Contents

BREAKING ADVANCES

3733 Highlights from Recent Cancer Literature

REVIEW

3735 Roles of Sildenafil in Enhancing Drug Sensitivity in Cancer
Zhi Shi, Amit K. Tiwari, Atish S. Patel, Li-Wu Fu, and Zhe-Sheng Chen

PERSPECTIVE

3739 Evolved Tumor Suppression: Why Are We So Good at Not Getting Cancer?
James DeGregori

CLINICAL STUDIES

3745 Serial Magnetic Resonance Spectroscopy Reveals a Direct Metabolic Effect of Cediranib in Glioblastoma
Heisoog Kim, Ciprian Catana, Eva-Maria Ratai, Ovidiu C. Andronesi, Dominique L. Jennings, Tracy T. Batchelor, Rakesh K. Jain, and A. Gregory Sorensen

P/ précis: Metabolic changes in the tumor and brain tissue during anti-VEGF therapy can serve as imaging biomarkers for predicting treatment response in patients with recurrent malignant glioblastomas.

INTEGRATED SYSTEMS AND TECHNOLOGIES

3753 Preclinical Validation of Electrochemotherapy as an Effective Treatment for Brain Tumors
Birgit Agerholm-Larsen, Helle K. Iversen, Per Ihse, Jakob M. Moller, Faisal Mahmood, Kurt Svarre Jensen, and Julie Gehl

P/ précis: Enhancing drug uptake through the use of a novel electrode technology can achieve high rates of complete response in a rat model of brain cancer.

MICROENVIRONMENT AND IMMUNOLOGY

3763 Chronic Inflammatory IFN-γ Signaling Suppresses Hepatocarcinogenesis in Mice by Sensitizing Hepatocytes for Apoptosis
Stefan Lüth, Jörg Schrader, Stefan Zander, Antonella Carambia, Juliane Buchkremer, Samuel Huber, Kurt Reifenberg, Ken-Ichi Yamamura, Peter Schirmacher, Ansgar W. Lohse, and Johannes Herkel

P/ précis: Findings highlight the central role of interferon-γ in determining cancer-promoting versus cancer-suppressing inflammation.

3772 A Requirement of STAT3 DNA Binding Precludes Th-1 Immunostimulatory Gene Expression by NF-κB in Tumors
Heehyoung Lee, Jiehui Deng, Hong Xin, Yong Liu, Drew Pardoll, and Hua Yu

P/ précis: This study addresses paradoxes concerning the role of STAT3 and NF-κB as pro-oncogenic yet also immunostimulatory to T-cell responses against cancer.

3781 Proangiogenic Factor PlGF Programs CD11b⁺ Myelomonocytes in Breast Cancer during Differentiation of Their Hematopoietic Progenitors
Julien Laurent, Eveline Faes-van’t Hull, Cedric Touvrey, François Kuonen, Qiang Lan, Girieca Lorusso, Marie-Agnes Doucey, Laura Ciarroni, Natsuko Imaizumi, Gian Carlo Alghisi, Ernesta Fajiani, Khalil Zaman, Roger Stupp, Masabumi Shibuya, Jean-François Delaloye, Gerhard Christofori, and Curzio Ruegg

P/ précis: Findings reveal a previously unrecognized activity of placental growth factor, a proangiogenic factor that contributes to tumor angiogenesis and progression in many types of cancer.

3792 Exosomes Released by Melanoma Cells Prepare Sentinel Lymph Nodes for Tumor Metastasis
Joshua L. Hood, Susana San Roman, and Samuel A. Wickline

P/ précis: Preparation of the metastatic niche in lymph nodes relies in part on the ability of a primary tumor to secrete nanovesicles that can remodel the nodal microenvironment and permit its colonization by tumor cells.
CD24 Offers a Therapeutic Target for Control of Bladder Cancer Metastasis Based on a Requirement for Lung Colonization
Jonathan B. Overdevest, Shibu Thomas, Glen Kristiansen, Donna E. Hansel, Steven C. Smith, and Dan Theodorescu

Précis: Findings offer preclinical proof-of-concept for antibody targeting of a marker of metastatic progression as a potential new adjuvant therapy for clinical investigation.

