

## BREAKING INSIGHTS

- 6029** Highlights from Recent Cancer Literature

## REVIEWS

- 6031** Glioma Cell Secretion: A Driver of Tumor Progression and a Potential Therapeutic Target  
Damian A. Almiron Bonnin, Matthew C. Havrda, and Mark A. Israel

- 6040** Reactive Oxygen and Nitrogen Species–Induced Protein Modifications: Implication in Carcinogenesis and Anticancer Therapy  
Nurbubu T. Moldogazieva, Sergey V. Lutsenko, and Alexander A. Terentiev

- 6048** Zebrafish: Speeding Up the Cancer Drug Discovery Process  
Patricia Letrado, Irene de Miguel, Iranzu Lamberto, Roberto Díez-Martínez, and Julen Oyarzabal

## METABOLISM AND CHEMICAL BIOLOGY

- 6059** Gene Expression Integration into Pathway Modules Reveals a Pan-Cancer Metabolic Landscape  
Cankut Cubuk, Marta R. Hidalgo, Alicia Amadoz, Miguel A. Pujana, Francesca Mateo, Carmen Herranz, Jose Carbonell-Caballero, and Joaquin Dopazo  
*Significance:* Combining gene expression with metabolic modules identifies molecular mechanisms of cancer undetected on an individual gene level and allows discovery of new potential therapeutic targets.

## MOLECULAR CELL BIOLOGY

- 6073** HER2/EGFR–AKT Signaling Switches TGF $\beta$  from Inhibiting Cell Proliferation to Promoting Cell Migration in Breast Cancer  
Fei Huang, Qiaoni Shi, Yuzhen Li, Linlin Xu, Chi Xu, Fenfang Chen, Hai Wang, Hongwei Liao, Zai Chang, Fang Liu, Xiang H.-F. Zhang, Xin-Hua Feng, Jing-Dong J. Han, Shiwen Luo, and Ye-Guang Chen  
*Significance:* TGF $\beta$  signaling can shift from inhibiting to promoting breast cancer development via HER2/EGFR AKT-mediated phosphorylation of Smad3 at S208, enhancing its nuclear accumulation and upregulation of EMT-related genes.

- 6086** Emerin Deregulation Links Nuclear Shape Instability to Metastatic Potential



Mariana Reis-Sobreiro, Jie-Fu Chen, Tatiana Novitskaya, Sungyong You, Samantha Morley, Kenneth Steadman, Navjot Kaur Gill, Adel Eskaros, Mirja Rotinen, Chia-Yi Chu, Leland W.K. Chung, Hisashi Tanaka, Wei Yang, Beatrice S. Knudsen, Hsian-Rong Tseng, Amy C. Rowat, Edwin M. Posadas, Andries Zijlstra, Dolores Di Vizio, and Michael R. Freeman

*Significance:* This study identifies a novel mechanism integrating the control of nuclear structure with the metastatic phenotype, and our inclusion of two types of human specimens (cancer tissues and circulating tumor cells) demonstrates direct relevance to human cancer.

- 6098** Heterozygosity of Chaperone Grp78 Reduces Intestinal Stem Cell Regeneration Potential and Protects against Adenoma Formation

Jooske F. van Lidth de Jeude, Claudia N. Spaan, Bartolomeus J. Meijer, Wouter L. Smit, Tanya T.D. Soeratrarn, Mattheus C.B. Wielenga, B. Florian Westendorp, Amy S. Lee, Sander Meisner, Jacqueline L.M. Vermeulen, Manon E. Wildenberg, Gijs R. van den Brink, Vanesa Muncan, and Jarom Heijmans

*Significance:* Heterozygous disruption of chaperone protein Grp78 reduces tissue regeneration and expansive growth and protects from tumor formation without affecting intestinal homeostasis.

