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BREAKING ADVANCES

- 2375 **Highlights from Recent Cancer Literature**

REVIEW

- 2377 **Cancer Cell Lines for Drug Discovery and Development**
Jennifer L. Wilding and Walter F. Bodmer

PRIORITY REPORT

- 2385 **COX-2 Drives Metastatic Breast Cells from Brain Lesions into the Cerebrospinal Fluid and Systemic Circulation**
Joshua E. Allen, Akshal S. Patel, Varun V. Prabhu, David T. Dicker, Jonas M. Sheehan, Michael J. Glantz, and Wafik S. El-Deiry
Précis: These important findings suggest that COX-2 inhibitors should be investigated in breast cancer patients with brain metastases as a simple immediate strategy to prevent systemic recurrence.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2391 **An Integrated Computational Model of the Bone Microenvironment in Bone-Metastatic Prostate Cancer**
Arturo Araujo, Leah M. Cook, Conor C. Lynch, and David Basanta
Précis: This work establishes a computational model that can be tailored for rapid assessment of experimental therapies and delivery of precision medicine to prostate cancer patients with bone metastases.

MICROENVIRONMENT AND IMMUNOLOGY

- 2402 **Endothelial-Specific Notch Blockade Inhibits Vascular Function and Tumor Growth through an eNOS-Dependent Mechanism**
Alexandre Patenaude, Megan Fuller, Linda Chang, Fred Wong, Grigorios Paliouras, Rebecca Shaw, Alastair H. Kyle, Patricia Umlandt, Jennifer H.E. Baker, Erika Diaz, Jade Tong, Andrew I. Minchinton, and Aly Karsan
Précis: This study uncovers a novel mechanism of nitric oxide production in endothelial cells in tumors, with implications for understanding the peculiar character of tumor blood vessels.

- 2412 **Combined Anti-CD40 and Anti-IL-23 Monoclonal Antibody Therapy Effectively Suppresses Tumor Growth and Metastases**
Bianca von Scheidt, Patrick S.K. Leung, Michelle C.R. Yong, Yu Zhang, Jennifer E. Towne, Mark J. Smyth, and Michele W.L. Teng
Précis: Therapies that tip the IL-12/23 balance in established tumors can effectively suppress their growth and metastases.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 2422 **Tumor Suppressor VHL Functions in the Control of Mitotic Fidelity**
Michael P. Hell, Maria Duda, Thomas C. Weber, Holger Moch, and Wilhelm Krek
Précis: This study reveals a function for the von Hippel-Lindau protein in spatially oriented cell division and faithful mitotic checkpoint function in renal epithelium, where this tumor suppressor has a pivotal role in blocking tumorigenesis.
- 2432 **miR-28-5p Promotes Chromosomal Instability in VHL-Associated Cancers by Inhibiting Mad2 Translation**
Michael P. Hell, Claudio R. Thoma, Niklaus Fankhauser, Yann Christinat, Thomas C. Weber, and Wilhelm Krek
Précis: By identifying a potential mediator of chromosomal instability in VHL-associated cancers, this study suggests a novel microRNA-based therapeutic strategy to target aneuploid cells in VHL-associated cancers.
- 2444 **JNK Signaling Mediates EPHA2-Dependent Tumor Cell Proliferation, Motility, and Cancer Stem Cell-like Properties in Non-Small Cell Lung Cancer**
Wenqiang Song, Yufang Ma, Jialiang Wang, Dana Brantley-Sieders, and Jin Chen
Précis: This study identifies a cell adhesion receptor-based signaling pathway that controls the function of cancer stem-like cells in lung adenocarcinoma.
- 2455 **Hypoxia-Inducible Factor-1 Promotes Pancreatic Ductal Adenocarcinoma Invasion and Metastasis by Activating Transcription of the Actin-Bundling Protein Fascin**
Xiao Zhao, Song Gao, He Ren, Wei Sun, Huan Zhang, Jianwei Sun, Shengyu Yang, and Jihui Hao
Précis: This study highlights a mechanism by which the hypoxic microenvironment may promote invasion and metastasis, with implications for defining a new candidate target to block the early progression in this disease.


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- 2465** **SWI/SNF Factors Required for Cellular Resistance to DNA Damage Include ARID1A and ARID1B and Show Interdependent Protein Stability**
Reiko Watanabe, Ayako Ui, Shin-ichiro Kanno, Hideaki Ogiwara, Takahiro Nagase, Takashi Kohno, and Akira Yasui
Précis: Cancer cells lacking in the expression of SWI/SNF transcription factors are deficient in DNA repair and potentially vulnerable to DNA damage, with implications for predicting cytotoxic drug responses and addressing resistance.