An EGFR-ERK-SOX9 Signaling Cascade Links Urothelial Development and Regeneration to Cancer
Shizhang Ling, Xiaofei Chang, Luciana Schultz, Thomas K. Lee, Alcides Chaux, Luigi Marchionni, George J. Netto, David Sidransky, and David M. Berman

Précis: Cells undergoing injury turn on EGF ligand production, which induces the developmental transcription factor SOX9 and supports emergence of a migratory, invasive phenotype.

Epithelial Cell Organization Suppresses Myc Function by Attenuating Myc Expression
David R. Simpson, Min Yu, Siyuan Zheng, Zhongming Zhao, Senthil K. Muthuswamy, and William P. Tansey

Précis: This study finds that epithelial cell organization does not pose a barrier to Myc oncogenicity, pointing to roles for tumor suppression mechanisms other than threedimensional structure in antagonizing Myc during carcinogenesis.

Bone Marrow Stroma–Secreted Cytokines Protect JAK2V617F-Mutated Cells from the Effects of a JAK2 Inhibitor
Taghi Manshouri, Zeev Estrov, Alfonso Quintás-Cardama, Jan Burger, Ying Zhang, Ana Livun, Liza Knez, David Harris, Chad J. Creighton, Hagop M. Kantarjian, and Srdan Verstovsek

Précis: Myeloproliferative neoplasms rely on support from stromal cells in the bone marrow microenvironment that release IL-6, FGF, and CXCL10.

A Genome-Wide Search for Promoters That Respond to Increased MYCN Reveals Both New Oncogenic and Tumor Suppressor MicroRNAs Associated with Aggressive Neuroblastoma
Jason M. Shohet, Rajib Ghosh, Cristian Coarfa, Andrew Ludwig, Ashley L. Benham, Zaowen Chen, Danielle M. Patterson, Eveline Barbieri, Pieter Mestdagh, Denae N. Sikorski, Aleksandar Milosavljevic, Eugene S. Kim, and Preethi H. Gunaratne

Précis: N-Myc activation is associated with direct repression of a microRNA program that is not generally suppressive to neuroblastoma cells, with possible implications for how to better attack this aggressive pediatric cancer.

The Melanoma-Upregulated Long Noncoding RNA SPRY4-IT1 Modulates Apoptosis and Invasion
Divya Khaitan, Marcel E. Dinger, Joseph Mazar, Joanna Crawford, Martin A. Smith, John S. Mattick, and Ranjan J. Perera

Précis: Long noncoding RNAs (lncRNAs) are a rapidly emerging area of cancer research because of their suspected roles in interacting with messenger RNAs, regulatory microRNAs, and proteins and modulating their functions.

Mutationally Activated BRAFV600E Elicits Papillary Thyroid Cancer in the Adult Mouse
Roch-Philippe Charles, Gioia Iezza, Elena Amendola, David Dankort, and Martin McMahon

Précis: Studies of thyroid cancer, the most common endocrine cancer, will benefit from the development of a high-penetrance, genetically-engineered mouse model, which recapitulates key features of the genetics and pathophysiology of the human disease.

Mild Elevation of Body Temperature Reduces Tumor Interstitial Fluid Pressure and Hypoxia and Enhances Efficacy of Radiotherapy in Murine Tumor Models
Arindam Sen, Maegan L. Capitano, Joseph A. Spernyak, John T. Schueckler, Seneca Thomas, Anurag K. Singh, Sharon S. Evans, Bonnie L. Hylander, and Elizabeth A. Repasky

Précis: Preclinical findings show how mild systemic hyperthermia in mice bearing tumors can increase tumor blood flow and improve the efficacy radiation therapy, prompting immediate attention for clinical evaluation.
A Multistage Association Study Identifies a Breast Cancer Genetic Locus at \textit{NCOA7}


\textit{Précis:} A large genetic association study of growth factor signaling and estrogen metabolism defines a variant in an estrogen receptor-binding transcriptional co-activator that may confer a reduced risk of breast cancer.

Physical Activity after Diagnosis and Risk of Prostate Cancer Progression: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor

Erin L. Richman, Stacey A. Kenfield, Meir J. Stampfer, Alan Paciorek, Peter R. Carroll, and June M. Chan

\textit{Précis:} Brisk walking after diagnosis may inhibit or delay prostate cancer progression among men diagnosed with clinically localized prostate cancer.

