

Contents

Cancer Research

March 15, 2013 • Volume 73 • Number 6

BREAKING ADVANCES

- 1647 | **Highlights from Recent Cancer Literature**

REVIEW

- 1649 | **Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy**
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

MEETING REPORT

- 1658 | **Ion Channels and Transporters in Cancer: Pathophysiology, Regulation, and Clinical Potential**
Stine F. Pedersen and Christian Stock

PRIORITY REPORTS

- 1662 | **G-protein Inactivator RGS6 Mediates Myocardial Cell Apoptosis and Cardiomyopathy Caused By Doxorubicin**
Jianqi Yang, Biswanath Maity, Jie Huang, Zhan Gao, Adele Stewart, Robert M. Weiss, Mark E. Anderson, and Rory A. Fisher
Précis: This important study suggests a rational approach to limiting the well-known cardiotoxic effects of doxorubicin (adriamycin), one of the most effective and widely used cytotoxic chemotherapy drugs for cancer treatment.
- 1668 | **Trp53 Inactivation in the Tumor Microenvironment Promotes Tumor Progression by Expanding the Immunosuppressive Lymphoid-like Stromal Network**
Gang Guo, Luis Marrero, Paulo Rodriguez, Luis Del Valle, Augusto Ochoa, and Yan Cui
Précis: Findings reveal a previously unappreciated function for p53 in maintaining an immunological microenvironment that can suppress tumorigenesis and progression.

CLINICAL STUDIES

- 1676 | **Phase I Trial of Recombinant Modified Vaccinia Ankara Encoding Epstein-Barr Viral Tumor Antigens in Nasopharyngeal Carcinoma Patients**
Edwin P. Hui, Graham S. Taylor, Hui Jia, Brigitte B.Y. Ma, Stephen L. Chan, Rosalie Ho, Wai-Lap Wong, Steven Wilson, Benjamin F. Johnson, Ceri Edwards, Deborah D. Stocken, Alan B. Rickinson, Neil M. Steven, and Anthony T.C. Chan
Précis: Vaccination of nasopharyngeal carcinoma patients targeting two pathogenic viral antigens produces potent immune responses after they have completed chemo/radiotherapy.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 1689 | **Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model**
Sunitha V. Bachawal, Kristin C. Jensen, Amelie M. Lutz, Sanjiv S. Gambhir, Francois Tranquart, Lu Tian, and Jürgen K. Willmann
Précis: This study lays the foundation for the development of a novel ultrasound-based imaging approach for earlier detection of breast cancer and paves the way for translational clinical trials in the future.
- 1699 | **Collections of Simultaneously Altered Genes as Biomarkers of Cancer Cell Drug Response**
David L. Masica and Rachel Karchin
Précis: New methods are offered to improve the identification of drug response biomarkers in cancer cells.

MICROENVIRONMENT AND IMMUNOLOGY

- 1709 | **Therapeutic Efficacy of Bifunctional siRNA Combining TGF- β 1 Silencing with RIG-I Activation in Pancreatic Cancer**
Jonathan Ellermeier, Jiwu Wei, Peter DUEWELL, Sabine Hoves, Mareike R. Stieg, Tina Adunka, Daniel Noerenberg, Hans-Joachim Anders, Doris Mayr, Hendrik Poeck, Gunther Hartmann, Stefan Endres, and Max Schnurr
Précis: The potency of a therapeutic siRNA can be increased by a parallel strategy to combinatorially activate an RNA helicase that triggers inflammatory responses to double-stranded viral RNA, with implications for understanding how to reprogram the tumor microenvironment to destroy tumor cells.

1721 **LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis**

Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melisa W-Y. Ho, Georgina Lang, and Janine T. Erler

Précis: The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.

1733 **Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma**

Sofia Lyford-Pike, Shiwen Peng, Geoffrey D. Young, Janis M. Taube, William H. Westra, Belinda Akpeng, Tullia C. Bruno, Jeremy D. Richmon, Hao Wang, Justin A. Bishop, Lieping Chen, Charles G. Drake, Suzanne L. Topalian, Drew M. Pardoll, and Sara I. Pai

Précis: HPV-associated oropharyngeal cancers, which are increasing in incidence in the developed world, evade immune surveillance through an escape pathway that is actively being targeted in clinical trials.

1742 **IFN- γ -Mediated Downregulation of LXA4 Is Necessary for the Maintenance of Nonresolving Inflammation and Papilloma Persistence**

Chunhui Wang, Mingjie Xiao, Xiaoman Liu, Chen Ni, Jianhong Liu, Ulrike Erben, and Zhihai Qin

Précis: By helping resolve an inflammatory response, IFN γ blockade can promote tumor regression by reprogramming the inflammatory microenvironment.

