Cancer Research

Table of Contents

AACR American Association for Cancer Research

May 1, 2017 • Volume 77 • Number 9

BREAKING ADVANCES

2177 Highlights from Recent Cancer Literature

REVIEWS

2179 Genomic Instability in Cancer: Teetering on the Limit of Tolerance
Noemi Andor, Carlo C. Maley, and Hanlee P. Ji

2186 Master Transcriptional Regulators in Cancer: Discovery via Reverse Engineering Approaches and Subsequent Validation
Bruce Moran, Arman Rahman, Katja Palonen, Fiona T. Lanigan, and William M. Gallagher

PERSPECTIVE

2191 Whither Radioimmunotherapy: To Be or Not To Be?
Damian J. Green and Oliver W. Press

MEETING REPORT

2197 Regulatory Aspects of Optical Methods and Exogenous Targets for Cancer Detection
Willemieke S. Tummers, Jason M. Warram, Kiranya E. Tipirneni, John Fengler, Paula Jacobs, Lalitha Shankar, Lori Henderson, Betsy Ballard, T. Joshua Pfefer, Brian W. Pogue, Jamey P. Weichert, Michael Bouvet, Jonathan Sorger, Christopher H. Contag, John V. Frangioni, Michael F. Tweedle, James P. Basilion, Sanjiv S. Gambhir, and Eben L. Rosenthal

PRIORITY REPORT

2207 A Pyrrole-Imidazole Polyamide Is Active against Enzalutamide-Resistant Prostate Cancer
Alexis A. Kurmis, Fei Yang, Timothy R. Welch, Nicholas G. Nickols, and Peter B. Dervan

Précis: *This study defines a small molecule–based strategy to treat prostate cancers that become resistant to enzalutamide, an antiandrogen that is initially effective but to which malignant cells inevitably evolve around.*

CLINICAL STUDIES

2213 Intrinsic Subtypes and Gene Expression Profiles in Primary and Metastatic Breast Cancer
Juan M. Cejalvo, Eduardo Martínez de Dueñas, Patricia Galván, Susana García-Recio, Octavio Burgués Gasión, Laia Paré, Silvia Antolín, Rosella Martinello, Isabel Blancas, Barbara Adamo, Ángel Guerrero-Zotano, Montserrat Muñoz, Paolo Nucíforo, María Vidal, Ramón M. Pérez, José I. Chacón López-Muniz, Rosalía Caballero, Vicente Peg, Eva Carrasco, Federico Rojo, Charles M. Perou, Javier Cortés, Vincenzo Adamo, Joan Albanell, Roger R. Gomis, Ana Lluch, and Aleix Prat

Précis: *A study of paired metastatic and primary breast tumors suggests how micrometastasis in primary disease may evolve towards a more aggressive phenotype with time, with possible implications for prognosis and treatment.*

2222 Circulating Tumor Cells with Aberrant *ALK* Copy Number Predict Progression-Free Survival during Crizotinib Treatment in *ALK*-Rearranged Non–Small Cell Lung Cancer Patients
Emma Pailler, Marianne Oulhen, Isabelle Borget, Jordi Remon, Kirsty Ross, Nathalie Auger, Fanny Billiot, Maud Ngo Camus, Frédéric Commo, Colin R. Lindsay, David Planchard, Jean-Charles Soria, Benjamin Besse, and Françoise Farace

Précis: *Circulating tumor cells offer a highly tractable resource for the development of real-time markers to monitor and prognose solid tumors, as developed in this study of ALK-rearranged lung adenocarcinomas.*

INTEGRATED SYSTEMS AND TECHNOLOGIES

2231 Cellular Hierarchy as a Determinant of Tumor Sensitivity to Chemotherapy
Ignacio A. Rodriguez-Brenes, Antonina V. Kurtova, Christopher Lin, Yu-Cheng Lee, Jing Xiao, Martha Mims, Keith Syson Chan, and Dominik Wodarz

Précis: *In bladder cancer, feedback regulatory mechanisms from underlying healthy tissue are found to determine resistance to chemotherapy.*

Downloaded from cancerres.aacrjournals.org on June 20, 2021. © 2017 American Association for Cancer Research.

