

BREAKING ADVANCES

- 507** Highlights from Recent Cancer Literature


CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES

- 509** Fat, Calories, and Cancer
Yves A. DeClerck
- 511** Observations on Radiation-Induced Lymphoid Tumors of Mice
Rakesh Kumar


REVIEW

- 513** A Breakthrough: Macrophage-Directed Cancer Immunotherapy
Charles D. Mills, Laurel L. Lenz, and Robert A. Harris

PRIORITY REPORT

- 517** VEGF-A/VEGFR Inhibition Restores Hematopoietic Homeostasis in the Bone Marrow and Attenuates Tumor Growth
 Rebekah K. O'Donnell, Beverly Falcon, Jeff Hanson, Whitney E. Goldstein, Carole Perruzzi, Shahin Rafii, William C. Aird, and Laura E. Benjamin
Précis: This study provides preclinical proof of concept that the bone marrow hematopoietic niche can be directly targeted and opposed by antiangiogenic therapy.


CLINICAL STUDIES

- 525** Identification of Patients with Recurrent Glioblastoma Who May Benefit from Combined Bevacizumab and CCNU Therapy: A Report from the BELOB Trial
 Lale Erdem-Eraslan, Martin J. van den Bent, Youri Hoogstrate, Hina Naz-Khan, Andrew Stubbs, Peter van der Spek, René Böttcher, Ya Gao, Maurice de Wit, Walter Taal, Hendrika M. Oosterkamp, Annemiek Walenkamp, Laurens V. Beerepoot, Monique C.J. Hanse, Jan Buter, Aafke H. Honkoop, Bronno van der Holt, René M. Vernhout, Peter A.E. Sillevius Smitt, Johan M. Kros, and Pim J. French
Précis: Learning how a subset of glioblastoma patients responds to combined bevacizumab and CCNU therapy prompts further investigations into the use of novel biomarkers to predict treatment benefits and survival outcomes.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 535** Modeling Spontaneous Metastasis following Surgery: An *In Vivo-In Silico* Approach
Sebastien Benzekry, Amanda Tracz, Michalis Mastro, Ryan Corbelli, Dominique Barbolosi, and John M.L. Ebos
Précis: A data-based mathematical model that assesses the impact of surgery on metastatic potential may have clinical uses to individualize adjuvant therapies that can extend cancer remission.

MICROENVIRONMENT AND IMMUNOLOGY

- 548** Citrullinated Vimentin Presented on MHC-II in Tumor Cells Is a Target for CD4⁺ T-Cell-Mediated Antitumor Immunity
 Victoria A. Brentville, Rachael L. Metheringham, Barbara Gunn, Peter Symonds, Ian Daniels, Mohamed Gijon, Katherine Cook, Wei Xue, and Lindy G. Durrant
Précis: Results show how CD4 cells can mediate potent antitumor responses against modified self-epitopes presented on tumor cells, and they illustrate for the first time how the citrullinated peptides may offer especially attractive subjects for cancer vaccine development.

MOLECULAR AND CELLULAR PATHOBIOLOGY


- 561** Balancing Protein Stability and Activity in Cancer: A New Approach for Identifying Driver Mutations Affecting CBL Ubiquitin Ligase Activation
 Minghui Li, Stephen C. Kales, Ke Ma, Benjamin A. Shoemaker, Juan Crespo-Barreto, Andrew L. Cangelosi, Stanley Lipkowitz, and Anna R. Panchenko
Précis: This study describes a new computational approach to identify the functional consequences of cancer mutations using the ubiquitin ligase CBL as a model for proof of concept.
- 572** HEATR1 Negatively Regulates Akt to Help Sensitize Pancreatic Cancer Cells to Chemotherapy
Tongzheng Liu, Yuan Fang, Haoxing Zhang, Min Deng, Bowen Gao, Nifang Niu, Jia Yu, SeungBaek Lee, JungJin Kim, Bo Qin, Fang Xie, Debra Evans, Liewei Wang, Wenhui Lou, and Zhenkun Lou
Précis: This study offers several lines of evidence for a new predictive and prognostic biomarker of chemotherapy response and outcome in pancreatic cancer patients, with additional implications for methods to sensitize pancreatic tumors to therapeutic eradication.

