  
*Précis:* This study shows how efficacious antibody-drug conjugates can be prepared based on a novel, polymer-based conjugation approach that overcomes physicochemical limitations, enabling higher drug-antibody ratios and therefore uses for less potent drug payloads.

- 3373** **Depleting MET-Expressing Tumor Cells by ADCC Provides a Therapeutic Advantage over Inhibiting HGF/MET Signaling**  
Anna Hultberg, Virginia Morello, Leander Huyghe, Natalie De Jonge, Christophe Blanchetot, Valérie Hanssens, Gitte De Boeck, Karen Silence, Els Festjens, Raimond Heukers, Benjamin Roux, Fabienne Lamballe, Christophe Ginestier, Emmanuelle Charafe-Jauffret, Flavio Maina, Peter Brouckaert, Michael Saunders, Alain Thibault, Torsten Dreier, Hans de Haard, and Paolo Michieli  
*Précis:* These findings offer evidence that killing MET-expressing cancer cells by ADCC is therapeutically more advantageous than simply inhibiting HGF/MET signaling, based on studies of a novel ADCC-enhanced anti-MET antibody entering clinical development.

## TUMOR AND STEM CELL BIOLOGY

- 3384** **Oncogenic G Protein GNAQ Induces Uveal Melanoma and Intravasation in Mice**  
 Jenny Li-Ying Huang, Oscar Urtatiz, and Catherine D. Van Raamsdonk  
*Précis:* This study reports the first transgenic mouse model of uveal melanoma, one of the most aggressive cancers, which will be useful for developing in vivo understanding of etiology and metastatic progression of this disease.
- 3398** **Diverse Targets of  $\beta$ -Catenin during the Epithelial–Mesenchymal Transition Define Cancer Stem Cells and Predict Disease Relapse**  
Yi-Wen Chang, Ying-Jhen Su, Michael Hsiao, Kuo-Chen Wei, Wei-Hsin Lin, Chi-Jung Liang, Shin-Cheh Chen, and Jia-Lin Lee  
*Précis:* In discovering that Wnt signaling must accompany the epithelial-mesenchymal transition to generate cancer stem-like cells, this study defines a five-gene signature for these cells that may be a valuable prognostic marker in lung cancer patients.
- 3411** **PML/RAR $\alpha$ -Regulated miR-181a/b Cluster Targets the Tumor Suppressor RASSF1A in Acute Promyelocytic Leukemia**  
Daniela Bräuer-Hartmann, Jens-Uwe Hartmann, Alexander Arthur Wurm, Dennis Gerloff, Christiane Katzerke, Maria Vittoria Verga Falzacappa, Pier Giuseppe Pelicci, Carsten Müller-Tidow, Daniel G. Tenen, Dietger Niederwieser, and Gerhard Behre  
*Précis:* These findings identify a pivotal microRNA cluster and tumor suppressor gene as determinants of the outgrowth versus effective therapeutic control of acute promyelocytic leukemias.

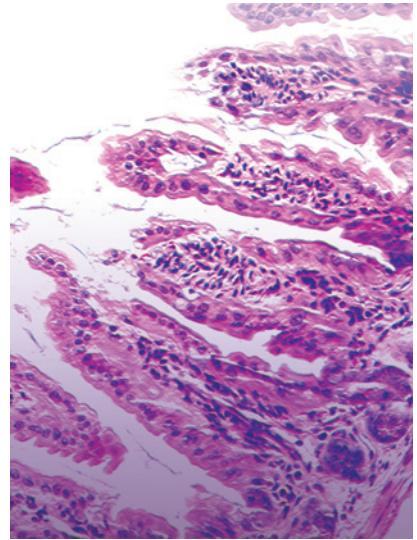
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# Table of Contents

## ABOUT THE COVER

Radiation-induced gastrointestinal toxicity is highly relevant to the treatment of pancreatic cancer with radiation. To determine if pharmacological ascorbate changes the response of the gastrointestinal tract following radiation in a clinically meaningful way, a crypt cell assay was performed. The addition of pharmacological ascorbate partially reversed the decreases in jejunal crypt regeneration in both the 10 Gy and 13 Gy groups of mice, suggesting that ascorbate may protect the gastrointestinal tract from the damaging effects of radiation. For details, see article by Du and colleagues on page 3314.



# Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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