

## BREAKING ADVANCES

- 7015 | **Highlights from Recent Cancer Literature**

## CLINICAL STUDIES

- 7017 | **MRE11 Expression Is Predictive of Cause-Specific Survival following Radical Radiotherapy for Muscle-Invasive Bladder Cancer**  
Ananya Choudhury, Louisa D. Nelson, Mark T.W. Teo, Sameer Chilka, Selina Bhattarai, Colin F. Johnston, Faye Elliott, Johanna Lowery, Claire F. Taylor, Michael Churchman, Johanne Bentley, Margaret A. Knowles, Patricia Harnden, Robert G. Bristow, D. Timothy Bishop, and Anne E. Kiltie

*Précis:* Findings define a biopsy marker that may predict the type of therapy most likely to cure individual patients of invasive bladder cancer.

## REVIEW

- 7027 | **The Promise of MicroRNA Replacement Therapy**  
Andreas G. Bader, David Brown, and Matthew Winkler

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 7031 | **Visible Drug Delivery by Supramolecular Nanocarriers Directing to Single-Platformed Diagnosis and Therapy of Pancreatic Tumor Model**  
Sachiko Kaida, Horacio Cabral, Michiaki Kumagai, Akihiro Kishimura, Yasuko Terada, Masaki Sekino, Ichio Aoki, Nobuhiro Nishiyama, Toru Tani, and Kazunori Kataoka

*Précis:* Study illustrates how cytotoxic nanoparticle therapies can incorporate an approved MRI contrast agent for superior noninvasive imaging in vivo, easing analysis of preclinical and clinical pharmacology.

## MICROENVIRONMENT AND IMMUNOLOGY

- 7042 | **The Sympathetic Nervous System Induces a Metastatic Switch in Primary Breast Cancer**  
Erica K. Sloan, Saul J. Priceman, Benjamin F. Cox, Stephanie Yu, Matthew A. Pimentel, Veera Tangkanangnukul, Jesusa M.G. Arevalo, Kouki Morizono, Breanne D.W. Karanikolas, Lily Wu, Anil K. Sood, and Steven W. Cole

*Précis:* Metastasis promoted by macrophages may be assisted by the sympathetic nervous system and thus blocked by drugs that antagonize adrenergic signaling.

- 7053 | **Quantitative Imaging of Lymphatic Function with Liposomal Indocyanine Green**  
Steven T. Proulx, Paola Luciani, Stefanie Derzsi, Matthias Rinderknecht, Viviane Mumprecht, Jean-Christophe Leroux, and Michael Detmar

*Précis:* Quantitative noninvasive imaging of lymphatic flow will greatly assist the study of experimental cancer drugs being developed to target lymphatics, as well as the ability to image lymphedema and sentinel lymph nodes in cancer.

- 7063 | **Loss of Osteoclasts Contributes to Development of Osteosarcoma Pulmonary Metastases**  
Liliana Endo-Munoz, Andrew Cumming, Danny Rickwood, Danielle Wilson, Claudia Cueva, Charlotte Ng, Geoffrey Stratton, A. Ian Cassady, Andreas Evdokiou, Scott Sommerville, Ian Dickinson, Alexander Guminski, and Nicholas A. Saunders

*Précis:* Findings suggest that osteoclast-preserving therapies may help prevent or delay metastatic development in osteosarcoma.