Table of Contents

582 **Aberrant Activation of Notch Signaling Inhibits PROX1 Activity to Enhance the Malignant Behavior of Thyroid Cancer Cells**

Dongwon Choi, Swapnika Ramu, Eunkyung Park, Eunson Jung, Sara Yang, Wonhyeuk Jung, Inho Choi, Sunju Lee, Kyu Eui Kim, Young Jin Seong, Mingu Hong, George Daghlian, Daniel Kim, Eugene Shin, Jung In Seo, Vicken Khatchadourian, Mengchen Zou, Wei Li, Roger De Filippo, Paul Kokorowski, Andy Chang, Steve Kim, Ana Bertoni, Tania Weber Furlanetto, Sung Shin, Meng Li, Yibu Chen, Alex Wong, Chester Koh, Jan Geliebter, and Young-Kwon Hong

Précis: This study provides new insights into a potentially actionable molecular alteration underlying progression of aggressive thyroid cancers.

594 **DNA Hypomethylation and Histone Variant macroH2A1 Synergistically Attenuate Chemotherapy-Induced Senescence to Promote Hepatocellular Carcinoma Progression**

Michela Borghesan, Caterina Fusilli, Francesca Rappa, Concetta Panebianco, Giovanni Rizzo, Jude A. Oben, Gianluigi Mazzoccoli, Chris Faulkes, Illar Pata, Antonella Agodi, Farhad Rezaee, Shane Minogue, Alessandra Warren, Abigail Peterson, John M. Sedivy, Julien Douet, Marcus Buschbeck, Francesco Cappello, Tommaso Mazza, Valerio Pazienza, and Manlio Vinciguerra

Précis: Epigenetic synergy between DNA methylation and histone variants contributes to the refractoriness of liver cancer cells to chemotherapy, with implications for identification of a biomarker of drug-induced senescent cells that may predict disease progression.

607 **SIGMAR1 Regulates Membrane Electrical Activity in Response to Extracellular Matrix Stimulation to Drive Cancer Cell Invasiveness**

David Crottès, Raphael Rapetti-Mauss, Francisca Alcaraz-Perez, Mélanie Tichet, Giuseppina Gariano, Sonia Martial, Hélène Guizouarn, Bernard Pellissier, Agnès Loubat, Alexandra Popa, Agnès Paquet, Marco Presta, Sophie Tartare-Deckert, Maria Luisa Cayuela, Patrick Martin, Franck Borgese, and Olivier Soriani

Précis: An important regulator of ion channel activity in cancer cells is found to promote aggressive and invasive behaviors, with potential implications for new therapeutic approaches to treat cancer.

619 **PBX3 and MEIS1 Cooperate in Hematopoietic Cells to Drive Acute Myeloid Leukemias Characterized by a Core Transcriptome of the MLL-Rearranged Disease**

Zejuan Li, Ping Chen, Rui Su, Chao Hu, Yuanyuan Li, Abdel G. Elkahoun, Zhixiang Zuo, Sandeep Gurbuxani, Stephen Arnovitz, Hengyou Weng, Yungui Wang, Shenglai Li, Hao Huang, Mary Beth Neilly, Gang Greg Wang, Xi Jiang, Paul P. Liu, Jie Jin, and Jianjun Chen

Précis: A gene expression signature stimulated by two homeobox transcription factors in hematopoietic precursor offers intriguing new insights into how acute myeloid leukemias may arise.

PREVENTION AND EPIDEMIOLOGY

630 **Systemic Chromosome Instability Resulted in Colonic Transcriptomic Changes in Metabolic, Proliferation, and Stem Cell Regulators in Sgo1^{-/+} Mice**

Chinthalapally V. Rao, Saira Sanghera, Yuting Zhang, Laura Biddick, Arun Reddy, Stan Lightfoot, Naveena B. Janakiram, Altaf Mohammed, Wei Dai, and Hiroshi Y. Yamada

Précis: A mouse model of chromosome instability reveals aberrant regulation of unexpected pathways and offers new targets for therapeutic and preventive strategies.

