BREAKING ADVANCES
1589 Highlights from Recent Cancer Literature

REVIEWS
1591 Shedding Light on Melanocyte Pathobiology In Vivo
M. Raza Zaidi, Edward C. De Fabo, Frances P. Noonan, and Glenn Merlino

Mechanisms of Ploidy Increase in Human Cancers: A New Role for Cell Cannibalism
Matej Krajcovic and Michael Overholtzer

PERSPECTIVE
1602 Ribosome Biogenesis and Control of Cell Proliferation: p53 Is Not Alone
Giulio Donati, Lorenzo Montanaro, and Massimo Derenzini

PRIORITY REPORTS
1608 PARP-1 Inhibition as a Targeted Strategy to Treat Ewing’s Sarcoma
J. Chad Brenner, Felix Y. Feng, Sumin Han, Sonam Patel, Siddharth V. Goyal, Laura M. Bou-Maroun, Meilan Liu, Robert Lonigro, John R. Prensner, Scott A. Tomlins, and Arul M. Chinnaiyan

Precis: This study prompts immediate attention to reposition small-molecule inhibitors of the DNA damage response protein PARP-1, a new class of experimental agents currently in trials in the adult oncology clinic, for treatment of a particularly aggressive and deadly class of pediatric sarcomas.

1614 Receptor Tyrosine Kinase Genes Amplified in Glioblastoma Exhibit a Mutual Exclusivity in Variable Proportions Reflective of Individual Tumor Heterogeneity
Suzanne E. Little, Sergey Popov, Alexa Jury, Dorine A. Bax, Lawrence Doey, Safa Al-Sarraj, Juliane E. Jurisch, and Chris Jones

Precis: A major challenge facing the development of molecular cancer therapeutics is the complex heterogeneity of tumors at the cellular level, a factor poorly modeled in preclinical systems currently used in drug development, where molecular variegation in key pathways can limit a targeting principle depending on its proportional involvement in the tumor.

CLINICAL STUDIES
1621 Oncolytic Immunotherapy of Advanced Solid Tumors with a CD40L-Expressing Replicating Adenovirus: Assessment of Safety and Immunologic Responses in Patients

Precis: Clinical translation of oncolytic virotherapy has been mainly disappointing, but this study describes a modification that may improve the ability to trigger tumor clearance by defeating immune escape.

INTEGRATED SYSTEMS AND TECHNOLOGIES
1632 Combinatorial Chemotherapeutic Efficacy in Non-Hodgkin Lymphoma Can Be Predicted by a Signaling Model of CD20 Pharmacodynamics
John M. Harrold, Robert M. Straubinger, and Donald E. Mager

Precis: This study offers a mathematical model that can predict the efficacy of combinatorial chemotherapy regimens, which include the CD20 agonist rituximab, a drug that is being used to treat an increasing number of human cancers.

MICROENVIRONMENT AND IMMUNOLOGY
1642 Dissection of T-cell Antigen Specificity in Human Melanoma
Rikke Sick Andersen, Charlotte Albeck Thrue, Niels Junker, Rikke Lyngaa, Marco Donia, Eva Ellebæk, Inge Marie Svane, Ton N. Schumacher, Per thor Straten, and Sine Reker Hadrup

Precis: By defining the antigens recognized by tumor-infiltrating lymphocytes, one might improve their efficacy and, in turn, improve adoptive cell therapy in cancer.
Oncolytic Virus and Anti-4-1BB Combination Therapy Elicits Strong Antitumor Immunity against Established Cancer


Précis: The preclinical proof-of-concept offered by this study suggests a strategy to improve the clinical efficacy of oncolytic viruses for cancer immunotherapy by combining them with an immune agonist antibody that may help overcome tumor-mediated immune suppression.

Preclinical Evaluation of TriMix and Antigen mRNA-Based Antitumor Therapy

Sandra Van Lint, Cleo Goyvaerts, Sarah Maenhout, Lode Goethals, Aurélie Disy, Daphné Benteyn, Joeri Pen, Aude Bonehill, Carlo Heirman, Karine Breckpot, and Kris Thielemans

Précis: This study presents important progress in the rapid development of simpler kinds of dendritic cell vaccines, the first ever of which was approved for patient treatment in the United States last year.

