

## BREAKING ADVANCES

- 3685** Highlights from Recent Cancer Literature

## REVIEWS

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

- 3692** NF- $\kappa$ B: Regulation by Methylation  
Tao Lu and George R. Stark

## MEETING REPORT

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

## PRIORITY REPORTS

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

- 3706** Real-time Imaging of the Resection Bed Using a  
Handheld Probe to Reduce Incidence of  
Microscopic Positive Margins in Cancer Surgery  
Sarah J. Erickson-Bhatt, Ryan M. Nolan,  
Nathan D. Shemonski, Steven G. Adie, Jeffrey Putney,  
Donald Darga, Daniel T. McCormick,  
Andrew J. Cittadine, Adam M. Zysk, Marina Marjanovic,  
Eric J. Chaney, Guillermo L. Monroy, Fredrick A. South,  
Kimberly A. Craddock, Z. George Liu, Magesh Sundaram,  
Partha S. Ray, and Stephen A. Boppart  
*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 cleaner surgical margins in a real-time setting that contribute to reduced morbidity and mortality from cancer.

- 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. Socci, and  
Joan Massagué

*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.

- 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,  
Saravana Mohan Dhanasekaran, Nallasivam 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 Arul M. Chinnaiyan

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

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 3728** TANRIC: An Interactive Open Platform to  
Explore the Function of lncRNAs in Cancer

Jun Li, Leng Han, Paul Roebuck, Lixia Diao,  
Lingxiang Liu, Yuan Yuan, John N. Weinstein, and  
Han Liang

*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** Pulsed High-Intensity Focused Ultrasound  
Enhances Delivery of Doxorubicin in a  
Preclinical Model of Pancreatic Cancer

Tong Li, Yak-Nam Wang, Tatiana D. Khokhlova,  
Samantha D'Andrea, Frank Starr, Hong Chen,  
Jeannine S. McCune, Linda J. Risler,  
Afshin Mashadi-Hosseini, and Joo Ha Hwang

*Précis:* An ultrasound-based delivery method that causes tissue cavitation can greatly improve locally targeted delivery of drugs to tumors, such as pancreatic cancer, that have dense stroma and are poorly permeable to small molecule therapies.

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## MICROENVIRONMENT AND IMMUNOLOGY

**3747** Aberrant Expression of MHC Class II in Melanoma Attracts Inflammatory Tumor-Specific CD4<sup>+</sup> T-Cells, Which Dampen CD8<sup>+</sup> T-cell Antitumor Reactivity

Marco Donia, Rikke Andersen, Julie W. Kjeldsen, Paolo Fagone, Shamaila Munir, Ferdinando Nicoletti, Mads Hald Andersen, Per thor Straten, and Inge Marie Svane

*Précis:* These results illustrate a novel immune escape mechanism used in melanoma cells that aberrantly express MHC class II molecules, which by attracting CD4<sup>+</sup> T cells generate a local inflammatory response dominated by TNF, which thereby inhibits cytotoxic CD8<sup>+</sup> T cells.

**3760** Mast Cells Infiltrating Inflamed or Transformed Gut Alternatively Sustain Mucosal Healing or Tumor Growth

Alice Rigoni, Lucia Bongiovanni, Alessia Burocchi, Sabina Sangaletti, Luca Danelli, Carla Guarnotta, Amy Lewis, Aroldo Rizzo, Andrew R. Silver, Claudio Tripodo, and Mario P. Colombo

*Précis:* 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.

**3771** 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 Salem Chouaib

*Précis:* These findings offer a preclinical rationale to investigate the use of miR-210 inhibitory 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, Jurandy M. de Andrade, Gislaïne A. Martins, and João S. Silva

*Précis:* IL17 blockade represents an attractive approach for the control of invasive breast tumors.

**3800** A Threshold Level of Intratumor CD8<sup>+</sup> T-cell PD1 Expression Dictates Therapeutic Response to Anti-PD1

Shin Foong Ngiow, Arabella Young, Nicolas Jacquelot, Takahiro Yamazaki, David Enot, Laurence Zitvogel, and Mark J. Smyth

*Précis:* This study shows how PD1 levels in CD8<sup>+</sup> 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.

