

## BREAKING INSIGHTS

- 5721** Highlights from Recent Cancer Literature

## REVIEW

- 5723** Promoting Scientist–Advocate Collaborations in Cancer Research: Why and How  
 Jeannine M. Salamone, Wanda Lucas, Shelley B. Brundage, Jamie N. Holloway, Sherri M. Stahl, Nora E. Carbine, Margery London, Naomi Greenwood, Rosa Goyes, Deborah Charles Chisholm, Erin Price, Roberta Carlin, Susan Winarsky, Kirsten B. Baker, Julia Maues, and Ayesha N. Shajahan-Haq

## CANCER RESEARCH HIGHLIGHTS

- 5729** Choosing the Best Chemotherapy Agent to Boost Immune Checkpoint Inhibition Activity  
 Marina Chiara Garassino, Valter Torri, Mario Paolo Colombo, and Antonio Sica  
*See related article, p. 5891*

## PRIORITY REPORT

- 5731** Epigenetic Reprogramming with Antisense Oligonucleotides Enhances the Effectiveness of Androgen Receptor Inhibition in Castration-Resistant Prostate Cancer  
 Lanbo Xiao, Jean C. Tien, Josh Vo, Mengyao Tan, Abhijit Parolia, Yajia Zhang, Lisha Wang, Yuanyuan Qiao, Sudhanshu Shukla, Xiaoju Wang, Heng Zheng, Fengyun Su, Xiaojun Jing, Esther Luo, Andrew Delekta, Kristin M. Juckette, Alice Xu, Xuhong Cao, Ajjai S. Alva, Youngsoo Kim, A. Robert MacLeod, and Arul M. Chinnaiyan  
*Significance: Simultaneous targeting of lysine methyltransferase EZH2 and the androgen receptor with antisense oligonucleotides proves a novel and effective therapeutic strategy in patients with CRPC.*

## GENOME AND EPIGENOME

- 5741** A Polysome-Based microRNA Screen Identifies miR-24-3p as a Novel Promigratory miRNA in Mesothelioma



Stefania Oliveto, Roberta Alfieri, Annarita Miluzio, Alessandra Scagliola, Raissa S. Secli, Pierluigi Gasparini, Stefano Grosso, Luciano Cascione, Luciano Mutti, and Stefano Biffo

*Significance: Subcellular localization of miRNAs may predict their role in cancer and identify novel oncogenic miRNAs involved in cancer progression.*

- 5754** Dual Inhibition of DNA and Histone Methyltransferases Increases Viral Mimicry in Ovarian Cancer Cells

Minmin Liu, Stacey L. Thomas, Ashley K. DeWitt, Wanding Zhou, Zachary B. Madaj, Hitoshi Ohtani, Stephen B. Baylin, Gangning Liang, and Peter A. Jones

*Significance: Dual inhibition of DNA methylation and histone H3 lysine 9 dimethylation by 5-aza-CdR and G9A results in synergistic upregulation of ERV and induces an antiviral response, serving as a basis for exploring this novel combination treatment in patients with ovarian cancer.*

## MOLECULAR CELL BIOLOGY

- 5767** MYBL2 Supports DNA Double Strand Break Repair in Hematopoietic Stem Cells



Rachel Bayley, Daniel Blakemore, Laila Cancian, Stephanie Dumon, Giacomo Volpe, Carl Ward, Ruba Almaghrabi, Jidnyasa Gujar, Natasha Reeve, Manoj Raghavan, Martin R. Higgs, Grant S. Stewart, Eva Petermann, and Paloma Garcia

*Significance: These findings suggest MYBL2 levels may be used as a biological biomarker to determine the DNA repair capacity of hematopoietic stem cells from patients with MDS and as a clinical biomarker to inform decisions regarding patient selection for treatments that target DNA repair.*

- 5780** Cancer-Associated MORC2-Mutant M276I Regulates an hnRNPM-Mediated CD44 Splicing Switch to Promote Invasion and Metastasis in Triple-Negative Breast Cancer

Fang-Lin Zhang, Jin-Ling Cao, Hong-Yan Xie, Rui Sun, Li-Feng Yang, Zhi-Ming Shao, and Da-Qiang Li

*Significance: A gain-of-function effect of a single mutation on MORC2 promotes metastasis of triple-negative breast cancer by regulating CD44 splicing.*

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**5793** Targeting STAT5 or STAT5-Regulated Pathways Suppresses Leukemogenesis of Ph<sup>+</sup> Acute Lymphoblastic Leukemia

Valentina Minieri, Marco De Dominicis, Patrizia Porazzi, Samanta A. Mariani, Orietta Spinelli, Alessandro Rambaldi, Luke F. Peterson, Pierluigi Porcu, Marja T. Nevalainen, and Bruno Calabretta

*Significance:* Suppression of STAT5 by BCL2 and PIM kinase inhibitors reduces leukemia burden in mice and constitutes a new potential therapeutic approach against Ph<sup>+</sup> ALL, especially in tyrosine kinase inhibitor-resistant disease.

