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**ACR**  
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## BREAKING ADVANCES

- 6375 **Highlights from Recent Cancer Literature**

## REVIEWS

- 6377 **A Genome-wide View of Microsatellite Instability: Old Stories of Cancer Mutations Revisited with New Sequencing Technologies**  
Tae-Min Kim and Peter J. Park
- 6383 **Chimeric Antigen Receptor T-cell Therapy to Target Hematologic Malignancies**  
Saad Sirop Kenderian, Marco Ruella, Saar Gill, and Michael Kalos

## PRIORITY REPORT

- 6390 **Discrepancies in Cancer Genomic Sequencing Highlight Opportunities for Driver Mutation Discovery**  
 Andrew M. Hudson, Tim Yates, Yaoyong Li, Eleanor W. Trotter, Shameem Fawdar, Phil Chapman, Paul Lorigan, Andrew Biankin, Crispin J. Miller, and John Brognard  
*Précis:* These findings highlight major discrepancies in mutational profiles of identical cancer cell lines sequenced by two different institutes, with implications for identifying previously undiscovered driver mutations.


## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6397 **Mathematical Modeling of Tumor Growth and Metastatic Spreading: Validation in Tumor-Bearing Mice**  
Niklas Hartung, Séverine Mollard, Dominique Barbolosi, Assia Benabdallah, Guillemette Chapuisat, Gerard Henry, Sarah Giacometti, Athanassios Iliadis, Joseph Ciccolini, Christian Faivre, and Florence Hubert  
*Précis:* This work advances efforts to predict metastatic spreading during the earliest stages of cancer, at points that could help clinicians make the best decisions on treatment strategies.

- 6408 **Direct Chemosensitivity Monitoring *Ex Vivo* on Undissociated Melanoma Tumor Tissue by Impedance Spectroscopy**  
Heinz-Georg Jahnke, Sarah Poenick, Jan Maschke, Michael Kendler, Jan C. Simon, and Andrea A. Robitzki

*Précis:* This study presents a novel and more accurate tissue-based method to determine chemotherapeutic drug sensitivity using small fragments of tumor tissue, addressing a need to personalize therapy for patients to improve treatment outcomes.

## MICROENVIRONMENT AND IMMUNOLOGY

- 6419 **CXM: A New Tool for Mapping Breast Cancer Risk in the Tumor Microenvironment**  
Michael J. Flister, Bradley T. Endres, Nathan Rudemiller, Allison B. Sarkis, Stephanie Santarriaga, Ishan Roy, Angela Lemke, Aron M. Geurts, Carol Moreno, Sophia Ran, Shirng-Wern Tsaih, Jeffery De Pons, Daniel F. Carlson, Wenfang Tan, Scott C. Fahrenkrug, Zelmira Lazarova, Jozef Lazar, Paula E. North, Peter S. LaViolette, Michael B. Dwinell, James D. Shull, and Howard J. Jacob  
*Précis:* These results establish the utility of a novel model of breast cancer that can localize genetic variants that affect breast cancer risk through actions on the tumor microenvironment, rather than the tumor cell itself.
- 6430 **Ag-Presenting CpG-Activated pDCs Prime Th17 Cells That Induce Tumor Regression**  
 Leslie Guéry, Juan Dubrot, Carla Lippens, Dale Brighthouse, Pauline Malinge, Magali Irla, Caroline Pot, Walter Reith, Jean-Marc Waldburger, and Stéphanie Hugues  
*Précis:* This study identifies a new antigen-presenting strategy that may improve cancer immunotherapy involving Th17 cells.
- 6441 **SA-4-IBBL and Monophosphoryl Lipid A Constitute an Efficacious Combination Adjuvant for Cancer Vaccines**  
Abhishek K. Srivastava, Gunes Dinc, Rajesh K. Sharma, Esma S. Yolcu, Hong Zhao, and Haval Shirwan  
*Précis:* These results offer preclinical proof of concept for the use of a powerful new adjuvant system for tumor antigen-based cancer vaccines, with immediate implications for its clinical evaluation in the oncology clinic.

