

## BREAKING ADVANCES

- 6135** Highlights from Recent Cancer Literature

## CANCER RESEARCH 75<sup>TH</sup> ANNIVERSARY COMMENTARIES

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- 6140** KIT Oncogenic Mutations: Biologic Insights, Therapeutic Advances, and Future Directions  
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- 6143** Commentary on microRNA Fingerprint in Human Epithelial Ovarian Cancer  
Marilena V. Iorio and Carlo M. Croce


## REVIEWS

- 6146** Metabolite and Microbiome Interplay in Cancer Immunotherapy  
Caroline H. Johnson, Mary E. Spilker, Laura Goetz, Scott N. Peterson, and Gary Siuzdak
- 6153** Humanized Mouse Xenograft Models: Narrowing the Tumor–Microenvironment Gap  
J. Jason Morton, Gregory Bird, Yosef Refaeli, and Antonio Jimeno

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- 6159** Connecting (T)issues: How Research in Fascia Biology Can Impact Integrative Oncology  
 Helene M. Langevin, Patricia Keely, Jun Mao, Lisa M. Hodge, Robert Schleip, Gary Deng, Boris Hinz, Melody A. Swartz, Beverley A. de Valois, Suzanna Zick, and Thomas Findley
- 6163** PET and MRI: Is the Whole Greater than the Sum of Its Parts?  
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## MEETING REPORT

- 6167** Big Data–Led Cancer Research, Application, and Insights  
 James A.L. Brown, Triona Ni Chonghaile, Kyle B. Matchett, Niamh Lynam-Lennon, and Patrick A. Kiely

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6171** EpCAM-Regulated Transcription Exerts Influences on Nanomechanical Properties of Endometrial Cancer Cells That Promote Epithelial-to-Mesenchymal Transition  
Ya-Ting Hsu, Pawel Osmulski, Yao Wang, Yi-Wen Huang, Lu Liu, Jianhua Ruan, Victor X. Jin, Nameer B. Kirma, Maria E. Gaczynska, and Tim Hui-Ming Huang
- Précis:* This study advances understanding of how the biophysical properties of cancer cells must be altered to achieve an epithelial-mesenchyme transition in their status, a pivotal step in gaining invasive properties that can elude normal tissue barriers.

## MICROENVIRONMENT AND IMMUNOLOGY

- 6183** BPTF Depletion Enhances T-cell–Mediated Antitumor Immunity  
Kimberly Mayes, Suehyb G. Alkhatib, Kristen Peterson, Aiman Alhazmi, Carolyn Song, Vivian Chan, Tana Blevins, Mark Roberts, Catherine I. Dumur, Xiang-Yang Wang, and Joseph W. Landry
- Précis:* The results of this study document a novel chromatin regulator, which, when inhibited, improves antitumor immunity.
- 6193** Nutritional Stress Induced by Tryptophan-Degrading Enzymes Results in ATF4-Dependent Reprogramming of the Amino Acid Transporter Profile in Tumor Cells  
 Elina Timosenko, Hemza Ghadbane, Jonathan D. Silk, Dawn Shepherd, Uzi Gileadi, Lauren J. Howson, Robert Laynes, Qi Zhao, Robert L. Strausberg, Lars R. Olsen, Stephen Taylor, Francesca M. Buffa, Richard Boyd, and Vincenzo Cerundolo
- Précis:* These findings reveal the mechanisms by which cancer cells but not T cells can compensate for tryptophan deprivation in a tumor microenvironment by upregulating the expression of amino acid transporters that mediate cellular tryptophan uptake.