643 **Bereavement Is Associated with an Increased Risk of HPV Infection and Cervical Cancer: An Epidemiological Study in Sweden**

Donghao Lu, Karin Sundström, Pär Sparén, Katja Fall, Arvid Sjölander, Joakim Dillner, Nathalie Ylitalo Helm, Hans-Olov Adami, Unnur Valdimarsdóttir, and Fang Fang

Précis: Women who experience the loss of an immediate family member are at a higher risk of developing cervical cancer, possibly related to an increased incidence of oncogenic HPV infections, with implications for identifying at-risk individuals who could benefit from increased screening.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

652 **Hydroxamic Acid and Benzoic Acid–Based STAT3 Inhibitors Suppress Human Glioma and Breast Cancer Phenotypes *In Vitro* and *In Vivo***

Peibin Yue, Francisco Lopez-Tapia, David Paladino, Yifei Li, Chih-Hong Chen, Andrew T. Namanja, Tyvette Hilliard, Yuan Chen, Marcus A. Tius, and James Turkson

Précis: STAT3 offers an attractive target for cancer therapy, but small molecule inhibitors with appealing pharmacologic and biologic properties in animals have been elusive.

Table of Contents

664 Elucidation and Pharmacological Targeting of Novel Molecular Drivers of Follicular

Lymphoma Progression

Brygida Bisikirska, Mukesh Bansal, Yao Shen, Julie Teruya-Feldstein, Raju Chaganti, and Andrea Califano

Précis: Computational interrogation of human B-cell regulatory networks enables the identification of key drivers of follicular lymphoma and provides a generalized approach for the systematic analysis of drug combinations that may offer the strongest antitumor responses.

675 Modulation of EZH2 Expression by MEK-ERK or PI3K-AKT Signaling in Lung Cancer Is Dictated by Different KRAS Oncogene Mutations

Erick Riquelme, Carmen Behrens, Heather Y. Lin, George Simon, Vassiliki Papadimitrakopoulou, Julie Izzo, Cesar Moran, Neda Kalhor, J. Jack Lee, John D. Minna, and Ignacio I. Wistuba

Précis: For those lung cancer patients whose tumors harbor KRAS mutations, the specific type of mutation determines which kinase effector signaling pathways to target along with the histone methyltransferase EZH2, defined here as a novel KRAS effector.

686 Deguelin Analogue SH-1242 Inhibits Hsp90 Activity and Exerts Potent Anticancer Efficacy with Limited Neurotoxicity

Su-Chan Lee, Hye-Young Min, Hoon Choi, Song Yi Bae, Kwan Hee Park, Seung Yeob Hyun, Ho Jin Lee, Jayoung Moon, Shin-Hyung Park, Jun Yong Kim, Hongchan An, So-Jung Park, Ji Hae Seo, Seungbeom Lee, Young-Myeong Kim, Hyun-Ju Park, Sang Kook Lee, Jeewoo Lee, Jeeyeon Lee, Kyu-Won Kim, Young-Ger Suh, and Ho-Young Lee

Précis: This study reports an important advance in the development of Hsp90 inhibitors as cancer therapeutics, a drug class that is appealing in principle but limited to date by significant toxic side-effects that have impeded clinical development.

700 Agonists of the TRAIL Death Receptor DR5 Sensitize Intestinal Stem Cells to Chemotherapy-Induced Cell Death and Trigger Gastrointestinal Toxicity

Niklas K. Finnberg, Prashanth Gokare, Arunasalam Navaraj, Krystle A. Lang Kuhs, George Cerniglia, Hideo Yagita, Kazuyoshi Takeda, Noboru Motoyama, and Wafik S. El-Deiry

Précis: These findings suggest a strategy to reduce gastrointestinal toxicities that arise from combining chemotherapy with TRAIL death receptor agonists, with clinical implications for developing these agents for cancer therapy.

TUMOR AND STEM CELL BIOLOGY

713 Therapeutic Targeting of Tumor-Derived R-Spondin Attenuates β -Catenin Signaling and Tumorigenesis in Multiple Cancer Types

Cecile Chartier, Janak Raval, Fumiko Axelrod, Chris Bond, Jennifer Cain, Cristina Dee-Hoskins, Shirley Ma, Marcus M. Fischer, Jalpa Shah, Jie Wei, May Ji, Andrew Lam, Michelle Stroud, Wan-Ching Yen, Pete Yeung, Belinda Cancilla, Gilbert O'Young, Min Wang, Ann M. Kapoun, John Lewicki, Timothy Hoey, and Austin Gurney

Précis: R-spondin proteins are defined as enhancers of tumorigenic Wnt/ β -catenin signaling, suggesting a novel mechanistic strategy to target β -catenin-driven cancers.

