

BREAKING ADVANCES

- 6107 | **Highlights from Recent Cancer Literature**

REVIEW

- 6109 | **Monitoring of Natural Killer Cell Immunotherapy Using Noninvasive Imaging Modalities**
Priyanka Jha, Daniel Golovko, Sukhmine Bains, Daniel Hostetter, Reinhard Meier, Michael F. Wendland, and Heike E. Daldrup-Link

MEETING REPORT

- 6114 | **Cyclins, Cdks, E2f, Skp2, and More at the First International RB Tumor Suppressor Meeting**
Rod Bremner and Eldad Zacksenhaus

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6119 | **A Novel Imaging Approach for Early Detection of Prostate Cancer Based on Endogenous Zinc Sensing**
Subrata K. Ghosh, Pilhan Kim, Xiao-an Zhang, Seok-Hyun Yun, Anna Moore, Stephen J. Lippard, and Zdravka Medarova
- Précis:* This paper illustrates how differences in zinc levels in normal and cancerous prostates can be exploited for purposes of non-invasive imaging, with the potential for rapid clinical translation.

- 6128 | **A Microfluidic Platform for Systems Pathology: Multiparameter Single-Cell Signaling Measurements of Clinical Brain Tumor Specimens**
Jing Sun, Michael D. Masterman-Smith, Nicholas A. Graham, Jing Jiao, Jack Mottahedeh, Dan R. Laks, Minoru Ohashi, Jason DeJesus, Ken-ichiro Kamei, Ki-Bum Lee, Hao Wang, Zeta T.F. Yu, Yi-Tsung Lu, Shuang Hou, Keyu Li, Max Liu, Nangang Zhang, Shutao Wang, Brigitte Angenieux, Eduard Panosyan, Eric R. Samuels, Jun Park, Dirk Williams, Vera Konkankit, David Nathanson, R. Michael van Dam, Michael E. Phelps, Hong Wu, Linda M. Liao, Paul S. Mischel, Jorge A. Lazareff, Harley I. Kornblum, William H. Yong, Thomas G. Graeber, and Hsian-Rong Tseng

Précis: This study describes a microfluidic imaging technology that can enhance pathological analysis of tumor biopsies.

MICROENVIRONMENT AND IMMUNOLOGY

- 6139 | **Gr-1+CD11b+ Myeloid Cells Tip the Balance of Immune Protection to Tumor Promotion in the Premetastatic Lung**
Hannah H. Yan, Michael Pickup, Yanli Pang, Agnieszka E. Gorska, Zhaoyang Li, Anna Chytil, Yipeng Geng, Jerome W. Gray, Harold L. Moses, and Li Yang
- Précis:* Findings promote the concept that blocking the activity of myeloid derived suppressor cells could normalize the pre-metastatic lung environment, strengthening immune surveillance that prevents metastasis.
- 6150 | **Receptor Activator of NF- κ B Ligand Enhances Breast Cancer-Induced Osteolytic Lesions through Upregulation of Extracellular Matrix Metalloproteinase Inducer/CD147**
Nadia Rucci, Danilo Millimaggi, Marianna Mari, Andrea Del Fattore, Mauro Bologna, Anna Teti, Adriano Angelucci, and Vincenza Dolo
- Précis:* A cancer cell surface molecule plays a critical role in supporting breast cancer metastasis to bone, validating a target for therapeutic blockade of this process.

6161 **Antigen-Experienced CD4⁺ T Cells Limit Naïve T-Cell Priming in Response to Therapeutic Vaccination *In vivo***

Chris Schiering, Jlenia Guarnerio, Veronica Basso, Luca Muzio, and Anna Mondino

Précis: Results emphasize limitations imposed by tumor-primed CD4⁺ T lymphocytes that block the ability of cancer vaccines to generate immunogenicity.

6171 **Antiangiogenic Agents Can Increase Lymphocyte Infiltration into Tumor and Enhance the Effectiveness of Adoptive Immunotherapy of Cancer**

Rajeev K. Shrimali, Zhiya Yu, Marc R. Theoret, Dhanalakshmi Chinnasamy, Nicholas P. Restifo, and Steven A. Rosenberg

Précis: Findings rationalize testing of a combination of antiangiogenic agents with cell transfer immunotherapies in clinical oncology trials.