Table of Contents

2242 **Defining Cancer Subpopulations by Adaptive Strategies Rather Than Molecular Properties Provides Novel Insights into Intratumoral Evolution**
Arig Ibrahim-Hashim, Mark Robertson-Tessi, Pedro M. Enriquez-Navas, Mehdi Damaghi, Yoganand Balagurunathan, Jonathan W. Wojtkowiak, Shonagh Russell, Kam Yoonseok, Mark C. Lloyd, Marilyn M. Bui, Joel S. Brown, Alexander R.A. Anderson, Robert J. Gillies, and Robert A. Gatenby

Précis: *Mutliple murine cancer models support the use of mathematical models to understand intratumoral evolution based on environmental selection forces and cancer cell adaptive strategies.*

2255 **Genomic and Epigenomic Heterogeneity of Hepatocellular Carcinoma**
De-Chen Lin, Anand Mayakonda, Huy Q. Dinh, Pinbo Huang, Lehang Lin, Xiaoping Liu, Ling-wen Ding, Jie Wang, Benjamin P. Berman, Er-Wei Song, Dong Yin, and H. Phillip Koeffler

Précis: *Liver cancer exhibits widespread intratumoral heterogeneity at genomic and epigenomic levels, increasing the challenges for personalized patient treatment and molecular-based biomarkers.*

MICROENVIRONMENT AND IMMUNOLOGY

2266 **Cellular and Molecular Identity of Tumor-Associated Macrophages in Glioblastoma**
Zhihong Chen, Xi Feng, Cameron J. Herting, Virginia Alvarez Garcia, Kai Nie, Winnie W. Pong, Rikke Rasmussen, Bhakti Dwivedi, Sandra Seby, Susanne A. Wolf, David H. Gutmann, and Dolores Hambardzumyan

Précis: *Most tumor-associated macrophoage in glioblastoma are derived from bone marrow myeloid cells, infiltrating the tumor bed at early times when they are crucial for malignant outgrowth.*

2279 **Soluble IL6R Expressed by Myeloid Cells Reduces Tumor-Specific Th1 Differentiation and Drives Tumor Progression**
Hirotake Tsukamoto, Koji Fujieda, Masatoshi Hirayama, Tokunori Ikeda, Akira Yuno, Keiko Matsumura, Daiki Fukuma, Kimi Araki, Hiroshi Mizuta, Hideki Nakayama, Satoru Senju, and Yasuharu Nishimura

Précis: *These findings offer a mechanistic rationale to manipulate levels of the soluble IL6 receptor in cancer patients to improve T-cell-based cancer immunotherapy.*

2292 **Local Activation of p53 in the Tumor Microenvironment Overcomes Immune Suppression and Enhances Antitumor Immunity**
Gang Guo, Miao Yu, Wei Xiao, Esteban Celis, and Yan Cui

Précis: *These findings show how activating p53 in host cells of the tumor microenvironment, for example by direct or DNA damaging strategies, could improve locoregional antitumor immunity and perhaps leverage the efficacy of systemic immunotherapy.*

2306 **MYC Mediates Large Oncosome-Induced Fibroblast Reprogramming in Prostate Cancer**
Valentina R. Minciacchi, Cristiana Spinelli, Mariana Reis-Sobreiro, Lorenzo Cavallini, Sungyong You, Mandana Zandian, Xiaohong Li, Rajeev Mishra, Paola Chiarugi, Rosalyn M. Adam, Edwin M. Posadas, Giuseppe Viglietto, Michael R. Freeman, Emanuele Cocucci, Neil A. Bhowmick, and Dolores Di Vizio

Précis: *Large exosomes secreted by cancer cells that are termed oncosomes are reported to stimulate endothelial tube formation via a MYC-driven stromal reprogramming event.*

2318 **Granzyme B PET Imaging as a Predictive Biomarker of Immunotherapy Response**
Benjamin M. Larimer, Eric Wehrenberg-Klee, Frank Dubois, Anila Mehta, Taylor Kalomeris, Keith Flaherty, Genevieve Boland, and Umar Mahmood

Précis: *These findings offer a preclinical proof of concept for a novel PET imaging agent that can predict antitumor immune responses prior to tumor volume changes, with immediate implications for clinical translation.*

MOLECULAR AND CELLULAR PATHOBIOLOGY

2328 **Tankyrase-Binding Protein TNKS1BP1 Regulates Actin Cytoskeleton Rearrangement and Cancer Cell Invasion**
Tomokazu Ohishi, Haruka Yoshida, Masamichi Katori, Toshiro Migita, Yukiko Muramatsu, Mao Miyake, Yuichi Ishikawa, Akio Saiura, Shun-ichiro Iemura, Tohru Natsume, and Hiroyuki Seimiya

Précis: *These findings show how a PARP-like enzyme activates a cytoskeletal modification pathway to promote cancer cell invasion.*

Downloaded from cancerres.aacrjournals.org on June 20, 2021. © 2017 American Association for Cancer Research.

