## Breaking Advances

**Highlights from Recent Cancer Literature**

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## Reviews

**From Integrative Genomics to Therapeutic Targets**
Rachael Natrajan and Paul Wilkerson

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**HER2 and Breast Cancer Stem Cells: More than Meets the Eye**
Hasan Korkaya and Max S. Wicha

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## Perspective

**APOBEC3 Cytidine Deaminases in Double-Strand DNA Break Repair and Cancer Promotion**
Roni Nowarski and Moshe Kotler

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## Clinical Studies

**Immune Infiltrates Are Prognostic Factors in Localized Gastrointestinal Stromal Tumors**

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## Integrated Systems and Technologies

**Kinetic Modeling-Based Detection of Genetic Signatures That Provide Chemoresistance via the E2F1-p73/DNp73-miR-205 Network**
Julio Vera, Ulf Schmitz, Xin Lai, David Engelmann, Faiz M. Khan, Olaf Wolkenhauer, and Brigitte M. Pitzer

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**Mathematical Modeling of Tumor Cell Proliferation Kinetics and Label Retention in a Mouse Model of Lung Cancer**
Yanyan Zheng, Helen Moore, Alexandra Piryatinska, Trinidad Solis, and E. Alejandro Sweet-Cordero

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**Tumor–Immune Dynamics Regulated in the Microenvironment Inform the Transient Nature of Immune-Induced Tumor Dormancy**
Kathleen P. Wilkie and Philip Hahnfeldt

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## Microenvironment and Immunology

**Booster Vaccinations against Cancer Are Critical in Prophylactic but Detrimental in Therapeutic Settings**
Alessia Ricupito, Matteo Grioni, Arianna Calciniotto, Rodrigo Hess Michelini, Renato Longhi, Anna Mondino, and Matteo Bellone

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**Precis:** These findings encourage the prospective validation of immune biomarkers for optimal risk stratification of GIST, and they prompt clinical use of immunomodulators in conjunction with imatinib used to treat this disease.
A Novel Model for Evaluating Therapies Targeting Human Tumor Vasculature and Human Cancer Stem–like Cells

BMP-6 in Renal Cell Carcinoma

Dual Blockade of PD-1 and CTLA-4

Enhanced Effector Responses in Activated CD8+ T Cells Deficient in Diacylglycerol Kinases

SOCS3 Transactivation by PPAR

Enhanced Effector Responses in Activated CD8+ T Cells Deficient in Diacylglycerol Kinases

YAP/TEAD–Mediated Transcription Controls Cellular Senescence

ATF3 Suppresses Metastasis of Bladder Cancer by Regulating Gelsolin-Mediated Remodeling of the Actin Cytoskeleton

Nkx2-8 Downregulation Promotes Angiogenesis and Activates NF-κB in Esophageal Cancer

Targeting ROR1 Inhibits Epithelial–Mesenchymal Transition and Metastasis

As a pivotal step in what converts curable benign tumors to untreatable malignant cancers, the cellular process of EMT and the key factors regulating it remain an important focus of attention in identifying cancer-specific therapies.
**TUMOR AND STEM CELL BIOLOGY**

**3692**  
Inhibition of c-Met Reduces Lymphatic Metastasis in RIP-Tag2 Transgenic Mice  
Barbara Sennino, Toshina Ishiguro-Oonuma, Brian J. Schriver, James G. Christensen, and Donald M. McDonald  
 préc: VEGF inhibition increases expression of c-Met, which can promote lymph node metastases, with consequences for understanding how resistance arises to antiangiogenic therapies.

**3704**  
Antioxidant Enzymes Mediate Survival of Breast Cancer Cells Deprived of Extracellular Matrix  
 préc: This study offers evidence that blocking antioxidant enzymes may help kill cancer cells that are poised to metastasize, a finding that is counterintuitive in light of a large body of literature encouraging antioxidant treatments to prevent cancer.