1752 **Myeloid-Specific Expression of Ron Receptor Kinase Promotes Prostate Tumor Growth**

Devikala Gurusamy, Jerilyn K. Gray, Peterson Pathrose, Rishikesh M. Kulkarni, Fred D. Finkleman, and Susan E. Waltz

Précis: This study suggests a new strategy to treat prostate tumors, by blocking a tyrosine kinase that supports tumor-associated macrophages that drive immune escape.

1764 **HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients**

Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Mørch Frøsig, Stine Kiaer Larsen, Tobias Wrenfeldt Klausen, Inge Marie Svane, and Mads Hald Andersen

Précis: PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immunotherapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.

1777 **A Chimeric Receptor with NKG2D Specificity Enhances Natural Killer Cell Activation and Killing of Tumor Cells**

Yu-Hsiang Chang, John Connolly, Noriko Shimasaki, Kousaku Mimura, Koji Kono, and Dario Campana

Précis: Findings illustrate how to increase the antitumor efficacy of NK cell therapy, a strategy that may be used to fight nearly any kind of human cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

1787 **Transcription Factor YY1 Contributes to Tumor Growth by Stabilizing Hypoxia Factor HIF-1 α in a p53-Independent Manner**

Shourong Wu, Vivi Kasim, Mitsunobu R. Kano, Sayaka Tanaka, Shinsuke Ohba, Yutaka Miura, Kanjiro Miyata, Xueying Liu, Ako Matsuhashi, Ung-il Chung, Li Yang, Kazunori Kataoka, Nobuhiro Nishiyama, and Makoto Miyagishi

Précis: Findings suggest a mechanistic strategy to block a core hypoxia-driven progression pathway regardless of p53 status.

1800 **Arkadia Regulates Tumor Metastasis by Modulation of the TGF- β Pathway**

Marco A. Briones-Orta, Laurence Levy, Chris D. Madsen, Debipriya Das, Yigit Erker, Erik Sahai, and Caroline S. Hill

Précis: An E3 ubiquitin ligase in the TGF- β signaling pathway is not required to regulate tumor growth but to colonize metastasis sites, suggesting novel antimetastatic strategies.

1811 **Phosphorylation of Ribosomal Protein S6 Attenuates DNA Damage and Tumor Suppression during Development of Pancreatic Cancer**

Abed Khalaileh, Avigail Dreazen, Areej Khatib, Roy Apel, Avital Swisa, Norma Kidess-Bassir, Anirban Maitra, Oded Meyuhas, Yuval Dor, and Gideon Zamir

Précis: Findings reveal that a key mTOR effector molecule is crucial for initiation of K-Ras-induced pancreatic cancers, illuminating the centrality of this mTOR pathway to evade p53-mediated tumor suppression in this setting.

1821

Dormant Cancer Cells Contribute to Residual Disease in a Model of Reversible Pancreatic Cancer

Wan-chi Lin, Nirakar Rajbhandari, Chengbao Liu, Kazuhito Sakamoto, Qian Zhang, Aleata A. Triplett, Surinder K. Batra, Rene Opavsky, Dean W. Felsner, Dominick J. DiMaio, Michael A. Hollingsworth, John P. Morris 4th, Matthias Hebrok, Agnieszka K. Witkiewicz, Jonathan R. Brody, Hallgeir Rui, and Kay-Uwe Wagner

Précis: A novel mouse model reveals essential roles for deregulated c-Myc in the initiation, progression, maintenance, and recurrence of pancreatic ductal adenocarcinoma.

1831

Proliferation-Independent Control of Tumor Glycolysis by PDGFR-Mediated AKT Activation

Cong Ran, Huan Liu, Yasuyuki Hitoshi, and Mark A. Israel

Précis: Findings argue that tyrosine kinase growth factor signaling directly affects glucose metabolism in glioma and is not a secondary response to enhanced proliferation, as suggested in other cancer models.

1844

Telomere Length and Telomerase Activity Impact the UV Sensitivity Syndrome Xeroderma Pigmentosum C

Gerdine J. Stout and Maria A. Blasco

Précis: Findings reveal a role for the DNA repair protein XPC in telomere stability and how activation occurs for the ALT pathway of telomere maintenance, a broadly important aspect of tumor formation.

