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, Hanxian Wan, Bo Tang, Jingjing Liu, Yahan Fan, Suming Wang, Yuyun Wu, Qiang Lin, Michael X. Zhu, John M. Carethers, Hui Dong, and Shiming Yang

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, Jaclyn F. Hechtman, Efsevia Vakian, 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

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

6551 Clonality, Heterogeneity, and Evolution of Synchronous Bilateral Ovarian Cancer
Xia Yin, Ying Jing, Mei-Chun Cai, Pengfei Ma, Yi Zhang, Cong Xu, Meiying Zhang, Wen Di, and Guanglei Zhuang

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.
## TUMOR AND STEM CELL BIOLOGY

### 6576

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

### 6589

R-Spondin1/LGR5 Activates TGFβ 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, Kayo Suzuki, Takaharu Nakao, Hiroyuki Okazaki, Masahiko Kutsukake, Shiro Fukumori, Yasuhiro Tuji, and Hideo 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, Marilynn Chow, Samantha Savage, Jeffrey W. Tyner, De-Chen Lin, and H. Phillip Koefler  
**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

### 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, Arnauld Sergé, Samuel Gzanjeaud, Laurent Pouyet, Camille Montiersino, Anne-Sophie Chretien, Marie-Joelle Moziconacci, Remy Castellano, Ghislain Bidaut, Jean-Marie Boher, Yves Collette, Stéphane J.C. Mancini, Norbert Vey, and Michel Aurand-Lions  
**Précis:** These findings define a gene signature for tumor-initiating cells in the early heterogeneous population of acute myeloid leukemias, with implications for fighting disease relapse.

### 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 Ciamparocero, Srievani Arisa, Piergiorgio Pettazzoni, Giulio F. Draetta, Mukund Seshadri, Bradley Hancock, Milan Radovich, Janaiah Kota, Michael Buck, Heike Krillich, Brian P. McCanhy, Scott A. Persohn, Paul R. Territo, Yong Zang, Joseph Insalayaraj, 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  
Punushottam Larnichhan, Lavakumar Karyampudi, Barath Shreeder, James Krempski, Deborah Bahr, Joshua Daunm, 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.
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, Osama Tawfik, Hongying Dai, Yelizaveta Shnayder, Kieran 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

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, Xiaoming Hao, Fang Yan, Pengping Zhu, Jiyi Wu, Guanling Huang, Yinhui 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, Hesed M. Padilla-Nash, M. Margarita Bernardo, Shijie Sheng, Thomas Ried, and Reji 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 Trottinger, 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. Purdie, Neal D. Freedman, Eric J. Jacobs, Susan M. Capstur, 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.
Corrections

Correction: miR-103/107 Promote Metastasis of Colorectal Cancer by Targeting the Metastasis Suppressors DAPK and KLF4

Correction: Myc Induces miRNA-Mediated Apoptosis in Response to HDAC Inhibition in Hematologic Malignancies

Correction: CRLX101, a Nanoparticle–Drug Conjugate Containing Camptothecin, Improves Rectal Cancer Chemoradiotherapy by Inhibiting DNA Repair and HIF1α

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.
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