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- 6205** **Snail1-Dependent Activation of Cancer-Associated Fibroblast Controls Epithelial Tumor Cell Invasion and Metastasis**  
Lorena Alba-Castellón, Rubén Olivera-Salguero, Aida Mestre-Farrera, Raúl Peña, Mercedes Herrera, Félix Bonilla, J. Ignacio Casal, Josep Baulida, Cristina Peña, and Antonio García de Herreros  
*Précis:* Eliminating Snail1 function in tumor stromal fibroblasts prevent the invasive capacity of epithelial tumor cells.
- 6218** **Interleukin-30 Promotes Breast Cancer Growth and Progression**  
 Irma Airoidi, Claudia Cocco, Carlo Sorrentino, Domenico Angelucci, Serena Di Meo, Lamberto Manzoli, Silvia Esposito, Domenico Ribatti, Maria Bertolotto, Laura Iezzi, Clara Natoli, and Emma Di Carlo  
*Précis:* This study describes the breast cancer-promoting activity of endogenous IL30 in the tumor microenvironment, which promotes tumor cell proliferation, migration, and inflammatory characters associated with a metastatic program, with potential biomarker and therapeutic implications.
- 6230** **Ccl22 Diverts T Regulatory Cells and Controls the Growth of Melanoma**  
Jared Klarquist, Kristen Tobin, Peyman Farhangi Oskuei, Steven W. Henning, Manuel F. Fernandez, Emilia R. Dellacecca, Flor C. Navarro, Jonathan M. Eby, Shilpak Chatterjee, Shikhar Mehrotra, Joseph I. Clark, and I. Caroline Le Poole  
*Précis:* These findings offer preclinical proof of concept for the potential utility of the chemokine CCL22, as delivered by local injection, to enhance the efficacious response of immune checkpoint therapy in melanoma patients while suppressing the autoimmune side-effects of the treatment.
- 6241** **Thymic Stromal Chemokine TSLP Acts through Th2 Cytokine Production to Induce Cutaneous T-cell Lymphoma**  
Naomi Takahashi, Makoto Sugaya, Hiraku Suga, Tomonori Oka, Makiko Kawaguchi, Tomomitsu Miyagaki, Hideki Fujita, and Shinichi Sato  
*Précis:* A growth-reinforcing cycle reported in atopic dermatitis also functions in cutaneous T-cell lymphoma, not only inducing a Th2-dominant tumor environment but also stimulating tumor cell proliferation in this malignancy.
- 6253** **Trametinib Drives T-cell–Dependent Control of KRAS-Mutated Tumors by Inhibiting Pathological Myelopoiesis**  
Michael J. Allegrezza, Melanie R. Rutkowski, Tom L. Stephen, Nikolaos Svoronos, Alfredo Perales-Puchalt, Jenny M. Nguyen, Kyle K. Payne, Sunil Singhal, Evgeniy B. Eruslanov, Julia Tchou, and Jose R. Conejo-Garcia  
*Précis:* This study reveals a new perspective on the antitumor activity of FDA-approved MEK inhibitors, revealing that they enhance protective immunity in vivo by influencing multiple cell types in divergent ways, acting overall to prevent the accumulation of immunosuppressive leukocytes in tumor beds.
- 6266** **Agonistic CD40 mAb-Driven IL12 Reverses Resistance to Anti-PD1 in a T-cell–Rich Tumor**  
Shin Foong Ngjow, Arabella Young, Stephen J. Blake, Geoffrey R. Hill, Hideo Yagita, Michele W.L. Teng, Alan J. Korman, and Mark J. Smyth  
*Précis:* This study offers a proof-of-concept framework to systematically identify immune conditioning agents that can convert PD1<sup>hi</sup> T cells to PD1<sup>lo</sup> T cells, with clinical implications for the management of patients resistant to anti-PD1 immune checkpoint antibodies.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 6278** **Wnt Signaling Promotes Breast Cancer by Blocking ITCH-Mediated Degradation of YAP/TAZ Transcriptional Coactivator WBP2**  
Shen Kiat Lim, Ssu Yi Lu, Shin-Ae Kang, Hock Jin Tan, Zilin Li, Zhen Ning Adrian Wee, Jye Swee Guan, Vishnu Priyanka Reddy Chichili, J. Sivaraman, Thomas Putti, Aye Aye Thihe, Puay Hoon Tan, Marius Sudol, David M. Virshup, Siew Wee Chan, Wanjin Hong, and Yoon Pin Lim  
*Précis:* This study identifies how a new oncogene in breast cancer is normally suppressed to prevent aberrant growth but becomes activated to promote cancer, with potential implications to understand and therapeutically exploit a critical interface between the WNT and Hippo signaling pathways that drive this disease.
- 6290** **MXN1 Is Oncogenically Upregulated in African-American Prostate Cancer**  
Li Zhang, Jianghua Wang, Yongquan Wang, Yiqun Zhang, Patricia Castro, Longjiang Shao, Arun Sreekumar, Nagireddy Putluri, Nilanjan Guha, Saligrama Deepak, Arunkumar Padmanaban, Chad J. Creighton, and Michael Ittmann  
*Précis:* An oncogene regulated by androgen and AKT is activated in prostate cancers relatively more frequently in African-American men, potentially offering a novel therapeutic target to address the increased incidence of aggressive disease in this patient population.

