

Contents

Cancer Research

June 1, 2012 • Volume 72 • Number 11

BREAKING ADVANCES

- 2693 | **Highlights from Recent Cancer Literature**

REVIEWS

- 2695 | **Genetically Engineered Mouse Models: Closing the Gap between Preclinical Data and Trial Outcomes**
Mallika Singh, Christopher L. Murriel, and Leisa Johnson
- 2701 | **The Changing View of High-Grade Serous Ovarian Cancer**
Els M.J.J. Berns and David D. Bowtell

PRIORITY REPORTS

- 2705 | **Estrogen Promotes ER-Negative Tumor Growth and Angiogenesis through Mobilization of Bone Marrow-Derived Monocytes**
Vandana Iyer, Ina Klebba, Jessica McCreedy, Lisa M. Arendt, Monica Betancur-Boissel, Meng-Fen Wu, Xiaomei Zhang, Michael T. Lewis, and Charlotte Kuperwasser
Précis: Estrogen recruits a proangiogenic myeloid cell population from the bone marrow that drives cancer development, with implications for the development and use of antiestrogen therapies to treat ER-negative cancers in premenopausal women.
- 2714 | **Smurf2 Regulates the Senescence Response and Suppresses Tumorigenesis in Mice**
Charusheila Ramkumar, Yahui Kong, Hang Cui, Suyang Hao, Stephen N. Jones, Rachel M. Gerstein, and Hong Zhang
Précis: This study offers a genetic proof in mice for a tumor suppressor role of an E3 ubiquitin ligase that regulates the expression of p16 and its pivotal function in cell senescence, extending understanding of this universal pathway of tumor suppression.

CLINICAL STUDIES

- 2720 | **Nanocytology of Rectal Colonocytes to Assess Risk of Colon Cancer Based on Field Cancerization**
Dhwanil Damania, Hemant K. Roy, Hariharan Subramanian, David S. Weinberg, Douglas K. Rex, Michael J. Goldberg, Joseph Muldoon, Lusik Cherkazy, Yuanjia Zhu, Laura K. Bianchi, Dhiren Shah, Prabhakar Pradhan, Monica Borkar, Henry Lynch, and Vadim Backman
Précis: A novel noninvasive imaging method may offer a sensitive prescreening option to consider before colonoscopy, an expensive but effective technique to prevent colon cancer, perhaps leading to a more cost-effective strategy for risk stratification.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2728 | **Identification of an Epigenetic Profile Classifier That Is Associated with Survival in Head and Neck Cancer**
Graham M. Poage, Rondi A. Butler, E. Andrés Houseman, Michael D. McClean, Heather H. Nelson, Brock C. Christensen, Carmen J. Marsit, and Karl T. Kelsey
Précis: A novel approach that integrates genetic and epigenetic information reveals prognostic biomarkers for head and neck cancer that are independent of HPV status, thus enabling clinical stratification of patient subpopulations and suggesting new candidates for targeted therapies.
- 2738 | **In Vivo Diagnosis of Melanoma and Nonmelanoma Skin Cancer Using Oblique Incidence Diffuse Reflectance Spectrometry**
Alejandro Garcia-Urbe, Jun Zou, Madeleine Duvic, Jeong Hee Cho-Vega, Victor G. Prieto, and Lihong V. Wang
Précis: This study reports a novel in vivo imaging method that can quickly and accurately diagnose malignant melanomas and skin carcinomas from benign pigmented skin lesions in the clinical setting, helping reduce the number of invasive, expensive, and tedious biopsies needed from patients with suspected skin cancers.