\textit{LIN28B} Polymorphisms Influence Susceptibility to Epithelial Ovarian Cancer


\textit{Précis:} Common inherited variants in \textit{miRNA} biogenesis genes may be useful to identify high-risk populations and to develop novel cancer diagnostic, prognostic, and therapeutic strategies.

Identification of an Unintended Consequence of Nrf2-Directed Cytoprotection against a Key Tobacco Carcinogen plus a Counteracting Chemopreventive Intervention

Joseph D. Paonessa, Yi Ding, Kristen L. Randall, Rex Munday, Dayana Argoti, Paul Vouros, and Yuesheng Zhang

\textit{Précis:} An important cytoprotective factor is found to sensitize the bladder to a major tobacco carcinogen, but a chemopreventive strategy is suggested to limit this pitfall.

Combining Histone Deacetylase Inhibitor Vorinostat with Aurora Kinase Inhibitors Enhances Lymphoma Cell Killing with Repression of \textit{c-Myc}, \textit{hTERT}, and \textit{microRNA} Levels

Leo Kretzner, Anna Scuto, Pamela M. Dino, Claudia M. Kowolik, Jun Wu, Patrick Ventura, Richard Jove, Stephen J. Forman, Yun Yen, and Mark H. Kirschbaum

\textit{Précis:} Proof-of-concept and mechanistic findings prompt clinical evaluation for a novel drug combination that could improve cancer treatment.

Histone Methyltransferase KMT1A Restrains Entry of Alveolar Rhabdomyosarcoma Cells into a Myogenic Differentiated State

Min-Hyang Lee, Mathivahan Jothi, Andrei V. Gudkov, and Asoke K. Mal

\textit{Précis:} Results address the longstanding question of how an aggressive childhood cancer might be prompted to undergo terminal differentiation, suggesting new strategies to improve therapy.

Erlotinib-Mediated Inhibition of EGFR Signaling Induces Metabolic Oxidative Stress through NOX4


\textit{Précis:} Findings suggest that the cytotoxicity of EGFR kinase inhibitors in cancer cells may be based in large part on induction of oxidative stress via hydrogen peroxide produced by NOX4 signaling.
ErbB3 Ablation Impairs PI3K/Akt-Dependent Mammary Tumorigenesis
Rebecca S. Cook, Joan T. Garrett, Violeta Sánchez, Jamie C. Stanford, Christian Young, Anindita Chakrabarty, Cammie Rinehart, Yixian Zhang, Yaming Wu, Lee Greenberger, Ivan D. Horak, and Carlos L. Arteaga

**Précis:** Findings offer preclinical proof-of-concept that ErbB3 disruption may be therapeutically effective in PI3K/Akt-driven breast cancers.

Comparison of Neuropathy-Inducing Effects of Eribulin Mesylate, Paclitaxel, and Ixabepilone in Mice
Krystyna M. Wozniak, Kenichi Nomoto, Rena G. Lapidus, Ying Wu, Valentina Carozzi, Guido Cavaletti, Kazuhiro Hayakawa, Satoru Hosokawa, Murray J. Towle, Bruce A. Littlefield, and Barbara S. Slusher

**Précis:** Compared to taxanes and epothilones, the two major classes of antimitotic drugs used in cancer treatment, a new FDA approved antitubulin drug may cause far less debilitating nerve damage in cancer survivors.

Convection-Enhanced Delivery of Topotecan into a PDGF-Driven Model of Glioblastoma Prolongs Survival and Ablates Both Tumor-Initiating Cells and Recruited Glial Progenitors
Kim A. Lopez, Aaron M. Tannenbaum, Marcela C. Assanah, Katy Linskey, Jonathan Yun, Alayar Kangarlu, Orlando D. Gil, Peter Canoll, and Jeffrey N. Bruce

**Précis:** The findings of this study suggest that chemotherapy may prime later recurrence by decreasing recruitment of normal glial progenitor cells into a brain tumor microenvironment.