- 6107** p63-Dependent Dickkopf3 Expression Promotes Esophageal Cancer Cell Proliferation via CKAP4

Chihiro Kajiwara, Katsumi Fumoto, Hirokazu Kimura, Satoshi Nojima, Keita Asano, Kazuki Odagiri, Makoto Yamasaki, Hayato Hikita, Tetsuo Takehara, Yuichiro Doki, Eiichi Morii, and Akira Kikuchi

*Significance:* In esophageal cancer, findings identify DKK3 as a poor prognostic indicator and demonstrate CKAP4 inhibition as an effective therapeutic strategy.

- 6121** A Nonpump Function of Sodium Iodide Symporter in Thyroid Cancer via Cross-talk with PTEN Signaling

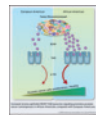
Fang Feng, Lamis Yehia, Ying Ni, Yi Seok Chang, Sissy Meihua Jhiang, and Charis Eng

*Significance:* A novel pump-independent protumorigenic role of nonmembranous NIS challenges the presumption that radioiodine treatment of thyroid cancer is ineffective when transmembrane NIS is not expressed.

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## TUMOR BIOLOGY AND IMMUNOLOGY

### 6134 Elevation of Stromal-Derived Mediators of Inflammation Promote Prostate Cancer Progression in African-American Men



Marc Gillard, Rodrigo Javier, Yuan Ji, S. Lilly Zheng, Jianfeng Xu, Charles B. Brendler, Susan E. Crawford, Brandon L. Pierce, Donald J. Vander Griend, and Omar E. Franco

**Significance:** These findings suggest that stromal cells in the tumor microenvironment of African-American men promote progression of prostate cancer by increasing levels of a specific set of proinflammatory molecules compared with European-American men.

### 6146 Tobacco Carcinogen-Induced Production of GM-CSF Activates CREB to Promote Pancreatic Cancer



Supriya Srinivasan, Tulasigeri Totiger, Chanjuan Shi, Jason Castellanos, Purushottam Lamichhane, Austin R. Dosch, Fanuel Messaggio, Nilesh Kashikar, Kumaraswamy Honnenahally, Yuguang Ban, Nipun B. Merchant, Michael VanSaun, and Nagaraj S. Nagathihalli

**Significance:** These findings identify GM-CSF-induced CREB as a driver of pancreatic cancer in smokers and demonstrate the therapeutic potential of targeting CREB to reduce PDAC tumor growth.

### 6159 Human Papilloma Virus Specific Immunogenicity and Dysfunction of CD8<sup>+</sup> T Cells in Head and Neck Cancer



Sri Krishna, Peaches Ulrich, Eric Wilson, Falguni Parikh, Pooja Narang, Shanshan Yang, Amelia K. Read, Seunghee Kim-Schulze, Jin G. Park, Marshall Posner, Melissa A. Wilson Sayres, Andrew Sikora, and Karen S. Anderson

**Significance:** This study evaluates the HPV antigen T-cell immunogenicity role of inhibitory receptors and other exhaustion markers in the cytotoxic function of HPV antigen-specific CTLs and identifies combined inhibition of PD-1/IDO-1 as a strategy to enhance CTL targeting of HPV<sup>+</sup>HNSCC.

### 6171 Intrathecal Viral Vector Delivery of Trastuzumab Prevents or Inhibits Tumor Growth of Human HER2-Positive Xenografts in Mice

William T. Rothwell, Peter Bell, Laura K. Richman, Maria P. Limberis, Anna P. Tretiakova, Mingyao Li, and James M. Wilson

**Significance:** Intrathecal delivery of trastuzumab via adeno-associated virus has the potential to become a novel, integral part of adjuvant therapy for patients with HER2-positive breast cancer brain metastases.

### 6183 Therapeutically Active RIG-I Agonist Induces Immunogenic Tumor Cell Killing in Breast Cancers



David L. Elion, Max E. Jacobson, Donna J. Hicks, Bushra Rahman, Violeta Sanchez, Paula I. Gonzales-Ericsson, Olga Fedorova, Anna M. Pyle, John T. Wilson, and Rebecca S. Cook

**Significance:** These findings describe the first in vivo delivery of RIG-I mimetics to tumors, demonstrating a potent immunogenic and therapeutic effect in the context of otherwise poorly immunogenic breast cancers.

