**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-κB: 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. Ludtwig, Noah Sorrelle, GzyHaaland, Tone Sandal, Renate Ranasesrera, Jason E. Toombs, Xiaoa Wang, Sean P. Dineen, David Mickle, 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

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, Moni Pirun, Agnes Viale, Nicholas D. Soeci, and Joan Massagué

Précis: 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.

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, Nallasiyam Painelisamy, Javed Siddiqui, Xuhong Cao, Fengyun Su, Rui Wang, Hong Xiao, Lakshmi P. Kunju, Rohit Mehta, Scott A. Tomlins, Douglas Randall Fullen, Christopher Keram Bichakjian, Timothy M. Johnson, Andrzezej 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 IncRNAs in Cancer
Jun Li, Leng Han, Paul Roebuck, Lixia Dao, 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. Khoikhlova, Samantha D’Andrea, Frank Statt, 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**

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<td>Aberrant Expression of MHC Class II in Melanoma Attracts Inflammatory Tumor-Specific CD4+ T-Cells, Which Dampen CD8+ T-cell Antitumor Reactivity</td>
<td>Marco Donia, Rikke Andersen, Julie W. Kjeldsen, Paolo Fagone, Shamaila Munir, Ferdinando Nicoletti, Mads Hald Andersen, Per thor Straten, and Inge Marie Svane</td>
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<td><em>Précis:</em> 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>
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<td>3760</td>
<td>Mast Cells Infiltrating Inflamed or Transformed Gut Alternatively Sustain Mucosal Healing or Tumor Growth</td>
<td>Alice Rigoni, Lucia Bongiovanni, Alessia Barocchi, Sabina Sangaletti, Luca Danelli, Carla Guarnotta, Amy Lewis, Aroldo Rizzo, Andrew R. Silver, Claudio Tripodo, and Mario P. Colombo</td>
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<td><em>Précis:</em> 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.</td>
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<td>3771</td>
<td>Tumor-Promoting Effects of Myeloid-Derived Suppressor Cells Are Potentiated by Hypoxia-Induced Expression of miR-210</td>
<td>Muhammad Zaeem Noman, Bassam Janji, Shijun Hu, Joseph C. Wu, Fabio Martelli, Vincenzo Boente, and Salem Chouaib</td>
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<td><em>Précis:</em> These findings offer a preclinical rationale to investigate the use of miR-210 inhibitors 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.</td>
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<td>IL17 Promotes Mammary Tumor Progression by Changing the Behavior of Tumor Cells and Eliciting Tumorigenic Neutrophils Recruitment</td>
<td>Luciana Benevides, Denise Morais da Fonseca, Paula Barbim Donate, Daniel Guimarães Tiezzi, Daniel D. De Carvalho, Jurandyr M. de Andrade, Gislaine A. Martins, and João S. Silva</td>
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<td><em>Précis:</em> IL17 blockade represents an attractive approach for the control of invasive breast tumors.</td>
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<td>A Threshold Level of Intratumor CD8+ T-cell PD1 Expression Dictates Therapeutic Response to Anti-PD1</td>
<td>Shin Foong Ngio, Arabella Young, Nicolas Jacquelot, Takahiro Yamaoka, David Enot, Laurence Zitvogel, and Mark J. Smyth</td>
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<td><em>Précis:</em> 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.</td>
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<td>3823</td>
<td>Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway</td>
<td>Adam von Wittek, Lucas T. Goertler, Ralf Marienfeld, Holger Barth, André Lechel, Kevin Mellert, Michael Böhm, Marko Kornmann, Regine Mayer-Steinacker, Alexandra von Baer, Markus Schulteis, Adrienne M. Flanagan, Peter Möller, Silke Bruderlein, and Thomas F.E. Barth</td>
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<td><em>Précis:</em> 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.</td>
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<td>Loss of RACK1 Promotes Metastasis of Gastric Cancer by Inducing a miR-302c/IL8 Signaling Loop</td>
<td>Ling Chen, Lingsheng Min, Xuemei Wang, Junjie Zhao, Hua Chen, Jing Qin, Weidong Chen, Zhenbin Shen, Zhaosong Tang, Qiangjun Gan, Yuanyan Ruan, Yihong Sun, Xinyu Qin, and Jianxin Gu</td>
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<td><em>Précis:</em> 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.</td>
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**TUMOR AND STEM CELL BIOLOGY**

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<td>CD38 in Hairy Cell Leukemia Is a Marker of Poor Prognosis and a New Target for Therapy</td>
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- 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
- ABCG2 Transporter Expression Impacts Group 3 Medulloblastoma Response to Chemotherapy
- miR-634 Activates the Mitochondrial Apoptosis Pathway and Enhances Chemotherapy-Induced Cytotoxicity
- Hypoxia Drives Breast Tumor Malignancy through a TET–TNFα–p38–MAPK Signaling Axis
DNp63a 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 DNp63a 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.

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 Setién,Alberto Villanueva,Catia Mouzinho,Anna Martínez-Cárdis,Sebastián Moran,Maria Berdasco,Antonio Gomez,Enrique Vidal,Marta Soler,Holger Heyn,Alejandro Vaquerod,Carolina de la Torre, Silvia Barceló-Batlori, August Vidal, Luca Rox, Ugol Pastorino,Katalin Szakaszn, Guntram Bocek, Conceição S. Moura,Fátima Carneiro, Ilse Zondervan,Suvi Savola,Reika Iwakawa,Takashi Kohno,Yoko Takata,Sally Gaddis,Jianjun Shen,Marcos R. Estecio,Aysegül A. Sahin, and C. Marcelo Aldaz

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


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, Ezequiel Lacunza, Matias Butti, Yoko Takata, Sally Gaddis, Jianjun Shen, Marcos R. Estecio, Aysegül 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.

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

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

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

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

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

LETTERS TO THE EDITOR

CORRECTIONS

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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.