

BREAKING ADVANCES

- 5585** Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

- 5587** β -Catenin Mutations: Insights into the APC Pathway and the Power of Genetics
Patrice J. Morin, Kenneth W. Kinzler, and Andrew B. Sparks
- 5590** Blood Worth Bottling: Circulating Tumor DNA as a Cancer Biomarker
Elizabeth L. Christie, Sarah-Jane Dawson, and David D.L. Bowtell

REVIEWS

- 5592** Visualizing Epithelial–Mesenchymal Transition Using the Chromobody Technology
Julia Maier, Bjoern Traenkle, and Ulrich Rothbauer
- 5597** The Emerging Role of B Cells in Tumor Immunity
Peiling Tsou, Hiroyuki Katayama, Edwin J. Ostrin, and Samir M. Hanash

PERSPECTIVES

- 5602** Commentary on Almassalha et al., "The Greater Genomic Landscape: The Heterogeneous Evolution of Cancer"
Henry T. Lynch, Marc Rendell, Trudy G. Shaw, Peter Silberstein, and Binh T. Ngo
- 5605**  The Greater Genomic Landscape: The Heterogeneous Evolution of Cancer
Luay M. Almassalha, Greta M. Bauer, John E. Chandler, Scott Gladstein, Igal Szeleifer, Hemant K. Roy, and Vadim Backman
- 5610** The Challenge of Developing Autophagy Inhibition as a Therapeutic Strategy
David A. Gewirtz

PRIORITY REPORTS

- 5615** *RBM5-AS1* Is Critical for Self-Renewal of Colon Cancer Stem-like Cells
Serena Di Cecilia, Fan Zhang, Ana Sancho, SiDe Li, Francesca Aguiló, Yifei Sun, Madhumitha Rengasamy, Weijia Zhang, Luigi Del Vecchio, Francesco Salvatore, and Martin J. Walsh
Précis: These findings show how a little studied long non-coding RNA enables the function of cancer stem-like cells in the colon, as mediated by direct physical interactions with β -catenin in the WNT signaling pathway.
- 5628** RNA Sequencing Identifies Transcriptionally Viable Gene Fusions in Esophageal Adenocarcinomas
Andrew E. Blum, Srividya Venkitachalam, Yan Guo, Ann Marie Kieber-Emmons, Lakshmeswari Ravi, Apoorva K. Chandar, Prasad G. Iyer, Marcia I. Canto, Jean S. Wang, Nicholas J. Shaheen, Jill S. Barnholtz-Sloan, Sanford D. Markowitz, Joseph E. Willis, Yu Shyr, Amitabh Chak, Vinay Varadan, and Kishore Guda
Précis: A chimeric protein expressed from a *RPS6KB1-VMP1* gene fusion discovered in this global RNA expression study promotes esophageal adenocarcinoma by modulating autophagy-related processes, offering a new perspective on the molecular pathogenesis of this aggressive cancer.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 5634** Estrogen Receptor α Promotes Breast Cancer by Reprogramming Choline Metabolism
Min Jia, Trygve Andreassen, Lasse Jensen, Tone Frost Bathen, Indranil Sinha, Hui Gao, Chunyan Zhao, Lars-Arne Haldosen, Yihai Cao, Leonard Gimita, Siver Andreas Moestue, and Karin Dahlman-Wright
Précis: These findings offer a preclinical proof of concept for the exploration of the ER α target gene product CHPT1 as a promising therapeutic target in breast cancer.
- 5647** Imaging of Esophageal Lymph Node Metastases by Desorption Electrospray Ionization Mass Spectrometry
Nima Abbassi-Ghadi, Ottmar Golf, Sacheen Kumar, Stefan Antonowicz, James S. McKenzie, Juzheng Huang, Nicole Strittmatter, Hiromi Kudo, Emrys A. Jones, Kirill Veselkov, Robert Goldin, Zoltan Takats, and George B. Hanna
Précis: These findings illustrate the ability of an ambient mass spectrometry technique to accurately determine the presence of metastases in a lymph node specimen based on its lipid profile.

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MICROENVIRONMENT AND IMMUNOLOGY