### 6196 HORMAD1 Is a Negative Prognostic Indicator in Lung Adenocarcinoma and Specifies Resistance to Oxidative and Genotoxic Stress

Brandt A. Nichols, Nathaniel W. Oswald, Elizabeth A. McMillan, Kathleen McGlynn, Jingsheng Yan, Min S. Kim, Janapriya Saha, Prema L. Mallipeddi, Sydney A. LaDuke, Pamela A. Villalobos, Jaime Rodriguez-Canales, Ignacio I. Wistuba, Bruce A. Posner, Anthony J. Davis, John D. Minna, John B. MacMillan, and Angelique W. Whitehurst

**Significance:** This study uses a chemigenomics approach to demonstrate that anomalous expression of the cancer testis antigen HORMAD1 specifies resistance to oxidative stress and promotes homologous recombination to support tumor cell survival in NSCLC.

### 6209 Comprehensive Phenotypic Characterization of Human Invasive Lobular Carcinoma Cell Lines in 2D and 3D Cultures

Nilgun Tasdemir, Emily A. Bossart, Zheqi Li, Li Zhu, Matthew J. Sikora, Kevin M. Levine, Britta M. Jacobsen, George C. Tseng, Nancy E. Davidson, and Steffi Oesterreich

**Significance:** These findings provide the breast cancer research community with a comprehensive assessment of human invasive lobular carcinoma (ILC) cell line signaling and behavior in various culture conditions, aiding future endeavors to develop therapies and to ultimately improve survival in patients with ILC.

### 6223 Development, Function, and Clinical Significance of Plasmacytoid Dendritic Cells in Chronic Myeloid Leukemia

Sabrina Inselmann, Ying Wang, Susanne Saussele, Lea Fritz, Christin Schütz, Magdalena Huber, Simone Liebler, Thomas Ernst, Dali Cai, Sarah Botschek, Cornelia Brendel, Raffaele A. Calogero, Dinko Pavlinic, Vladimir Benes, Edison T. Liu, Andreas Neubauer, Andreas Hochhaus, and Andreas Burchert

**Significance:** CML-pDC originates from low-level BCR-ABL expressing stem cells into a functional immunogenic DC-population regulating antileukemic immunity and treatment outcome in CML.

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## TRANSLATIONAL SCIENCE

**6235** Inverse Correlation of STAT3 and MEK Signaling Mediates Resistance to RAS Pathway Inhibition in Pancreatic Cancer



Nagaraj S. Nagathihalli, Jason A. Castellanos, Purushottam Lamichhane, Fanuel Messaggio, Chanjuan Shi, Xizi Dai, Priyamvada Rai, Xi Chen, Michael N. VanSaun, and Nipun B. Merchant

**Significance:** This report describes an inverse correlation between MEK and STAT3 signaling as key mechanisms of resistance in PDAC and shows that combined inhibition of MEK and STAT3 overcomes this resistance and provides an improved therapeutic strategy to target the RAS pathway in PDAC.

**6247** CD44-Targeting PLGA Nanoparticles Incorporating Paclitaxel and FAK siRNA Overcome Chemoresistance in Epithelial Ovarian Cancer



Yeongseon Byeon, Jeong-Won Lee, Whan Soo Choi, Ji Eun Won, Ga Hee Kim, Min Gi Kim, Tae In Wi, Jae Myeong Lee, Tae Heung Kang, In Duk Jung, Young-Jae Cho, Hyung Jun Ahn, Byung Cheol Shin, Young Joo Lee, Anil K. Sood, Hee Dong Han, and Yeong-Min Park

**Significance:** These findings demonstrate the efficacy of a novel, selective, two-in-one delivery system to overcome chemoresistance in epithelial ovarian cancer.

