

BREAKING ADVANCES

- 4171 | **Highlights from Recent Cancer Literature**

REVIEWS

- 4173 | **Cooperation and Antagonism among Cancer Genes: The Renal Cancer Paradigm**
Samuel Peña-Llopis, Alana Christie, Xian-Jin Xie, and James Brugarolas

- 4180 | **Lessons from Functional Analysis of Genome-Wide Association Studies**
Inderpreet Sur, Sari Tuupanen, Thomas Whittington, Lauri A. Aaltonen, and Jussi Taipale

MEETING REPORT

- 4185 | **Exploiting Tumor Vulnerabilities: Epigenetics, Cancer Metabolism and the mTOR Pathway in the Era of Personalized Medicine**
Cristina Muñoz-Pinedo, Eva González-Suárez, Anna Portela, Antonio Gentilella, and Manel Esteller

PRIORITY REPORT

- 4190 | **Evaluation of LDH-A and Glutaminase Inhibition *In Vivo* by Hyperpolarized ¹³C-Pyruvate Magnetic Resonance Spectroscopy of Tumors**
Prasanta Dutta, Anne Le, David L. Vander Jagt, Takashi Tsukamoto, Gary V. Martinez, Chi V. Dang, and Robert J. Gillies
Précis: This is the first study to report the ability to monitor biomarkers of antimetabolic therapy in real time, paving the way for clinical development of imaging biomarkers to monitor metabolic pharmacodynamics.

MICROENVIRONMENT AND IMMUNOLOGY

- 4196 | **Tumor MMP-1 Activates Endothelial PAR1 to Facilitate Vascular Intravasation and Metastatic Dissemination**
Anna Juncker-Jensen, Elena I. Deryugina, Ivo Rimann, Ewa Zajac, Tatyana A. Kupriyanova, Lars H. Engelholm, and James P. Quigley
Précis: Therapeutic targeting of a newly unraveled tumor pathway with connections to a thrombin receptor on endothelial cells is effective in preventing carcinoma cell intravasation, the earliest step of tumor metastasis.

- 4212 | **VEGF-C and VEGF-D Blockade Inhibits Inflammatory Skin Carcinogenesis**
Annamari K. Alitalo, Steven T. Proulx, Sinem Karaman, David Aebischer, Stefania Martino, Manuela Jost, Nicole Schneider, Maija Bry, and Michael Detmar

Précis: These findings show that less-studied isoforms of VEGF shape the inflammatory tumor microenvironment and support the use of VEGF-C/D antagonists to inhibit both early and late stages of tumor growth.

- 4222 | **Intestinal Bacteria Modify Lymphoma Incidence and Latency by Affecting Systemic Inflammatory State, Oxidative Stress, and Leukocyte Genotoxicity**
Mitsuko L. Yamamoto, Irene Maier, Angeline Tilly Dang, David Berry, Jared Liu, Paul M. Ruegger, Jiue-in Yang, Phillip A. Soto, Laura L. Presley, Ramune Reliene, Aya M. Westbrook, Bo Wei, Alexander Loy, Christopher Chang, Jonathan Braun, James Borneman, and Robert H. Schiestl

Précis: This potentially seminal study reveals the powerful effects that intestinal microbiota can exert on lymphoma penetrance in genetically susceptible mice, with possible implications for preventing this cancer in individuals who are at risk of disease.

- 4233 | **Bone Marrow-Derived CD11b⁺Jagged2⁺ Cells Promote Epithelial-to-Mesenchymal Transition and Metastasization in Colorectal Cancer**
Francisco Caiado, Tânia Carvalho, Isadora Rosa, Leonor Remédio, Ana Costa, João Matos, Beate Heissig, Hideo Yagita, Koichi Hattori, João Pereira da Silva, Paulo Fidalgo, António Dias Pereira, and Sérgio Dias

Précis: These findings suggest that quantifying the number of circulating bone marrow cells expressing JAG2 might define metastatic development in colorectal cancer patients.