- 7073 **Hyaluronan Deficiency in Tumor Stroma Impairs Macrophage Trafficking and Tumor Neovascularization**  
Nobutaka Kobayashi, Seiji Miyoshi, Takahide Mikami, Hiroshi Koyama, Masato Kitazawa, Michiko Takeoka, Kenji Sano, Jun Amano, Zenzo Isogai, Shumpei Niida, Kayoko Oguri, Minoru Okayama, John A. McDonald, Koji Kimata, Shun'ichiro Taniguchi, and Naoki Itano  
*Précis:* Stromal hyaluronan serves as a microenvironmental signal for recruitment of tumor-associated macrophages, which are key cells involved in tumor neovascularization.
- 7084 **Dacarbazine Treatment before Peptide Vaccination Enlarges T-Cell Repertoire Diversity of Melan-A-Specific, Tumor-Reactive CTL in Melanoma Patients**  
Belinda Palermo, Duilia Del Bello, Alessandra Sottini, Federico Serana, Claudia Ghidini, Novella Gualtieri, Virginia Ferraresi, Caterina Catricalà, Filippo Belardelli, Enrico Proietti, Pier Giorgio Natali, Luisa Imberti, and Paola Nisticò  
*Précis:* Clinical findings support the concept that the use of chemotherapy before a cancer vaccine can promote renewal of tumor-reactive T cells and extend survival.
- 7093 **IFN $\gamma$  Markedly Cooperates with Intratumoral Dendritic Cell Vaccine in Dog Tumor Models**  
Kai Mito, Kikuya Sugiura, Kana Ueda, Takako Hori, Takashi Akazawa, Jyoji Yamate, Hiroshi Nakagawa, Shingo Hatoya, Muneo Inaba, Norimitsu Inoue, Susumu Ikehara, and Toshio Inaba  
*Précis:* Findings suggest a mechanism through which caveolin-1 can mediate antimetastatic effects in melanoma.
- 7102 **Chemotherapy-Induced Genotoxic Stress Promotes Sensitivity to Natural Killer Cell Cytotoxicity by Enabling Missing-Self Recognition**  
Jason H. Fine, Peter Chen, Aruz Mesci, David S.J. Allan, Stephan Gasser, David H. Raulet, and James R. Carlyle  
*Précis:* Genotoxic and cell-stressing chemicals sensitize tumor cells to MHC-independent missing-self recognition by NK cells.
- 7114 **PTEN Loss Accelerates Kras<sup>G12D</sup>-Induced Pancreatic Cancer Development**  
Reginald Hill, Joseph Hargan Calvopina, Christine Kim, Ying Wang, David W. Dawson, Timothy R. Donahue, Sarah Dry, and Hong Wu  
*Précis:* Cooperation between K-ras activation and PTEN loss during pancreatic carcinogenesis occurs at the early stage of acinar-to-ductal metaplasia.
- 7125 **The Neutrophil Elastase Inhibitor Elafin Triggers Rb-Mediated Growth Arrest and Caspase-Dependent Apoptosis in Breast Cancer**  
Joseph A. Caruso, Kelly K. Hunt, and Khandan Keyomarsi  
*Précis:* Findings suggest applications of a neutrophil protease inhibitor that can attack breast cancer cells without affecting normal proliferating cells.
- 7137 **hnRNP A2/B1 Modulates Epithelial-Mesenchymal Transition in Lung Cancer Cell Lines**  
Jordi Tauler, Enrique Zudaire, Huaitian Liu, Joanna Shih, and James L. Mulshine  
*Précis:* Findings contribute to growing evidence that modification of hnRNP A2/B1 expression exerts a major impact on the proliferation and invasive capacity of lung cancer cells.
- 7148 **Spontaneous Tumorigenesis in Mice Overexpressing the p53-Negative Regulator Mdm4**  
Shunbin Xiong, Vinod Pant, Young-Ah Suh, Carolyn S. Van Pelt, Yongxing Wang, Yasmine A. Valentin-Vega, Sean M. Post, and Guillermina Lozano  
*Précis:* Findings offer preclinical genetic proof that an Mdm2 relative is a critical regulator of p53 and thus a valid therapeutic target to activate p53 in tumors.

7155 **BRCA1-Associated Epigenetic Regulation of p73 Mediates an Effector Pathway for Chemosensitivity in Ovarian Carcinoma**

Nageatte Ibrahim, Lei He, Chee-Onn Leong, Deyin Xing, Beth Y. Karlan, Elizabeth M. Swisher, Bo R. Rueda, Sandra Orsulic, and Leif W. Ellisen

*Précis:* Results define a regulatory mechanism that supports contributions of the p53-related protein p73 as a key mediator of the response to platinum chemotherapy in certain ovarian carcinomas.

7166 **Cyclin-Dependent Kinase-Mediated Phosphorylation Plays a Critical Role in the Oncogenic Functions of PELP1**

Binoj C. Nair, Sujit S. Nair, Dimple Chakravarty, Rambabu Challa, Bramanandam Manavathi, P. Renee Yew, Rakesh Kumar, Rajeshwar Rao Tekmal, and Ratna K. Vadlamudi

*Précis:* Results define a key intersection between cell cycle control and estrogen receptor signaling that has implications for breast cancer progression.

7176 **Oncogenic Wip1 Phosphatase Is Inhibited by miR-16 in the DNA Damage Signaling Pathway**

Xinna Zhang, Guohui Wan, Sizolwenkosi Mlotshwa, Vicki Vance, Franklin G. Berger, Hexin Chen, and Xiongbin Lu

*Précis:* Findings define a mechanism by which a DNA damage-induced microRNA controls a nodal regulator of DNA damage signaling.