6181 **Single-Cell Analysis of T-Cell Receptor Repertoire of HTLV-1 Tax-Specific Cytotoxic T Cells in Allogeneic Transplant Recipients with Adult T-Cell Leukemia/Lymphoma**

Yukie Tanaka, Hideki Nakasone, Rie Yamazaki, Ken Sato, Miki Sato, Kiriko Terasako, Shun-ichi Kimura, Shinya Okuda, Shinichi Kako, Kumi Oshima, Aki Tanihara, Junji Nishida, Toshiaki Yoshikawa, Tetsuya Nakatsura, Haruo Sugiyama, and Yoshinobu Kanda

Précis: This study suggests a basis to understand the efficacy of allogeneic hematopoietic stem cell transplantation as a treatment for HTLV-1-associated T cell leukemia.

6205 **FOXO3 Encodes a Carcinogen-Activated Transcription Factor Frequently Deleted in Early-Stage Lung Adenocarcinoma**

Oliver R. Mikse, Daniel C. Blake, Jr., Nathan R. Jones, Yuan-Wan Sun, Shantu Amin, Carla J. Gallagher, Philip Lazarus, Judith Weisz, and Christopher R. Herzog

Précis: Findings identify deletions of a suspected tumor suppressor gene in the setting of lung adenocarcinoma.

6216 **Tumor Cells Secrete Galectin-1 to Enhance Endothelial Cell Activity**

Victor L. Thijssen, Batya Barkan, Hiroki Shoji, Ingrid M. Aries, Véronique Mathieu, Louise Deltour, Tilman M. Hackeng, Robert Kiss, Yoel Kloog, Françoise Poirier, and Arjan W. Griffioen

Précis: This study identifies a novel angiogenic growth factor function for galectin-1 opening a new window for angiostatic cancer therapy.

6225 **Joint Loss of PAX2 and PTEN Expression in Endometrial Precancers and Cancer**

Nicolas M. Monte, Kaitlyn A. Webster, Donna Neuberger, Gregory R. Dressler, and George L. Mutter

Précis: Combined loss of a tumor suppressor and a differentiation factor may drive the majority of sporadic endometrial cancers.

6233 **Met Receptor Sequence Variants R970C and T992I Lack Transforming Capacity**

Jeffrey W. Tyner, Luke B. Fletcher, Ellen Q. Wang, Wayne F. Yang, Michael L. Rutenberg-Schoenberg, Carol Beadling, Motomi Mori, Michael C. Heinrich, Michael W. Deininger, Brian J. Druker, and Marc M. Loriaux

Précis: Findings illustrate the importance of distinguishing oncogenic mutations from normal polymorphisms in tumor cells before an oncogene-targeted drug strategy is justified.

6238 **Circadian Rhythm of Transferrin Receptor 1 Gene Expression Controlled by c-Myc in Colon Cancer-Bearing Mice**

Fumiyasu Okazaki, Naoya Matsunaga, Hiroyuki Okazaki, Naoki Utoguchi, Ryo Suzuki, Kazuo Maruyama, Satoru Koyanagi, and Shigehiro Ohdo

Précis: c-Myc controlled circadian rhythms that regulate colon cancer gene expression may promote new concepts in dosing regimens for cancer therapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6193 **The ITK-SYK Fusion Oncogene Induces a T-Cell Lymphoproliferative Disease in Mice Mimicking Human Disease**

Christine Dierks, Francisco Adrian, Paul Fisch, Hong Ma, Helga Maurer, Dieter Herchenbach, Christine Ulrike Forster, Clara Sprissler, Guoxun Liu, Sabine Rottmann, Gui-Rong Guo, Zirlik Katja, Hendrik Veelken, and Markus Warmuth

Précis: Findings argue that Syk kinase fusions present in peripheral T-cell lymphomas might be effective therapeutic targets.

6247 **Phosphomimetic Mutants of Pigment Epithelium-Derived Factor with Enhanced Antiangiogenic Activity as Potent Anticancer Agents**
Alexander Konson, Sunila Pradeep, and Rony Seger

Précis: Findings may encourage the development of a specific neovascularization-targeting anticancer agent.

6258 **DNA Damage-Induced Cytotoxicity Is Dissociated from BRCA1's DNA Repair Function but Is Dependent on Its Cytosolic Accumulation**
Hong Wang, Eddy S. Yang, Juhong Jiang, Somaira Newsheen, and Fen Xia

Précis: BRCA1 nucleocytoplasmic shuttling may serve as marker of tumor response and possibly a mechanistic focus to sensitize cancer cells to DNA damage-based therapy.

6268 **6-Thioguanine Selectively Kills BRCA2-Defective Tumors and Overcomes PARP Inhibitor Resistance**
Natalia Issaeva, Huw D. Thomas, Tatjana Djurenovic, Janneke E. Jaspers, Iyavlo Stoimenov, Suzanne Kyle, Nicholas Pedley, Ponnari Gottipati, Rafal Zur, Kate Sleeth, Vicky Chatzakos, Evan A. Mulligan, Cecilia Lundin, Evgenia Gubanova, Ariena Kersbergen, Adrian L. Harris, Ricky A. Sharma, Sven Rottenberg, Nicola J. Curtin, and Thomas Helleday

Précis: Strategies to anticipate and address resistance to PARP inhibitors that target tumors defective in BRCA1 or BRCA2 will extend patient survival and may help rationalize more effective combinatorial treatments.