PREVENTION AND EPIDEMIOLOGY

- 2476** **Telomere Length in Peripheral Blood Leukocytes and Lung Cancer Risk: A Large Case–Control Study in Caucasians**
Beatriz Sanchez-Espiridion, Meng Chen, Joe Y. Chang, Charles Lu, David W. Chang, Jack A. Roth, Xifeng Wu, and Jian Gu
Précis: This large epidemiologic study addresses a controversy concerning an association between telomere length in peripheral blood leukocytes and lung cancer susceptibility, revealing that risk is associated differentially with different histologic subtypes.
- 2487** **Curcumin Promotes Autophagic Survival of a Subset of Colon Cancer Stem Cells, Which Are Ablated by DCLK1-siRNA**
Carla Kantara, Malaney O’Connell, Shubhashish Sarkar, Stephanie Moya, Robert Ullrich, and Pomila Singh
Précis: These interesting findings suggest a use for the spice curcumin, which has chemopreventive properties for colon cancer, by combining it with therapies that target colon cancer stem-like cells to promote more durable remissions in this setting.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 2499** **Activation of the Glutamate Receptor GRM1 Enhances Angiogenic Signaling to Drive Melanoma Progression**
 Yu Wen, Jiadong Li, Jasmine Koo, Seung-Shick Shin, Yong Lin, Byeong-Seon Jeong, Janice M. Mehnert, Suzie Chen, Karine A. Cohen-Sola, and James S. Goydos
Précis: These findings offer a mechanistic rationale for combinatorial therapy of melanoma with GRM1 inhibitors, with immediate implications on trial designs for the clinical development of this class of antimetabolic agents.

- 2510** **WEE1 Inhibition Alleviates Resistance to Immune Attack of Tumor Cells Undergoing Epithelial–Mesenchymal Transition**
Duane H. Hamilton, Bruce Huang, Romaine I. Fernando, Kwong-Yok Tsang, and Claudia Palena
Précis: This study describes a therapeutic rationale to correct a mechanism of immune escape associated with epithelial–mesenchymal transition in cancer cells, a pivotal step enabling invasion and metastatic prowess.

- 2520** **Auranofin Induces Lethal Oxidative and Endoplasmic Reticulum Stress and Exerts Potent Preclinical Activity against Chronic Lymphocytic Leukemia**
Warren Fiskus, Nakhle Saba, Min Shen, Mondana Ghias, Jinyun Liu, Soumyasri Das Gupta, Lata Chauhan, Rekha Rao, Sumedha Gunewardena, Kevin Schorno, Christopher P. Austin, Kami Maddocks, John Byrd, Ari Melnick, Peng Huang, Adrian Wiestner, and Kapil N. Bhalla
Précis: This study provides a rationale to immediately reposition the approved drug Auranofin for clinical evaluation in the therapy of relapsed forms of chronic lymphocytic leukemia.

- 2533** **Global Gene Repression by the Steroid Receptor Coactivator SRC-1 Promotes Oncogenesis**
Claire A. Walsh, Jarlath C. Bolger, Christopher Byrne, Sinead Cocchiglia, Yuan Hao, Ailis Fagan, Li Qin, Aoife Cahalin, Damian McCartan, Marie McLroy, Peadar O’Gaora, Jianming Xu, Arnold D. Hill, and Leonie S. Young
Précis: These findings deepen understanding of a key partner of the estrogen regulator, with implications for how gene expression is controlled in breast cancer cells through a novel role in gene repression.

- 2545** **Comparative Functional Analysis of DPYD Variants of Potential Clinical Relevance to Dihydropyrimidine Dehydrogenase Activity**
Steven M. Offer, Croix C. Fossum, Natalie J. Wegner, Alexander J. Stuflesser, Gabriel L. Butterfield, and Robert B. Diasio
Précis: Clinical testing for deficient DPYD variations might dramatically improve current predictive tests for 5-FU sensitivity, especially in individuals of non-European descent

- 2555** **Maintaining Glycogen Synthase Kinase-3 Activity Is Critical for mTOR Kinase Inhibitors to Inhibit Cancer Cell Growth**
Junghui Koo, Ping Yue, Anthony A. Gal, Fadlo R. Khuri, and Shi-Yong Sun
Précis: These findings reveal a critical factor in determining the therapeutic effect of mTOR kinase inhibitors, with potential implications for a biomarker of clinical response.

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- 2569** **Curative Properties of Noninternalizing Antibody–Drug Conjugates Based on Maytansinoids**
Elena Perrino, Martina Steiner, Nikolaus Krall, Gonçalo J.L. Bernardes, Francesca Pretto, Giulio Casi, and Dario Neri

Précis: *This study offers the first preclinical demonstration that antibody–drug conjugates targeting the microenvironment can be fully curative and that cancer cell internalization is not necessary for the efficacy of this emerging class of cancer therapeutics.*

- 2579** **STAT3-Mediated Autophagy Dependence Identifies Subtypes of Breast Cancer Where Autophagy Inhibition Can Be Efficacious**
Paola Maycotte, Christy M. Gearheart, Rebecca Barnard, Suraj Aryal, Jean M. Mulcahy Levy, Susan P. Fosmire, Ryan J. Hansen, Michael J. Morgan, Christopher C. Porter, Daniel L. Gustafson, and Andrew Thorburn