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**6452 Host Deficiency in Caveolin-2 Inhibits Lung Carcinoma Tumor Growth by Impairing Tumor Angiogenesis**

Yajun Liu, Sungchan Jang, Leike Xie, and Grzegorz Sowa

**Précis:** Loss of a protein that helps organize lipid rafts on the plasma membrane reduces cancerous cell growth, with possible implications for a generalized approach to cancer targeting.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

**6463 Histone H1.3 Suppresses H19 Noncoding RNA Expression and Cell Growth of Ovarian Cancer Cells**

Magdalena Medrzycki, Yunzhe Zhang, Weijia Zhang, Kaixiang Cao, Chenyi Pan, Nathalie Lailler, John F. McDonald, Eric E. Bouhassira, and Yuhong Fan

**Précis:** These results provide new information about the regulation of a noncoding RNA in ovarian cancer cells, advancing work in a timely new area of RNA physiology and cancer.

**6474 Oncogenic Properties of a Spermatogenic Meiotic Variant of Fer Kinase Expressed in Somatic Cells**

Etai Yaffe, Elad Hikri, Yoav Elkis, Ortal Cohen, Ariela Segal, Adar Makovski, Alexander Varvak, Sally Shpungin, and Uri Nir

**Précis:** This provocative study reveals a molecular alteration in the mitochondria of cancer cells that may represent a common pathophysiological root, with possible implications for broad-based treatments.

**6486 BRG1/SMARCA4 Inactivation Promotes Non-Small Cell Lung Cancer Aggressiveness by Altering Chromatin Organization**

Tess Orvis, Austin Hepperla, Vonn Walter, Shujie Song, Jeremy Simon, Joel Parker, Matthew D. Wilkerson, Nisarg Desai, Michael B. Major, D. Neil Hayes, Ian J. Davis, and Bernard Weissman

**Précis:** These results offer direct evidence of a tumor suppressor role for a core ATPase found in SWI/SNF chromatin regulatory complexes, the inactivation of which contributes to lung cancer aggressiveness by altering nucleosome positioning and expression at many cancer-associated genes.

**6499 Deubiquitination of  $\gamma$ -Tubulin by BAP1 Prevents Chromosome Instability in Breast Cancer Cells**

Reihaneh Zarrizi, Julien Albert Menard, Mattias Belting, and Ramin Massoumi

**Précis:** These findings illuminate a core mechanism preventing genomic instability, with implications for understanding malignant progression.

**6509 The Notch Pathway Inhibits TGF $\beta$  Signaling in Breast Cancer through HEYL-Mediated Crosstalk**

Liangfeng Han, Adam Diehl, Nguyen K. Nguyen, Preethi Korangath, Weiwen Teo, Soonweng Cho, Scott Kominsky, David L. Huso, Lionel Feigenbaum, Alan Rein, Pedram Argani, Goran Landberg, Manfred Gessler, and Saraswati Sukumar

**Précis:** These findings identify a particular mechanism of TGF $\beta$  signaling as a key element in the development of drug resistance in breast cancer.

**6519 STAT1 Drives Tumor Progression in Serous Papillary Endometrial Cancer**

Budiman Kharma, Tsukasa Baba, Noriomi Matsumura, Hyun Sook Kang, Junzo Hamanishi, Ryusuke Murakami, Melissa M. McConechy, Samuel Leung, Ken Yamaguchi, Yuko Hosoe, Yumiko Yoshioka, Susan K. Murphy, Masaki Mandai, David G. Hunstman, and Ikuro Konishi

**Précis:** This study identifies a molecular signature and root oncogenic driver of serous papillary endometrial cancer, a relatively rare and poorly characterized form of uterine cancer that arises in post-menopausal women, with implications for improving its prognosis and treatment.

**6531 IGF2 Preserves Osteosarcoma Cell Survival by Creating an Autophagic State of Dormancy That Protects Cells against Chemotherapeutic Stress**

Takatsune Shimizu, Eiji Sugihara, Sayaka Yamaguchi-Iwai, Sakura Tamaki, Yuko Koyama, Walied Kamel, Arisa Ueki, Tomoki Ishikawa, Tatsuyuki Chiyoda, Satoru Osuka, Nobuyuki Onishi, Hiroko Ikeda, Junzo Kamei, Koichi Matsuo, Yumi Fukuchi, Toshihiro Nagai, Junya Toguchida, Yoshiaki Toyama, Akihiro Muto, and Hideyuki Saya

**Précis:** This study provides a mechanistic rationale for blunting IGF/insulin-mediated survival signals in osteosarcoma, a pediatric tumor notorious for its intrinsic therapeutic resistance, as a strategy to improve treatment outcomes.

