


## BREAKING ADVANCES


- 6471** Highlights from Recent Cancer Literature

## REVIEWS

- 6473** Precision Oncology: Between Vaguely Right and Precisely Wrong  
Amy Brock and Sui Huang
- 6480** The Biology of Cancer Exosomes: Insights and New Perspectives  
Carolina F. Ruivo, Bárbara Adem, Miguel Silva, and Sónia A. Melo
- 6489** Recent Advances of Cell-Cycle Inhibitor Therapies for Pediatric Cancer  
Christopher C. Mills, EA. Kolb, and Valerie B. Sampson

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 6499** Calcium Promotes Human Gastric Cancer via a Novel Coupling of Calcium-Sensing Receptor and TRPV4 Channel  
 Rui Xie, Jingyu Xu, Yufeng Xiao, Jilin Wu, Hanxing Wan, Bo Tang, Jingjing Liu, Yahan Fan, Suming Wang, Yuyun Wu, Tobias Xiao Dong, Michael X. Zhu, John M. Carethers, Hui Dong, and Shiming Yang  
*Précis:* These results raise the possibility that daily calcium supplements may be harmful to patients at risk for gastric cancer.
- 6513** Mechanisms of Acquired Resistance to BRAF V600E Inhibition in Colon Cancers Converge on RAF Dimerization and Are Sensitive to Its Inhibition  
Rona Yaeger, Zhan Yao, David M. Hyman, Jaelyn F. Hechtman, Efsevia Vakiani, HuiYong Zhao, Wenjing Su, Lu Wang, Andrew Joelson, Andrea Cercek, Jose Baselga, Elisa de Stanchina, Leonard Saltz, Michael F. Berger, David B. Solit, and Neal Rosen  
*Précis:* Colorectal cancer resistance to combination inhibition of EGFR and mutant RAF converges on formation of RAF dimers, such that targeting RAF dimers together with EGFR may effectively treat these resistant cancers.

- 6524** Loss of FOXO1 Cooperates with Tmprss2-ERG Overexpression to Promote Prostate Tumorigenesis and Cell Invasion  


Yinhui Yang, Alexandra M. Blee, Dejie Wang, Jian An, Yunqian Pan, Yuqian Yan, Tao Ma, Yundong He, Joseph Dugdale, Xiaonan Hou, Jun Zhang, S. John Weroha, Wei-Guo Zhu, Y. Alan Wang, Ronald A. DePinho, Wanhai Xu, and Haojie Huang

*Précis:* This study identifies a signaling pathway that promotes prostate cancer, suggesting new directions to limit progression of this disease, which is the key issue in promoting patient survival.

- 6538** Integrated Analysis of Whole-Genome ChIP-Seq and RNA-Seq Data of Primary Head and Neck Tumor Samples Associates HPV Integration Sites with Open Chromatin Marks

Dylan Z. Kelley, Emily L. Flam, Evgeny Izumchenko, Ludmila V. Danilova, Hildegard A. Wulf, Theresa Guo, Dzov A. Singman, Bahman Afsari, Alyza M. Skaist, Michael Considine, Jane A. Welch, Elena Stavrovskaya, Justin A. Bishop, William H. Westra, Zubair Khan, Wayne M. Koch, David Sidransky, Sarah J. Wheelan, Joseph A. Califano, Alexander V. Favorov, Elana J. Fertig, and Daria A. Gaykalova

*Précis:* This study is the first to describe global relationships between chromatin organization and HPV integration sites in head and neck cancers, with implications for more effective prognosis and treatment.

- 6551** Clonality, Heterogeneity, and Evolution of Synchronous Bilateral Ovarian Cancer

Xia Yin, Ying Jing, Mei-Chun Cai, Pengfei Ma, Yi Zhang, Cong Xu, Meiyang Zhang, Wen Di, and Guanglei Zhuang

*Précis:* Bilateral ovarian cancers are more likely to form by pelvic spread rather than independent multifocal oncogenesis, with the early characteristic metastasis in this disease mainly a function of dynamic mutational processes and divergent evolution.