**6257** Dose and Schedule Determine Distinct Molecular Mechanisms Underlying the Efficacy of the p53-MDM2 Inhibitor HDM201



Sébastien Jeay, Stéphane Ferretti, Philipp Holzer, Jeanette Fuchs, Emilie A. Chapeau, Markus Wartmann, Dario Sterker, Vincent Romanet, Masato Murakami, Grainne Kerr, Eric Y. Durand, Swann Gaulis, Marta Cortes-Cros, Stephan Ruetz, Therese-Marie Stachyra, Joerg Kallen, Pascal Furet, Jens Würthner, Nelson Guerreiro, Ensar Halilovic, Astrid Jullion, Audrey Kauffmann, Emil Kuriakose, Marion Wiesmann, Michael R. Jensen, Francesco Hofmann, and William R. Sellers

**Significance:** Pulsed high doses versus sustained low doses of the p53-MDM2 inhibitor HDM201 elicit a proapoptotic response from wild-type p53 cancer cells, offering guidance to current clinical trials with this and other drugs that exploit the activity of p53.

**6268** Preclinical Evaluation of the Hsp70 Peptide Tracer TPP-PEG<sub>24</sub>-DFO [<sup>89</sup>Zr] for Tumor-Specific PET/CT Imaging



Stefan Stangl, Lorenzo Tei, Francesco De Rose, Sybille Reder, Jonathan Martinelli, Wolfgang Sievert, Maxim Shevtsov, Rupert Öllinger, Roland Rad, Markus Schwaiger, Calogero D'Alessandria, and Gabriele Multhoff

**Significance:** A novel peptide-based PET tracer against the oligomerization domain of Hsp70 has potential for universal tumor-specific imaging in vivo across many tumor types.

**6282** Systematic Analysis of Compounds Specifically Targeting Telomeres and Telomerase for Clinical Implications in Cancer Therapy



Hee-Sheung Lee, Mar Carmena, Mikhail Liskovych, Emma Peat, Jung-Hyun Kim, Mitsuo Oshimura, Hiroshi Masumoto, Marie-Paule Teulade-Fichou, Yves Pommier, William C. Earnshaw, Vladimir Larionov, and Natalay Kouprina

**Significance:** An assay provides a unique opportunity to screen thousands of chemical compounds for their ability to inactivate replication of telomeric ends in cancer cells and holds potential to lay the foundation for the discovery of new treatments for cancer.

**6297** RAS-MAPK Pathway-Driven Tumor Progression Is Associated with Loss of CIC and Other Genomic Aberrations in Neuroblastoma

Thomas F. Eleveld, Linda Schild, Jan Koster, Danny A. Zwijnenburg, Lindy K. Alles, Marli E. Ebus, Richard Volckmann, Godelieve A. Tijtgat, Peter van Sluis, Rogier Versteeg, and Jan J. Molenaar

**Significance:** This work identifies CIC as a powerful tumor suppressor affecting the RAS-MAPK pathway in neuroblastoma and reinforces the importance of mutation-driven activation of this pathway in cancer.

**6308** Evaluation of Explant Responses to STING Ligands: Personalized Immunosurgical Therapy for Head and Neck Squamous Cell Carcinoma

Jason R. Baird, R. Bryan Bell, Victoria Troesch, David Friedman, Shelly Bambina, Gwen Kramer, Tiffany C. Blair, Terry Medler, Yaping Wu, Zhaoyu Sun, Tanja D. de Gruijl, Rieneke van de Ven, Rom S. Leidner, Marka R. Crittenden, and Michael J. Gough

**Significance:** Delivery of immunotherapy directly to resection sites via a gel-based biomaterial prevents locoregional recurrence of head and neck squamous cell carcinoma.