724 Recurrent MLK4 Loss-of-Function Mutations Suppress JNK Signaling to Promote Colon Tumorigenesis

Anna A. Marusiak, Natalie L. Stephenson, Hayeon Baik, Eleanor W. Trotter, Yaoyong Li, Karen Blyth, Susan Mason, Phil Chapman, Lorena A. Puto, Jon A. Read, Claire Brassington, Hannah K. Pollard, Chris Phillips, Isabelle Green, Ross Overman, Matthew Collier, Ewelina Testoni, Crispin J. Miller, Tony Hunter, Owen J. Sansom, and John Brognard

Précis: This study establishes a tumor suppressor role for a kinase that is frequently inactivated by mutation in colon cancer, leading to inactivation of JNK pathway signaling, aberrant cell proliferation, and enhanced tumor growth.

736 Myc Induces miRNA-Mediated Apoptosis in Response to HDAC Inhibition in Hematologic Malignancies

Clare M. Adams, Scott W. Hiebert, and Christine M. Eischen

Précis: This study highlights a surprising role for Myc in activating a miRNA-mediated apoptotic program, the implications of which increase understanding of how HDAC inhibitors selectively target malignant cells.

Table of Contents

749 Integrated Genomic Analysis of Pancreatic Ductal Adenocarcinomas Reveals Genomic Rearrangement Events as Significant Drivers of Disease

Stephen J. Murphy, Steven N. Hart, Geoffrey C. Halling, Sarah H. Johnson, James B. Smadbeck, Travis Drucker, Joema Felipe Lima, Fariborz Rakhshan Rohakhtar, Faye R. Harris, Farhad Kosari, Subbaya Subramanian, Gloria M. Petersen, Timothy D. Wiltshire, Benjamin R. Kipp, Mark J. Truty, Robert R. McWilliams, Fergus J. Couch, and George Vasmatazis

Précis: Large genomic rearrangements may perturb signaling pathways that drive pancreatic cancer initiation, affecting progression to the same extent as point mutations, underscoring the need for comprehensive genomic analysis to elucidate disease mechanisms.

CORRECTION

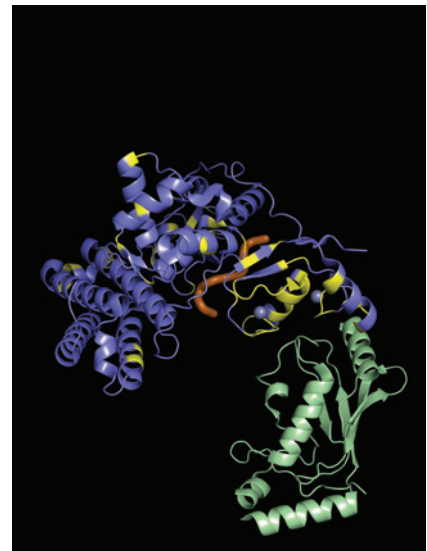
762 Correction: Development of a New Tracking Tool for the Human Monomeric Laminin- γ 2 Chain *In Vitro* and *In Vivo*

 AC icon indicates Author Choice

For more information please visit www.aacrjournals.org

ABOUT THE COVER

The monomeric Casitas B-lineage lymphoma (c-Cbl, CBL) RING finger ubiquitin ligase (blue) can bind to phosphorylated RTK (orange peptide) via the TKBD domain. Upon phosphorylation, CBL undergoes a large conformational change that positions the ubiquitin-conjugating enzyme E2 (green) active site close to RTK. Cancer mutation sites are mapped on the structure of the complex and are shown in yellow; Zn ions are shown as blue balls. Other stages of the CBL activation cycle are depicted in Figure 1 of the article. For details, see article by Li and colleagues on page 561.



Cancer Research

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

76 (3)

Cancer Res 2016;76:507-762.

Updated version Access the most recent version of this article at:
<http://cancerres.aacrjournals.org/content/76/3>

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/76/3>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.