

BREAKING ADVANCES

- 3657** Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

- 3659** ErbB2: From an EGFR Relative to a Central Target for Cancer Therapy
Nancy E. Hynes
- 3663** Commentary on "Participation of p53 Protein in the Cellular Response to DNA Damage"
Michael B. Kastan

REVIEW

- 3666** OncomiR or Tumor Suppressor? The Duplicity of MicroRNAs in Cancer
Alexander A. Svoronos, Donald M. Engelman, and Frank J. Slack

MEETING REPORT

- 3671** Thrombosis in Cancer: Research Priorities Identified by a National Cancer Institute/National Heart, Lung, and Blood Institute Strategic Working Group
Nigel S. Key, Alok A. Khorana, Nigel Mackman, Owen J.T. McCarty, Gilbert C. White, Charles W. Francis, Keith R. McCrae, Joseph S. Palumbo, Gary E. Raskob, Andrew T. Chan, and Anil K. Sood

PRIORITY REPORTS

- 3676** Genomic Landscape Established by Allelic Imbalance in the Cancerization Field of a Normal Appearing Airway
Yasminka Jakubek, Wenhua Lang, Selina Vattathil, Melinda Garcia, Li Xu, Lili Huang, Suk-Young Yoo, Li Shen, Wei Lu, Chi-Wan Chow, Zachary Weber, Gareth Davies, Jing Huang, Carmen Behrens, Neda Kalhor, Cesar Moran, Junya Fujimoto, Reza Mehran, Randa El-Zein, Stephen G. Swisher, Jing Wang, Jerry Fowler, Avrum E. Spira, Erik A. Ehli, Ignacio I. Wistuba, Paul Scheet, and Humam Kadara
- Précis: Molecular alterations in normal-appearing, yet mutagenized, airway cells offer a model to interrogate the biology of lung cancer and to identify targets for early treatment and chemoprevention of this malignancy.*

- 3684** ICOS Promotes the Function of CD4⁺ Effector T Cells during Anti-OX40-Mediated Tumor Rejection

Todd C. Metzger, Hua Long, Shobha Potluri, Thomas Pertel, Samantha L. Bailey-Bucktrout, John C. Lin, Tihui Fu, Padmanee Sharma, James P. Allison, and Reid M.R. Feldman

Précis: These findings identify a novel combination approach for immunotherapy, which activates complimentary costimulatory pathways to enhance CD4⁺ T-cell-dependent rejection of tumors.

CLINICAL STUDIES

- 3690**  Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study


Jennifer J. Wheler, Filip Janku, Aung Naing, Yali Li, Bettzy Stephen, Ralph Zinner, Vivek Subbiah, Siqing Fu, Daniel Karp, Gerald S. Falchook, Apostolia M. Tsimberidou, Sarina Piha-Paul, Roosevelt Anderson, Danxia Ke, Vincent Miller, Roman Yelensky, J. Jack Lee, David S. Hong, and Razelle Kurzrock

Précis: As one of the first completed prospective trials to use next-generation sequencing for matching therapy in patients with diverse advanced cancers, this study offers a proof of concept for the notion that this type of genomic profiling can improve outcome parameters.

- 3702** Improved Survival of HER2⁺ Breast Cancer Patients Treated with Trastuzumab and Chemotherapy Is Associated with Host Antibody Immunity against the HER2 Intracellular Domain

Keith L. Knutson, Raphael Clynes, Barath Shreeder, Patrick Yeramian, Kathleen P. Kemp, Karla Ballman, Kathleen S. Tenner, Courtney L. Erskine, Nadine Norton, Donald Northfelt, Winston Tan, Carmen Calfa, Mark Pegram, Elizabeth A. Mittendorf, and Edith A. Perez

Précis: These findings underscore a trend in discovering that intracellular antibodies are fully capable of eradicating tumors, including to improve outcomes in breast cancers treated with HER2 therapy.


- 3711**  Clonotypic Diversification of Intratumoral T Cells Following Sipuleucel-T Treatment in Prostate Cancer Subjects

Nadeem Sheikh, Jason Cham, Li Zhang, Todd DeVries, Simon Letarte, Jeff Pufnock, David Hamm, James Trager, and Lawrence Fong

Précis: These findings offer the first analysis of T-cell clonotype changes induced by an FDA-approved cancer vaccine, with implications for understanding and improving active immunotherapies under development for cancer treatment.