4247

***Rb1* Haploinsufficiency Promotes
Telomere Attrition and Radiation-
Induced Genomic Instability**

Iria Gonzalez-Vasconcellos, Natasa Anastasov,
Bahar Sanli-Bonazzi, Olena Klymenko,
Michael J. Atkinson, and Michael Rosemann

Précis: These findings suggest that telomere maintenance is a noncanonical caretaker function of the retinoblastoma protein, such that its deficiency in cancer may act beyond simply deregulating cell-cycle control.

4256



**Extracellular DNA in Pancreatic
Cancer Promotes Cell Invasion
and Metastasis**

Fushi Wen, Alex Shen, Andrew Choi,
Eugene W. Gerner, and Jiaqi Shi

Précis: This study offers a provocative set of observations, suggesting that the accumulation of extracellular DNA in the microenvironment of pancreatic tumors triggers a feed-forward inflammatory signal that strongly promotes invasive and metastatic behavior.

4267



**Radioresistant Cancer Cells Can Be
Conditioned to Enter Senescence by
mTOR Inhibition**

Hae Yun Nam, Myung Woul Han,
Hyo Won Chang, Yoon Sun Lee, Myungjin Lee,
Hyang Ju Lee, Byoung Wook Lee, Hee Jin Lee,
Kyung Eun Lee, Min Kyo Jung, Hyesung Jeon,
Seung-Ho Choi, Neung Hwa Park,
Sang Yoon Kim, and Seong Who Kim

Précis: By revealing that mTOR inhibition can promote cellular senescence in radio-resistant cancer cells through activation of the RB pathway, this study provides a novel mechanistic perspective on how mTOR inhibitors can be used combinatorially to improve cancer therapy.

4278



**PML-RAR α and Its Phosphorylation
Regulate PML Oligomerization and
HIPK2 Stability**

Yutaka Shima, Yuki Honma, and
Issay Kitabayashi

Précis: These findings offer mechanistic insights into the basis for the most common prodifferentiation therapies used to treat acute promyelocytic leukemia in the clinic.

4289

**HMGA2 Is a Driver of Tumor
Metastasis**

Asahiro Morishita, M. Raza Zaidi, Akira Mito, Devipriya Sankarasharma, Matthias Szabolcs, Yasunori Okada, Jeanine D'Armiento, and Kiran Chada

Précis: These results define a key function in cancer invasion and metastasis for a nonhistone chromatin-binding protein that activates EMT by upregulating the TGF β signaling pathway.

4300

**ATR-Dependent Phosphorylation of
FANCM at Serine 1045 Is Essential for
FANCM Functions**

Thiyam Ramsing Singh, Abdullah Mahmood Ali,
Manikandan Paramasivam, Arun Pradhan,
Kebola Wahengbam, Michael M. Seidman, and
Amom Ruhikanta Meetei

Précis: These findings help unravel the intricacies of a central pathway of DNA damage response and repair.

4311

**Autophagy Plays a Critical Role in the
Degradation of Active RHOA, the
Control of Cell Cytokinesis, and
Genomic Stability**

Amine Belaid, Michaël Cerezo,
Abderrahman Chargui,
Elisabeth Corcelle-Termeau,
Florence Pedeutour, Sandy Giuliano, Marius Ilie,
Isabelle Rubera, Michel Tauc, Sophie Barale,
Corinne Bertolotto, Patrick Brest,
Valérie Vouret-Craviari, Daniel J. Klionsky,
Georges F. Carle, Paul Hofman, and
Baharia Mograbi

Précis: Autophagy may act in part as a safeguard mechanism in cancer cells by maintaining RHOA levels at the midbody needed for faithful completion of cytokinesis and genome inheritance.