**3812** 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

*Précis:* STAT3 inhibitors may improve the therapeutic benefits of anthracyclines through augmenting cancer cell-autonomous type I IFN response.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

**3823** Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway

Adrian von Witzleben, Lukas T. Goertler, Ralf Marienfeld, Holger Barth, André Lechel, Kevin Mellert, Michael Böhm, Marko Kormmann, Regine Mayer-Steinacker, Alexandra von Baer, Markus Schultheiss, Adrienne M. Flanagan, Peter Möller, Silke Brüderlein, and Thomas F.E. Barth

*Précis:* 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, Lingqiang Min, Xuefei Wang, Junjie Zhao, Hua Chen, Jing Qin, Weidong Chen, Zhenbin Shen, Zhaoqing Tang, Qiangjun Gan, Yuanjuan Ruan, Yihong Sun, Xinyu Qin, and Jianxin Gu

*Précis:* 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.

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## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 3842** **Small-Molecule NSC59984 Restores p53 Pathway Signaling and Antitumor Effects against Colorectal Cancer via p73 Activation and Degradation of Mutant p53**  
Shengliang Zhang, Lanlan Zhou, Bo Hong, A. Pieter J. van den Heuvel, Varun V. Prabhu, Noel A. Warfel, Christina Leah B. Kline, David T. Dicker, Levy Kopelovich, and Wafik S. El-Deiry  
*Précis:* The p53 pathway-activating compound reported in this study is highly novel, not only stimulating p73 expression and function but also targeting gain-of-function mutants of p53 that are expressed widely in human cancers, with potentially broad-reaching implications for cancer treatment.
- 3853** **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 Derniame, 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  
*Précis:* 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.
- 3865** **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**  
Bhavatarini Vangamudi, Thomas A. Paul, Parantu K. Shah, Maria Kost-Alimova, Lisa Nottebaum, Xi Shi, Yanai Zhan, Elisabetta Leo, Harshad S. Mahadeshwar, Alexei Protopopov, Andrew Futreal, Trang N. Tieu, Mike Peoples, Timothy P. Heffernan, Joseph R. Marszalek, Carlo Toniatti, Alessia Petrocchi, Dominique Verhelle, Dafydd R. Owen, Giulio Draetta, Philip Jones, Wylie S. Palmer, Shikhar Sharma, and Jannik N. Andersen  
*Précis:* These findings directly inform drug discovery efforts to translate synthetic lethal strategies into effective drugs and useful biomarkers in cancers that are driven by a mutated SWI/SNF transcription factor.

- 3879** **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. Sorrentino, John D. Schuetz, and Martine F. Roussel  
*Précis:* 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.
- 3890** **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  
*Précis:* 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.
- 3902** **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 Galiègue-Zouitina, and Carl Simon Shelley  
*Précis:* 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.

## TUMOR AND STEM CELL BIOLOGY

- 3912** **Hypoxia Drives Breast Tumor Malignancy through a TET-TNF $\alpha$ -p38-MAPK Signaling Axis**  
Min-Zu Wu, Su-Feng Chen, Shin Nieh, Christopher Benner, Luo-Ping Ger, Chia-Ing Jan, Li Ma, Chien-Hung Chen, Tomoaki Hishida, Hong-Tai Chang, Yaoh-Shiang Lin, Nuria Montserrat, Pedro Gascon, Ignacio Sancho-Martinez, and Juan Carlos Izpisua Belmonte  
*Précis:* 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**  $\Delta$ Np63 $\alpha$  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  $\Delta$ Np63 $\alpha$  can initiate pro-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 Moutinho, Anna Martínez-Cardús, Sebastian Moran, Maria Berdasco, Antonio Gomez, Enrique Vidal, Marta Soler, Holger Heyn, Alejandro Vaquero, Carolina de la Torre, Silvia Barceló-Batllo, August Vidal, Luca Roz, Ugo Pastorino, Katalin Szaksszon, Guntram Borck, Conceição S. Moura, Fátima Carneiro, 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 Mujagic, Benjamin Jakupovic, Jessica B. Back, Eric Van Buren, Xiang Han, Ivory Dean, Yong Q. Chen, Elisabeth Heath, Wael Sakr, 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

**3991** G-CSF Is a Cancer Stem Cell-Specific Growth Factor—Letter

John M. Maris, Jason Healy, Julie Park, Ruth Ladenstein, and Ulrike Pötschger

**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  $\kappa$ B Activation by Tumor Necrosis Factor  $\alpha$  in Cancer Cells

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## ABOUT THE COVER

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.



# Cancer Research

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