1855

xCT Inhibition Depletes CD44v-Expressing Tumor Cells That Are Resistant to EGFR-Targeted Therapy in Head and Neck Squamous Cell Carcinoma

Momoko Yoshikawa, Kenji Tsuchihashi, Takatsugu Ishimoto, Toshifumi Yae, Takeshi Motohara, Eiji Sugihara, Nobuyuki Onishi, Takashi Masuko, Kunio Yoshizawa, Shuichi Kawashiri, Makio Mukai, Seiji Asoda, Hiromasa Kawana, Taneaki Nakagawa, Hideyuki Saya, and Osamu Nagano

Précis: Cells that express variant isoforms of the stem cell-determining factor CD44 rely on the activity of a cystine transporter subunit that affects redox status and EGFR function.

PREVENTION AND EPIDEMIOLOGY

1867

MicroRNA-Related Genetic Variants Associated with Clinical Outcomes in Early-Stage Non-Small Cell Lung Cancer Patients

Xia Pu, Jack A. Roth, Michelle A.T. Hildebrandt, Yuanqing Ye, Hua Wei, John D. Minna, Scott M. Lippman, and Xifeng Wu

Précis: This large study of non-small cell lung cancer suggests that miRNA-related polymorphisms can predict clinical outcomes at a level that may be superior to other markers developed previously.

1876

Genetic Variation in Transforming Growth Factor Beta 1 and Mammographic Density in Singapore Chinese Women

Eunjung Lee, David Van den Berg, Chris Hsu, Giske Ursin, Woon-Puay Koh, Jian-Min Yuan, Daniel O. Stram, Mimi C. Yu, and Anna H. Wu

Précis: Host genetic polymorphisms in a key growth factor in breast cancer may help identify women at an increased risk of breast cancer.

1883

Identification of Inherited Genetic Variations Influencing Prognosis in Early-Onset Breast Cancer

Sajjad Rafiq, William Tapper, Andrew Collins, Sofia Khan, Ioannis Politopoulos, Sue Gerty, Carl Blomqvist, Fergus J. Couch, Heli Nevanlinna, Jianjun Liu, and Diana Eccles

Précis: This study maps host genetic variations that affect risks of poor prognosis in early onset breast cancer patients, with implications for how aggressive treatments should be used to improve survival outcomes.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

1892

Focused Ultrasound Delivers Targeted Immune Cells to Metastatic Brain Tumors

Ryan Alkins, Alison Burgess, Milan Ganguly, Giulio Francia, Robert Kerbel, Winfried S. Wels, and Kullervo Hynynen

Précis: Noninvasive MRI-guided focused ultrasound allows targeted natural killer cells to circumvent the blood-brain barrier and treat HER2-amplified breast metastasis in the brain.

1900

Caveolin-1-LRP6 Signaling Module Stimulates Aerobic Glycolysis in Prostate Cancer

Salahaldin A. Tahir, Guang Yang, Alexei Goltsov, Ki-Duk Song, Chengzhen Ren, Jianxiang Wang, Wenjun Chang, and Timothy C. Thompson

Précis: This study offers mechanistic insights into how aerobic glycolysis is increased in prostate cancer, possibly revealing critical targets for effective antimetabolic therapy in this setting.

1912 **Mixed Lineage Kinase MLK4 Is Activated in Colorectal Cancers Where It Synergistically Cooperates with Activated RAS Signaling in Driving Tumorigenesis**

Miriam Martini, Mariangela Russo, Simona Lamba, Elisa Vitiello, Emily Hannah Crowley, Francesco Sassi, Davide Romanelli, Milo Frattini, Antonio Marchetti, and Alberto Bardelli

Précis: Findings support the development of small molecule inhibitors of the kinase MLK4 to treat the significant number of KRAS-mutant colorectal cancers that arise in humans.

1922 **A Novel Inhibitor of STAT3 Homodimerization Selectively Suppresses STAT3 Activity and Malignant Transformation**

Xiaolei Zhang, Ying Sun, Roberta Pireddu, Hua Yang, Murali K. Urlam, Harshani R. Lawrence, Wayne C. Guida, Nicholas J. Lawrence, and Saïd M. Sebti

Précis: STAT3 provides critical support in cancer cells and the immune microenvironment in tumors, but bioactive small molecule inhibitors that offer tractable qualities for clinical translation have been elusive.

1934 **Alkaline Phosphatase ALPPL-2 Is a Novel Pancreatic Carcinoma-Associated Protein**

Pooja Dua, Hye Suk Kang, Seung-Mo Hong, Ming-Sound Tsao, Soyoun Kim, and Dong-ki Lee

Précis: An aptamer selection strategy identifies an enzyme that may be useful for blood-based detection of pancreatic cancer.