MICROENVIRONMENT AND IMMUNOLOGY

2746 **Modulation of Microenvironment Acidity Reverses Anergy in Human and Murine Tumor-Infiltrating T Lymphocytes**

Arianna Calcinotto, Paola Filipazzi, Matteo Grioni, Manuela Iero, Angelo De Milito, Alessia Ricupito, Agata Cova, Rossella Canese, Elena Jachetti, Monica Rossetti, Veronica Huber, Giorgio Parmiani, Luca Generoso, Mario Santinami, Martina Borghi, Stefano Fais, Matteo Bellone, and Licia Rivoltini

Précis: Important findings show how acidification in the tumor microenvironment promotes immune escape by blunting T-cell immunity, and suggest how PPIs used clinically to treat gastric acid reflux might be applied immediately as low-risk adjuvants to improve the efficacy of any immunotherapy or immunochemotherapy regimen.

2757 **Cancer-Induced Immunosuppression: IL-18–Elicited Immunoablative NK Cells**

Magali Terme, Evelyn Ullrich, Laetitia Aymeric, Kathrin Meinhardt, Jérôme D. Coudert, Mélanie Desbois, François Ghiringhelli, Sophie Viaud, Bernard Ryffel, Hideo Yagita, Lieping Chen, Salaheddine Mécheri, Gilles Kaplanski, Armelle Prévost-Blondel, Masashi Kato, Joachim L. Schultze, Eric Tartour, Guido Kroemer, Mariapia Degli-Esposti, Nathalie Chaput, and Laurence Zitvogel

Précis: This study reveals that the proinflammatory cytokine IL-18 produced by tumors can induce expansion of a population of natural killer cells with immunosuppressive properties, revealing an important new mechanism of immune escape.

2768 **CCL2 Mediates Cross-talk between Cancer Cells and Stromal Fibroblasts That Regulates Breast Cancer Stem Cells**

Akihiro Tsuyada, Amy Chow, Jun Wu, George Somlo, Peiguo Chu, Sofia Loera, Thehang Luu, Arthur Xuejun Li, Xiwei Wu, Wei Ye, Shuan Chen, Weiyang Zhou, Yang Yu, Yuan-Zhong Wang, Xiubao Ren, Hui Li, Peggy Scherle, Yukio Kuroki, and Shizhen Emily Wang

Précis: Cancer stem cell regulation by the microenvironment is shown to be mediated by the chemokine CCL2, also known as MIP-1 α , which offers a therapeutic target to block CSC-mediated disease progression.

2780 **High Expression of IL-13 Receptor α 2 in Colorectal Cancer Is Associated with Invasion, Liver Metastasis, and Poor Prognosis**

Rodrigo Barderas, Rubén A. Bartolomé, María Jesús Fernandez-Aceñero, Sofia Torres, and J. Ignacio Casal

Précis: Signaling through a cytokine decoy receptor is found to play a critical role in the adhesion, invasion, and colonization of highly metastatic colorectal cancer cells, with potential implications for their therapeutic management.

2791 **Inhibiting Systemic Autophagy during Interleukin 2 Immunotherapy Promotes Long-term Tumor Regression**

Xiaoyan Liang, Michael E. De Vera, William J. Buchser, Antonio Romo de Vivar Chavez, Patricia Loughran, Donna Beer Stolz, Per Basse, Tao Wang, Bennett Van Houten, Herbert J. Zeh III, and Michael T. Lotze

Précis: The preclinical study shows how the inexpensive autophagy inhibitor chloroquine might be repositioned to greatly enhance the antitumor effects of IL-2, a central growth and survival factor for T cells used for melanoma treatment, while limiting the toxicity that has restricted its broad use in clinic.

MOLECULAR AND CELLULAR PATHOBIOLOGY

2802 **Human Nuclease/Helicase DNA2 Alleviates Replication Stress by Promoting DNA End Resection**

Guang Peng, Hui Dai, Wei Zhang, Hui-Ju Hsieh, Mei-Ren Pan, Yun-Yong Park, Robert Yu-Lin Tsai, Isabelle Bedrosian, Ju-Seog Lee, Grzegorz Ira, and Shiaw-Yih Lin

Précis: This study provides insights into the function of a nuclease and helicase protein that is overexpressed in a variety of human cancers, with implications of its definition as a possible generalized therapeutic target in prevention and therapy.