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- 6542 CtBP2 Modulates the Androgen Receptor to Promote Prostate Cancer Progression**  
Ken-ichi Takayama, Takashi Suzuki,  
Tetsuya Fujimura, Tomohiko Urano,  
Satoru Takahashi, Yukio Homma, and Satoshi Inoue

**Précis:** A transcriptional corepressor linked to prostate cancer susceptibility is found here to be an androgen-regulated gene that modulates pro-cancerous downstream signals from the androgen receptor.

- 6554 Genetic Evidence of a Precisely Tuned Dysregulation in the Hypoxia Signaling Pathway during Oncogenesis**  
Sophie Couvé, Charline Ladrone, Elodie Laine,  
Karène Mahtouk, Justine Guégan, Sophie Gad,  
Hélène Le Jeune, Marion Le Gentil, Gregory Nuel,  
William Y. Kim, Bernard Lecomte,  
Jean-Christophe Pagès, Christine Collin,  
Françoise Lasne, Patrick R. Benusiglio,  
Brigitte Bressac-de Paillerets, Jean Feunteun,  
Vladimir Lazar, Anne-Paule Gimenez-Roqueplo,  
Nathalie M. Mazure, Philippe Dessen,  
Luba Tchertanov, David R. Mole, William Kaelin,  
Peter Ratcliffe, Stéphane Richard, and Betty Gardie

**Précis:** These findings offer evidence in humans to validate the "continuum" model of tumor suppression, advancing work beyond the mouse in developing a successor to the classic "two-hit" model in the field.

- 6565 In Vivo Disruption of an Rb-E2F-Ezh2 Signaling Loop Causes Bladder Cancer**  
Mirentxu Santos, Mónica Martínez-Fernández,  
Marta Dueñas, Ramón García-Escudero,  
Begoña Alfaya, Felipe Villacampa,  
Cristina Saiz-Ladera, Clotilde Costa, Marta Oteo,  
José Duarte, Victor Martínez,  
M<sup>a</sup> José Gómez-Rodríguez, M<sup>a</sup> Luisa Martín,  
Manoli Fernández, Patrick Viatour,  
Miguel A. Morcillo, Julien Sage, Daniel Castellano,  
Jose L. Rodriguez-Peralto, Federico de la Rosa, and  
Jesús M Paramio

**Précis:** This study addresses the gap in knowledge concerning the genetic and epigenetic underpinnings of bladder cancer development, which still remain relatively obscure.

- 6578 Suppression of Deacetylase SIRT1 Mediates Tumor-Suppressive NOTCH Response and Offers a Novel Treatment Option in Metastatic Ewing Sarcoma**



Jozef Ban, Dave N.T. Aryee, Argyro Fourtouna,  
Wietske van der Ent, Max Kauer, Stephan Niedan,  
Isidro Machado, Carlos Rodriguez-Galindo,  
Oscar M. Tirado, Raphaela Schwentner, Piero Picci,  
Adrienne M. Flanagan, Verena Berg,  
Sandra J. Strauss, Katia Scotlandi,  
Elizabeth R. Lawlor, Ewa Snaar-Jagalska,  
Antonio Llombart-Bosch, and Heinrich Kovar

**Précis:** These findings offer a mechanistic rationale for the use of pharmacological inhibitors of a p53 deacetylase to treat cancers in which NOTCH acts a tumor suppressor.

## PREVENTION AND EPIDEMIOLOGY

- 6589 High Serum Iron Is Associated with Increased Cancer Risk**

Chi Pang Wen, June Han Lee, Ya-Ping Tai,  
Christopher Wen, Shiu-an Be Wu, Min Kuang Tsai,  
Dennis P.H. Hsieh, Hung-Che Chiang,  
Chao Agnes Hsiung, Chung Y. Hsu, and Xifeng Wu

**Précis:** This large cohort study reveals that high levels of iron in blood serum is a risk marker for a variety of adult cancer, most dramatically in conferring a 3-fold increased risk for liver cancer.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 6598 Microenvironment-Derived HGF Overcomes Genetically Determined Sensitivity to Anti-MET Drugs**

Selma Pennacchietti, Manuela Cazzanti,  
Andrea Bertotti, William M. Rideout III, May Han,  
Jeno Gyuris, Timothy Perera, Paolo M. Comoglio,  
Livio Trusolino, and Paolo Michieli

**Précis:** This study offers preclinical proof of concept for the use of antibodies that neutralize hepatocyte growth factor along with MET-targeting agents as a more effective therapeutic strategy to treat MET-dependent tumors.

