BREAKING ADVANCES

7015 | Highlights from Recent Cancer Literature

MICROENVIRONMENT AND IMMUNOLOGY

7042 | The Sympathetic Nervous System Induces a Metastatic Switch in Primary Breast Cancer

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

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 Bhattacharai, 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

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

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

REVIEW

7042 | The Sympathetic Nervous System Induces a Metastatic Switch in Primary Breast Cancer

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Steven T. Proulx, Paola Luciani, Stefanie Derzsi, Matthias Rinderknecht, Viviane Mumprecht, Jean-Christophe Leroux, and Michael Detmar

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 Strutton, A. Ian Cassidy, Andreas Evdokiou, Scott Sommerville, Ian Dickinson, Alexander Guminski, and Nicholas A. Saunders

INTEGRATED SYSTEMS AND TECHNOLOGIES

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

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 Guaitieri, 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.

IFNγ 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 antimeetastic effects in melanoma.

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. 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.

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.

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.

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.

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 Guillermima 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.
**CANCER RESEARCH**

**THE PREVENTION AND EPIDEMIOLOGY SECTION**

**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 Challu, Bramanandam Manavathi, P. Renee Yew, Bakesh Kumar, Rajeswar 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 Molotswana, 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.

**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, Kazumori 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.

**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.

**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-1 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 Fargnoli, 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 Procaspsase-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.
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<td>7242</td>
<td>Crucial Roles for Protein Kinase C Isoforms in Tumor-Specific Killing by Apoptin</td>
<td>Jie Jiang, Daryl Cole, Nigel Westwood, Lee Macpherson, Farzin Farzaneh, Ghulam Mufti, Madhavshavlessi, and Joop Gáken</td>
<td>Précis: Mechanistic studies reveal the basis for a cancer-selective cell death pathway that might be exploited to improve the treatment of multiple myeloma.</td>
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<td>Colorectal Tumors Are Effectively Eradicated by Combined Inhibition of β-Catenin, KRAS, and the Oncogenic Transcription Factor ITF2</td>
<td>Luca Mologni, Hafedh Dekhil, Monica Ceccor, Stefania Purgante, Cathy Lan, Loredana Cleris, Vera Magistroni, Franca Formelli, and Carlo B. Gambacorti-Passerini</td>
<td>Précis: Findings offer preclinical proof of concept for a highly effective combinatorial therapy for colorectal tumors which targets three key oncoproteins.</td>
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<td>Deficiency of Splicing Factor 1 Suppresses the Occurrence of Testicular Germ Cell Tumors</td>
<td>Rui Zhu, Jason Heaney, Joseph H. Nadeau, Sara Ali, and Angabin Matin</td>
<td>Précis: Findings strengthen the emerging evidence that alterations in RNA splicing occurring widely in cancer cells functionally contributes to malignant development.</td>
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<td>Angiopoietin-4 Promotes Glioblastoma Progression by Enhancing Tumor Cell Viability and Angiogenesis</td>
<td>Melissa K. Brunckhorst, Hui Wang, Rong Lu, and Qin Yu</td>
<td>Précis: Findings identify the Ang-4/Tie-2 receptor axis as an attractive therapeutic target to treat aggressive brain cancers.</td>
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<td>Cancer-Associated Fibroblasts Enhance the Gland-Forming Capability of Prostate Cancer Stem Cells</td>
<td>Chun-Peng Liao, Helty Adisetiyo, Mengmeng Lian, and Pradip Roy-Burman</td>
<td>Précis: Cancer-associated fibroblasts may exert their robust contributions to malignant phenotype by promoting the tumorigenic potential of cancer stem cells.</td>
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<td>Coactivated Platelet-Derived Growth Factor Receptor α and Epidermal Growth Factor Receptor Are Potential Therapeutic Targets in Intimal Sarcoma</td>
<td>Barbara Dewaele, Giuseppe Floris, Julio Finalet-Ferreiro, Christopher D. Fletcher, Jean-Michel Coindret, Louis Guillou, Pancras C.W. Hogendoorn, Agnieszka Wozniak, Vanessa Vanspauwen, Patrick Schöffski, Peter Marynen, Peter Vandenberghe, Raf Sciort, and Maria Debiec-Rychter</td>
<td>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.</td>
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<td>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</td>
<td>Hoe Suk Kim, Hye Rim Cho, Seung Hong Choi, Ji Su Woo, and Woo Kyung Moon</td>
<td>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.</td>
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A Specific Need for CRKL in p210BCR-ABL–Induced Transformation of Mouse Hematopoietic Progenitors
Ji-Huei Seo, Lisa J. Wood, Anupriya Agarwal, Thomas O'Hare, Collin R. Elsea, 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.

Modifying Akt Signaling in B-Cell Chronic Lymphocytic Leukemia Cells
Sebastian W. Hofbauer, Josefina D. Piñón, Gabriele Brachtl, Lucia Haginger, Wei Wang, Karin Jöhrrer, 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-β2-adrenergic receptor (green), anti-F4/80 (red), and nuclear counterstaining (blue) were used to visualize 66c14 mammary tumor cryosections from control and stressed mice. For details, see the article by Sloan and colleagues on page 7042 of this issue.