2814 **Mre11-Dependent Degradation of Stalled DNA Replication Forks Is Prevented by BRCA2 and PARP1**

Songmin Ying, Freddie C. Hamdy, and Thomas Helleday

Précis: Findings provide mechanistic insight into the interaction between BRCA2 and PARP1 at stalled replication forks, revealing why these genes exhibit synthetic lethality in cancer cells.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2822 **A Novel Tankyrase Inhibitor Decreases Canonical Wnt Signaling in Colon Carcinoma Cells and Reduces Tumor Growth in Conditional APC Mutant Mice**

Jo Waaler, Ondrej Machon, Lucie Tumova, Huyen Dinh, Vladimir Korinek, Steven Ray Wilson, Jan Erik Paulsen, Nina Marie Pedersen, Tor J. Eide, Olga Machonova, Dietmar Gradl, Andrey Voronkov, Jens Peter von Kries, and Stefan Krauss

Précis: This preclinical proof-of-concept study suggests a new strategy to treat colon cancer by increasing the degradation of β -catenin, which drives this disease.

TUMOR AND STEM CELL BIOLOGY

2833 **Suppression of Tak1 Promotes Prostate Tumorigenesis**

Min Wu, Lihong Shi, Adela Cimic, Lina Romero, Guangchao Sui, Cynthia J. Lees, J. Mark Cline, Darren F. Seals, Joseph S. Sirintrapun, Thomas P. McCoy, Wennuan Liu, Jin Woo Kim, Gregory A. Hawkins, Donna M. Peehl, Jianfeng Xu, and Scott D. Cramer

Précis: This study interrogates the tumor suppressor function of Tak1 in a novel stem cell model of prostate cancer, establishing that its loss causes increased growth, invasion, and tumorigenesis.

2844 **HSP DNAJB8 Controls Tumor-Initiating Ability in Renal Cancer Stem-like Cells**

Satoshi Nishizawa, Yoshihiko Hirohashi, Toshihiko Torigoe, Akari Takahashi, Yasuaki Tamura, Takashi Mori, Takayuki Kanaseki, Kenjiro Kamiguchi, Hiroko Asanuma, Rena Morita, Alice Sokolovskaya, Junichi Matsuzaki, Ren Yamada, Reona Fujii, Harm H. Kampinga, Toru Kondo, Tadashi Hasegawa, Isao Hara, and Noriyuki Sato

Précis: Immunological targeting of a heat shock protein that maintains cancer stem-like cells in tumors might offer a novel immunotherapeutic approach to destroy a core wellspring of tumor growth.

2855 **Loss of the Ceramide Transfer Protein Augments EGF Receptor Signaling in Breast Cancer**

Johanna Heering, Nicole Weis, Monika Holeiter, Felix Neugart, Annette Staebler, Tanja N. Fehm, Annabell Bischoff, Jürgen Schiller, Stephan Duss, Simone Schmid, Thomas Korte, Andreas Herrmann, and Monilola A. Olayioye

Précis: Findings define a novel link between sphingomyelin homeostasis at the Golgi complex and growth factor receptor signaling at the plasma membrane, suggesting novel therapies to treat aggressive triple-negative breast cancers.

2867 **MIF Produced by Bone Marrow-Derived Macrophages Contributes to Teratoma Progression after Embryonic Stem Cell Transplantation**

Xi Wang, Tianxiang Chen, Lin Leng, Jianqing Fan, Kai Cao, Zhaoxia Duan, Xijing Zhang, Changshun Shao, Mingmei Wu, Iman Tadmori, Tianyi Li, Li Liang, Dongming Sun, Shusen Zheng, Andreas Meinhardt, Wise Young, Richard Bucala, and Yi Ren

Précis: Infiltrating bone marrow-derived macrophages form niche microenvironments that may be a crucial driving force in the initiation and progression of teratomas after stem cell transplantation.