4323

**Integration of High-Resolution
Methylome and Transcriptome
Analyses to Dissect Epigenomic
Changes in Childhood Acute
Lymphoblastic Leukemia**

Stephan Busche, Bing Ge, Ramon Vidal,
Jean-François Spinella, Virginie Saillour,
Chantal Richer, Jasmine Healy,
Shu-Huang Chen, Arnaud Droit, Daniel Sinnett,
and Tomi Pastinen

Précis: A multilevel genome-wide profiling approach defines key biomarkers and driver elements in major subtypes of childhood pre-B acute lymphoblastic leukemia.

4337

**Loss of ARF Sensitizes Transgenic
BRAF^{V600E} Mice to UV-Induced
Melanoma via Suppression of XPC**

Chi Luo, Jinghao Sheng, Miaofen G. Hu,
Frank G. Haluska, Rutao Cui, Zhengping Xu,
Philip N. Tschlis, Guo-Fu Hu, and
Philip W. Hinds

Précis: Mutations in p19^{ARF} and BRAF^{V600E} cooperate to suppress DNA repair during melanoma formation, promoting disease beyond effects on p53 function and senescence, which are minimally affected.

4349 **PPAR δ Induces Estrogen Receptor-Positive Mammary Neoplasia through an Inflammatory and Metabolic Phenotype Linked to mTOR Activation**
Hongyan Yuan, Jin Lu, Junfeng Xiao, Geeta Upadhyay, Rachel Umans, Bhaskar Kallakury, Yuhzi Yin, Michael E. Fant, Levy Kopelovich, and Robert I. Glazer
Précis: These findings identify a targetable transcription factor that drives the pathogenesis of breast cancer through mTOR activation, with implications for new therapeutic approaches to prevent and treat this disease.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4362 **Structure-Specific Endonucleases Xpf and Mus81 Play Overlapping but Essential Roles in DNA Repair by Homologous Recombination**
Koji Kikuchi, Takeo Narita, Van T. Pham, Junko Iijima, Kouji Hirota, Islam Shamima Keka, Mohiuddin, Katsuya Okawa, Tetsuya Hori, Tatsuo Fukagawa, Jeroen Essers, Roland Kanaar, Matthew C. Whitby, Kaoru Sugasawa, Yoshihito Taniguchi, Katsumi Kitagawa, and Shunichi Takeda
Précis: These findings address gaps in knowledge concerning how DNA repair mediated by homologous recombination can influence the sensitivity of cancer cells to genotoxic chemotherapeutic agents, with potential therapeutic implications.

4372 **The Exomes of the NCI-60 Panel: A Genomic Resource for Cancer Biology and Systems Pharmacology**
Ogan D. Abaan, Eric C. Polley, Sean R. Davis, Yuelin J. Zhu, Sven Bilke, Robert L. Walker, Marbin Pineda, Yevgeniy Gindin, Yuan Jiang, William C. Reinhold, Susan L. Holbeck, Richard M. Simon, James H. Doroshow, Yves Pommier, and Paul S. Meltzer
Précis: Making whole exome sequence data part of the NCI-60 tumor cell line database will provide the ability to quickly identify expression correlates of anticancer drug response, with immediate relevance to translational and clinical research.

4383 **Therapeutic Destruction of Insulin Receptor Substrates for Cancer Treatment**
Hadas Reuveni, Efrat Flashner-Abramson, Lilach Steiner, Kirill Makedonski, Renduo Song, Alexei Shir, Meenhard Herlyn, Menashe Bar-Eli, and Alexander Levitzki
Précis: This important study offers preclinical proof of concept for a family of small-molecule inhibitors that cause destruction of insulin receptor substrates as broad-acting drugs for cancer treatment, including deadly melanomas that become resistant to BRAF inhibitors.

4395 **4-Hydroxytamoxifen Induces Autophagic Death through K-Ras Degradation**
Latika Kohli, Niroop Kaza, Tatjana Coric, Stephanie J. Byer, Nicole M. Brossier, Barbara J. Klocke, Mary-Ann Bjornsti, Steven L. Carroll, and Kevin A. Roth
Précis: A novel mechanism of autophagic death triggered by tamoxifen in tumor cells may make this common breast cancer drug more broadly useful in cancer therapy.

