### BREAKING ADVANCES

**3685** Highlights from Recent Cancer Literature

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### REVIEWS

**3687** Tumors and Mitochondrial Respiration: A Neglected Connection
Andrea Viale, Denise Corti, and Giulio F. Draetta

**3692** NF-κB: Regulation by Methylation
Tao Lu and George R. Stark

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### MEETING REPORT

**3696** Meeting Report: Inaugural Chemotherapy-Induced Peripheral Neuropathy Symposium, Santa Barbara, CA, February 2015
Jennifer A. Smith and Sarah J. Benbow

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### PRIORITY REPORTS

**3699** Warfarin Blocks Gas6-Mediated Axl Activation Required for Pancreatic Cancer Epithelial Plasticity and Metastasis
Amanda Kirane, Kathleen F. Ludwigg, Noah Sorrelle, Gzy Haaland, Tone Sandal, Renate Ranasesva, Jason E. Toombs, Xiaoxi Wang, Sean P. Dineen, David Micklem, Michael T. Dellinger, James B. Lorens, and Rolf A. Brekken

**3706** Real-time Imaging of the Resection Bed Using a Handheld Probe to Reduce Incidence of Microscopic Positive Margins in Cancer Surgery

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### INTEGRATED SYSTEMS AND TECHNOLOGIES

**3728** TANRIC: An Interactive Open Platform to Explore the Function of IncRNAs in Cancer
Jun Li, Leng Han, Paul Roebuck, Lisa Diao, Lingxiang Liu, Yuan Yuan, John N. Weinstein, and Han Liang

**3738** Pulsed High-Intensity Focused Ultrasound Enhances Delivery of Doxorubicin in a Preclinical Model of Pancreatic Cancer
Tong Li, Yik-Nam Wang, Tatiana D. Khokhlova, Samantha D’Andrea, Frank Starr, Hong Chen, Jeannine S. McCune, Linda J. Risler, Afshin Mashadi-Hossein, and Joo Ha Hwang

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**3713** Metastatic Competence Can Emerge with Selection of Preexisting Oncogenic Alleles without a Need of New Mutations
Leni S. Jacob, Sakari Vanharanta, Anna C. Obenauf, Mono Pirun, Agnes Viale, Nicholas D. Soce, and Joan Massague

**3720** The Distinctive Mutational Spectra of Polyomavirus-Negative Merkel Cell Carcinoma
Paul William Harms, Pankaj Vats, Monique Elise Verhaegen, Dan R. Robinson, Yi-Mi Wu, Saravanan Mohan Dhanasekar, Nallalasivam Palanisamy, Javed Siddiqui, Xuhong Cao, Fengyun Su, Rui Wang, Hong Xiao, Lakshmi P. Kunju, Rohit Mehra, Scott A. Tomlins, Douglas Randall Fullen, Christopher Keram Bichakjian, Timothy M. Johnson, Andrzej Antoni Dlugosz, and Anul M. Chinnaiyan

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**3728** Précis: These findings offer an explanation for the long-standing anecdotal anticancer effects of warfarin and support directed clinical evaluation of low dose warfarin and other Axl-targeting agents in cancer patients.

**3738** Précis: This study presents a unique web resource that enables high-quality analyses to investigate the full spectrum of long-noncoding RNAs in cancer, reducing existing barriers for biomedical researchers to access the complex genomic data, generate testable hypotheses, and make translational discoveries.

**3738** Précis: This study offers a proof of concept for the use of a handheld imaging device during wide-area resections of solid tumors to assure cancer patients of reduced morbidity and mortality from cancer.

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**3713** Précis: Changes in the ecology of metastatic niche microenvironments may be sufficient to select for metastatic capacity, without any need of for selection of new mutations in cancer cells themselves, heightening evidence of the primacy of the host microenvironment in directing cancer progression.

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**3720** Précis: Next-generation sequencing analysis suggests two molecularly distinct etiologies for MCC, characterized by either viral-dependent or UV-dependent tumorigenic pathways.
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MICROENVIRONMENT AND IMMUNOLOGY

3747 aberrant expression of MHC class II in melanoma attracts inflammatory tumor-specific CD4+ T-cells, which dampen CD8+ T-cell antitumor reactivity
Marco Donia, Rikke Andersen, Julie W. Kjeldsen, Paolo Fagone, Shamaaila Mumir, Ferdinand Nicoletti, Mads Hald Andersen, Per thor Straten, and Inge Marie Svane
Precisé: these results illustrate a novel immune escape mechanism used in melanoma cells that aberrantly express MHC class II molecules, which, by attracting CD4+ T-cells, generate a local inflammatory response dominated by TNF, which thereby inhibits cytotoxic CD8+ T-cells.