2879 **RANK Induces Epithelial-Mesenchymal Transition and Stemness in Human Mammary Epithelial Cells and Promotes Tumorigenesis and Metastasis**

Marta Palafox, Irene Ferrer, Pasquale Pellegrini, Sergi Vila, Sara Hernandez-Ortega, Ander Urruticoechea, Fina Climent, Maria Teresa Soler, Purificación Muñoz, Francesc Viñals, Mark Tometsko, Dan Branstetter, William C. Dougall, and Eva González-Suárez

Précis: Findings provide insight into the role played by the RANK pathway in the development of breast cancer stem cells and epithelial-mesenchymal transition, and establish an association between its high expression and poor prognosis in breast cancer.

2889

ESE3/EHF Controls Epithelial Cell Differentiation and Its Loss Leads to Prostate Tumors with Mesenchymal and Stem-like Features

Domenico Albino, Nicole Longoni, Laura Curti, Maurizia Mello-Grand, Sandra Pinton, Gianluca Civenni, George Thalmann, Gioacchino D'Ambrosio, Manuela Sarti, Fausto Sessa, Giovanna Chiorino, Carlo V. Catapano, and Giuseppina M. Carbone

Précis: An ETS transcription factor is shown to regulate the balance between differentiation and self-renewal of prostate epithelial cells, and therefore plays a key role in the pathogenesis of a subset of low-expressing prostate tumors.

2901

The RASSF3 Candidate Tumor Suppressor Induces Apoptosis and G₁-S Cell-Cycle Arrest via p53

Takumi Kudo, Mitsunobu Ikeda, Misa Nishikawa, Zeyu Yang, Kikuo Ohno, Kentaro Nakagawa, and Yutaka Hata

Précis: Findings define the mechanisms through which a tumor suppressor with potentially broad impact in many human cancers appear to act.

LETTERS TO THE EDITOR

2912

Targeting Taspase1 for Cancer Therapy—Letter

Roland H. Stauber, Carolin Bier, and Shirley K. Knauer

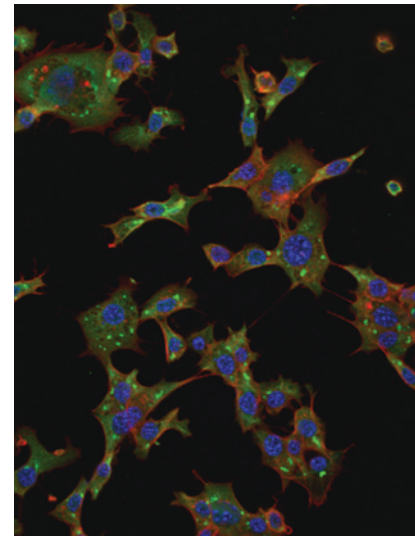
2913

Targeting Taspase1 for Cancer Therapy—Response

David Y. Chen, Shugaku Takeda, Toshinao Oyama, and James J. Hsieh

ABOUT THE COVER

Inhibiting autophagy during interleukin-2 immunotherapy. Autophagic flux and diminished apoptosis are noted in established tumor cell lines, conferring resistance to chemotherapy, radiation therapy, and immunotherapy with interleukin 2. Chloroquine administration *in vivo* or, as shown here, *in vitro* can inhibit this process by preventing fusion of the autophagosome with the lysosome, allowing accumulation in the cytosol. Murine MC38 colorectal adenocarcinoma tumor cells were cultured and treated with 200 μ M chloroquine for four hours. Immunofluorescence staining was done for LC3-II (green), actin (phalloidin; red) and nuclei (DAPI; blue). Chloroquine increased LC3-II puncta in both the MC38 tumor as well as the murine pancreatic adenocarcinoma Panc02 cells (not shown). For details, see article by Liang and colleagues on page 2791.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

72 (11)

Cancer Res 2012;72:2693-2913.

Updated version Access the most recent version of this article at:
<http://cancerres.aacrjournals.org/content/72/11>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/72/11>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.