4406 **KEAP1 Is a Redox Sensitive Target That Arbitrates the Opposing Radiosensitive Effects of Parthenolide in Normal and Cancer Cells**
Yong Xu, Fang Fang, Sumitra Miriyala, Peter A. Crooks, Terry D. Oberley, Luksana Chaiswing, Teresa Noel, Aaron K. Holley, Yanming Zhao, Kelley K. Kiningham, Daret K. St. Clair, and William H. St. Clair
Précis: These findings establish a principle through which it is possible to develop agents that can radiosensitize tumor cells but radioprotect normal cells, with important implications for the development of cancer-specific drugs.

4418 **A Survivin-Associated Adaptive Response in Radiation Therapy**
David J. Grdina, Jeffrey S. Murley, Richard C. Miller, Helena J. Mauceri, Harold G. Sutton, Jian Jian Li, Gayle E. Woloschak, and Ralph R. Weichselbaum
Précis: Very low-dose radiation used increasingly in imaging tumors subjected to irradiation is reported in this study to trigger adaptive responses that could adversely affect treatment outcomes, a possibility requiring attention by radiation oncologists.


4429 **Metformin Decreases Glucose Oxidation and Increases the Dependency of Prostate Cancer Cells on Reductive Glutamine Metabolism**
Sarah-Maria Fendt, Eric L. Bell, Mark A. Keibler, Shawn M. Davidson, Gregory J. Wirth, Brian Fiske, Jared R. Mayers, Matthias Schwab, Gary Bellingier, Alfredo Csibi, Akash Patnaik, Marie Jose Blouin, Lewis C. Cantley, Leonard Guarente, John Blenis, Michael N. Pollak, Aria F. Olumi, Matthew G. Vander Heiden, and Gregory Stephanopoulos
Précis: These results suggest a strategy to improve upon the powerful anticancer effects of metformin, a widely used diabetes drug, through a coordinate inhibition of glutamine metabolism.

4439 **Antitumor Activity of a Humanized, Bivalent Immunotoxin Targeting Fn14-Positive Solid Tumors**
Hong Zhou, Walter N. Hittelman, Hideo Yagita, Lawrence H. Cheung, Stuart S. Martin, Jeffrey A. Winkles, and Michael G. Rosenblum
Précis: These findings offer a preclinical proof of concept for the use of an immune targeting principle that may be both highly specific to cancer and broadly applicable to many different disease types.

4451 **Visualizing Inhibition of Nucleosome Mobility and Transcription by Cisplatin–DNA Interstrand Crosslinks in Live Mammalian Cells**
Guangyu Zhu, Lina Song, and Stephen J. Lippard
Précis: A minor DNA adduct formed by cisplatin may confer the most significant effects of this drug on tumor cells, as revealed by this study of nucleosome structure and DNA transcription in live cells.

TUMOR AND STEM CELL BIOLOGY

4461 **CX3CL1 Promotes Breast Cancer via Transactivation of the EGF Pathway**
Manuel Tardáguila, Emilia Mira, Miguel A. García-Cabezas, Anna M. Feijoo, Miguel Quintela-Fandino, Iñigo Azcoitia, Sergio A. Lira, and Santos Mañes
Précis: A chemokine that is induced by IL-1, a central proinflammatory cytokine in the tumor microenvironment, promotes HER2⁺ breast cancers by supporting expression of the EGF receptor.