**3716**  
FGFR1 Is Essential for Prostate Cancer Progression and Metastasis  
Feng Yang, Yongyou Zhang, Steven J. Ressler, Michael M. Ittmann, Gustavo E. Ayala, Truong D. Dang, Fen Wang, and David R. Rowley  
 préc: Fibroblast growth factor signaling in prostate cancer is emerging as an important area of therapeutic potential, as shown in this study of FGFR1, which suggests a rationale to attack metastatic tumors.

**3725**  
Androgen Receptor-Independent Function of FoxA1 in Prostate Cancer Metastasis  
Hong-Jian Jin, Jonathan C. Zhao, Irene Ogden, Raymond C. Bergan, and Jindan Yu  
 préc: This study may explain why recurrent FoxA1 mutations that have been found to occur in prostate cancer contribute to malignant progression in this disease.

**3737**  
NF-κB Regulates Radioresistance Mediated by β1 Integrin in Three-Dimensional Culture of Breast Cancer Cells  
Kazi Mokim Ahmed, Hui Zhang, and Catherine C. Park  
 préc: The results of this study suggest a novel approach to radiosensitize malignant breast cancers by targeting a forward feedback cell adhesion pathway.

**3749**  
ING5 Is a Tip60 Cofactor That Acetylates p53 in Response to DNA Damage  
Nansong Liu, Jiadong Wang, Jifeng Wang, Rukai Wang, Zhongle Liu, Yao Yu, and Hong Lu  
 préc: This study illuminates one of the mechanisms through which cells determine whether to undergo cell-cycle arrest or apoptosis after p53 activation.

**3761**  
MTA1 Promotes STAT3 Transcription and Pulmonary Metastasis in Breast Cancer  
 préc: Endogenous levels of a prometastatic transcriptional coregulator are sufficient to support its function in metastasis, whether or not it is overexpressed in cancer.
DDB2 Suppresses Epithelial-to-Mesenchymal Transition in Colon Cancer
Nilotpal Roy, Prashant V. Bommi, Uppoor G. Bhat, Shaumick Bhattacharjee, Indira Elangovan, Jing Li, Krushna C. Patra, Dragana Kopanja, Adam Blunier, Richard Benya, Srilata Bagchi, and Pradip Raychaudhuri

**Précis:** A nucleotide excision repair protein is found to function as an inhibitor of EMT, a phenotypic change in transformed epithelial cells that facilitates invasion and metastasis, suggesting a direct link between these processes during tumorigenesis.

GDNF–RET Signaling in ER-Positive Breast Cancers Is a Key Determinant of Response and Resistance to Aromatase Inhibitors
Andrea Morandi, Lesley-Ann Martin, Qiong Gao, Sunil Pancholi, Alan Mackay, David Robertson, Marketa Zvelebil, Mitch Dowsett, Ivan Plaza-Menacho, and Clare M. Isacke

**Précis:** This study addresses the clinical challenge of therapeutic resistance in oncology, in this case by defining an important tractable pathway of resistance to aromatase inhibitors used to fight ER-positive breast cancer.

Sox2 Requirement in Sonic Hedgehog-Associated Medulloblastoma
Julia Ahlfeld, Rebecca Favaro, Pierfrancesco Pagella, Hans A. Kretzschmar, Silvia Nicolis, and Ulrich Schuller

**Précis:** This study links a core pathogenic driver of an aggressive pediatric tumor to a central regulator of cancer stem-like function, with potential therapeutic implications.

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**ABOUT THE COVER**

Inhibition of VEGF signaling reduces angiogenesis and slows tumor growth, but can also promote lymph node metastasis in some preclinical models. Studies of RIP-Tag2 transgenic mice revealed that inhibition of VEGF signaling by a function blocking anti-VEGF antibody or the receptor tyrosine kinase inhibitor sunitinib increased the number of intratumoral lymphatics, the proportion of lymphatics with tumor cells inside, and the incidence of lymph node metastasis. After the treatment, c-Met was upregulated in lymphatics in and around the tumors. Importantly, inhibition of c-Met by PF-04217903 administered with the angiogenesis inhibitor significantly reduced the abundance of intratumoral lymphatics, tumor cells inside lymphatics, and lymph node metastases. For details, see article by Sennino and colleagues on page 3692.