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INTEGRATED SYSTEMS AND TECHNOLOGIES

- 3719** **Exome-Scale Discovery of Hotspot Mutation Regions in Human Cancer Using 3D Protein Structure**
 Collin Tokheim, Rohit Bhattacharya, Noushin Niknafs, Derek M. Gygax, Rick Kim, Michael Ryan, David L. Masica, and Rachel Karchin
Précis: Consideration of three-dimensional protein structure offers the potential to change the way genetic investigators look for new driver mutations in cancer.

- 3732** **Three-Dimensional Breast Cancer Models Mimic Hallmarks of Size-Induced Tumor Progression**
Manjulata Singh, Shilpa Mukundan, Maria Jaramillo, Steffi Oesterreich, and Shilpa Sant
Précis: Three-dimensional in vitro tumor models such as the one described in this study that can mimic the tumor microenvironment can offer more effective tools to study tumor biology and discover cancer drugs.

MICROENVIRONMENT AND IMMUNOLOGY

- 3744** **Disrupting Hypoxia-Induced Bicarbonate Transport Acidifies Tumor Cells and Suppresses Tumor Growth**
 Alan McIntyre, Alzbeta Hulikova, Ioanna Ledaki, Cameron Snell, Dean Singleton, Graham Steers, Peter Seden, Dylan Jones, Esther Bridges, Simon Wigfield, Ji-Liang Li, Angela Russell, Pawel Swietach, and Adrian L. Harris
Précis: This study explores a metabolic rationale behind a simple intervention to relieve the common resistance of hypoxic tumors to anticancer therapy, addressing a widespread clinical problem in many advanced solid malignancies.

- 3756** **Systemic DC Activation Modulates the Tumor Microenvironment and Shapes the Long-Lived Tumor-Specific Memory Mediated by CD8⁺ T Cells**
Kanako Shimizu, Satoru Yamasaki, Jun Shinga, Yusuke Sato, Takashi Watanabe, Osamu Ohara, Kiyotaka Kuzushima, Hideo Yagita, Yoshiko Komuro, Miki Asakura, and Shin-Ichiro Fujii
Précis: The findings of this study inform a next-generation platform for the development of more efficacious cancer vaccines.

- 3767** **Burden of Nonsynonymous Mutations among TCGA Cancers and Candidate Immune Checkpoint Inhibitor Responses**
Leandro M. Colli, Mitchell J. Machiela, Timothy A. Myers, Lea Jessop, Kai Yu, and Stephen J. Chanock
Précis: These findings strongly rationalize the use of immune checkpoint inhibitors in bladder, colon, gastric, and endometrial cancers, based on their higher relative burden of mutations shown to be associated with efficacy to these agents.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 3773** **Comparative Cistromics Reveals Genomic Cross-Talk between FOXA1 and ER α in Tamoxifen-Associated Endometrial Carcinomas**
Marjolein Droog, Ekaterina Nevedomskaya, Yongsoo Kim, Tesa Severson, Koen D. Flach, Mark Opdam, Karianne Schuurman, Patrycja Gradowska, Michael Hauptmann, Gwen Dackus, Harry Hollema, Marian Mourits, Petra Nederlof, Hester van Boven, Sabine C. Linn, Lodewyk Wessels, Flora E. van Leeuwen, and Wilbert Zwart
Précis: Breast cancer patients receiving the estrogen receptor antagonist tamoxifen are at risk of later endometrial cancers, for reasons now illuminated by the results of a whole genome transcriptional analysis performed here.


- 3785** **Downregulation of the TGF β Pseudoreceptor BAMBI in Non-Small Cell Lung Cancer Enhances TGF β Signaling and Invasion**
 Sebastian Marwitz, Sofia Depner, Dmytro Dvornikov, Ruth Merkle, Magdalena Szczygieł, Karin Müller-Decker, Philippe Lucarelli, Marvin Wäsch, Heimo Mairbäurl, Klaus F. Rabe, Christian Kugler, Ekkehard Vollmer, Martin Reck, Svetlana Scheufele, Maren Kröger, Ole Ammerpohl, Reiner Siebert, Torsten Goldmann, and Ursula Klingmüller
Précis: These results demonstrate how attenuated expression of a negative regulator of TGF β signaling drives invasiveness in lung adenocarcinomas, highlighting this signaling pathway as a candidate therapeutic target in this aggressive disease.