Intracellular Tumor-Associated Antigens Represent Effective Targets for Passive Immunotherapy


Précis: Contrary to a widely held but incorrect belief in the field, intracellular tumor antigens can offer highly effective targets for monoclonal antibody–directed therapy, as shown by this preclinical study.

Reprogramming Tumor-Associated Dendritic Cells In Vivo Using miRNA Mimetics Triggers Protective Immunity against Ovarian Cancer


Précis: Findings suggest it may be feasible to modulate microRNA activities in leukocytes in the tumor microenvironment without need of viral vectors or difficult clinical implementations.

Vascular Normalization by Loss of Siah2 Results in Increased Chemotherapeutic Efficacy

Christina S.F. Wong, Jaclyn Sceneay, Colin M. House, Heloise M. Halse, Mira C.P. Liu, Joshy George, Titaina C.U. Potdevin Hunnam, Belinda S. Parker, Izak Haviv, Ze’ev Ronai, Carleen Cullinane, David D. Bowtell, and Andreas Möller

Précis: Findings offer preclinical proof-of-concept that targeting the Siah2 ubiquitin ligase that regulates the hypoxia response factor HIF-1α can relieve hypoxia, normalize tumor vasculature, and improve responses to chemotherapy.

Vanilloid Receptor-1 Regulates Neurogenic Inflammation in Colon and Protects Mice from Colon Cancer

Amaya G. Vinuesa, Rocío Sancho, Carmen García-Limones, Axel Behrens, Peter ten Dijke, Marco A. Calzado, and Eduardo Muñoz

Précis: This important study offers compelling genetic support for the intriguing concept that neuronally controlled processes of inflammation may underlie the root inflammatory microenvironment that drives the development and progression of colon cancer, with implications for targeting neuroinflammatory receptors that control these processes as a wholly novel strategy to prevent or treat this major disease.

Cancer Vaccination Drives Nanog-Dependent Evolution of Tumor Cells toward an Immune-Resistant and Stem-like Phenotype

Kyung Hee Noh, Young-Ho Lee, Ju-Hong Jeon, Tae Heung Kang, Chih-Ping Mao, T.-C. Wu, and Tae Woo Kim

Précis: An important stem cell transcription factor is found to drive development of tumoral immune resistance after therapeutic vaccinations, suggesting possible strategies to enhance cancer immunotherapy.

RORα Suppresses Breast Tumor Invasion by Inducing SEMA3F Expression

Gaofeng Xiong, Chi Wang, B. Mark Evers, Binhua P. Zhou, and Ren Xu

Précis: Findings point to an important role for the Th17 immune transcription factor RORα in preventing the establishment of an immune-suppressive tumor microenvironment in mammary tissue.
Hypoxia-Induced Autophagy Promotes Tumor Cell Survival and Adaptation to Antiangiogenic Treatment in Glioblastoma


Précis: This important study has immediate clinical implications because it suggests ways that autophagy inhibitors such as chloroquine might be combined with antiangiogenic therapies to limit a mechanism of resistance and thereby extend efficacy.
### CHEMICAL BIOLOGY

**Paclitaxel Enhances Therapeutic Efficacy of the F8-IL2 Immunocytokine to EDA-Fibronectin–Positive Metastatic Human Melanoma Xenografts**

Michele Moschetta, Francesca Protto, Alexander Berndt, Kerstin Galler, Petra Richter, Andrea Bassi, Paolo Oliva, Edoardo Micotti, Giovanni Valentini, Kathrin Schwager, Manuela Kaspar, Eveline Trachsel, Hartwig Kosmehl, Maria Rosa Bani, Dario Neri, and Raffaele Giavazzi

**Precise:** Findings offer a preclinical proof-of-concept for an effective application of IL-2-based immunocytokine to fibronectin, an extracellular matrix protein expressed by many melanomas.

---

### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**Enhanced Apoptosis and Tumor Growth Suppression Elicited by Combination of MEK (Selumetinib) and mTOR Kinase Inhibitors (AZD8055)**

Sarah V. Holt, Armelle Logie, Barry R. Davies, Denis Alferez, Sarah Runswick, Sarah Fenton, Christine M. Chresta, Yi Gu, Jingchuan Zhang, Yi-Long Wu, Robert W. Wilkinson, Christine A. Miron, Petras Tumin, and Andrew Rees

**Precise:** Findings establish a significant association between genotoxic variants at 19p13.1 and triple-negative breast cancer, providing convincing evidence that there is a genetic susceptibility to different breast tumor subtypes and that they arise through distinct etiologic pathways.