3759 mast cells infiltrating inflamed or transformed gut alternatively sustain mucosal healing or tumor growth
Alice Rigoni, Lucia Bongiovanni, Alessia Burrochi, Sabine Sangaletti, Luca Danelli, Carla Guarnotta, Amy Lewis, Aroldo Rizzo, Andrew R. Silver, Claudio Tripodo, and Mario P. Colombo
Precisé: this study reveals that mast cells can favor colon tissue repair during inflammation but also promote high-grade tumors once they are initiated, with implications for understanding immune contributions during colon tumorigenesis.

3760 tumor-promoting effects of myeloid-derived suppressor cells are potentiated by hypoxia-induced expression of miR-210
Muhammad Zaeem Noman, Bassam Janji, Shijun Hu, Joseph C. Wu, Fabio Martelli, Vincenzo Bronte, and Muhammad Zaeem Noman
Precisé: these findings offer a preclinical rationale to investigate the use of miR-210 inhibitors or oligonucleotides as adjuvants to boost immunotherapeutic responses in cancer patients, based on their ability to blunt the potent immunosuppressive effects of MDSC in the tumor microenvironment.

3788 IL17 promotes mammary tumor progression by changing the behavior of tumor cells and eliciting tumorigenic neutrophils recruitment
Luciana Benevides, Denise Morais da Fonseca, Paula Barbim Donate, Daniel Guimarães Tiezzi, Daniel D. De Carvalho, Juvandyr M. de Andrade, Gislaine A. Martins, and João S. Silva
Precisé: IL17 blockade represents an attractive approach for the control of invasive breast tumors.

3800 a threshold level of intratumor CD8+ T-cell PD1 expression dictates therapeutic response to anti-PD1
Shin Foong Ngio, Arabella Young, Nicolas Jacquelot, Takahiro Yamazaki, David Enot, Laurence Zitvogel, and Mark J. Smyth
Precisé: this study shows how PD1 levels in CD8+ T cells that are present in tumors can predict the treatment response to PD1 antibodies and how regulatory T cells participate in controlling this sensitivity, with immediate implications for addressing the timely question of which patients will respond best to this exciting immune checkpoint therapy.

3810 STAT3 inhibition enhances the therapeutic efficacy of immunogenic chemotherapy by stimulating type 1 interferon production by cancer cells
Heng Yang, Takahiro Yamazaki, Federico Pietrocola, Heng Zhou, Laurence Zitvogel, Yuting Ma, and Guido Kroemer
Precisé: STAT3 inhibitors may improve the therapeutic benefits of anthracyclines through augmenting cancer cell-autonomous type I IFN response.

MOLECULAR AND CELLULAR PATHOBIOLOGY

3820 Preclinical characterization of novel chordoma cell systems and their targeting by pharmacological inhibitors of the CDK4/6 cell-cycle pathway
Adrian von Witteleben, Lukas T. Goerttler, Ralf Marienfeld, Holger Barth, André Lechel, Kevin Mellert, Michael Böhm, Marko Kornmann, Regine Mayer-Steinacker, Alexandra von Baer, Markus Schulteiss, Adrienne M. Flanagan, Peter Möller, Silke Brüderlein, and Thomas F.E. Barth
Precisé: this study describes the characterization of a valuable new tool for studies of chordoma, a deadly and little understood tumor arising at vertebral bodies and the base of the skull, along with the identification of a candidate prognostic biomarker and molecular targeting strategy.

3832 Loss of RACK1 promotes metastasis of gastric cancer by inducing a miR-302c/IL8 signaling loop
Ling Chen, Lingshiang Min, Xuelei Wang, Junjie Zhao, Hua Chen, Jing Qin, Weidong Chen, Zhenbin Shen, Zhaoqing Tang, Qiangjun Gan, Yauyuan Ruan, Yihong Sun, Xinyu Qin, and Jiabin Gu
Precisé: this study connects epigenetics and inflammatory cytokine control during tumorigenesis in gastric tissue, showing how an epithelium state affects key mediators in establishing a master-slave relationship in the tumor microenvironment.
Small-Molecule NSC59984 Restores p53 Pathway Signaling and Antitumor Effects against Colorectal Cancer via p73 Activation and Degradation of Mutant p53


Precis: This study demonstrates that a small-molecule compound can reactivate a p53 pathway in cells with mutant p53, which is commonly found in colorectal cancer. The compound stimulates p73 expression and function, and also targets gain-of-function mutants of p53 that are expressed widely in human cancers, with potentially broad-reaching implications for cancer treatment.