Table of Contents

2339 **Noncoding Effects of Circular RNA CCDC66 Promote Colon Cancer Growth and Metastasis**
Kuei-Yang Hsiao, Ya-Chi Lin, Sachin Kumar Gupta, Ning Chang, Laising Yen, H. Sunny Sun, and Shaw-Jenq Tsai

Précis: *Peculiar circular RNA molecules found in cancer cells can function as "microRNA sponges," which can upregulate expression of multiple oncogenes, suggesting their potential use as prognostic markers and candidate therapeutic targets.*

2351 **Hypercholesterolemia Increases Colorectal Cancer Incidence by Reducing Production of NKT and γδ T Cells from Hematopoietic Stem Cells**
Guodong Tie, Jinglian Yan, Lyne Khair, Julia A. Messina, April Deng, Joonsoo Kang, Thomas Fazzio, and Louis M. Messina

Précis: *Hypercholesterolemia appears to reduce the lineage priming of hematopoietic stem cells towards innate immune cells, thereby impairing immunosurveillance against colorectal cancer.*

2363 **Loss of NDRG2 Expression Confers Oral Squamous Cell Carcinoma with Enhanced Metastatic Potential**
Tomohiro Tamura, Tomonaga Ichikawa, Shingo Nakahata, Yudai Kondo, Yuri Tagawa, Koji Yamamoto, Kentaro Nagai, Takashi Baba, Ryoji Yamaguchi, Mitsuru Futakuchi, Yoshihiro Yamashita, and Kazuhiro Morishita

Précis: *These findings establish NDRG2 as a candidate prognostic factor and molecular therapeutic target in the most common type of aggressive oral cancer.*

2375 **NR4A3 Suppresses Lymphomagenesis through Induction of Proapoptotic Genes**
Alexander J.A. Deutsch, Beate Rinner, Martin Pichler, Katharina Prochazka, Katrin Pansy, Marco Bischof, Karoline Fechter, Stefan Hatzl, Julia Feichtinger, Kerstin Wenzl, Marie-Therese Frisch, Verena Stiegelbauer, Andreas Prokesch, Anne Krogsdam, Heinz Sill, Gerhard G. Thallinger, Hildegard T. Greinix, Chenguang Wang, Christine Beham-Schmid, and Peter Neumeister

Précis: *A little characterized nuclear receptor exerts a robust tumor suppressor function of similar impact to a much better established family member in aggressive lymphomas.*

2387 **Krüppel-like Transcription Factor KLF10 Suppresses TGFβ-Induced Epithelial-to-Mesenchymal Transition via a Negative Feedback Mechanism**
Vivek Kumar Mishra, Malayannan Subramaniam, Vijayalakshmi Kari, Kevin S. Pitel, Simon J. Baumgart, Ryan M. Naylor, Sankari Nagarajan, Florian Wegwitz, Volker Ellenrieder, John R. Hawse, and Steven A. Johnsen

Précis: *New results suggest a molecular basis for the dichotomy of TGFβ function as a positive or negative regulator of malignancy at different stages of tumor progression.*

2401 **Genetic Manipulation of *Helicobacter pylori* Virulence Function by Host Carcinogenic Phenotypes**
Giovanni Suarez, Judith Romero-Gallo, Johanna C. Sierra, M. Blanca Piazuelo, Uma S. Krishna, Martin A. Gomez, Keith T. Wilson, and Richard M. Peek Jr

Précis: *Identification of potential new targets and therapeutic strategies against* H. pylori *may reduce the risk of cancer caused by this pathogen.*

2413 **Endothelin Promotes Colorectal Tumorigenesis by Activating YAP/TAZ**
Zhen Wang, Peng Liu, Xin Zhou, Tianxiang Wang, Xu Feng, Yi-Ping Sun, Yue Xiong, Hai-Xin Yuan, and Kun-Liang Guan

Précis: *This study mechanistically connects the Hippo and endothelin receptor signaling pathways, two important signaling pathways in cancer.*

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2424 **HuR Small-Molecule Inhibitor Elicits Differential Effects in Adenomatosis Polyposis and Colorectal Carcinogenesis**
Michaela Lang, David Berry, Katharina Passecker, Ildiko Mesteri, Sabin Bhuju, Florian Ebner, Vitaly Sedlyarov, Rayko Evstatiev, Kyle Dammann, Alexander Loy, Orest Kuzyk, Pavel Kovarik, Vineeta Khare, Martin Beibel, Guglielmo Roma, Nicole Meisner-Kober, and Christoph Gasche

Précis: *These results provide a preclinical proof of concept for HuR inhibition as an effective means of chemoprevention in familial adenomatosis polyposis, with cautions advised in the setting of inflammatory bowel disease.*