4474  **β-Catenin Signaling Is a Critical Event in ErbB2-Mediated Mammary Tumor Progression**
Babette Schade, Robert Lesurf, Virginie Sanguin-Gendreau, Tung Bui, Geneviève Deblois, Sandra A. O'Toole, Ewan K.A. Millar, Sara J. Zardawi, Elena Lopez-Knowles, Robert L. Sutherland, Vincent Giguère, Michael Kahn, Michael Hallett, and William J. Muller
Précis: A mouse model that faithfully recapitulates many genetic features of the basal subset of ErbB2-positive breast cancers identifies the Wnt pathway as an essential driver and candidate therapeutic target for this aggressive disease.

4488 **EYA1 Phosphatase Function Is Essential to Drive Breast Cancer Cell Proliferation through Cyclin D1**
Kongming Wu, Zhaoming Li, Shaoxin Cai, Lifeng Tian, Ke Chen, Jing Wang, Junbo Hu, Ye Sun, Xue Li, Adam Ertel, and Richard G. Pestell
Précis: The homolog of a fruitfly regulator of retinal development that is overexpressed in the luminal B subtype of breast cancers appears to be an essential pathogenic driver in this setting, with implications in other cancers where this regulator is also overexpressed.

4500 **Microtubule-Associated Histone Deacetylase 6 Supports the Calcium Store Sensor STIM1 in Mediating Malignant Cell Behaviors**
Ying-Ting Chen, Yih-Fung Chen, Wen-Tai Chiu, Kuan-Yu Liu, Yu-Lin Liu, Jang-Yang Chang, Hsien-Chang Chang, and Meng-Ru Shen
Précis: Targeting calcium-based cellular physiology offers an appealing general strategy to disrupt cancer cell function, if a disease-specific approach can be identified.

4510 **c-Src Modulates Estrogen-Induced Stress and Apoptosis in Estrogen-Deprived Breast Cancer Cells**
Ping Fan, Obi L. Griffith, Fadeke A. Agboke, Pavana Anur, Xiaojun Zou, Russell E. McDaniel, Karen Creswell, Sung Hoon Kim, John A. Katzenellenbogen, Joe W. Gray, and V. Craig Jordan
Précis: In revealing a role for c-Src tyrosine kinase in estrogen-induced apoptosis, this study offers a mechanistic rationale for a new approach in the treatment of endocrine-resistant breast cancer.

4521 **The ShcA PTB Domain Functions as a Biological Sensor of Phosphotyrosine Signaling during Breast Cancer Progression**
Ryuhjin Ahn, Valerie Sabourin, Jacqueline R. Ha, Sean Cory, Gordana Maric, Young Kyuen Im, W. Rod Hardy, Hong Zhao, Morag Park, Michael Hallett, Peter M. Siegel, Tony Pawson, and Josie Ursini-Siegel
Précis: In the receptor tyrosine kinase adapter protein Shc, the phosphotyrosine-binding PTB domain rather than the SH2 domain appears to be the critical intersection for transmitting effector signals that control breast cancer development.

4533 **ETS Transcription Factor ESE1/ELF3 Orchestrates a Positive Feedback Loop That Constitutively Activates NF-κB and Drives Prostate Cancer Progression**

Nicole Longoni, Manuela Sarti, Domenico Albino, Gianluca Civenni, Anastasia Malek, Erica Orтели, Sandra Pinton, Maurizia Mello-Grand, Paola Ostano, Gioacchino D'Ambrosio, Fausto Sessa, Ramon Garcia-Escudero, George N. Thalmann, Giovanna Chiorino, Carlo V. Catapano, and Giuseppina M. Carbone

Précis: In extending the importance of ETS transcription functions in prostate cancer, this study defines an important new mechanism connecting inflammatory signaling, NF-κB activation, and prostate cancer progression.

4548 **Gankyrin Activates IL-8 to Promote Hepatic Metastasis of Colorectal Cancer**

Zhaofang Bai, Yanhong Tai, Weihua Li, Cheng Zhen, Weiting Gu, Zhao Jian, Qianyi Wang, Jieru E. Lin, Qing Zhao, Weili Gong, Bing Liang, Chenguang Wang, and Tao Zhou

Précis: This potentially seminal study suggests readily tractable targets to prevent or treat hepatic metastasis of colorectal cancer, the chief form of the advanced state in this disease.

