

## 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. Grealley, Jean-Pierre Issa, Peter W. Laird, Kornelia Polyak, Benjamin Tycko, and Peter A. Jones, for the AACR Cancer Epigenome Task Force

## REVIEWS

- 6325 | **Role of Chemokines and Chemokine Receptors in Shaping the Effector Phase of the Antitumor Immune Response**  
Katarzyna Franciszkiewicz, 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**  
Isaac S. Chan, Cynthia D. Guy, Yuping Chen, Jiuyi Lu, Marzena Swiderska-Syn, Gregory A. Michelotti, Gamze Karaca, Guanhua Xie, Leandi Krüger, Wing-Kin Syn, Blair R. Anderson, Thiago A. Pereira, Steve S. Choi, Albert S. Baldwin, and Anna Mae Diehl
- Précis:* Myofibroblasts in the microenvironment of liver carcinoma rely on Hedgehog signals, suggesting new diagnostic and therapeutic targets to exploit in this disease.

## 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<sup>+</sup> Monocytes That Can Induce Tumor Vessel Normalization and Inhibit Tumor Growth**  
Alessandro Carrer, Silvia Moimas, Serena Zacchigna, Lucia Pattarini, Lorena Zentilin, Giulia Ruozi, 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

6382 **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, Mingjun Zhang, Pei Lin, Zhen Cai, Robert Z. Orlowski, 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.

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, Altaf A. Dar, Sharanjot Saini, Sumit Arora, Varahram Shahryari, Mohd Saif Zaman, Inik Chang, Soichiro Yamamura, Yuichiro Tanaka, Guoren Deng, and Rajvir Dahiya  
*Précis:* This study documents the diagnostic, prognostic, and functional significance of microRNA-23b as a tumor suppressor gene in prostate cancer.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

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.

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 PP2A family phosphatase in tumors may predict therapeutic responses to a promising new class of anticancer agents currently in clinical trials.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

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.I. 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.

6468

**eIF4E/4E-BP Ratio Predicts the Efficacy of mTOR Targeted Therapies**

Tommy Alain, Masahiro Morita, Bruno D. Fonseca, Akiko Yanagiya, Nadeem Siddiqui, Mamatha Bhat, Domenick Zammit, Victoria Marcus, Peter Metrakos, Lucie-Anne Voyer, Valentina Gandin, Yi Liu, Ivan Topisirovic, and Nahum Sonenberg

*Précis:* This report establishes that a ratio of the translational regulatory factors eIF4E and 4E-BP, rather than simply their individual levels or phosphorylation status, may serve as a generalized marker to predict the clinical therapeutic response to mTOR inhibitors in any cancer setting.

6502

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

Yan Feng, Ye Wang, Zuoyun 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, Haiquan 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.

6512

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

Shun X. Ren, Alfred S.L. Cheng, Ka F. To, Joanna H.M. Tong, May S. Li, Jin Shen, Clover C.M. Wong, Lin Zhang, Ruby L.Y. Chan, Xiao J. Wang, Simon S.M. Ng, Lawrence C.M. Chiu, Victor E. Marquez, Richard L. Gallo, Francis K.L. Chan, Jun Yu, Joseph J.Y. Sung, William K.K. Wu, and Chi H. Cho

*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.

**TUMOR AND STEM CELL BIOLOGY**

6477

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

Nelson E. Brown, Rinath Jeselsohn, Teeru Bihani, Miaofen G. Hu, Parthena Foltopoulou, Charlotte Kuperwasser, 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.

6490

**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

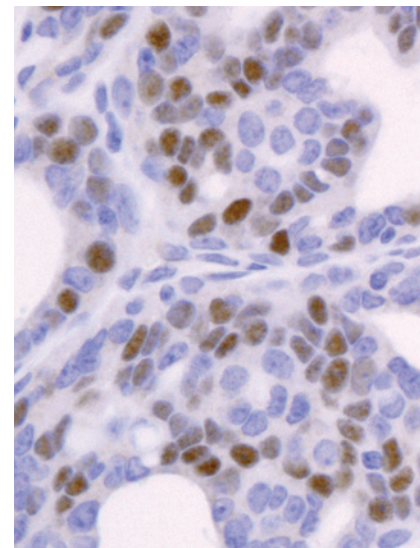
*Précis:* Striking findings may help explain why obese postmenopausal women have relatively increased risks of breast cancer.

**CORRECTION**

6524

**Correction: The Kynurenine Pathway in Brain Tumor Pathogenesis****ABOUT THE COVER**

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.



# Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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