**Contents**

**Cancer Research**
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### BREAKING ADVANCES

6317  
Highlights from Recent Cancer Literature

---

### EPIGENOME CONSORTIUM

6319  
A Blueprint for an International Cancer Epigenome Consortium. A Report from the AACR Cancer Epigenome Task Force  
Stephan Beck, Bradley E. Bernstein, Robert M. Campbell, Joseph F. Costello, Dashyant Dhanak, Joseph R. Ecker, John M. Greally, Jean-Pierre Issa, Peter W. Laird, Kornelia Polyak, Benjamin Tycko, and Peter A. Jones, for the AACR Cancer Epigenome Task Force

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### REVIEWS

6325  
Role of Chemokines and Chemokine Receptors in Shaping the Effector Phase of the Antitumor Immune Response  
Katarzyna Franciszkiwicz, Alexandre Boissonnas, Marie Boutet, Christophe Combadière, and Fathia Mami-Chouaib

6333  
TLRs as miRNA Receptors  
Muller Fabbri

6338  
Cytokine Stimulation of Epithelial Cancer Cells: The Similar and Divergent Functions of IL-4 and IL-13  
Miranda A. Hallett, Katherine T. Venmar, and Barbara Fingleton

---

### PRIORITY REPORT

6344  
Paracrine Hedgehog Signaling Drives Metabolic Changes in Hepatocellular Carcinoma  
**Précis:** Myofibroblasts in the microenvironment of liver carcinoma rely on Hedgehog signals, suggesting new diagnostic and therapeutic targets to exploit in this disease.

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### INTEGRATED SYSTEMS AND TECHNOLOGIES

6351  
An Integrated Genome-Wide Approach to Discover Tumor-Specific Antigens as Potential Immunologic and Clinical Targets in Cancer  
Qing-Wen Xu, Wei Zhao, Yue Wang, Maureen A. Sartor, Dong-Mei Han, Jixin Deng, Rakesh Ponnala, Jiang-Ying Yang, Qing-Yun Zhang, Guo-Qing Liao, Yi-Mei Qu, Lu Li, Fang-Fang Liu, Hong-Mei Zhao, Yan-Hui Yin, Wei-Feng Chen, Yu Zhang, and Xiao-Song Wang  
**Précis:** This important paper reports an integrated technology to uncover the cancer-specific antigen genome as a reservoir for novel immunological and clinical targets.

6362  
Evolutionary Approaches to Prolong Progression-Free Survival in Breast Cancer  
Ariosto S. Silva, Yoonseok Kam, Zayar P. Khin, Susan E. Minton, Robert J. Gillies, and Robert A. Gatenby  
**Précis:** This work challenges the paradigm of maximum tolerated dose for drug treatment in cancer by proposing a combination strategy to burden chemoresistant cells with a chronic futile efflux of noncytotoxic drugs, with only the minimal chemotherapy dose needed to block tumor growth.

### MICROENVIRONMENT AND IMMUNOLOGY

6371  
Neuropilin-1 Identifies a Subset of Bone Marrow Gr1+ Monocytes That Can Induce Tumor Vessel Normalization and Inhibit Tumor Growth  
Alessandro Carrer, Silvia Motimas, Serenac Zacchigna, Lucia Pattarini, Lorena Zentilin, Giulia Ruozzi, Miguel Mano, Milena Sinigaglia, Federica Maione, Guido Serini, Enrico Giraudo, Federico Bussolino, and Mauro Giacca  
**Précis:** Neuropilin-1 expressing monocytes (NEM) are able to stabilize the tumor vasculature, thereby improving tumor oxygenation and reducing tumor malignancy, invasiveness, and resistance to chemotherapy.
TWIST1 Is an ERK1/2 Effector That Promotes Invasion and Regulates MMP-1 Expression in Human Melanoma Cells

Michele B. Weiss, Ethan V. Abel, Melanie M. Mayberry, Kevin J. Basile, Adam C. Berger, and Andrew E. Aplin

Précis: Findings define the mechanism of action of a core regulator of EMT in tumor cell invasion through its action in a previously unrecognized signaling cascade that may have general implications in cancer.