4559 **Chromatin Regulator PRC2 Is a Key Regulator of Epigenetic Plasticity in Glioblastoma**

Atsushi Natsume, Motokazu Ito, Keisuke Katsushima, Fumiharu Ohka, Akira Hatanaka, Keiko Shinjo, Shinya Sato, Satoru Takahashi, Yuta Ishikawa, Ichiro Takeuchi, Hiroki Shimogawa, Motonari Uesugi, Hideyuki Okano, Seung U. Kim, Toshihiko Wakabayashi, Jean-Pierre J. Issa, Yoshitaka Sekido, and Yutaka Kondo

Précis: A modifier complex that controls tumor cell plasticity may provide a target to restrict the functional heterogeneity in tumors, a core challenge to all cancer cell-centric drugs, given the huge reservoir of resistance mechanisms that such heterogeneity confers.

4571 **Vitronectin-αvβ3 Integrin Engagement Directs Hypoxia-Resistant mTOR Activity and Sustained Protein Synthesis Linked to Invasion by Breast Cancer Cells**

Carolina Pola, Silvia C. Formenti, and Robert J. Schneider

Précis: These findings suggest a mechanistic rationale to target a nodal driver of breast cancer invasion to bone, in a hypoxic tissue microenvironment where this common but little-understood step in progression occurs.

4579 **Neuropilin-2 Promotes Extravasation and Metastasis by Interacting with Endothelial α5 Integrin**

Ying Cao, Luke H. Hoepfner, Steven Bach, Guangqi E, Yan Guo, Enfeng Wang, Jianmin Wu, Mark J. Cowley, David K. Chang, Nicola Waddell, Sean M. Grimmond, Andrew V. Biankin, Roger J. Daly, Xiaohui Zhang, and Debabrata Mukhopadhyay

Précis: This important study defines a mechanism of extravasation, which is needed for metastasis but remains little understood at the molecular level.

LETTERS TO THE EDITOR

4591 **Tumor Growth Control with IDO-Silencing *Salmonella*—Letter**
Robert M. Hoffman

4592 **Tumor Growth Control with IDO-Silencing *Salmonella*—Reply**
Edwin R. Manuel, Bruce R. Blazar, and Don J. Diamond

CORRECTION

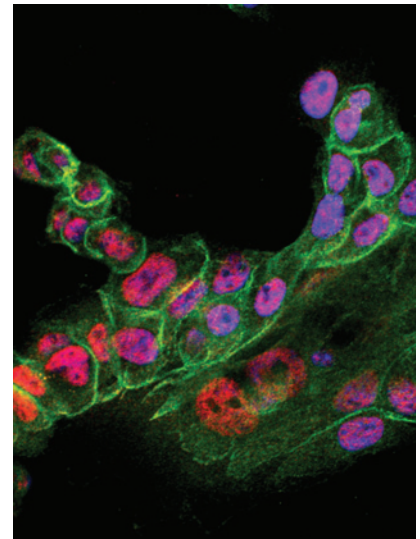
4594 **Correction: Critical Role for the Receptor Tyrosine Kinase EPHB4 in Esophageal Cancers**

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ABOUT THE COVER

β -catenin is a multifunctional protein that plays a vital structural role in cadherin-based cell adhesion and is an important transcriptional activator of canonical Wnt-mediated gene expression. Dysregulation or mutational activation of the β -catenin signaling is a critical event in the development of human cancer, including breast cancer. Immunofluorescence staining was used to visualize localization of β -catenin and activated β -catenin in human ERBB2-overexpressing ER-negative breast cancer cells (HCC202). The presence of nuclear-activated β -catenin in these breast cancer cells was correlated with a decrease in cell proliferation upon inhibition of β -catenin signaling. For details, see article by Schade and colleagues on page 4474.



Cancer Research

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