1946 **mTOR Complex 2 Is Involved in Regulation of Cbl-Dependent c-FLIP Degradation and Sensitivity of TRAIL-Induced Apoptosis**

Liquan Zhao, Ping Yue, Fadlo R. Khuri, and Shi-Yong Sun

Précis: Findings show how mTORC2 stabilizes the FLIP apoptotic regulators, thereby connecting mTORC2 signaling to death receptor-mediated apoptosis.

1958 **Phenotypic Profiling of DPYD Variations Relevant to 5-Fluorouracil Sensitivity Using Real-time Cellular Analysis and In Vitro Measurement of Enzyme Activity**

Steven M. Offer, Natalie J. Wegner, Croix Fossum, Kangsheng Wang, and Robert B. Diasio

Précis: An understanding of the contribution of DPYD alleles to 5-FU toxicity will facilitate the generation of clinically relevant predictive tests and promote the individualization of treatment based on genotype.

1969 **Involvement of Lyn and the Atypical Kinase Sgk269/PEAK1 in a Basal Breast Cancer Signaling Pathway**

David R. Croucher, Falko Hochgräfe, Luxi Zhang, Ling Liu, Ruth J. Lyons, Danny Rickwood, Carole M. Tactacan, Brigid C. Browne, Naveid Ali, Howard Chan, Robert Shearer, David Gallego-Ortega, Darren N. Saunders, Alexander Swarbrick, and Roger J. Daly

Précis: This study addresses a rationale to target basal breast cancers, also known as triple negative breast cancers, which present a major clinical challenge due to their aggressive nature and lack of targeted treatments.

1981 **FOXC2 Expression Links Epithelial-Mesenchymal Transition and Stem Cell Properties in Breast Cancer**

Brett G. Hollier, Agata A. Timmiello, Steven J. Werden, Kurt W. Evans, Joseph H. Taube, Tapasree Roy Sarkar, Nathalie Sphyris, Maryam Shariati, Sreedevi V. Kumar, Venkata L. Battula, Jason I. Herschkowitz, Rudy Guerra, Jeffrey T. Chang, Naoyuki Miura, Jeffrey M. Rosen, and Sendurai A. Mani

Précis: Findings of this study suggest a rational new target for anti-EMT therapy of cancer stem cells, perhaps relevant to many types of malignancy.

1993 **Characterization of a Novel PERK Kinase Inhibitor with Antitumor and Antiangiogenic Activity**

Charity Atkins, Qi Liu, Elisabeth Minthorn, Shu-Yun Zhang, David J. Figueroa, Katherine Moss, Thomas B. Stanley, Brent Sanders, Aaron Goetz, Nathan Gaul, Anthony E. Choudhry, Hasan Alsaïd, Beat M. Jucker, Jeffrey M. Axten, and Rakesh Kumar

Précis: Inhibition of PERK kinase, which controls the unfolded protein response (UPR), a near universally elevated process in cancer cells, was also found unexpectedly to affect amino acid metabolism, blood vessel density, and vascular perfusion in tumors.

2003 **Genetic Amplification of the NOTCH Modulator LNX2 Upregulates the WNT/ β -Catenin Pathway in Colorectal Cancer**

Jordi Camps, Jason J. Pitt, Georg Emons, Amanda B. Hummon, Chanelle M. Case, Marian Grade, Tamara L. Jones, Quang T. Nguyen, B. Michael Ghadimi, Tim Beissbarth, Michael J. Difilippantonio, Natasha J. Caplen, and Thomas Ried

Précis: Notch and Wnt signaling pathways are upregulated by overexpression of a ligand for the endocytic adaptor protein Numb, a Notch inhibitory protein, coordinately stimulating both of these critical oncogenic pathways in colorectal cancer.

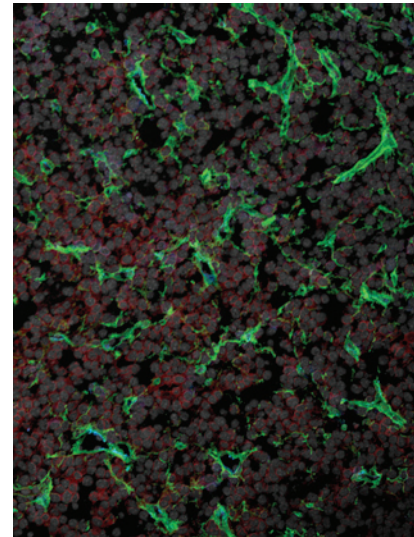
CORRECTION

2014

**Corrections: 2012 San Antonio Breast
Cancer Symposium Abstracts**

ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and α -SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.



Cancer Research

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

73 (6)

Cancer Res 2013;73:1647-2022.

Updated version Access the most recent version of this article at:
<http://cancerres.aacrjournals.org/content/73/6>

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/73/6>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.