6277 **Poly(ADP-Ribose) Polymerase Inhibitor Induces Accelerated Senescence in Irradiated Breast Cancer Cells and Tumors**
Elena V. Efimova, Helena J. Mauceri, Daniel W. Golden, Edwardine Labay, Vytautas P. Bindokas, Thomas E. Darga, Chaitali Chakraborty, Juan Camilo Barreto-Andrade, Clayton Crawley, Harold G. Sutton, Stephen J. Kron, and Ralph R. Weichselbaum

Précis: These studies suggest a novel mechanism for radiosensitization by PARP inhibitors, mediated by persistent DNA damage response resulting in accelerated cellular senescence both in vitro and in vivo, with significant implications for cancer therapy.

6283 **Transplanting Normal Vascular Proangiogenic Cells to Tumor-Bearing Mice Triggers Vascular Remodeling and Reduces Hypoxia in Tumors**
Junpei Sasajima, Yusuke Mizukami, Yoshiaki Sugiyama, Kazumasa Nakamura, Toru Kawamoto, Kazuya Koizumi, Rie Fujii, Wataru Motomura, Kazuya Sato, Yasuaki Suzuki, Satoshi Tanno, Mikihiro Fujiya, Katsunori Sasaki, Norihiko Shimizu, Hidenori Karasaki, Toru Kono, Jun-ichi Kawabe, Masaaki Ii, Hiroki Yoshiara, Naohisa Kamiyama, Toshifumi Ashida, Nabeel Bardeesy, Daniel C. Chung, and Yutaka Kohgo

Précis: This study describes a microfluidic imaging technology that can enhance pathological analysis of tumor biopsies.

6293 **Construction and Characterization of a Bispecific Anti-CD20 Antibody with Potent Antitumor Activity against B-Cell Lymphoma**
Bohua Li, Xunming Zhang, Shu Shi, Lei Zhao, Dapeng Zhang, Weizhu Qian, Lei Zheng, Jie Gao, Hao Wang, and Yajun Guo

Précis: A bispecific anti-CD20 antibody that engages both apoptosis and complement dependent cytotoxicity offers a promising agent to improve treatment of B cell neoplasms.

6303 **EGFRvIII Antibody-Conjugated Iron Oxide Nanoparticles for Magnetic Resonance Imaging-Guided Convection-Enhanced Delivery and Targeted Therapy of Glioblastoma**
Costas G. Hadjipanayis, Revaz Machaidze, Milota Kaluzova, Liya Wang, Albert J. Schuette, Hongwei Chen, Xinying Wu, and Hui Mao

Précis: Target directed magnetic nanoparticles are being developed for MRI contrast enhancement and treatment of brain tumors.

6313 **Vorinostat and Sorafenib Increase CD95 Activation in Gastrointestinal Tumor Cells through a Ca²⁺-De novo Ceramide-PP2A-Reactive Oxygen Species-Dependent Signaling Pathway**
Margaret A. Park, Clint Mitchell, Guo Zhang, Adly Yacoub, Jeremy Allegood, Dieter Häussinger, Roland Reinehr, Andrew Larner, Sarah Spiegel, Paul B. Fisher, Christina Voelkel-Johnson, Besim Ogretmen, Steven Grant, and Paul Dent

Précis: Mechanistic investigations reveal the critical steps through which a combination of targeted therapies now entering clinical trials activates a central cancer cell death pathway.

TUMOR AND STEM CELL BIOLOGY

6325 **A Chemosensitization Screen Identifies TP53RK, a Kinase that Restrains Apoptosis after Mitotic Stress**

David Peterson, James Lee, Xingye C. Lei, William F. Forrest, David P. Davis, Peter K. Jackson, and Lisa D. Belmont

Précis: A novel chemo-sensitization screen identifies a molecule that may confer taxane resistance and serve as a novel therapeutic target.

6336 **Reprogramming Human Cancer Cells in the Mouse Mammary Gland**

Karen M. Bussard, Corinne A. Boulanger, Brian W. Booth, Robert D. Bruno, and Gilbert H. Smith

Précis: Findings argue that human cancer cells can be reprogrammed to a non-cancerous phenotype by the microenvironment of a regenerating mammary gland.