- 6610 Targeting Cancer Stem-like Cells as an Approach to Defeating Cellular Heterogeneity in Ewing Sarcoma**

Sandrine Cornaz-Buros, Nicolo Riggi,  
Claudio DeVito, Alexandre Sarre, Igor Letovanec,  
Paolo Provero, and Ivan Stamenkovic

**Précis:** These results suggest a broadly and immediately applicable approach to improve the treatment of solid tumors that are marked by extensive cellular heterogeneity, likely driven by the plastic nature of cancer stem-like cells, with immediate applications for clinical evaluation.

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**6623 MPHOSPH1: A Potential Therapeutic Target for Hepatocellular Carcinoma**

Xinran Liu, Yafan Zhou, Xinyuan Liu, Anlin Peng, Hao Gong, Lizi Huang, Kaige Ji, Robert B. Petersen, Ling Zheng, and Kun Huang

**Précis:** *These results highlight a critical role for a mitotic kinesin as a critical oncogenic driver and candidate therapeutic target in liver cancer.*

**6635 Plk1 Inhibition Enhances the Efficacy of Androgen Signaling Blockade in Castration-Resistant Prostate Cancer**

Zhe Zhang, Xianzeng Hou, Chen Shao, Junjie Li, Ji-Xin Cheng, Shihuan Kuang, Nihal Ahmad, Timothy Ratliff, and Xiaoqi Liu

**Précis:** *These results offer a mechanistic rationale for evaluating Plk1 inhibitors in clinical development to enhance the efficacy of androgen signaling inhibitors in patients with castration-resistant prostate cancer.*

## TUMOR AND STEM CELL BIOLOGY

**6648 MicroRNA100 Inhibits Self-Renewal of Breast Cancer Stem-like Cells and Breast Tumor Development**



Lu Deng, Li Shang, Shoumin Bai, Ji Chen, Xueyan He, Rachel Martin-Trevino, Shanshan Chen, Xiao-yan Li, Xiaojie Meng, Bin Yu, Xiaolin Wang, Yajing Liu, Sean P. McDermott, Alexa E. Ariazi, Christophe Ginestier, Ingrid Ibarra, Jia Ke, Tahra Luther, Shawn G. Clouthier, Liang Xu, Ge Shan, Erwei Song, Herui Yao, Gregory J. Hannon, Stephen J. Weiss, Max S. Wicha, and Suling Liu

**Précis:** *These studies provide insight into the mechanisms by which a microRNA gene regulates the self-renewal and tumor-forming potential of cancer stem-like cells, suggesting theranostic applications for this microRNA in identifying and targeting these cells for cancer treatment.*

**6661 RABL6A Promotes G<sub>1</sub>-S Phase Progression and Pancreatic Neuroendocrine Tumor Cell Proliferation in an Rb1-Dependent Manner**

Jussara Hagen, Viviane P. Muniz, Kelly C. Falls, Sara M. Reed, Agshin F. Taghiyev, Frederick W. Quelle, Françoise A. Gourronc, Aloysius J. Klingelhutz, Heather J. Major, Ryan W. Askeland, Scott K. Sherman, Thomas M. O'Dorisio, Andrew M. Bellizzi, James R. Howe, Benjamin W. Darbro, and Dawn E. Quelle

**Précis:** *These findings provide insights into Rb1 regulation and cell proliferation in pancreatic neuroendocrine tumors, potentially offering new targets for diagnosis and therapy of this disease.*

**6671 A Hypusine-eIF5A-PEAK1 Switch Regulates the Pathogenesis of Pancreatic Cancer**

Ken Fujimura, Tracy Wright, Jan Strnad, Sharmeela Kaushal, Cristina Metildi, Andrew M. Lowy, Michael Bouvet, Jonathan A. Kelber, and Richard L. Klemke

**Précis:** *A selective posttranslational modification important for the development of pancreatic cancers may offer a new therapeutic strategy to treat this disease.*