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**6299** **lncRNA HOXA11-AS Promotes Proliferation and Invasion of Gastric Cancer by Scaffolding the Chromatin Modification Factors PRC2, LSD1, and DNMT1**

Ming Sun, Fengqi Nie, Yunfei Wang, Zhihong Zhang, Jiakai Hou, Dandan He, Min Xie, Lin Xu, Wei De, Zhaoxia Wang, and Jun Wang

*Précis:* New therapeutic directions are suggested by this mechanistic study of a gastric cancer-associated long noncoding RNA, which coordinates tumor suppressor functions.

**6311** **Posttranscriptional Upregulation of p53 by Reactive Oxygen Species in Chronic Lymphocytic Leukemia**

Jesvin Samuel, Sandrine Jayne, Yixiang Chen, Aneela Majid, Alice Wignall, Timothy Wormull, Hishyar Najeeb, Jin-Li Luo, George D.D. Jones, Salvador Macip, and Martin J.S. Dyer

*Précis:* These findings suggest that reactivation of the full transcriptional activities of p53 in proliferating chronic lymphocytic leukemia may offer a possible therapeutic strategy.

**6320** **BET Inhibitors Suppress ALDH Activity by Targeting ALDH1A1 Super-Enhancer in Ovarian Cancer**

Yuhki Yokoyama, Hengrui Zhu, Jeong Heon Lee, Andrew V. Kossenkov, Sherry Y. Wu, Jayamanna M. Wickramasinghe, Xiangfan Yin, Katherine C. Palozola, Alessandro Gardini, Louise C. Showe, Kenneth S. Zaret, Qin Liu, David Speicher, Jose R. Conejo-Garcia, James E. Bradner, Zhiguo Zhang, Anil K. Sood, Tamas Ordog, Benjamin G. Bitler, and Rugang Zhang

*Précis:* BET inhibitors offer a novel strategy to target ALDH activity, a functional marker in cancer stem-like cells, which in combination with platinum-based therapies are shown to have efficacious effects in ovarian cancer.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**6331** **Preclinical Efficacy of the Auristatin-Based Antibody–Drug Conjugate BAY 1187982 for the Treatment of FGFR2-Positive Solid Tumors**



Anette Sommer, Charlotte Kopitz, Christoph A. Schatz, Carl F. Nising, Christoph Mahler, Hans-Georg Lerchen, Beatrix Stelte-Ludwig, Stefanie Hammer, Simone Greven, Joachim Schuhmacher, Manuela Braun, Ruprecht Zierz, Sabine Wittemer-Rump, Axel Harrenga, Frank Dittmer, Frank Reetz, Heiner Apeler, Rolf Jautelat, Hung Huynh, Karl Ziegelbauer, and Bertolt Kreft

*Précis:* These findings offer a sound preclinical rationale to clinically translate a novel antibody-drug conjugate to target a growth factor receptor that is overexpressed in a variety of drug-refractory solid tumor types, including gastric, breast, and ovarian cancers.

**6340** **RK-33 Radiosensitizes Prostate Cancer Cells by Blocking the RNA Helicase DDX3**

Min Xie, Farhad Vesuna, Saritha Tantravedi, Guus M. Bol, Marise R. Heerma van Voss, Katriana Nugent, Reem Malek, Kathleen Gabrielson, Paul J. van Diest, Phuoc T. Tran, and Venu Raman

*Précis:* These findings offer preclinical proof of concept for a candidate small-molecule therapy that can increase the efficacy of radiotherapy without increasing apparent side effects.

**6351** **Ovarian Cancer Chemoresistance Relies on the Stem Cell Reprogramming Factor PBX1**

Jin-Gyoung Jung, Ie-Ming Shih, Joon Tae Park, Emily Gerry, Tae Hoen Kim, Ayse Ayhan, Karen Handschuh, Ben Davidson, Amanda N. Fader, Licia Selleri, and Tian-Li Wang

*Précis:* These findings offer a mechanistic rationale to target the PBX1/STAT3 axis in ovarian cancers to defeat a key mechanism of chemoresistance, which emerges in nearly every patient after first-line treatment.

**6362** **Histone H3K27 Trimethylation Modulates 5-Fluorouracil Resistance by Inhibiting PU.1 Binding to the DPYD Promoter**

Rentian Wu, Qian Nie, Erin E. Tapper, Calvin R. Jerde, Garrett S. Dunlap, Shikshya Shrestha, Tarig A. Elraiyah, Steven M. Offer, and Robert B. Diasio

*Précis:* These findings suggest new biomarkers with potential clinical utility to identify patients who could benefit most from aggressive adjuvant chemotherapy.