**5808** Amplification of Glyceronephosphate O-Acyltransferase and Recruitment of USP30 Stabilize DRP1 to Promote Hepatocarcinogenesis

Li Gu, Yahui Zhu, Xi Lin, Yajun Li, Kaisa Cui, Edward V. Prochownik, and Youjun Li

*Significance:* This study identifies and establishes the role of the enzyme GNPAT in liver cancer progression, which may serve as a potential therapeutic target for liver cancer.

**5820** Transcription Factor PROX1 Suppresses Notch Pathway Activation via the Nucleosome Remodeling and Deacetylase Complex in Colorectal Cancer Stem-like Cells

Jenny Högström, Sarika Heino, Pauliina Kallio, Marianne Lähde, Veli-Matti Leppänen, Diego Balboa, Zoltán Wiener, and Kari Alitalo

*Significance:* These findings address the role of the PROX1 homeobox factor as a downstream effector of Wnt/ $\beta$ -catenin signaling in colorectal cancer stem cells and show that PROX1 inhibits the Notch pathway and helps to enforce the stem cell phenotype and inhibit differentiation

**5833** A Mutant p53-Dependent Embryonic Stem Cell Gene Signature Is Associated with Augmented Tumorigenesis of Stem Cells



Gabriela Koifman, Yoav Shetzer, Shay Eizenberger, Hilla Solomon, Ron Rotkopf, Alina Molchadsky, Giuseppe Lonetto, Naomi Goldfinger, and Varda Rotter

*Significance:* Mesenchymal cancer stem cell-like cell lines express a mutant p53-dependent embryonic stem cell gene signature, which can serve as a potential prognostic biomarker and therapeutic target in cancer.

**5848** CSTF2-Induced Shortening of the RAC1 3'UTR Promotes the Pathogenesis of Urothelial Carcinoma of the Bladder

Xin Chen, Jia-Xing Zhang, Jun-Hang Luo, Song Wu, Gang-Jun Yuan, Ning-Fang Ma, Yong Feng, Mu-Yan Cai, Ri-Xin Chen, Jun Lu, Li-Juan Jiang, Jie-Wei Chen, Xiao-Han Jin, Hai-Liang Liu, Wei Chen, Xin-Yuan Guan, Tie-Bang Kang, Fang-Jian Zhou, and Dan Xie

*Significance:* These findings demonstrate that the short isoform of RAC1 is critical in UCB tumorigenesis and may have implications for developing new therapeutic strategies to treat this disease.

**5863** PTTG and PBF Functionally Interact with p53 and Predict Overall Survival in Head and Neck Cancer

Martin L. Read, Bhavika Modasia, Alice Fletcher, Rebecca J. Thompson, Katie Brookes, Peter C. Rae, Hannah R. Nieto, Vikki L. Poole, Sally Roberts, Moray J. Campbell, Kristien Boelaert, Andrew S. Turnell, Vicki E. Smith, Hisham Mehanna, and Christopher J. McCabe

*Significance:* These findings reveal a complex and novel interrelationship between the expression and function of PTTG, PBF, and p53 in human HNSCC that significantly influences patient outcome.

**5877** EGR1-Mediated Transcription of lncRNA-HNF1A-AS1 Promotes Cell-Cycle Progression in Gastric Cancer

Hai-Ting Liu, Sen Liu, Lei Liu, Ran-Ran Ma, and Peng Gao

*Significance:* This study provides novel insights into mechanisms by which the noncoding RNA HNF1A-AS1 contributes to gastric cancer progression through modulation of the cell cycle.

## TUMOR BIOLOGY AND IMMUNOLOGY

**5891** Paclitaxel Reduces Tumor Growth by Reprogramming Tumor-Associated Macrophages to an M1 Profile in a TLR4-Dependent Manner



Carlos W. Wanderley, David F. Colón, João Paulo M. Luiz, Francisco F. Oliveira, Paula R. Viacava, Caio A. Leite, Janaina A. Pereira, Camila M. Silva, Cassia R. Silva, Rangel L. Silva, Cesar A. Speck-Hernandez, José M. Mota, José C. Alves-Filho, Roberto C. Lima-Junior, Thiago M. Cunha, and Fernando Q. Cunha

*Significance:* This study provides new evidence that the antitumor effect of paclitaxel occurs in part via reactivation of the immune response against cancer, guiding tumor-associated macrophages toward the M1-like antitumor phenotype.