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- 3802** SIRT2-Mediated Deacetylation and Tetramerization of Pyruvate Kinase Directs Glycolysis and Tumor Growth
Seong-Hoon Park, Ozkan Ozden, Guoxiang Liu, Ha Yong Song, Yueming Zhu, Yufan Yan, Xianghui Zou, Hong-Jun Kang, Haiyan Jiang, Daniel R. Principe, Yong-Il Cha, Meejeon Roh, Athanassios Vassilopoulos, and David Gius
Précis: These findings suggest how the sirtuin molecule SIRT2 mediates tumor suppression by reprogramming the glycolytic metabolism and proliferation of cancer cells, offering an explanation for the tumor-permissive phenotype of SIRT2-deficient mice.
- 3813** RAR γ Downregulation Contributes to Colorectal Tumorigenesis and Metastasis by Derepressing the Hippo–Yap Pathway
Peng-Da Guo, Xing-Xing Lu, Wen-Juan Gan, Xiu-Ming Li, Xiao-Shun He, Shen Zhang, Qing-Hua Ji, Feng Zhou, Yue Cao, Jing-Ru Wang, Jian-Ming Li, and Hua Wu
Précis: These findings offer insights into how a retinoic acid receptor isoform drives colorectal cancer, with potential implications to prevent and treat this common disease.
- 3826** Rho GTPase Transcriptome Analysis Reveals Oncogenic Roles for Rho GTPase-Activating Proteins in Basal-like Breast Cancers
Campbell D. Lawson, Cheng Fan, Natalia Mitin, Nicole M. Baker, Samuel D. George, David M. Graham, Charles M. Perou, Keith Burridge, Channing J. Der, and Kent L. Rossman
Précis: Rho GTPase-activating proteins generally characterized as tumor suppressors actually act as oncogenes in basal-like breast cancers, an aggressive subtype of the disease.
- 3838** A Novel MIF Signaling Pathway Drives the Malignant Character of Pancreatic Cancer by Targeting NR3C2
Shouhui Yang, Peijun He, Jian Wang, Aaron Schetter, Wei Tang, Naotake Funamizu, Katsuhiko Yanaga, Tadashi Uwagawa, Abhay R. Satoskar, Jochen Gaedcke, Markus Bernhardt, B. Michael Ghadimi, Matthias M. Gaida, Frank Bergmann, Jens Werner, Thomas Ried, Nader Hanna, H. Richard Alexander, and S. Perwez Hussain
Précis: These results offer preclinical proof of concept for a strategy to target a newly described signaling axis for PDAC management.
- 3851** Constitutive Activation of PI3K in Oocyte Induces Ovarian Granulosa Cell Tumors
So-Youn Kim, Katherine Ebbert, Marilia H. Cordeiro, Megan M. Romero, Kelly A. Whelan, Adrian A. Suarez, Teresa K. Woodruff, and Takeshi Kurita
Précis: This study shows how perturbations of the interaction between oocytes and granulosa cells in the ovary can trigger tumor development by activating an autocrine growth circuit.

PREVENTION AND EPIDEMIOLOGY

- 3862** Circulating Omentin as a Novel Biomarker for Colorectal Cancer Risk: Data from the EPIC–Potsdam Cohort Study
Krasimira Aleksandrova, Romina di Giuseppe, Berend Isermann, Ronald Biemann, Matthias Schulze, Clemens Wittenbecher, Andreas Fritsche, Rainer Lehmann, Juliane Menzel, Cornelia Weikert, Tobias Pischon, and Heiner Boeing
Précis: A long-term prospective study identifies a proinflammatory cytokine secreted from visceral, but not subcutaneous, adipose tissue as a novel candidate biomarker for colorectal cancer risk.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY



- 3872** STAT3/IRF1 Pathway Activation Sensitizes Cervical Cancer Cells to Chemotherapeutic Drugs
Barbara Walch-Rückheim, Jennifer Pahne-Zeppenfeld, Jil Fischbach, Claudia Wickenhauser, Lars Christian Horn, Lars Tharun, Reinhard Büttner, Peter Mallmann, Peter Stern, Yoo-Jin Kim, Rainer Maria Bohle, Christian Rube, Russalina Ströder, Ingolf Juhasz-Böss, Erich-Franz Solomayer, and Sigrun Smola
Précis: These findings define a novel role for the oncoprotein STAT3 in sensitizing cervical tumors to radio/chemotherapy, proposing its downstream target IRF1 as a novel predictive marker for therapeutic response.
- 3884** Renalase Expression by Melanoma and Tumor-Associated Macrophages Promotes Tumor Growth through a STAT3-Mediated Mechanism
 Lindsay Hollander, Xiaojia Guo, Heino Velazquez, John Chang, Robert Safirstein, Harriet Kluger, Charles Cha, and Gary V. Desir
Précis: These results establish a role for the secreted flavoprotein renalase in promoting melanoma cell growth and CD163⁺ TAM in the tumor microenvironment, with potential therapeutic implications for the management of melanoma.
- 3895** M-COPA, a Golgi Disruptor, Inhibits Cell Surface Expression of MET Protein and Exhibits Antitumor Activity against MET-Addicted Gastric Cancers
 Yoshimi Ohashi, Mutsumi Okamura, Asaka Hirose, Naomi Tamaki, Akinobu Akatsuka, Kuo-Ming Wu, Hyeon-Wook Choi, Kentaro Yoshimatsu, Isamu Shiina, Takao Yamori, and Shingo Dan
Précis: These findings offer a preclinical proof of concept for the use of drugs that target the Golgi apparatus for treating certain aggressive stomach cancers, where effective therapeutic options are often lacking.

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3904 Mitochondria-Targeted Analogues of Metformin Exhibit Enhanced Antiproliferative and Radiosensitizing Effects in Pancreatic Cancer Cells

Gang Cheng, Jacek Zielonka, Olivier Ouari, Marcos Lopez, Donna McAllister, Kathleen Boyle, Christy S. Barrios, James J. Weber, Bryon D. Johnson, Micael Hardy, Michael B. Dwinell, and Balaraman Kalyanaraman

Précis: Mitochondria-targeting capabilities bestowed upon new analogs of metformin appear to improve upon its antitumor efficacy, strengthening the rationale to repurpose metformin as an anticancer agent.

3916 Dicer Elicits Paclitaxel Chemosensitization and Suppresses Cancer Stemness in Breast Cancer by Repressing AXL

Ting-Yu Chang, Hsin-An Chen, Ching-Feng Chiu, Yi-Wen Chang, Tsang-Chih Kuo, Po-Chun Tseng, Weu Wang, Mien-Chie Hung, and Jen-Liang Su

Précis: These findings define a mechanism of adenoviral E1A-mediated chemosensitization for paclitaxel, which is based upon the suppression of breast cancer stem-like cells, with potential implications for the diagnosis and treatment of breast cancer patients.

3929 In Situ Tumor Vaccination by Combining Local Radiation and Tumor-Specific Antibody or Immunocytokine Treatments

Zachary S. Morris, Emily I. Guy, David M. Francis, Monica M. Gressett, Lauryn R. Werner, Lakeesha L. Carmichael, Richard K. Yang, Eric A. Armstrong, Shyhmin Huang, Fariba Navid, Stephen D. Gillies, Alan Korman, Jacquelyn A. Hank, Alexander L. Rakhmilevich, Paul M. Harari, and Paul M. Sondel

Précis: Combining radiotherapy with an IL2-linked tumor-specific antibody can trigger durable eradications of large tumors and metastases, most powerfully with the further addition of immune checkpoint blockade, with immediate implications for clinical testing.

3942 A Novel Bispecific Antibody Targeting EGFR and cMet Is Effective against EGFR Inhibitor-Resistant Lung Tumors



Sheri L. Moores, Mark L. Chiu, Barbara S. Bushey, Kristen Chevalier, Leopoldo Luistro, Keri Dorn, Randall J. Brezski, Peter Haytko, Thomas Kelly, Sheng-Jiun Wu, Pauline L. Martin, Joost Neijssen, Paul W.H.I. Parren, Janine Schuurman, Ricardo M. Attar, Sylvie Laquerre, Matthew V. Lorenzi, and G. Mark Anderson

Précis: These findings offer preclinical proof of concept for use of a novel biologic to treat non-small cell lung cancers resistant to small-molecule inhibitors of EGFR, addressing an ongoing need in patients with this disease.

3954 Antibody-Targeted Chemotherapy for the Treatment of Melanoma

Wendy K. Nevala, Sarah A. Buhrow, Daniel J. Knauer, Joel M. Reid, Elena A. Atanasova, and Svetomir N. Markovic

Précis: This study provides a preclinical illustration of greater effectiveness of nab-paclitaxel (Abraxane) when it is attached noncovalently to a therapeutic antibody, with broad implications to improve cytotoxic therapy in many cancer types.

