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. Ludwig, Noah Sorrelle, Gzy Haaland, Tone Sandal, Renate Randeverra, Jason E. Toombs, Xiao Wang, Sean P. Dineen, David Micklem, Michael T. Dellen, 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

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

3738 Pulsed High-Intensity Focused Ultrasound Enhances Delivery of Doxorubicin in a Preclinical Model of Pancreatic Cancer
Tong Li, Ya-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

Précis: Next-generation sequencing analysis suggests two molecularly distinct etiologies for MCC, characterized by either viral-dependent or UV-dependent tumorigenic pathways.
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, Shamaila Munir, Ferdinando Nicoletti, Mads Hald Andersen, Per thor Straten, and Ingé 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+ T cells generate a local inflammatory response dominated by TNF, which thereby inhibits cytotoxic CD8+ 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 Paolo Fagone
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 Recruitmen
Luciana Benevides, Denise Morais da Fonseca, Paula BarbimDonate, Daniel Guimarães Tiezzi, Daniel D. De Carvalho, Jurandyr M. de Andrade, Gislaíme A. Martins, and João S. Silva
Précis: IL17 blockade represents an attractive approach for the control of invasive breast tumors.

MOLECULAR AND CELLULAR PATHOBIOLOGY

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.

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 1 IFN response.

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. Goerttler, Ralf Marienfeld, Holger Barth, André Lechel, 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, Lingshiang Min, Xuelei Wang, Junjie Zhao, Hua Chen, Jing Qin, Weidong Chen, Zhenbin Shen, Zhaoqiang Tang, Qiangjun Gan, Yuanynan Ruan, Yihong Sun, Xinyu Qin, and Jiuxin 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.
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

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 Demiame, Pierrick Potrel, Cécile Bas, Laetitia Lemaire, Roman Galetto, Cécile Bas, Céline Lebuhotel, Justin Eyquem, Gordon Weng-Kit Cheung, Ayméric Ducler, Agnès Gouble, Sylvain Arnauld, 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
Bhavatiranvi Vangamudi, Thomas A. Paul, Parantu K. Shah, Maria Kost-Alimova, Lisa Nottebaum, Xi Shi, Yanan Zhan, Elisabetta Leo, Harshad S. Mahadeshwar, Alexei Protopopov, Andrew Futral, Trang N. Tieu, Mike Peoples, Timothy P. Heffernan, Joseph R. Marszalek, Carlo Toniatti, Alessia Petrocchi, Dominique Verhelle, Dafydd R. Owen, Sylvain Arnould, Karl Peggs, Martin Pule, Andrew M. Scharenberg, and Julianne Smith

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 Kawachi, Anang A. Shelat, Clinton F. Stewart, Brian P. Sorrentino, John D. Schuetz, and Martine F. Rousel

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, Kouyou Tanimoto, Ken-ichi Kozaki, and Jouji 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 Quearnel, Xavier Troussard, Sylvie Galiligue-Zoutitina, 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–TNFα–p38–MAPK Signaling Axis
Min-Zu Wu, Su-Feng Chen, Shin Nieh, Christopher Benner, Jiao-Ping Ge, Chia-Iing Jan, Li Ma, Chien-Hung Chen, Tomoaki Hishida, Hong-Tai Chang, Yauh-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 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 Setien, Alberto Villanueva, Catia Mouzinho, Anna Martinez-Caridad, Sebastian Moran, Maria Berdasco, Antonio Gomez, Enrique Vidal, Marta Soler, Holger Heyn, Alejandro Vassallo, Carolina de la Torre, Silvia Barceló-Batllori, August Vidal, Luca Roz, Ugo Pastorino, Katalin Szakszon, Guntram Boock, Conceição S. Moura, 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.

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.

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

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

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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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