- 6562** DDB2 Is a Novel Regulator of Wnt Signaling in Colon Cancer

Shuo Huang, Damiano Fantini, Bradley J. Merrill, Srilata Bagchi, Grace Guzman, and Pradip Raychaudhuri

*Précis:* This study describes a novel regulatory element in WNT oncogenic signaling that expands the perspective on how colon cancers develop.

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**6576** *Sleeping Beauty* Insertional Mutagenesis in Mice Identifies Drivers of Steatosis-Associated Hepatic Tumors

Barbara R. Tschida, Nuri A. Temiz, Timothy P. Kuka, Lindsey A. Lee, Jesse D. Riordan, Carlos A. Tierrablanca, Robert Hullsiek, Sandra Wagner, Wendy A. Hudson, Michael A. Linden, Khalid Amin, Pauline J. Beckmann, Rachel A. Heuer, Aaron L. Sarver, Ju Dong Yang, Lewis R. Roberts, Joseph H. Nadeau, Adam J. Dupuy, Vincent W. Keng, and David A. Largaespada

*Précis:* Fatty liver disease is growing with the obesity epidemic and the inflammatory damage that it can create can influence the risks and genetic evolution of liver cancer, which is poised to increase in incidence in parallel with obesity.

**6627** JAM-C Identifies Src Family Kinase-Activated Leukemia-Initiating Cells and Predicts Poor Prognosis in Acute Myeloid Leukemia

Maria De Grandis, Florence Bardin, Cyril Fauriat, Christophe Zemmour, Abdessamad El-Kaoutari, Arnaud Sergé, Samuel Granjeaud, Laurent Pouyet, Camille MonTERSINO, Anne-Sophie Chretien, Marie-Joelle Mozziconacci, Remy Castellano, Chislain Bidaut, Jean-Marie Boher, Yves Collette, Stéphane J.C. Mancini, Norbert Vey, and Michel Aurrand-Lions

*Précis:* These findings define a gene signature for tumor-initiating cells in the early heterogenous population of acute myeloid leukemias, with implications for fighting disease relapse.

## TUMOR AND STEM CELL BIOLOGY

**6589** R-Spondin1/LGR5 Activates TGF $\beta$  Signaling and Suppresses Colon Cancer Metastasis



Xiaolin Zhou, Liying Geng, Degeng Wang, Haowei Yi, Geoffrey Talmon, and Jing Wang

*Précis:* These findings establish a novel cross-talk between an important adult intestinal stem cell marker and a well-established tumor suppressor pathway in colon cancer.

**6603** Administering xCT Inhibitors Based on Circadian Clock Improves Antitumor Effects

Fumiyasu Okazaki, Naoya Matsunaga, Kengo Hamamura, Kayoko Suzuki, Takaharu Nakao, Hiroyuki Okazaki, Masahiko Kutsukake, Shiro Fukumori, Yasuhiro Tsuji, and Hideto To

*Précis:* The circadian gene clock regulates the transcription of the essential cystine transporter xCT, the expression of which determines the effectiveness of the chemotherapy drug sulfasalazine.

**6614** Super-Enhancers Promote Transcriptional Dysregulation in Nasopharyngeal Carcinoma

Jiang Yuan, Yan-Yi Jiang, Anand Mayakonda, Moli Huang, Ling-Wen Ding, Han Lin, Fenggang Yu, Yanan Lu, Thomas Kwok Seng Loh, Marilyn Chow, Samantha Savage, Jeffrey W. Tyner, De-Chen Lin, and H. Phillip Koeffler

*Précis:* This study identifies a network of new candidate therapeutic targets in a cancer with high incidence in southeast Asia.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**6641** MYC Inhibition Depletes Cancer Stem-like Cells in Triple-Negative Breast Cancer

Aimin Yang, Shenghui Qin, Bradley A. Schulte, Stephen P. Ethier, Kenneth D. Tew, and Gavin Y. Wang

*Précis:* A natural product described in this study may offer an opportunity to selectively kill drug-resistant cancer stem-like cells in triple-negative breast cancer by triggering degradation of the c-MYC oncoprotein.