**6374** **Integrative Genomic Analysis Identifies the Core Transcriptional Hallmarks of Human Hepatocellular Carcinoma**

Coralie Allain, Gaëlle Angenard, Bruno Clément, and Cédric Coulouarn

*Précis:* These findings establish a rationale to pursue high-throughput meta-analysis of liver cancer patient specimens to develop and target common and subtype-specific cancer networks.

## TUMOR AND STEM CELL BIOLOGY

**6382** **Impaired Planar Germ Cell Division in the Testis, Caused by Dissociation of RHAMM from the Spindle, Results in Hypofertility and Seminoma**

Huaibiao Li, Lucien Frappart, Jürgen Moll, Anne Winkler, Torsten Kroll, Jana Hamann, Iris Kufferath, Marco Groth, Stefan Taudien, Moritz Schütte, Marie-Laure Yaspo, Heike Heuer, Bodo M.H. Lange, Matthias Platzer, Kurt Zatloukal, Peter Herrlich, and Aspasia Ploubidou

*Précis:* These findings identify the spindle-associated protein RHAMM as an intrinsic regulator of male germ cell fate and as a gatekeeper preventing initiation of testicular germ cell tumors.

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**6396** EGFL6 Regulates the Asymmetric Division, Maintenance, and Metastasis of ALDH<sup>+</sup> Ovarian Cancer Cells

Shoumei Bai, Patrick Ingram, Yu-Chih Chen, Ning Deng, Alex Pearson, Yashar S. Niknafs, Patrick O'Hayer, Yun Wang, Zhong-Yin Zhang, Elisa Boscolo, Joyce Bischoff, Euisik Yoon, and Ronald J. Buckanovich

*Précis:* These results offer preclinical proof of concept for a compelling new therapeutic target to improve the management of ovarian cancer.

**6410** TG2 and NF- $\kappa$ B Signaling Coordinates the Survival of Mantle Cell Lymphoma Cells via IL6-Mediated Autophagy

Han Zhang, Zheng Chen, Roberto N. Miranda, L. Jeffrey Medeiros, and Nami McCarty

*Précis:* These results illuminate a novel interconnected network of signaling and autophagy pathways in a clinically problematic form of non-Hodgkin lymphoma, the disruption of which may offer an effective therapeutic strategy.

**6424** Ablation of miR-10b Suppresses Oncogene-Induced Mammary Tumorigenesis and Metastasis and Reactivates Tumor-Suppressive Pathways

Jongchan Kim, Ashley N. Siverly, Dahu Chen, Min Wang, Yuan Yuan, Yumeng Wang, Hyemin Lee, Jinsong Zhang, William J. Muller, Han Liang, Boyi Gan, Xianbin Yang, Yutong Sun, M. James You, and Li Ma

*Précis:* These results establish the critical function of an oncomiR that drives metastasis, termed a metastamiR, and define the set of critical tumor suppressor mechanisms it overcomes to drive breast cancer progression.

## CORRECTION

**6436** Correction: miR-29b Mediates NF- $\kappa$ B Signaling in KRAS-Induced Non-Small Cell Lung Cancers

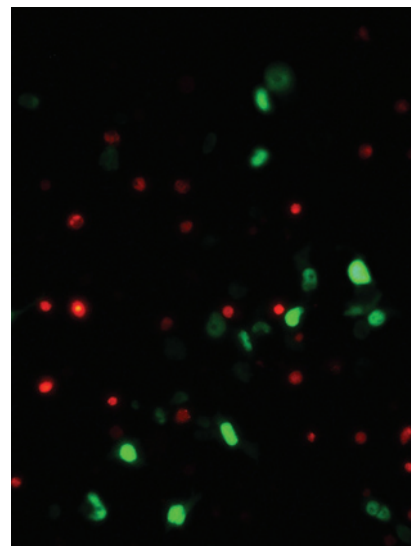


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## ABOUT THE COVER

Upregulation of the stem cell reprogramming factor PBX1 mediates resistance to platinum-based chemotherapy in ovarian cancer. Using an *in vitro* dual-color competition assay, PBX1-positive cells were labeled green and PBX1-negative cells were labeled red. It was found that PBX1-positive cells escaped the cytotoxic effects from a platinum-based agent, carboplatin, much more efficiently than did PBX1-negative cells, as demonstrated by an increased green to red ratio at several days following carboplatin treatment. For details, see article by Jung and colleagues on page 6351.



# Cancer Research

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

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