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## CONVERGENCE AND TECHNOLOGIES

**6320** **CANCERTOOL: A Visualization and Representation Interface to Exploit Cancer Datasets**



Ana R. Cortazar, Veronica Torrano, Natalia Martín-Martín, Alfredo Caro-Maldonado, Laura Camacho, Ivana Hermanova, Elizabeth Guruceaga, Luis F. Lorenzo-Martín, Ruben Caloto, Roger R. Gomis, Iñigo Apaolaza, Victor Quesada, Jan Trka, Antonio Gomez-Muñoz, Silvestre Vincent, Xose R. Bustelo, Francisco J. Planes, Ana M. Aransay, and Arkaitz Carracedo

*Significance:* In order to facilitate access of research groups without bioinformatics support to public transcriptomics data, we have developed a free online tool with an easy-to-use interface that allows researchers to obtain quality information in a readily publishable format.

## POPULATION AND PREVENTION SCIENCE

**6329** **Differential Burden of Rare and Common Variants on Tumor Characteristics, Survival, and Mode of Detection in Breast Cancer**



Jingmei Li, Emilio Ugalde-Morales, Wei Xiong Wen, Brennan Decker, Mikael Eriksson, Astrid Torstensson, Helene Nordahl Christensen, Alison M. Dunning, Jamie Allen, Craig Luccarini, Karen A. Pooley, Jacques Simard, Leila Dorling, Douglas F. Easton, Soo Hwang Teo, Per Hall, and Kamila Czene

*Significance:* These findings offer the potential to improve screening practices for breast cancer by providing a deeper understanding of how risk variants affect disease progression and mode of detection.

## LETTERS TO THE EDITOR

**6339** **JAM-C Expression as a Biomarker to Predict Outcome of Patients with Acute Myeloid Leukemia—Letter**

Malte von Bonin, Katharina Moll, Michael Kramer, Uta Oelschlägel, Martin Wermke, Christoph Röllig, Christian Thiede, Gerhard Ehninger, Alwin Krämer, Carsten Müller-Tidow, Ioannis Mitroulis, and Martin Bornhäuser

**6342** **JAM-C Expression as a Biomarker to Predict Outcome of Patients with Acute Myeloid Leukemia—Response**

Maria De Grandis, Stéphane J.C. Mancini, Norbert Vey, and Michel Aurrand-Lions

## CORRECTION

**6344** **Correction: MUC1 Oncoprotein Promotes Refractoriness to Chemotherapy in Thyroid Cancer Cells**

## RETRACTIONS

**6345** **Retraction: Inactivation of the Quinone Oxidoreductases NQO1 and NQO2 Strongly Elevates the Incidence and Multiplicity of Chemically Induced Skin Tumors**

Jun Shen, Roberto J. Barrios, and Anil K. Jaiswal

**6346** **Retraction: Low and High Dose UVB Regulation of Transcription Factor NF-E2-Related Factor 2**

Sankaranarayanan Kannan and Anil K. Jaiswal

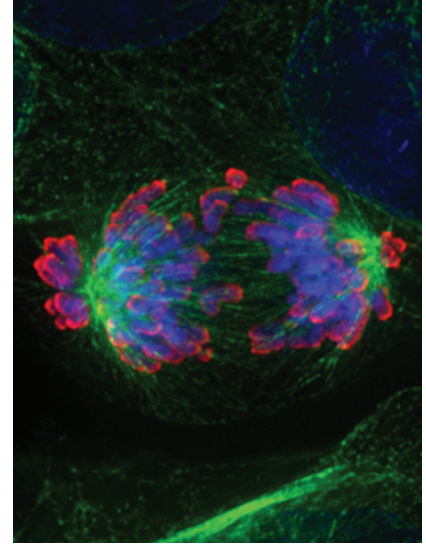
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## ABOUT THE COVER

A novel screen that allows the quantification of chromosome loss of human artificial chromosomes identified inhibitors of telomerase function that induce a high rate of aneuploidy. Using immunofluorescence, the authors characterized the defects in mitosis induced by the telomerase inhibitors. These include chromatin bridges and ultrafine bridges. For details, see article by Lee and colleagues on page 6282.



# Cancer Research

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

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