2439 **Sigma1 Targeting to Suppress Aberrant Androgen Receptor Signaling in Prostate Cancer**
Jeffrey D. Thomas, Charles G. Longen, Halley M. Oyer, Nan Chen, Christina M. Maher, Joseph M. Salvino, Blase Kania, Kelsey N. Anderson, William F. Ostrander, Karen E. Knudsen, and Felix J. Kim

Précis: *A small-molecule modulator of the signal scaffolding protein Sigma1 can be used to suppress splice variant and full-length androgen receptor function in prostate cancer cells, offering a new strategy to treat advanced prostate cancers.*

Downloaded from cancerres.aacrjournals.org on June 20, 2021. © 2017 American Association for Cancer Research.

Table of Contents

2453 **NR1D1 Recruitment to Sites of DNA Damage Inhibits Repair and Is Associated with Chemosensitivity of Breast Cancer**
Na-Lee Ka, Tae-Young Na, Hyelin Na, Min-Ho Lee, Han-Su Park, Sewon Hwang, Il Yong Kim, Je Kyung Seong, and Mi-Ock Lee

Précis: *These findings show how a nuclear receptor and its ligands blunts repair of double-strand DNA breaks, suggesting their candidacy as therapeutic targets in cancer patients.*

2464 **High-Throughput Genomic Profiling of Adult Solid Tumors Reveals Novel Insights into Cancer Pathogenesis**
Ryan J. Hartmaier, Lee A. Albacker, Juliann Chmielecki, Mark Bailey, Jie He, Michael E. Goldberg, Shakti Ramkissoon, James Suh, Julia A. Elvin, Samuel Chiacchia, Garrett M. Frampton, Jeffrey S. Ross, Vincent Miller, Philip J. Stephens, and Doron Lipson

Précis: *Publicly available data from 18,004 adult tumors can help accelerate discoveries of novel therapeutic targets, validate oncogenic mechanisms, guide treatment decisions, and design appropriate clinical trials to improve outcomes for cancer patients.*

2476 **Targeted Degradation of BET Proteins in Triple-Negative Breast Cancer**
Longchuan Bai, Bing Zhou, Chao-Yie Yang, Jiao Ji, Donna McEachern, Sally Przybranowski, Hui Jiang, Jiantao Hu, Fuming Xu, Yujun Zhao, Liu Liu, Ester Fernandez-Salas, Jing Xu, Yali Dou, Bo Wen, Duxin Sun, Jennifer Meagher, Jeanne Stuckey, Daniel F. Hayes, Shunqiang Li, Matthew J. Ellis, and Shaomeng Wang

Précis: *These findings provide a preclinical proof of concept for targeting BET protein degradation with small-molecule inhibitors as a promising therapeutic strategy for treatment of triple-negative breast cancers.*

2488 **Kinome-Wide RNA Interference Screen Reveals a Role for PDK1 in Acquired Resistance to CDK4/6 Inhibition in ER-Positive Breast Cancer**
Valerie M. Jansen, Neil E. Bhola, Joshua A. Bauer, Luigi Formisano, Kyung-Min Lee, Katherine E. Hutchinson, Agnieszka K. Witkiewicz, Preston D. Moore, Mónica Valéria Estrada, Violeta Sánchez, Paula G. Ericsson, Melinda E. Sanders, Paula R. Pohlmann, Michael J. Pishvaian, David A. Riddle, Teresa C. Dugger, Wenyi Wei, Erik S. Knudsen, and Carlos L. Arteaga

Précis: *These preclinical findings show how small-molecule inhibitors of the PI3K-PDK1 pathway can overcome acquired resistance to CDK4/6 inhibitors used to treat ER^+ breast cancers, with immediate implications for clinical evaluation.*

2500 **Energy Balance Modulation Impacts Epigenetic Reprogramming, ERα and ERβ Expression, and Mammary Tumor Development in MMTV-neu Transgenic Mice**
Emily L. Rossi, Sarah M. Dunlap, Laura W. Bowers, Subreen A. Khatib, Steven S. Doerstling, Laura A. Smith, Nikki A. Ford, Darcy Holley, Powel H. Brown, Marcos R. Estecio, Donna F. Kusewitt, Linda A. deGraffenried, Scott J. Bultman, and Stephen D. Hursting

Précis: *These findings offer a mechanistic rationale to reduce weight in overweight or obese women as a strategy to reduce their risks of HER2-positive breast cancer.*