Multiplex Genome-Edited T-cell Manufacturing Platform for "Off-the-Shelf" Adoptive T-cell Immunotherapies

Laurent Poirot, Brian Philip, Cécile Schiffer-Mannioui, Diane Le Clerre, Isabelle Chion-Sotinel, Sophie Demienne, Pierrick Potrel, Cécile Bas, Laetitia Lemaire, Roman Galetto, Céline Lebuhotel, Justin Eyquem, Gordon Weng-Kit Cheung, Aymeric Duclert, Agnès Gouble, Sylvain Arnould, Karl Peggs, Martin Pule, Andrew M. Scharenberg, and Julianne Smith

Precis: This study describes methods that overcome present limitations in generating patient-derived CAR T-cell therapy by using nonalloreactive T cells from third-party donors in a scalable manufacturing process that enables an "off-the-shelf" immunotherapy to be produced.

The SMARCA2/4 ATPase Domain Surpasses the Bromodomain as a Drug Target in SWI/SNF-Mutant Cancers: Insights from cDNA Rescue and PFI-3 Inhibitor Studies


Precis: This study shows how a little studied microRNA can alter the context in which cancer cells respond to chemotherapy-induced stress, improving efficacy in settings such as esophageal cancers, which are inherently resistant to chemotherapy.

ABCG2 Transporter Expression Impacts Group 3 Medulloblastoma Response to Chemotherapy

Marie Morfouace, Satish Cheepala, Sadhana Jackson, Yu Fukuda, Yogesh T. Patel, Soghra Fatima, Daisuke Kawauchi, Anang A. Shelat, Clinton F. Stewart, Brian P. Somrentino, John D. Schuetz, and Martine F. Rousset

Precis: These findings offer a preclinical rationale to block ABCG2 transporter activity as a strategy to enhance the therapeutic efficacy of topotecan used to treat Group 3 medulloblastoma, a pediatric brain tumor that is particularly challenging to address clinically.

miR-634 Activates the Mitochondrial Apoptosis Pathway and Enhances Chemotherapy-Induced Cytotoxicity

Naoto Fujiwara, Jun Inoue, Tatsuyuki Kawano, Kousuke Tanimoto, Ken-ichi Kozaki, and Johji Inazawa

Precis: This study shows how a little studied microRNA can alter the context in which cancer cells respond to chemotherapy-induced stress, improving efficacy in settings such as esophageal cancers, which are inherently resistant to chemotherapy.

CD38 in Hairy Cell Leukemia Is a Marker of Poor Prognosis and a New Target for Therapy

Nicolas Poret, Qiangwei Fu, Soizic Guihard, Meyling Cheok, Katie Miller, Gordon Zeng, Bruno Quesnel, Xavier Troussard, Sylvie Galiligue-Zoutitina, and Carl Simon Shelley

Precis: This study describes for the first time a biomarker that predicts the severity of hairy cell leukemia and provides preclinical proof that this same biomarker is a powerful new therapeutic target.

Hypoxia Drives Breast Tumor Malignancy through a TET–TNFα–p38–MAPK Signaling Axis

Min-Zu Wu, Su-Feng Chen, Shin Nieh, Christopher Benner, Luo-Ping Ge, Chia-Ing Jan, Li Ma, Chien-Hung Chen, Tomoaki Hishida, Hong-Tai Chang, Yao-Shiang Lin, Nuriya Montserrat, Pedro Gascon, Ignacio Sancho-Martinez, and Juan Carlos Izpisua Belmonte

Precis: These results shed new mechanistic light on how hypoxic tumor microenvironments affect epigenetic programs in cancer cells to drive stem-like character and metastasis, suggesting new ways to eradicate cancer stem-like cells that are nurtured by such microenvironments.
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## 3925

ΔNp63α Promotes Breast Cancer Cell Motility through the Selective Activation of Components of the Epithelial-to-Mesenchymal Transition Program  
Tuyen T. Dang, Matthew A. Esparza, Erin A. Maine, Jill M. Westcott, and Gray W. Pearson  
**Précis:** The transcription factor ΔNp63α can initiate migratory components of EMT while sustaining epithelial character, perhaps explaining the aggressive invasive behavior of certain epithelial-like cancers like basal cell breast cancers.