6-Bromoindirubin-3’-Oxime Inhibits JAK/STAT3 Signaling and Induces Apoptosis of Human Melanoma Cells
Lucy Liu, Sangkil Nam, Yan Tian, Fan Yang, Jun Wu, Yan Wang, Anna Scuto, Panos Polychronopoulos, Prokopios Magiatis, Leondros Skaltsounis, and Richard Jove

**Précis:** Inhibitors of the JAK/STAT3 signaling pathway represent a very appealing therapeutic direction because of the central importance of this pathway in tumor cells and the tumor microenvironment in sustaining malignant growth and progression.

Phosphorylation of Serine 68 of Twist1 by MAPKs Stabilizes Twist1 Protein and Promotes Breast Cancer Cell Invasiveness
Jun Hong, Jian Zhou, Junjiang Fu, Tao He, Jun Qin, Li Wang, Lan Liao, and Jianming Xu

**Précis:** Ras-activated MAP kinases promote invasion and metastasis by stabilizing a master regulator of epithelial-mesenchymal transition.

Aldehyde Dehydrogenase in Combination with CD133 Defines Angiogenic Ovarian Cancer Stem Cells That Portend Poor Patient Survival
Ines A. Silva, Shoumei Bai, Karen McLean, Kun Yang, Kent Griffith, Dayffd Thomas, Christophe Ginestier, Carolyn Johnston, Angela Kueck, R. Kevin Reynolds, Max S. Wha, and Ronald J. Buckanovich

**Précis:** This report identifies a pair of ovarian cancer stem cell markers that may be functionally critical for stem cell differentiation in cancers.

Hedgehog Overexpression Is Associated with Stromal Interactions and Predicts for Poor Outcome in Breast Cancer
Sandra A. O’Toole, Dorothy A. Machalek, Robert F. Shearer, Ewan K.A. Millar, Radhika Nair, Peter Schofield, Duncan McLeod, Caroline L. Cooper, Catriona M. McNeil, Andrea McFarland, Akira Nguyen, Christopher J. Ormandy, Min Ru Qiu, Brian Rabinevich, Luciano G. Martelotto, Duc Vu, Gregory E. Hannigan, Elizabeth A. Musgrove, Daniel Christ, Robert L. Sutherland, D. Neil Watkins, and Alexander Swarbrick

**Précis:** This study identifies an important prognostic role of Hedgehog pathway in breast cancer and highlights its potential as a novel therapeutic target in metastatic carcinoma.

The Hypoxia-Associated Factor Switches Cells from HIF-1α– to HIF-2α–Dependent Signaling Promoting Stem Cell Characteristics, Aggressive Tumor Growth and Invasion
Mei Yee Koh, Robert Lemos, Jr., Xiuping Liu, and Garth Powis

**Précis:** This study shows how tumor cells exposed to more intense periods of hypoxia in the microenvironment will respond to improve their likelihood of survival and progression, with implications for therapeutic targeting.
**EZH2-Mediated Concordant Repression of Wnt Antagonists Promotes \( \beta \)-Catenin–Dependent Hepatocarcinogenesis**


*Précis:* Mechanistic results reveal how the prometastatic transcription repressor EZH2 coordinately blocks Wnt antagonists, thereby promoting Wnt/\( \beta \)-catenin signaling in cancer.

**Uncoupling Cancer Mutations Reveals Critical Timing of p53 Loss in Sarcomagenesis**

Nathan P. Young, Denise Crowley, and Tyler Jacks

*Précis:* Altering the sequence of mutations in a mouse model of sarcomagenesis shows that mutation order dictates tumor phenotype.

**Correction:** Peptide Vaccination after T-Cell Transfer Causes Massive Clonal Expansion, Tumor Eradication, and Manageable Cytokine Storm

**Correction:** FLT3-Mediated \( \alpha \)-MAPK Activation Participates in the Control of Megakaryopoiesis in Primary Myelofibrosis

**Correction:** Functional Cooperation of RKTG with p53 in Tumorigenesis and Epithelial-Mesenchymal Transition

**ABOUT THE COVER**

Melanoma exosomes home to sentinel lymph nodes and induce microenvironmental responses that permit metastasis of melanoma cells. The figure demonstrates an increase in the number of melanoma cells (green) infiltrating a sentinel node (blue) for the larger melanoma exosome–induced sentinel node (bottom) in contrast to the smaller control liposome node (top) following serial injections of melanoma exosomes or control liposomes. For details, see the article by Hood and colleagues on page 3792 of this issue.