**6651** EZH2 Modifies Sunitinib Resistance in Renal Cell Carcinoma by Kinome Reprogramming

Remi Adelaiye-Ogala, Justin Budka, Nur P. Damayanti, Justine Arrington, Mary Ferris, Chuan-Chih Hsu, Sreenivasulu Chintala, Ashley Orillion, Kiersten Marie Miles, Li Shen, May Elbanna, Eric Ciamporcerro, Sreevani Arisa, Piergiorgio Pettazzoni, Giulio F. Draetta, Mukund Seshadri, Bradley Hancock, Milan Radovich, Janaiah Kota, Michael Buck, Heike Keilhack, Brian P. McCarthy, Scott A. Persohn, Paul R. Territo, Yong Zang, Joseph Irudayaraj, W. Andy Tao, Peter Hollenhorst, and Roberto Pili

*Précis:* These results offer a mechanistic rationale to target an oncogenic histone methyltransferase as a strategy to have an impact on sunitinib-resistance in kidney cancers.

## MICROENVIRONMENT AND IMMUNOLOGY

**6667** IL10 Release upon PD-1 Blockade Sustains Immunosuppression in Ovarian Cancer

Purushottam Lamichhane, Lavakumar Karyampudi, Barath Shreeder, James Krempsi, Deborah Bahr, Joshua Daum, Kimberly R. Kalli, Ellen L. Goode, Matthew S. Block, Martin J. Cannon, and Keith L. Knutson

*Précis:* These findings identify an actionable mechanism of resistance to anti-PD-1, with implications for broadening therapeutic responses to this immune checkpoint drug.



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- 6679** Secretory Autophagy in Cancer-Associated Fibroblasts Promotes Head and Neck Cancer Progression and Offers a Novel Therapeutic Target  
Jacob New, Levi Arnold, Megha Ananth, Sameer Alvi, Mackenzie Thornton, Lauryn Werner, Ossama Tawfik, Hongying Dai, Yelizaveta Shnyder, Kiran Kakarala, Terance T. Tsue, Douglas A. Girod, Wen-Xing Ding, Shrikant Anant, and Sufi Mary Thomas  
*Précis:* These results establish an oncogenic function for secretory autophagy in the stromal fibroblasts in head and neck cancers, with possible implications to prevent malignant progression in this and other cancer settings.
- 6692** Astrocytes Promote Medulloblastoma Progression through Hedgehog Secretion  
Yongqiang Liu, Larra W. Yuelling, Yuan Wang, Fang Du, Renata E. Gordon, Jenny A. O'Brien, Jessica M.Y. Ng, Shannon Robins, Eric H. Lee, Hailong Liu, Tom Curran, and Zeng-Jie Yang  
*Précis:* Astrocytes support the growth of medulloblastomas by secreting the developmental growth factor sonic hedgehog, enabling activation of a key progression pathway in this pediatric brain tumor.
- 6704** Mesenchymal Stem Cells Promote Hepatocarcinogenesis via lncRNA–MUF Interaction with ANXA2 and miR-34a  
Xinlong Yan, Dongdong Zhang, Wei Wu, Shuheng Wu, Jingfeng Qian, Yajing Hao, Fang Yan, Pingping Zhu, Jiayi Wu, Guanling Huang, Yinghui Huang, Jianjun Luo, Xinhui Liu, Benyu Liu, Xiaomin Chen, Ying Du, Runsheng Chen, and Zusen Fan  
*Précis:* These findings provide compelling evidence that long noncoding RNAs support liver carcinogenesis by facilitating contributions from mesenchymal stem cells in the tumor microenvironment.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6717** Chemotherapeutic Dose Scheduling Based on Tumor Growth Rates Provides a Case for Low-Dose Metronomic High-Entropy Therapies  
Jeffrey West and Paul K. Newton  
*Précis:* A game theory mathematical model shows how the effectiveness of cytotoxic drugs in killing cancer cells is affected more by changes in dose density than dose concentration, especially in faster growing tumors.