7199 **Human Papillomavirus Seropositivity Synergizes with MDM2 Variants to Increase the Risk of Oral Squamous Cell Carcinoma**

Xingming Chen, Erich M. Sturgis, Dapeng Lei, Kristina Dahlstrom, Qingyi Wei, and Guojun Li

*Précis:* Findings define a genetic marker elevating susceptibility to HPV-associated oral cancers, particularly in never smokers, never drinkers, and oropharyngeal cancer patients.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

7209 **Ligand-Independent Toll-like Receptor Signals Generated by Ectopic Overexpression of MyD88 Generate Local and Systemic Antitumor Immunity**

Zachary C. Hartman, Takuya Osada, Oliver Glass, Xiao Y. Yang, Gang-jun Lei, H. Kim Lyerly, and Timothy M. Clay

*Précis:* Ectopic expression of a common TLR adapter signaling protein can exert all the benefits of TLR signaling to antitumor immunity.

7221 **Differential Mechanisms of Acquired Resistance to Insulin-like Growth Factor-I Receptor Antibody Therapy or to a Small-Molecule Inhibitor, BMS-754807, in a Human Rhabdomyosarcoma Model**

Fei Huang, Warren Hurlburt, Ann Greer, Karen A. Reeves, Stephen Hillerman, Han Chang, Joseph Fagnoli, Friedrich Graf Finckenstein, Marco M. Gottardis, and Joan M. Carboni

*Précis:* Study offers the first definition and comparison of acquired resistance mechanisms for IGF-1R targeted therapies.

7232 **Discovery and Canine Preclinical Assessment of a Nontoxic Procaspase-3-Activating Compound**

Quinn P. Peterson, Danny C. Hsu, Chris J. Novotny, Diana C. West, Dewey Kim, Joanna M. Schmit, Levent Dirikolu, Paul J. Hergenrother, and Timothy M. Fan

*Précis:* Findings demonstrate that direct activation of procaspase-3 by a small molecule can be well tolerated and efficacious as an anticancer strategy.

## PREVENTION AND EPIDEMIOLOGY

7187 **Relationship between Radiation Exposure and Risk of Second Primary Cancers among Atomic Bomb Survivors**

Christopher I. Li, Nobuo Nishi, Jean A. McDougall, Erin O. Semmens, Hiromi Sugiyama, Midori Soda, Ritsu Sakata, Mikiko Hayashi, Fumiyoshi Kasagi, Akihiko Suyama, Kiyohiko Mabuchi, Scott Davis, Kazunori Kodama, and Kenneth J. Kopecky

*Précis:* Individuals with substantial exposure to radiation who are diagnosed with a first primary cancer should be carefully screened for second primary cancers, particularly those that are radiation sensitive.

7242 **Crucial Roles for Protein Kinase C Isoforms in Tumor-Specific Killing by Apoptin**  
Jie Jiang, Daryl Cole, Nigel Westwood, Lee Macpherson, Farzin Farzaneh, Ghulam Mufti, Mahvash Tavassoli, and Joop Gäken

*Précis: Mechanistic studies reveal the basis for a cancer-selective cell death pathway that might be exploited to improve the treatment of multiple myeloma.*

7253 **Colorectal Tumors Are Effectively Eradicated by Combined Inhibition of  $\beta$ -Catenin, KRAS, and the Oncogenic Transcription Factor ITF2**  
Luca Mologni, Hafedh Dekhil, Monica Ceccon, Stefania Purgante, Cathy Lan, Loredana Cleris, Vera Magistroni, Franca Formelli, and Carlo B. Gambacorti-Passerini

*Précis: Findings offer preclinical proof of concept for a highly effective combinatorial therapy for colorectal tumors which targets three key oncoproteins.*

7283 **Angiopoietin-4 Promotes Glioblastoma Progression by Enhancing Tumor Cell Viability and Angiogenesis**  
Melissa K. Brunckhorst, Hui Wang, Rong Lu, and Qin Yu

*Précis: Findings identify the Ang-4/Tie-2 receptor axis as an attractive therapeutic target to treat aggressive brain cancers.*

7294 **Cancer-Associated Fibroblasts Enhance the Gland-Forming Capability of Prostate Cancer Stem Cells**  
Chun-Peng Liao, Hely Adisetiyo, Mengmeng Liang, and Pradip Roy-Burman

*Précis: Cancer-associated fibroblasts may exert their robust contributions to malignant phenotype by promoting the tumorigenic potential of cancer stem cells.*