---

### TUMOR AND STEM CELL BIOLOGY

**Cancer Stem Cell Vaccination Confers Significant Antitumor Immunity**

Ning Ning, Qin Pan, Fang Zheng, Seagal Teitze-Tennenbaum, Martin Egenti, Ji Yet, Mu Li, Christophe Ginestier, Max S. Witcha, Jeffrey S. Moyer, Mark E.P. Prince, Yingxin Xu, Xiao-Lian Zhang, Shiang Huang, Alfred E. Chang, and Qiao Li

**Precise:** Vaccines that use purified cancer stem cells are highly immunogenic and trigger antitumor immunity with greater potency than that triggered by vaccines composed of unselected tumor cells.
miRNA Signatures Associate with Pathogenesis and Progression of Osteosarcoma

Kevin B. Jones, Zaidoun Salah, Sara Del Mare, Marco Galasso, Eugenio Gaudio, Gerard J. Nuovo, Francesca Lovat, Kimberly LeBlanc, Jeff Palatini, R. Lor Randall, Stefano Volinia, Gary S. Stein, Carlo M. Croce, Jane B. Lian, and Rami I. Aqeilan

 précis: Osteosarcoma is a leading cause of death in adolescents yet remains mainly devoid of development of sounder tools to improve prognosis or therapy.

Pten Loss and RAS/MAPK Activation Cooperate to Promote EMT and Metastasis Initiated from Prostate Cancer Stem/Progenitor Cells

David J. Mulholland, Naoko Kobayashi, Marcus Ruscetti, Allen Zhi, Linh M. Tran, Jiaoti Huang, Martin Gleave, and Hong Wu

 précis: Development of a prostate cancer model that addresses the major metastatic burden accompanying late-stage human disease addresses a gap in the field that may permit the development of more effective targeted treatment strategies.

Jab1/CSN5 Negatively Regulates p27 and Plays a Role in the Pathogenesis of Nasopharyngeal Carcinoma

Yunbao Pan, Qingshu Zhang, Ling Tian, Xin Wang, Xiaohang Fan, Huizhong Zhang, Francois X. Claret, and Huiling Yang

 précis: Definition of a cell-cycle regulatory role for a component of the signalosome, a protein turnover complex analogous to the proteosome but less understood, suggests new strategies to treat an aggressive cancer endemic in East Asia.

LETTERS TO THE EDITOR

Lactate-Induced IL-8 Pathway in Endothelial Cells—Letter

Céline Pinheiro, Adhemar Longatto-Filho, Rosete Nogueira, Fernando Schmitt, and Fátima Baltazar

Lactate-Induced IL-8 Pathway in Endothelial Cells—Response

Frédérique Végran, Emmanuel Seront, Pierre Sonveaux, and Olivier Feron

Correction: Significance of MAD2 Expression to Mitotic Checkpoint Control in Ovarian Cancer Cells

ABOUT THE COVER

Tumor metastasis represents a major cause of cancer mortality. Despite intense effort, strategies designed to inhibit metastasis have been unsuccessful, in part due to lack of understanding of mechanisms underlying the process. In this study, a shortened period of disease-free survival was observed after surgery in lung cancer patients showing high angiopoietin-like protein 2 (ANGPTL2) expression in tumor cells within primary tumor sites. Furthermore, tumor cell–derived ANGPTL2 increased tumor cell motility and invasive capacity in an autocrine/paracrine manner, resulting in acquisition of metastatic tumor phenotypes. In tumor cell–implanted mouse models, tumor cell–derived ANGPTL2 accelerated metastasis and shortened survival periods; conversely, decreasing ANGPTL2 expression in tumor cells significantly attenuated metastasis and extended survival periods. This image represents CD44-stained human breast tumor cells expressing ANGPTL2 in lung metastasis in mice. For details, see the article by Endo and colleagues on page 1784 of this issue.