Cancer Research
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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
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 Christianat, 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, Huei 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.
**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 Ogawa, 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.

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**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.

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**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 Ulrich, 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.

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**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.

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**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.

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**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, Jinyu Liu, Soumyasri Das Gupta, Lata Chauhan, Rekha Rao, Sumedha Cunewardena, 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.

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**Global Gene Repression by the Steroid Receptor Coactivator SRC-1 Promotes Oncogenesis**

Claire A. Walsh, Jarlath C. Bolger, Christopher Byrne, Sinead Cocciglia, Yuan Hao, Ailis Fagan, Li Qin, Aoife Cahalin, Damian McCartan, Marie McIlroy, 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.

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**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.
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**TUMOR AND STEM CELL BIOLOGY**

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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.