7304 **Coactivated Platelet-Derived Growth Factor Receptor  $\alpha$  and Epidermal Growth Factor Receptor Are Potential Therapeutic Targets in Intimal Sarcoma**

Barbara Dewaele, Giuseppe Floris, Julio Finalet-Ferreiro, Christopher D. Fletcher, Jean-Michel Coindre, Louis Guillou, Pancras C.W. Hogendoorn, Agnieszka Wozniak, Vanessa Vanspauwen, Patrick Schöffski, Peter Marynen, Peter Vandenberghe, Raf Sciote, and Maria Debiec-Rychter

*Précis: Findings suggest that mutationally activated and ligand activated forms of growth factor receptors regulate distinct transcription programs that differentially affect motility, stress response, and stem cell properties.*

## TUMOR AND STEM CELL BIOLOGY

7264 **Deficiency of Splicing Factor 1 Suppresses the Occurrence of Testicular Germ Cell Tumors**  
Rui Zhu, Jason Heaney, Joseph H. Nadeau, Sara Ali, and Angabin Matin

*Précis: Findings strengthen the emerging evidence that alterations in RNA splicing occurring widely in cancer cells functionally contributes to malignant development.*

7273 **Using the Transcription Factor Inhibitor of DNA Binding 1 to Selectively Target Endothelial Progenitor Cells Offers Novel Strategies to Inhibit Tumor Angiogenesis and Growth**  
Albert S. Mellick, Prue N. Plummer, Daniel J. Nolan, Dingcheng Gao, Kathryn Bambino, Mary Hahn, Raul Catena, Vivian Turner, Kevin McDonnell, Robert Benezra, Robert Brink, Alexander Swarbrick, and Vivek Mittal

*Précis: Findings establish a strategy to follow and target bone marrow-derived endothelial progenitor cells that are vital for tumor angiogenesis.*

7315 **In vivo Imaging of Tumor Transduced with Bimodal Lentiviral Vector Encoding Human Ferritin and Green Fluorescent Protein on a 1.5T Clinical Magnetic Resonance Scanner**  
Hoe Suk Kim, Hye Rim Cho, Seung Hong Choi, Ji Su Woo, and Woo Kyung Moon

*Précis: Simultaneous MRI and fluorescent imaging of tumors can be used to noninvasively monitor metastasis and response to cell or gene-based therapies with the use of an engineered lentiviral system.*

7325

**A Specific Need for CRKL in p210<sup>BCR-ABL</sup>-Induced Transformation of Mouse Hematopoietic Progenitors**

Ji-Heui Seo, Lisa J. Wood, Anupriya Agarwal, Thomas O'Hare, Collin R. Elosei, Ian J. Griswold, Michael W.N. Deininger, Akira Imamoto, and Brian J. Druker

***Précis:** Results reveal a previously undefined linkage in BCR-ABL effector signaling that is essential to drive transformation of hematopoietic progenitor cells.*

7336

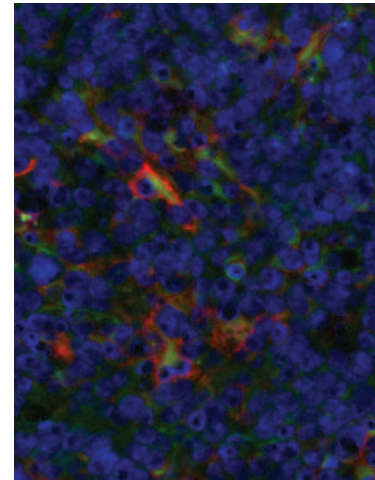
**Modifying Akt Signaling in B-Cell Chronic Lymphocytic Leukemia Cells**

Sebastian W. Hofbauer, Josefina D. Piñón, Gabriele Brachtl, Lucia Hagingler, Wei Wang, Karin Jöhner, Ingeborg Tinhofer, Tanja Nicole Hartmann, and Richard Greil

***Précis:** A survival pathway in chronic lymphocytic leukemia responding to antigenic and stromal support might be targeted by disrupting an Akt pathway mediating this support.*

**ABOUT THE COVER**

Chronic stress promotes adrenergic-dependent infiltration of macrophages into primary mammary tumors, leading to enhanced metastasis. In an immunofluorescence analysis, anti- $\beta$ 2-adrenergic receptor (green), anti-F4/80 (red), and nuclear counterstaining (blue) were used to visualize 66cl4 mammary tumor cryosections from control and stressed mice. For details, see the article by Sloan and colleagues on page 7042 of this issue.



# Cancer Research

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**AACR** American Association  
for Cancer Research

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