See related commentary, p. 5729

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**5901** **Reduced Expression of PROX1 Transitions Glioblastoma Cells into a Mesenchymal Gene Expression Subtype**



Kaveh M. Goudarzi, Jaime A. Espinoza, Min Guo, Jiri Bartek, Monica Nistér, Mikael S. Lindström, and Daniel Hägerstrand

*Significance:* These findings demonstrate the role and prognostic value of PROX1 in glioblastomas; low PROX1 levels correlate with a mesenchymal gene expression subtype and shorter survival in glioblastoma tumors.

**5917** **Ribonucleotide Excision Repair Is Essential to Prevent Squamous Cell Carcinoma of the Skin**

Björn Hiller, Anja Hoppe, Christa Haase, Christina Hiller, Nadja Schubert, Werner Müller, Martin A.M. Reijns, Andrew P. Jackson, Thomas A. Kunkel, Jörg Wenzel, Rayk Behrendt, and Axel Roers

*Significance:* Selective inactivation of ribonucleotide excision repair by loss of RNase H2 in the murine epidermis results in spontaneous DNA damage, type I interferon response, skin inflammation, and development of squamous cell carcinoma.

**5927** **Schwann Cells Augment Cell Spreading and Metastasis of Lung Cancer**

Yan Zhou, Galina V. Shurin, Hua Zhong, Yuri L. Bunimovich, Baohui Han, and Michael R. Shurin

*Significance:* This study increases our understanding of how nerves and, in particular, specific glial cells, Schwann cells, in the peripheral nervous system, may help promote tumor growth and metastasis.

## TRANSLATIONAL SCIENCE

**5940** **VEGFC Antibody Therapy Drives Differentiation of AML**

Kim R. Kampen, Frank J.G. Scherpen, Hasan Mahmud, Arja ter Elst, André B. Mulder, Victor Guryev, Han J.M.P. Verhagen, Kim De Keersmaecker, Linda Smit, Steven M. Komblau, and Eveline S.J.M. De Bont

*Significance:* These findings reveal VEGFC targeting as a promising new differentiation therapy in AML.

**5949** **A Novel Microtubule Inhibitor Overcomes Multidrug Resistance in Tumors**

Nannan Ning, Yamei Yu, Min Wu, Ruihong Zhang, Ting Zhang, Changjun Zhu, Lei Huang, Cai-Hong Yun, Cyril H. Benes, Jianming Zhang, Xianming Deng, Qiang Chen, and Ruibao Ren

*Significance:* Paclitaxel is a widely used chemotherapeutic drug in patients with multiple types of cancer. However, resistance to paclitaxel is a challenge. This study describes a novel class of microtubule inhibitors with the ability to circumvent multidrug resistance across multiple tumor cell lines.

**5958** **Patient-Derived Xenograft Models Reveal Intratumor Heterogeneity and Temporal Stability in Neuroblastoma**



Noémie Braekeveldt, Kristoffer von Stedingk, Susanne Fransson, Angela Martinez-Monleon, David Lindgren, Håkan Axelson, Fredrik Levander, Jakob Willforss, Karin Hansson, Ingrid Øra, Torbjörn Backman, Anna Börjesson, Siv Beckman, Javanshir Esfandyari, Ana P. Berbegall, Rosa Noguera, Jenny Karlsson, Jan Koster, Tommy Martinsson, David Gisselsson, Sven Pahlman, and Daniel Bexell

*Significance:* These findings underpin the complexity of PDX modeling as a means to advance translational applications against neuroblastoma.

**5970** **Spatially Resolved Transcriptomics Enables Dissection of Genetic Heterogeneity in Stage III Cutaneous Malignant Melanoma**



Kim Thrane, Hanna Eriksson, Jonas Maaskola, Johan Hansson, and Joakim Lundeberg

*Significance:* Applying ST technology to gene expression profiling in melanoma lymph node metastases reveals a complex transcriptional landscape in a spatial context, which is essential for understanding the multiple components of tumor progression and therapy outcome.