- 5657** Endoplasmic Reticulum Stress Protein GRP78 Modulates Lipid Metabolism to Control Drug Sensitivity and Antitumor Immunity in Breast Cancer
Katherine L. Cook, David R. Soto-Pantoja, Pamela A.G. Clarke, M. Idalia Cruz, Alan Zwart, Anni Wärrri, Leena Hilakivi-Clarke, David D. Roberts, and Robert Clarke
Précis: Targeting an endoplasmic reticulum chaperone protein triggers macrophage recruitment to tumors and lowers expression of the self-recognition marker CD47, potentiating an immune-dependent mechanism of cancer cell death.
- 5671** CCL2 Produced by the Glioma Microenvironment Is Essential for the Recruitment of Regulatory T Cells and Myeloid-Derived Suppressor Cells
Alan L. Chang, Jason Miska, Derek A. Wainwright, Mahua Dey, Claudia V. Rivetta, Dou Yu, Deepak Kanojia, Katarzyna C. Pituch, Jian Qiao, Peter Pytel, Yu Han, Meijing Wu, Lingjiao Zhang, Craig M. Horbinski, Atique U. Ahmed, and Maciej S. Lesniak
Précis: These findings show how the most aggressive form of brain cancer subverts the tissue microenvironment to recruit two potent mechanisms of immunosuppression that drive progression, with potential therapeutic implications to improve treatment.
- 5683** Stimulation of Natural Killer Cell-Mediated Tumor Immunity by an IL15/TGF β -Neutralizing Fusion Protein
Spencer Ng, Jiusheng Deng, Raghavan Chinnadurai, Shala Yuan, Andrea Pennati, and Jacques Galipeau
Précis: These results offer a preclinical proof of concept for the use of a new class of chimeric protein therapeutics that can coordinately neutralize the effects of immunosuppressive TGF β in the tumor microenvironment while empowering tumor immunity.
- 5696** Adaptive NK Cells with Low TIGIT Expression Are Inherently Resistant to Myeloid-Derived Suppressor Cells
Dhifaf Sarhan, Frank Cichocki, Bin Zhang, Ashley Yingst, Stephen R. Spellman, Sarah Cooley, Michael R. Verneris, Bruce R. Blazar, and Jeffrey S. Miller
Précis: This seminal study shows how antagonists of the immune suppression receptor TIGIT offer a novel type of checkpoint inhibitor to enhance natural killer cell-mediated attacks on tumor cells.

MOLECULAR AND CELLULAR PATHOBIOLOGY



- 5707** Heme Oxygenase-1 Controls an HDAC4-miR-206 Pathway of Oxidative Stress in Rhabdomyosarcoma
 Maciej Ciesla, Paulina Marona, Magdalena Kozakowska, Mateusz Jez, Marta Seczynska, Agnieszka Loboda, Karolina Bukowska-Strakova, Agata Szade, Magdalena Walawender, Magdalena Kusior, Jacek Stepniewski, Krzysztof Szade, Bart Krist, Oleksandr Yagensky, Aleksandra Urbanik, Bernarda Kazanowska, Jozef Dulak, and Alicja Jozkowicz
Précis: These findings offer novel insights into the pathogenesis of rhabdomyosarcoma, an aggressive muscle tumor, with implications for a novel differentiation treatment strategy.
- 5719** Recurrent PPP2R1A Mutations in Uterine Cancer Act through a Dominant-Negative Mechanism to Promote Malignant Cell Growth
Dorien Haesen, Layka Abbasi Asbagh, Rita Derua, Antoine Hubert, Stefanie Schrauwen, Yana Hoorne, Frédéric Amant, Etienne Waelkens, Anna Sablina, and Veerle Janssens
Précis: These results show how recurrent mutations in the α subunit of the tumor suppressive protein phosphatase PP2A promote oncogenic signaling in endometrial cancer cells, with implications for the improvement of treatment approaches.
- 5732** PAK4 Phosphorylates p53 at Serine 215 to Promote Liver Cancer Metastasis
Hai-Tao Xu, Wai-Lung Lai, Heong-Fai Liu, Leo Lap-Yan Wong, Irene Oi-Lin Ng, and Yick Pang Ching
Précis: These results highlight a kinase implicated in cell migratory behavior in conferring the metastatic behavior of aggressive liver cancers, with implications for their therapeutic management.
- 5743** Chromatin Remodeling Factor LSH Drives Cancer Progression by Suppressing the Activity of Fumarate Hydratase
 Xiaozhen He, Bin Yan, Shuang Liu, Jiantao Jia, Weiwei Lai, Xing Xin, Can-e Tang, Dixian Luo, Tan Tan, Yiqun Jiang, Ying Shi, Yating Liu, Desheng Xiao, Ling Chen, Shao Liu, Chao Mao, Gang Yin, Yan Cheng, Jia Fan, Ya Cao, Kathrin Muegge, and Yongguang Tao
Précis: Nasopharyngeal carcinoma, an EBV-associated cancer that is prevalent in China, is driven by a chromatin modeling factor that supports epithelial-mesenchyme transition in cancer cells through a metabolic pathway.

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5756 Metastatic Progression of Prostate Cancer Is Mediated by Autonomous Binding of Galectin-4-O-Glycan to Cancer Cells

Chin-Hsien Tsai, Sheue-Fen Tzeng, Tai-Kuang Chao, Chia-Yun Tsai, Yu-Chih Yang, Ming-Ting Lee, Jiuan-Jiuan Hwang, Yu-Ching Chou, Mong-Hsun Tsai, Tai-Lung Cha, and Pei-Wen Hsiao

Précis: During malignant progression, prostate cancers elevate expression of galectin-4 and a selected group of O-glycosylation enzymes that drive functions essential for metastasis, with implications for therapeutic targeting of advanced disease.