6393

p38 MAPK in Myeloma Cells Regulates Osteoclast and Osteoblast Activity and Induces Bone Destruction

Jin He, Zhiqiang Liu, Yuhuan Zheng, Jianfei Qian, Haiyan Li, Yong Lu, Jingda Xu, Bangxing Hong, Minjun Zhang, Pei Lin, Zhen Cai, Robert Z. Orlowskia, Larry W. Kwak, Qing Yi, and Jing Yang

Précis: Findings suggest that p38 MAPK inhibitors developed clinically should be repositioned to evaluate their use in treating osteolytic bone lesions in myeloma, with potentially broader implications to treat bone metastasis occurring in various cancers.

6403

Polyploidization of Murine Mesenchymal Cells Is Associated with Suppression of the Long Noncoding RNA H19 and Reduced Tumorigenicity

Ofer Shoshani, Hassan Massalha, Nir Shani, Sivan Kagan, Orly Ravid, Shalom Madar, Luba Trakhtenbrot, Dena Leshkowitz, Gideon Rechavi, and Dov Zipori

Précis: Findings reveal a critical link between a noncoding RNA and the polyploid character and low tumorigenicity of mesenchymal stromal cells.

6447

Systemic Delivery of Salmonella typhimurium Transformed with IDO shRNA Enhances Intratumoral Vector Colonization and Suppresses Tumor Growth

Céline A. Blache, Edwin R. Manuel, Teodora I. Kaltcheva, Andrea N. Wong, Joshua D.J. Ellenhorn, Bruce R. Blazar, and Don J. Diamond

Précis: IDO blockade can leverage hypoxia-targeting infections that recruit neutrophils with powerful tumor-killing capacity, further expanding the broad acting modifier effects of IDO on adaptive and innate mechanisms of immune escape in tumors.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6403

Polypliodization of Murine Mesenchymal Cells Is Associated with Suppression of the Long Noncoding RNA H19 and Reduced Tumorigenicity

Ofer Shoshani, Hassan Massalha, Nir Shani, Sivan Kagan, Orly Ravid, Shalom Madar, Luba Trakhtenbrot, Dena Leshkowitz, Gideon Rechavi, and Dov Zipori

Précis: Findings reveal a critical link between a noncoding RNA and the polyploid character and low tumorigenicity of mesenchymal stromal cells.

6414

Loss of PPP2R2A Inhibits Homologous Recombination DNA Repair and Predicts Tumor Sensitivity to PARP Inhibition

Peter Kalev, Michal Simicek, Iria Vazquez, Sebastian Munck, Liping Chen, Thomas Soin, Natasha Danda, Wen Chen, and Anna Sablina

Précis: Findings suggest that downregulation of a PPP2A family phosphatase in tumors may predict therapeutic responses to a promising new class of anticancer agents currently in clinical trials.

6425

Genetically Mediated Nf1 Loss in Mice Promotes Diverse Radiation-Induced Tumors Modeling Second Malignant Neoplasms

Grace Choi, Brian Huang, Emile Pinarbasi, Steve E. Braunstein, Andrew E. Horvai, Scott Kogan, Smita Bhatia, Bruce Faddegon, and Jean L. Nakamura

Précis: A mouse model of second malignant neoplasms reveals that loss of the Nf1 gene drives genotoxin-induced tumorigenesis in multiple tissue types. Concordant with this mouse model, genetically-mediated Nf1 loss also occurs in human second malignant neoplasms.

6435

miR-23b Represses Proto-oncogene Src Kinase and Functions as Methylation-Silenced Tumor Suppressor with Diagnostic and Prognostic Significance in Prostate Cancer

Shahana Majid, Aliaf A. Dar, Sharanjot Saini, Sumita Arora, Varahram Sabhly, Mohd Saif Zaman, Inik Chuang, Soichiro Yamamura, Yuichiro Tanaka, Guoren Deng, and Rajvir Dahya

Précis: This study documents the diagnostic, prognostic, and functional significance of microRNA-23b as a tumor suppressor gene in prostate cancer.