## CONVERGENCE AND TECHNOLOGIES

**5980** **Oxygen-Enhanced and Dynamic Contrast-Enhanced Optoacoustic Tomography Provide Surrogate Biomarkers of Tumor Vascular Function, Hypoxia, and Necrosis**



Michal R. Tomaszewski, Marcel Gehrung, James Joseph, Isabel Quiros-Gonzalez, Jonathan A. Disselhorst, and Sarah E. Bohndiek

*Significance:* Imaging biomarkers derived from optoacoustic tomography can be used as surrogate measures of tumor perfusion and hypoxia, potentially yielding rapid, multiparametric, and noninvasive cancer staging and therapeutic response monitoring in the clinic.

**5992** **In Vivo Estimation of Oncolytic Virus Populations within Tumors**

Mi-Yeon Jung, Chetan P. Offord, Matthew K. Ennis, Iris Kemler, Claudia Neuhauser, and David Dingli

*Significance:* These findings address a fundamental gap in our knowledge of oncolytic virotherapy by presenting technology that gives insight into the behavior of oncolytic viruses in vivo.

**6001** **Clinical Proteomics of Breast Cancer Reveals a Novel Layer of Breast Cancer Classification**

Gali Yanovich, Hadar Agmon, Michal Harel, Amir Sonnenblick, Tamar Peretz, and Tamar Geiger

*Significance:* These findings utilize extensive proteomics to identify a novel luminal breast cancer subtype, highlighting the added value of clinical proteomics in breast cancer to identify unique features not observable by genomic approaches.

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## POPULATION AND PREVENTION SCIENCE

### 6011 Pooled Analysis of Nine Cohorts Reveals Breast Cancer Risk Factors by Tumor Molecular Subtype

Mia M. Gaudet, Gretchen L. Gierach, Brian D. Carter, Juhua Luo, Roger L. Milne, Elisabete Weiderpass, Graham G. Giles, Rulla M. Tamimi, A. Heather Eliassen, Bernard Rosner, Alicja Wolk, Hans-Olov Adami, Karen L. Margolis, Susan M. Gapstur, Montserrat Garcia-Closas, and Louise A. Brinton

*Significance:* These findings comprise the largest study of prospective data to date and contribute to the accumulating evidence that etiological heterogeneity exists in breast carcinogenesis.

## LETTER TO THE EDITOR

### 6022 Innervation of the Tumor Microenvironment—Letter

Mark R. Goldstein and Luca Mascitelli

## CORRECTIONS

### 6023 Correction: MicroRNA-22 Suppresses DNA Repair and Promotes Genomic Instability through Targeting of MDC1

6024 Correction: RSF1 Is a Positive Regulator of NF $\kappa$ B-induced Gene Expression Required for Ovarian Cancer Chemoresistance

6025 Correction: Absence of the Full-Length Breast Cancer-Associated Gene-1 Leads to Increased Expression of Insulin-Like Growth Factor Signaling Axis Members

6026 Correction: Telomerase-dependent Virotherapy Overcomes Resistance of Hepatocellular Carcinomas against Chemotherapy and Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand by Elimination of Mcl-1

6027 Correction: A Telomerase-dependent Conditionally Replicating Adenovirus for Selective Treatment of Cancer

## RETRACTION

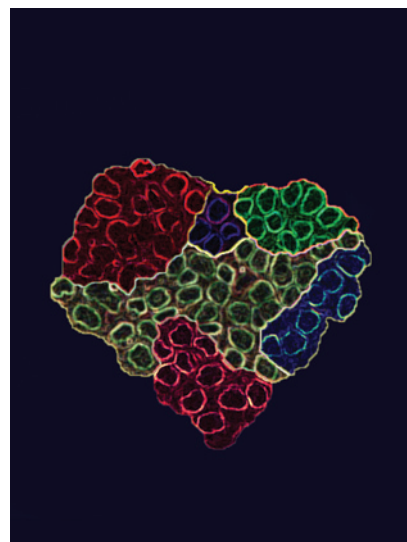
6028 Retraction: Down-regulation of Apurinic/Apyrimidinic Endonuclease 1/Redox Factor-1 Expression by Soy Isoflavones Enhances Prostate Cancer Radiotherapy *In vitro* and *In vivo*

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## ABOUT THE COVER

The cover art is based on a microscopic May-Grunwald-Giemsa staining of untreated control primary human CD34<sup>+</sup> AML blasts that were spotted on a glass slide and formed a heart-shaped structure. The image was taken with a Leica DM 3000 or Leica DM IL microscope with a Leica DFC420C camera (Leica Geosystems B.V.). This picture has been artistically modified in Photoshop to create an embracing colorful projection of the AML blasts. For details, see article by Kampen and colleagues on page 5940.



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