TUMOR AND STEM CELL BIOLOGY

3965 CD271 Expression on Patient Melanoma Cells Is Unstable and Unlinked to Tumorigenicity

Samantha E. Boyle, Clare G. Fedele, Vincent Corbin, Elisha Wybacz, Pacman Szeto, Jeremy Lewin, Richard J. Young, Annie Wong, Robert Fuller, John Spillane, David Speakman, Simon Donahoe, Miklos Pohl, David Gyorki, Michael A. Henderson, Ricky W. Johnstone, Anthony T. Papenfuss, and Mark Shackleton

Précis: This study presents evidence that calls into question a putative biomarker of melanoma stem cells, undermining an earlier rationale to explore its development as a therapeutic target.

3978 The Tumor-Associated Glycosyltransferase ST6Gal-I Regulates Stem Cell Transcription Factors and Confers a Cancer Stem Cell Phenotype

Matthew J. Schultz, Andrew T. Holdbrooks, Asmi Chakraborty, William E. Grizzle, Charles N. Landen, Donald J. Buchsbaum, Michael G. Conner, Rebecca C. Arend, Karina J. Yoon, Christopher A. Klug, Daniel C. Bullard, Robert A. Kesterson, Patsy G. Oliver, Amber K. O'Connor, Bradley K. Yoder, and Susan L. Bellis

Précis: These findings define a specific role for tumor cell sialylation in regulating stem cell-associated transcription factors and conferring a cancer stem-like cell phenotype.

3989 Molecular Insights of Pathways Resulting from Two Common PIK3CA Mutations in Breast Cancer

Poomima Bhat-Nakshatri, Chirayu P. Goswami, Sunil Badve, Luca Magnani, Mathieu Lupien, and Harikrishna Nakshatri

Précis: This study identifies a unique signaling network downstream of PIK3CA-E545K mutation in estrogen receptor-positive breast cancers, representing about 20% of cases, which dictates the response to estrogen treatment and PI3K inhibitors.

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- 4002** p27 Is a Candidate Prognostic Biomarker and Metastatic Promoter in Osteosarcoma
Yiting Li, Manjula Nakka, Aaron J. Kelly, Ching C. Lau, Mark Krailo, Donald A. Barkauskas, John M. Hicks, and Tsz-Kwong Man

Précis: Mislocalization of the cell-cycle kinase inhibitor p27 to the cytoplasm in metastatic osteosarcoma cells may exert prognostic and therapeutic impact, where both biomarkers and better treatments are sorely needed.

- 4012** miR-17-92/p38 α Dysregulation Enhances Wnt Signaling and Selects Lgr6⁺ Cancer Stem-like Cells during Lung Adenocarcinoma Progression
Anna Guinot, Feride Oeztuerk-Winder, and Juan-Jose Ventura

Précis: These results identify a specific stem-like cell population in non-small cell lung cancers, the elucidation of which may enable earlier prognosis and possibly the development of more effective targeted treatments.

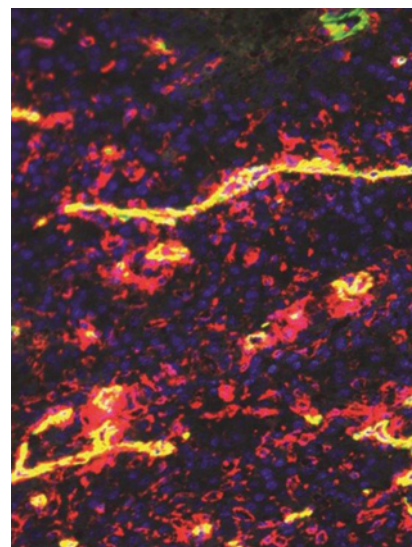


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ABOUT THE COVER

Immunotherapy with artificial adjuvant vector cells programs local immune responses by establishing tertiary lymphoid structures (TLS) composed of CXCL10-producing CD11c⁺ dendritic cells and antigen-specific CD8⁺ T cells around the CD31⁺VCAM-1⁺ICAM-1⁺ vessels seen in tumor sites. The image depicts immunofluorescence staining of the normalized vessels with CD31 (green), ICAM-1 (red), and DAPI (blue) at tumor sites. The TLS-associated vascular normalization at tumor sites may enable the trafficking of tumor-specific CTL into tumor-associated TLS. For details, see article by Shimizu and colleagues on page 3756.



Cancer Research

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

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Cancer Res 2016;76:3657-4022.

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