6344 **GlcNAcylation Plays an Essential Role in Breast Cancer Metastasis**

Yuchao Gu, Wenyi Mi, Yuqing Ge, Haiyan Liu, Qiong Fan, Cuifang Han, Jing Yang, Feng Han, Xinzhi Lu, and Wengong Yu

Précis: This study elucidates how a nuclear and cytoplasmic carbohydrate modification in breast cancer cells influences their malignant properties.

6352 **C11A Is a Novel Regulator of Detachment-Induced Cell Death**

Kwang Je Kim, Je-Wook Yu, Hyun Sub Hwang, and Eui-Ju Choi

Précis: Findings define a novel mechanistic realm to trigger anoikis in cancer cells as a possible therapeutic strategy.

6359 **Suppression of Integrin $\alpha 3 \beta 1$ in Breast Cancer Cells Reduces Cyclooxygenase-2 Gene Expression and Inhibits Tumorigenesis, Invasion, and Cross-Talk to Endothelial Cells**

Kara Mitchell, Kimberly B. Svenson, Whitney M. Longmate, Katerina Gkirtzimanaki, Rafal Sadej, Xianhui Wang, Jihe Zhao, Aristides G. Eliopoulos, Fedor Berditchevski, and C. Michael DiPersio

Précis: Findings reveal a novel role for COX-2 as a downstream effector of integrin $\alpha 3 \beta 1$ in tumor cells, identifying this integrin as a potential therapeutic target in breast cancer treatment.

6368 **Fructose Induces Transketolase Flux to Promote Pancreatic Cancer Growth**

Haibo Liu, Danshan Huang, David L. McArthur, Laszlo G. Boros, Nicholas Nissen, and Anthony P. Heaney

Précis: Dietary fructose which is commonly added to processed foods may promote pancreatic cancer growth, given a distinct metabolism relative to glucose that more strongly favors DNA and RNA synthesis.

6377 **Transforming Growth Factor- β (TGF- β)-Inducible Gene *TMEPAI* Converts TGF- β from a Tumor Suppressor to a Tumor Promoter in Breast Cancer**

Prajjal K. Singha, I-Tien Yeh, Manjeri A. Venkatachalam, and Pothana Saikumar

Précis: Findings suggest novel insights into how cancer cell responses to TGF-beta are converted from growth inhibitory to growth promoting in nature.

6384 **HERC2 Is an E3 Ligase That Targets BRCA1 for Degradation**

Wenwen Wu, Ko Sato, Ayaka Koike, Hiroyuki Nishikawa, Hirotaka Koizumi, Ashok R. Venkitaraman, and Tomohiko Ohta

Précis: This study identifies an E3 ligase that may balance regulation of BRCA1 stability and influence breast carcinogenesis.

LETTER TO THE EDITOR

6393 **Spontaneous Malignant Transformation of Human Mesenchymal Stem Cells Reflects Cross-Contamination: Putting the Research Field on Track – Letter**

Anja Torsvik, Gro V. Røslund, Agnete Svendsen, Anders Molven, Heike Immervoll, Emmet McCormack, Per Eystein Lønning, Monika Primon, Ewa Sobala, Joerg-Christian Tonn, Roland Goldbrunner, Christian Schichor, Josef Mysliwicz, Tamara T. Lah, Helena Motaln, Stian Knappskog, and Rolf Bjerkvig

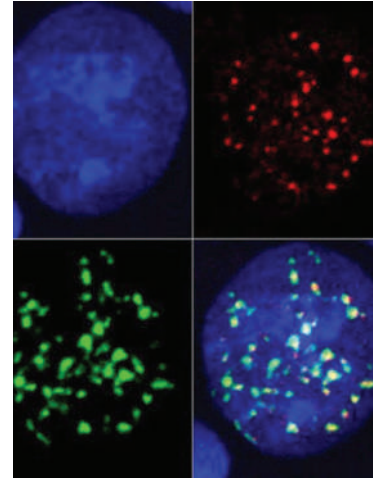
CORRECTIONS

6397 **Correction: Oncogenic Ras Promotes Reovirus Spread by Suppressing IFN- β Production through Negative Regulation of *RIG-I* Signaling**

6397 **Correction: Myc-Induced MicroRNAs Integrate Myc-Mediated Cell Proliferation and Cell Fate**

ABOUT THE COVER

DNA damage induced by 6-thioguanine is repaired by homologous recombination. Cells treated with 6-thioguanine were fixed, and DNA (blue), RAD51 (red), and γ H2AX (green) were visualized by immunofluorescence. RAD51 foci formed in V-C8+B2 cells and colocalized with γ H2AX foci. For details, see the article by Helleday and colleagues on page 6268 of this issue.



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