Précis: *This study shows how STAT3 makes triple-negative breast cancer cells dependent on autophagy for survival, even in nutrient-rich conditions, implicating this factor as a marker for autophagy addiction and efficacious responses to autophagy inhibitors.*

TUMOR AND STEM CELL BIOLOGY

- 2591** **Survival in Patients with High-Risk Prostate Cancer Is Predicted by miR-221, Which Regulates Proliferation, Apoptosis, and Invasion of Prostate Cancer Cells by Inhibiting IRF2 and SOCS3**



Burkhard Kneitz, Markus Krebs, Charis Kalogirou, Maria Schubert, Steven Joniau, Hein van Poppel, Evelyne Lerut, Susanne Kneitz, Claus Jürgen Scholz, Philipp Ströbel, Manfred Gessler, Hubertus Riedmiller, and Martin Spahn

Précis: *These results identify a microRNA with significant potential as a prognostic biomarker and therapeutic target for improving clinical management of patients with aggressive prostate cancer.*

- 2604** **GRHL1 Acts as Tumor Suppressor in Neuroblastoma and Is Negatively Regulated by MYCN and HDAC3**

Johannes Fabian, Marco Lodrini, Ina Oehme, Marie C. Schier, Theresa M. Thole, Thomas Hielscher, Annette Kopp-Schneider, Lennart Opitz, David Capper, Andreas von Deimling, Inga Wiegand, Till Milde, Ulrich Mahlknecht, Frank Westermann, Odilia Popanda, Frederik Roels, Barbara Hero, Frank Berthold, Matthias Fischer, Andreas E. Kulozik, Olaf Witt, and Hedwig E. Deubzer

Précis: *These findings suggest a new avenue of therapeutic intervention in neuroblastoma based on the application of small molecule inhibitors of histone deacetylases.*

- 2617** **Mechanistic Elucidation of the Antitumor Properties of Withaferin A in Breast Cancer**

Arumugam Nagalingam, Panjamurthy Kuppusamy, Shivendra V. Singh, Dipali Sharma, and Neeraj K. Saxena

Précis: *These findings reveal the key nodes of Withaferin A action in breast cancer to establish surrogate biomarkers for its efficacy and help in clinical development of this bioactive molecule.*

- 2630** **CD44v8-10 Is a Cancer-Specific Marker for Gastric Cancer Stem Cells**



Wen Min Lau, Eileen Teng, Hui Shan Chong, Kirsten Anne Pagaduan Lopez, Amy Yuh Ling Tay, Manuel Salto-Tellez, Asim Shabbir, Jimmy Bok Yan So, and Shing Leng Chan

Précis: *This study defines a variant form of the common stem cell marker CD44 with properties that may make it superior for practical clinical use in targeting cancer stem-like cells, with important therapeutic implications.*

- 2642** **Genetic Suppression of Inflammation Blocks the Tumor-Promoting Effects of TGF- β in Gastric Tissue**



Mitsuhiko Ota, Masahito Horiguchi, Victoria Fang, Kotaro Shibahara, Kyuichi Kadota, Cynthia Loomis, Michael Cammer, and Daniel B. Rifkin

Précis: *Genetic ablation of adaptive immunity eliminates the development of tumors in a mouse model of gastric cancer driven by TGF- β hypomorphism, highlighting the critical contribution of inflammation to TGF- β -mediated tumorigenesis.*

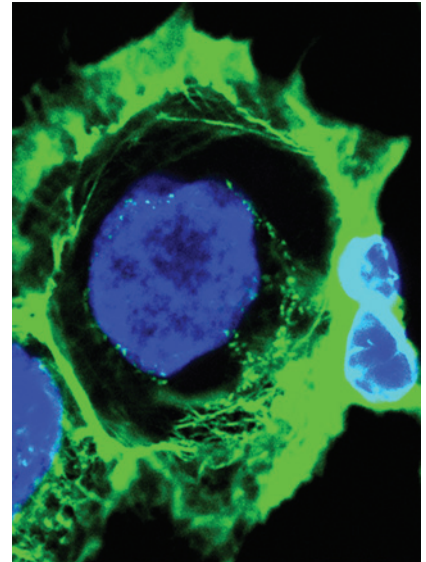
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ABOUT THE COVER

Aberrant expression of the T-box transcription factor brachyury in human carcinomas drives the phenomenon of epithelial-mesenchymal transition (EMT), a phenotypic modulation that facilitates tumor dissemination and resistance to conventional anti-neoplastic therapies. Hamilton and colleagues show that acquisition of a mesenchymal-like phenotype could also significantly reduce the susceptibility of cancer cells to lysis by both antigen-specific T cells and natural killer cells. This defect was observed even in the presence of a stable engagement between the immune effector cells and the tumor cells, as demonstrated by the effective polar actin polymerization observed at the interacting surface area. The phenomenon of immune resistance of mesenchymal-like cells was correlated to their decreased levels of cell cycle kinase CDK1, a defect that could be countered by treatment with a specific inhibitor of WEE1. For details, see article by Hamilton and colleagues on page 2510.



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