**6682 CD66<sup>+</sup> Cells in Cervical Precancers Are Partially Differentiated Progenitors with Neoplastic Traits**

Chitra Pattabiraman, Shiyuan Hong, Vignesh K. Gunasekharan, Annapurna Pranatharthi, Jeevisha Bajaj, Sweta Srivastava, H. Krishnamurthy, Aswathy Ammothumkandy, Venkat G. Giri, Laimonis A. Laimins, and Sudhir Krishna

**Précis:** *Neoplastic cell subsets in cervical cancer emerge early in the disease and are linked to the life cycle of HPV virus, which drives this disease.*

**6693 TRAP1 Is Involved in BRAF Regulation and Downstream Attenuation of ERK Phosphorylation and Cell-Cycle Progression: A Novel Target for BRAF-Mutated Colorectal Tumors**

Valentina Condelli, Annamaria Piscazzi, Lorenza Sisinni, Danilo Swann Matassa, Francesca Maddalena, Giacomo Lettini, Vittorio Simeon, Giuseppe Palladino, Maria Rosaria Amoroso, Stefania Trino, Franca Esposito, and Matteo Landriscina

**Précis:** *This study illuminates the regulation of the BRAF oncoprotein at the level of its posttranslational ubiquitination.*

**6705 Tumor-Derived Osteopontin Suppresses Antitumor Immunity by Promoting Extramedullary Myelopoiesis**

Eun-Kyung Kim, Insu Jeon, Hyungseok Seo, Young-Jun Park, Boyeong Song, Kyoo-A Lee, Yongwoo Jang, Yeonseok Chung, and Chang-Yuil Kang

**Précis:** *These findings unveil a novel immunosuppressive role for a factor widely associated with the inflammatory tumor microenvironment, with implications for a general therapeutic strategy in cancer treatment.*

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- 6717**    **GPx2 Suppression of H<sub>2</sub>O<sub>2</sub> Stress Links the Formation of Differentiated Tumor Mass to Metastatic Capacity in Colorectal Cancer**  
Benjamin L. Emmink, Jamila Laoukili, Anna P. Kipp, Jan Koster, Klaas M. Govaert, Szabolcs Fatrai, Andre Verheem, Ernst J.A. Steller, Regina Brigelius-Flohé, Connie R. Jimenez, Inne H.M. Borel Rinkes, and Onno Kranenburg

*Précis:* Results reveal an unexpected redox-controlled link between formation of a tumor mass and its capacity for metastasis.

## RETRACTION

- 6731**    **Retraction: Novel HSP90 Inhibitor NVP-HSP990 Targets Cell-Cycle Regulators to Ablate Olig 2-Positive Glioma Tumor-Initiating Cells**

## CORRECTIONS

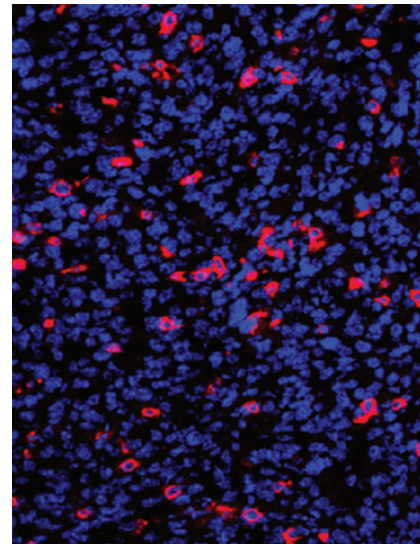
- 6733**    **Correction: Diffusion-Weighted Imaging in Cancer: Physical Foundations and Applications of Restriction Spectrum Imaging**
- 6734**    **Correction: A Novel Wnt Regulatory Axis in Endometrioid Endometrial Cancer**

 AC icon indicates Author Choice

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## ABOUT THE COVER

CD8<sup>+</sup> T cells are critical for elimination of cancer. A major limitation of therapeutic cancer vaccines is their inability to activate and mobilize CD8<sup>+</sup> T cells for infiltration into tumor. A vaccine formulation containing SA-4-1BBL and MPL as a novel adjuvant system shows robust efficacy in activating and recruiting CD8<sup>+</sup> T cells into the tumor, with subsequent effective tumor destruction in preclinical models. For details, see article by Srivastava and colleagues on page 6441.



# Cancer Research

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

## 74 (22)

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