- 6729** SMYD5 Controls Heterochromatin and Chromosome Integrity during Embryonic Stem Cell Differentiation  
Benjamin L. Kidder, Runsheng He, Darawalee Wangsa, Hesus M. Padilla-Nash, M. Margarida Bernardo, Shijie Sheng, Thomas Ried, and Keji Zhao  
*Précis:* Changes in a repressive chromatin structure in embryonic stem cells leads to genome instability during differentiation.
- 6746** Glutamine Addiction in Kidney Cancer Suppresses Oxidative Stress and Can Be Exploited for Real-Time Imaging  
Omran Abu Aboud, Samy L. Habib, Josephine Trott, Benjamin Stewart, Sitai Liang, Abhijit J. Chaudhari, Julie Sutcliffe, and Robert H. Weiss  
*Précis:* Glutamine consumed by clear cell renal tumors to support an antioxidant survival pathway can be exploited for functional PET imaging.
- 6759** Modeling Cytostatic and Cytotoxic Responses to New Treatment Regimens for Ovarian Cancer  
Francesca Falcetta, Francesca Bizzaro, Elisa D'Agostini, Maria Rosa Bani, Raffaella Giavazzi, and Paolo Ubezio  
*Précis:* A comparative preclinical study of several treatment regimens for ovarian cancer with paclitaxel, cisplatin, and bevacizumab alone or in combination decodes tumor growth curves via mathematical modeling of the proliferation process.

## PREVENTION AND EPIDEMIOLOGY

- 6770** Disparities in Prostate, Lung, Breast, and Colorectal Cancer Survival and Comorbidity Status among Urban American Indians and Alaskan Natives  
Marc A. Emerson, Matthew P. Banegas, Neetu Chawla, Ninah Achacoso, Stacey E. Alexeeff, Alyce S. Adams, and Laurel A. Habel  
*Précis:* These findings address a critical gap in information concerning the cancer experience of the majority of Native Americans and Alaskan Natives in the U.S. who live in urban areas.
- 6777** Oral Microbiome Composition Reflects Prospective Risk for Esophageal Cancers  
Brandilyn A. Peters, Jing Wu, Zhiheng Pei, Liying Yang, Mark P. Purdue, Neal D. Freedman, Eric J. Jacobs, Susan M. Gapstur, Richard B. Hayes, and Jiyoung Ahn  
*Précis:* A prospective study of the relationship between the oral microbiome and risks of developing esophageal cancers has potential implications for early detection and prevention.

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## CORRECTIONS

- 6788** Correction: miR-103/107 Promote Metastasis of Colorectal Cancer by Targeting the Metastasis Suppressors DAPK and KLF4
- 6789** Correction: Myc Induces miRNA-Mediated Apoptosis in Response to HDAC Inhibition in Hematologic Malignancies

- 6790** Correction: CRLX101, a Nanoparticle-Drug Conjugate Containing Camptothecin, Improves Rectal Cancer Chemoradiotherapy by Inhibiting DNA Repair and HIF1 $\alpha$

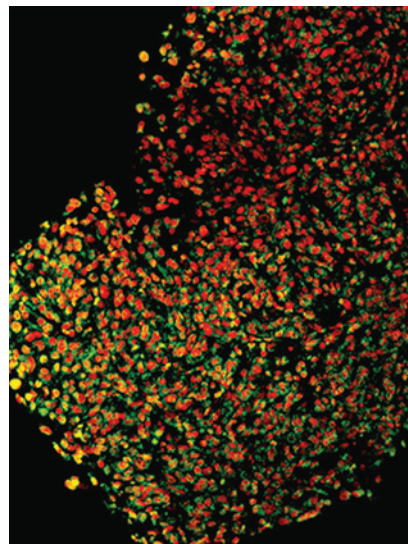


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## ABOUT THE COVER

8-Oxo7,8-dihydro-2'-deoxyguanosine (8-oxodG), an oxidized form of deoxyguanosine, is a major product of DNA oxidation and is used as a biomarker for oxidative stress in cancer. The level of 8-oxodG in cellular DNA reflects the balance between the rate of DNA damage and the efficiency of DNA repair. This merged image of double fluorescent-labeled murine xenografted human kidney cancer cells shows a high abundance of 8-oxodG (stained green with FITC) within the nuclei (identified by red propidium iodide staining of all DNA). A higher level of orange to green staining within the kidney tumor section as compared with the normal kidney (not shown) indicates more oxidative DNA damage within the tumor. The image was taken using a Nikon research microscope equipped for epifluorescence with excitation and band pass filters. For details, see article by Abu Aboud and colleagues on page 6746.



# Cancer Research

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