Highlights from Recent Cancer Literature

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

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

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

Warfarin Blocks Gas6-Mediated Axl Activation Required for Pancreatic Cancer Epithelial Plasticity and Metastasis
Amanda Kirane, Kathleen F. Ludwig, Noah Sorrelle, Gzy Hadlaid, Tone Sandal, Renate Ranasawa, Jason E. Toombs, Miao Wang, Sean P. Dineen, David Micklem, Michael T. Lorens, and Rolf A. Brekken

Prècis: 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.

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, Sean P. Dineen, David Micklem, Michael T. Dellinga, James B. Lorens, and Rolf A. Brekken

Prècis: 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.

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. Soeck, and Joan Massague

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

The Distinctive Mutational Spectra of Polyomavirus-Negative Merkel Cell Carcinoma
Paul William Harms, Pankaj Vats, Monique Elise Verhaegem, Dan R. Robinson, Yi-Mi Wu, Saravana Mohan Dhanasekaran, Nallasivam Palanisamy, Javed Siddiqui, Xuhong Cao, Pengyun Su, Rui Wang, Hong Xiao, Lakshmi P. Kunju, Rohit Mehra, Scott A. Tomlins, Douglas Randall Fallens, Christopher Kerem Bichajkian, Timothy M. Johnson, Andrzej Antoni Dlugoszz, and Arul M. Chinnaiyan

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

TANRIC: An Interactive Open Platform to Explore the Function of lncRNAs in Cancer
Jun Li, Leng Han, Paul Roebuck, Lixia Diao, Junxiang Liu, Yuan Yuan, John N. Weinstein, and Han Liang

Prècis: 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.

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-Hossein, and Joo Hwai Hwang

Prècis: 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.
<table>
<thead>
<tr>
<th>3747</th>
<th>Aberrant Expression of MHC Class II in Melanoma Attracts Inflammatory Tumor-Specific CD4(^+) T-Cells, Which Dampen CD8(^+) T-cell Antitumor Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marco Donia, Rikke Andersen, Julie W. Kjeldsen, Paolo Fagone, Shamaila Mumir, Ferdinand Nicoletti, Mads Hald Andersen, Per Thor Straten, and Inge Marie Svane</td>
<td></td>
</tr>
<tr>
<td>Précis: 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.</td>
<td></td>
</tr>
</tbody>
</table>

| 3760 | Mast Cells Infiltrating Inflamed or Transformed Gut Alternatively Sustain Mucosal Healing or Tumor Growth |
| Alice Rigoni, Lucia Bongiovanni, Alessia Burocchi, Sabina Sangalenti, Luca Danelli, Carla Guarnotta, Amy Lewis, Aroldo Rizzo, Andrew R. Silver, Claudio Tripotodo, 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 |
| Paula Barbim Donate, Daniel Guimarães Tiezzi, Daniel D. De Carvalho, Jurandyr M. de Andrade, Gisalene 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\(^+\) 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 |
| Précis: 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. |

| 3823 | Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway |
| Adrian von Witeleben, Lukas T. Goerttler, Ralf Marienfeld, Holger Barth, André Lechal, Kevin Meller, Michael Böhm, Marko Kornmann, 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, Xuelei Wang, Junjie Zhao, Hua Chen, Jing Qin, Weidong Chen, Zhenbin Shen, Zhaoqing Tang, Qiangjun Gan, Yuanynan 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. |
3842 Small-Molecule NSC59984 Restores p53 Pathway Signaling and Antitumor Effects against Colorectal Cancer via p73 Activation and Degradation of Mutant p53

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 Poiriot, Brian Philip, Cecile Schiffer-Mannioui, Diane Le Clerre, Isabelle Chion-Sotinel, Sophie Demiame, Pierrick Potrel, Célèce Bas, Laetitia Lemaire, Roman Galetto, Céline Lebuhotel, Justin Eyquem, Gordon Weng-Kit Cheung, Agnès Gouble, Sylvain Arnould, Karl Pegg, 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

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. Somerlito, 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 Cytoxicity
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, Gorden Zeng, Bruno Quessuel, Xavier Troussard, Sylvie Caligiure-Zoutina, 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.

3912 Hypoxia Drives Breast Tumor Malignancy through a TET–TNFa–p38–MAPK Signaling Axis
Min-Zu Wu, Su-Feng Chen, Shin Nieh, Christopher Benner, Lu-Ping Ger, Chia-Iing Jan, Li Ma, Chien-Hung Chen, Tstoami Hishida, Hong-Tai Chang, Yaw-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.
**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.

**KAT6B Is a Tumor Suppressor Histone H3 Lysine 23 Acetyltransferase Undergoing Genomic Loss in Small Cell Lung Cancer**

Laia Simó-Riudalbas, Montserrat Perez-Salvia, Fernando Setien, Alberto Villanueva, Catia Mouzinho, Anna Martinez-Cardis, Sebastian Moran, Maria Berdasco, Antonio Gomez, Enrique Vidal, Marta Soler, Holger Heyn, Alejandro Vazquez, Carolina de la Torre, Silvia Barcelo-Batlori, August 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.

**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.

**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.

**Maspin Expression in Prostate Tumor Cells Averts Stemness and Stratifies Drug Sensitivity**

M. Margarida Bernardo, Alexander Kaplun, Sijana H. Dzinic, Xiao Hu Li, Jonathan Irish, Adelina Muga, 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.

**A Molecular Portrait of High-Grade Ductal Carcinoma In Situ**

Martin C. Abba, Ting Gong, Yue Lu, Jaeho Lee, Yi Zhong, Ezequiél 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**

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

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

**G-CSF Is a Cancer Stem Cell–Specific Growth Factor**—Response

Eugene S. Kim, Saurabh Agarwal, and Jason M. Shohet

**CORRECTIONS**

**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

**Correction:** Mutant p53 Enhances Nuclear Factor κB Activation by Tumor Necrosis Factor α in Cancer Cells
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.