6447

Systemic Delivery of Salmonella typhimurium Transformed with IDO shRNA Enhances Intratumoral Vector Colonization and Suppresses Tumor Growth

Céline A. Blache, Edwin R. Manuel, Teodora I. Kaltcheva, Andrea N. Wong, Joshua D.J. Ellenhorn, Bruce R. Blazar, and Don J. Diamond

Précis: IDO blockade can leverage hypoxia-targeting infections that recruit neutrophils with powerful tumor-killing capacity, further expanding the broad acting modifier effects of IDO on adaptive and innate mechanisms of immune escape in tumors.

6457

Modulation of the ATPase and Transport Activities of Broad-Acting Multidrug Resistance Factor ABCC10 (MRP7)

Ekaterina V. Malofeeva, Natalya Domanitskaya, Mariya Gudima, and Elizabeth A. Hopper-Borge

Précis: Findings suggest that the approved multikinase inhibitor sorafenib may enhance chemotherapeutic efficacy of drugs that are effluxed by an important mediator of drug resistance in cancer cells.
**TUMOR AND STEM CELL BIOLOGY**

**Cyclin D1 Activity Regulates Autophagy and Senescence in the Mammary Epithelium**

Nelson E. Brown, Rinath Jeselsohn, Teeru Bihani, Miaofen G. Hu, Parthena Foltopoulou, Charlotte Kupervasser, and Philip W. Hinds

**Précis:** Mammary epithelial cells expressing a kinase defective cyclin D1 survive due to an upregulation of autophagy, which if blocked, results in senescence.

**Obesity and Overfeeding Affecting Both Tumor and Systemic Metabolism Activates the Progesterone Receptor to Contribute to Postmenopausal Breast Cancer**

Erin D. Giles, Elizabeth A. Wellberg, David P. Astling, Steven M. Anderson, Ann D. Thor, Sonali Jindal, Aik-Choon Tan, Pepper S. Schedin, and Paul S. MacLean

**Précis:** Striking findings may help explain why obese postmenopausal women have relatively increased risks of breast cancer.

**The CRTC1-NEDD9 Signaling Axis Mediates Lung Cancer Progression Caused by LKB1 Loss**

Yan Feng, Ye Wang, Zao yuan Wang, Zhaoyuan Fang, Fei Li, Yijun Gao, Hongyan Liu, Tian Xiao, Fuming Li, Yang Zhou, Qiwei Zhai, Xiaolong Liu, Yihua Sun, Nabeel Bardeesy, Kwok-kin Wong, Hailian Chen, Zhi-qi Xiong, and Hongbin Ji

**Précis:** Results decipher the mechanism through which mutation of the tumor suppressor LKB1 in lung cancer leads to progression and metastasis, offering mechanistic insights into how to attack these processes.

**Host Immune Defense Peptide LL-37 Activates Caspase-Independent Apoptosis and Suppresses Colon Cancer**


**Précis:** Findings suggest that a bacteriocidal factor secreted by macrophages, PMNs, and colonocytes contributes to colon cancer suppression by activating a novel pathway of apoptosis in colon cancer cells.

**Correction:** The Kynurenine Pathway in Brain Tumor Pathogenesis

**Correction:** The Kynurenine Pathway in Brain Tumor Pathogenesis

Obesity increases the risk for breast cancer after menopause. Animal studies reveal that obesity and ovariectomy-induced overfeeding converge to promote progesterone receptor (PR)-positive mammary tumors as shown by high nuclear PR immunohistochemical staining. Elevated PR expression positively correlated with tumor expression of glycolytic and lipogenic enzymes, glucose uptake, and proliferation markers. A similar relationship between PR expression and metabolic capacity was observed in tumors from postmenopausal women. Metformin treatment during the window of weight gain following ovariectomy caused PR downregulation and tumor regression. For details, see article by Giles and colleagues on page 6490.
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