## 3936

KAT6B Is a Tumor Suppressor Histone H3 Lysine 23 Acetyltransferase Undergoing Genomic Loss in Small Cell Lung Cancer  
Laia Simó-Riudalbas,Montserrat Pérez-Salvia, Fernando Setien, Alberto Villanueva, Catia Mouzinho, Anna Martínez-Caridi, Sebastian Moran, Maria Berdasco, Antonio Gomez, Enrique Vidal, Marta Soler, Holger Heyn, Alejandro Vaquero, Carolina de la Torre, Silvia Barceló-Batllori, August Vidal, Luca Roz, Ugo Pastorino, Katalin Szakszon, Ilse Zondervan, Suvi Savola, Reika Iwakawa, Takashi Kohno, Jun Yokota, and Manel Esteller  
**Précis:** Understanding how genetic defects in histone modifier genes contribute to human cancer can identify common pathogenic processes and new predictive and prognostic markers.

## 3946

Heparanase Enhances Tumor Growth and Chemoresistance by Promoting Autophagy  
Anna Shteingauz, Ilanit Boyango, Inna Naroditsky, Edward Hammond, Maayan Gruber, Ilana Doweck, Neta Ilan, and Israel Vlodavsky  
**Précis:** These findings illuminate the function of an enzyme implicated in tumor inflammation, angiogenesis, and metastasis in modulating autophagy in cells, thereby conferring cell growth advantages under stress and resistance to chemotherapy.

## 3958

Notch1 Activation or Loss Promotes HPV-Induced Oral Tumorigenesis  
Rong Zhong, Riyue Bao, Pieter W. Faber, Vytautas P. Bindokas, John Bechill, Mark W. Lingen, and Michael T. Spiotto  
**Précis:** Strikingly, a functional screen for candidate driver genes in HPV-associated squamous cancers revealed that either gain or loss of Notch1 can promote tumor growth, by distinct pathways, suggesting great caution in the interpretation of putative driver mutations linked to cancer development.

## 3970

Maspin Expression in Prostate Tumor Cells Averts Stemness and Stratifies Drug Sensitivity  
M. Margarida Bernardo, Alexander Kaplun, Sijana H. Dzinic, Xiaohua Li, Jonathan Irish, Adelina Mjugic, Benjamin Jakupovic, Jessica B. Back, Eric Van Buren, Xiang Han, Ivory Dean, Yong Q. Chen, Elisabeth Heath, Wael Saar, and Shijie Sheng  
**Précis:** These results offer evidence that the epithelial-specific molecule maspin limits tumor cell plasticity in the prostate, thereby dictating drug sensitivity and offering a biomarker in experimental screens for curative chemotherapy.

## 3980

A Molecular Portrait of High-Grade Ductal Carcinoma In Situ  
Martin C. Abba, Ting Gong, Yue Lu, Jaeho Lee, Yi Zhong, Ezequiel Lacunza, Matias Butti, Yoko Takata, Sally Gaddis, Jianjun Shen, Marcos R. Estecio, Aysegul A. Sahin, and C. Marcelo Aldaz  
**Précis:** This first comprehensive molecular profile of pre-invasive breast cancers identifies a subgroup of early-stage lesions with aggressive molecular profiles that are indistinguishable from invasive breast cancers, with immediate clinical implications for managing aggressive early-stage lesions at first diagnosis.

## LETTERS TO THE EDITOR

## 3990

G-CSF Is a Cancer Stem Cell–Specific Growth Factor—Letter  
John M. Maris, Jason Healy, Julie Park, Ruth Ladenstein, and Ulrike Potschger

## 3992

G-CSF Is a Cancer Stem Cell–Specific Growth Factor—Response  
Eugene S. Kim, Saurabh Agarwal, and Jason M. Shohet

## CORRECTIONS

## 3993

Correction: Identification of Cyclin D1 and Other Novel Targets for the von Hippel–Lindau Tumor Suppressor Gene by Expression Array Analysis and Investigation of Cyclin D1 Genotype as a Modifier in von Hippel–Lindau Disease

## 3994

Correction: Mutant p53 Enhances Nuclear Factor xB Activation by Tumor Necrosis Factor α in Cancer Cells
Mast cells located in the gut move in areas of mucosal damage during the process of resolution of acute inflammation and repair. Their activity helps the quenching of inflammatory stimuli, as demonstrated by the delayed tissue repair occurring in mast cell-deficient mice. Mucosal healing is restored upon reconstitution of tissues of mast cell-deficient mice with bone marrow-derived mast cells, as indicated by histology showing the recovered crypt architecture characterizing the intestinal mucosa of reconstituted mice. These pieces of information imply a positive role of the mast cell in the resolution of intestinal inflammation and mucosal healing, which eventually becomes detrimental when transformation towards cancer occurs. For details, see article by Rigoni and colleagues on page 3760.