2512 **Mcl-1 Degradation Is Required for Targeted Therapeutics to Eradicate Colon Cancer Cells**
Jingshan Tong, Peng Wang, Shuai Tan, Dongshi Chen, Zaneta Nikolovska-Coleska, Fangdong Zou, Jian Yu, and Lin Zhang

Précis: *These results show how degradation of the Bcl-2 family protein Mcl-1 in colon cancer cells determines their response to targeted therapeutics, providing new insights into a fundamental mechanism of drug resistance based in apoptosis suppression.*

TUMOR AND STEM CELL BIOLOGY

2522 **The Histone Methyltransferase DOT1L Promotes Neuroblastoma by Regulating Gene Transcription**
Matthew Wong, Andrew E.L. Tee, Giorgio Milazzo, Jessica L. Bell, Rebecca C. Poulos, Bernard Atmadibrata, Yuting Sun, Duohui Jing, Nicholas Ho, Dora Ling, Pei Yan Liu, Xu Dong Zhang, Stefan Hüttelmaier, Jason W.H. Wong, Jenny Wang, Patsie Polly, Giovanni Perini, Christopher J. Scarlett, and Tao Liu

Précis: *These findings offer a preclinical proof of concept for the use of DOT1L inhibitors as a strategy to disrupt the function of amplified N-MYC in neuroblastoma, a deadly type of pediatric cancer.*

2534 **WNT/β-Catenin Directs Self-Renewal Symmetric Cell Division of $hTERT^{high}$ Prostate Cancer Stem Cells**
Kai Zhang, Yanjing Guo, Xue Wang, Huifang Zhao, Zhongzhong Ji, Chaping Cheng, Li Li, Yuxiang Fang, Dawei Xu, Helen He Zhu, and Wei-Qiang Gao

Précis: *Interfering with the WNT3a/hTERT/β-catenin signaling axis can suppress expansion of $hTERT^{high}$ prostate cancer stem-like cells, offering a new therapeutic stratagy to eradicate advanced castration-resistant prostate cancers.*

Downloaded from cancerres.aacrjournals.org on June 20, 2021. © 2017 American Association for Cancer Research.

Table of Contents

LETTERS TO THE EDITOR

2548 Role of CBX4 in the Colorectal Carcinoma Metastasis—Letter
Valentina Sancisi and Alessia Ciarrocchi

2550 Role of CBX4 in the Colorectal Carcinoma Metastasis—Response
Xin Wang and Tiebang Kang

CORRECTIONS

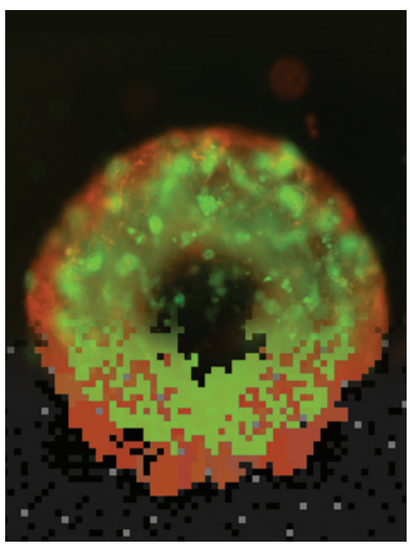
2552 Correction: Neutralization of Tumor Acidity Improves Antitumor Responses to Immunotherapy

2553 Correction: UTX and MLL4 Coordinately Regulate Transcriptional Programs for Cell Proliferation and Invasiveness in Breast Cancer Cells

AC icon indicates Author Choice
For more information please visit www.aacrjournals.org

ABOUT THE COVER

This image combines *in vitro* and *in silico* demonstrations of environmental niches that drive phenotypic segregation in mixed metabolic phenotype spheroids. *In vitro:* Coculture of low glycolytic MCF7-GFP and high glycolytic MDA-MB-231-RFP as spheroids started with a random mixture of both cells and over time each cell line moved to their favorable habitat, MDA-MB-231 to the edge and MCF7 to the center. *In silico:* Simulation of a mathematical model of tumor cells with low (green) and high (red) glycolytic phenotypes, subject to a gradient of nutrients similar to a spheroid. The simulation was initialized with equal numbers of both cell types, well-mixed. Over time, the glycolytic phenotypes moved to the edge in the simulation. For details, see article by Ibrahim-Hashim and colleagues on page 2242.



Downloaded from cancerres.aacrjournals.org on June 20, 2021. © 2017 American Association for Cancer Research.

AACR American Association for Cancer Research

Cancer Research

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

77 (9)

Cancer Res 2017;77:2177-2553.

Updated version	Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/77/9

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/77/9. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cancerres.aacrjournals.org on June 20, 2021. © 2017 American Association for Cancer Research.