PREVENTION AND EPIDEMIOLOGY

5768 Novel Association of Genetic Markers Affecting CYP2A6 Activity and Lung Cancer Risk

Yesha M. Patel, Sunghim L. Park, Younghun Han, Lynne R. Wilkens, Heike Bickeböller, Albert Rosenberger, Neil Caporaso, Maria Teresa Landi, Irene Brüske, Angela Risch, Yongyue Wei, David C. Christiani, Paul Brennan, Richard Houlston, James McKay, John McLaughlin, Rayjean Hung, Sharon Murphy, Daniel O. Stram, Christopher Amos, and Loïc Le Marchand

Précis: The present study is the first genome-wide association study to document lung cancer risks conferred by specific genetic variants in the chief enzyme that metabolizes nicotine.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5777 miR-1298 Inhibits Mutant KRAS-Driven Tumor Growth by Repressing FAK and LAMB3

Ying Zhou, Jason Dang, Kung-Yen Chang, Edwin Yau, Pedro Aza-Blanc, Jorge Moscat, and Tariq M. Rana

Précis: A large-scale microRNA screen in cancer cells driven by mutant KRAS identifies a new molecular mechanism of synthetic lethality that might be therapeutically exploited.

5788 Antitumor Properties of an IgG2-Enhanced Next-Generation MET Monoclonal Antibody That Degrades Wild-Type and Mutant MET Receptors

Yan Yang, Sreekala Mandiyan, Brett S. Robinson, and Gerald McMahon

Précis: This study highlights a second generation MET monoclonal antibody that acts by a novel mechanism to degrade the MET receptor in cancer cells, potentially offering a therapeutic tool to treat a broader range of human tumors involving common MET alleles.

5798 Evaluation of Alternative *In Vivo* Drug Screening Methodology: A Single Mouse Analysis

Brendan Murphy, Han Yin, John M. Maris, E. Anders Kolb, Richard Gorlick, C. Patrick Reynolds, Min H. Kang, Stephen T. Keir, Raushan T. Kurmasheva, Igor Dvorchik, Jianrong Wu, Catherine A. Billups, Nana Boateng, Malcolm A. Smith, Richard B. Lock, and Peter J. Houghton

Précis: This study describes a new approach for the use of patient-derived xenograft (PDX) models in drug discovery and development that may more efficiently and fully encompass tumor heterogeneity.

5810 Chromatin-Remodeling Complex SWI/SNF Controls Multidrug Resistance by Transcriptionally Regulating the Drug Efflux Pump ABCB1

Ramin Dubey, Andres M. Lebensohn, Zahra Bahrami-Nejad, Caleb Marceau, Magali Champion, Olivier Gevaert, Branimir I. Sikić, Jan E. Carette, and Rajat Rohatgi

Précis: These results illuminate a central mechanism through which cancer cells acquire multidrug resistance, by upregulating the expression of an chemotherapy efflux pump.

5822 Cytotoxic Properties of a DEPTOR-mTOR Inhibitor in Multiple Myeloma Cells

Yijiang Shi, Tracy R. Daniels-Wells, Patrick Frost, Jihye Lee, Richard S. Finn, Carolyn Bardeleben, Manuel L. Penichet, Michael E. Jung, Joseph Gera, and Alan Lichtenstein

Précis: These results offer a preclinical proof of concept for targeting a particular mTOR complex as a therapeutic strategy to eradicate multiple myeloma cells.

5832 Mesenchymal Stem Cell-Derived Exosomes Stimulate Cycling Quiescence and Early Breast Cancer Dormancy in Bone Marrow

Sarah A. Bliss, Garima Sinha, Oleta A. Sandiford, Lisa M. Williams, Daniel J. Engelberth, Khadidiatou Guiro, Leidy L. Isenalumhe, Steven J. Greco, Seda Ayer, Margarette Bryan, Rakesh Kumar, Nicholas M. Ponzio, and Pranela Rameshwar

Précis: Breast cancer cells induce changes in the miRNA stored in exosomes released from mesenchymal stem cells, helping establish tumor dormancy and chemoresistance in the bone marrow.

TUMOR AND STEM CELL BIOLOGY

5845 Acidosis Acts through HSP90 in a PHD/VHL-Independent Manner to Promote HIF Function and Stem Cell Maintenance in Glioma

Alina Filatova, Sascha Seidel, Nuray Böğürçü, Sabine Gräf, Boyan K. Garvalov, and Till Acker

Précis: These findings suggest that HSP90 offers an attractive druggable target to choke microenvironmental supports for cancer stem-like cells in deadly hypoxic tumors.

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5857 RANK Signaling Blockade Reduces Breast Cancer Recurrence by Inducing Tumor Cell Differentiation



Guillermo Yoldi, Pasquale Pellegrini, Eva M. Trinidad, Alex Cordero, Jorge Gomez-Miragaya, Jordi Serra-Musach, William C. Dougall, Purificación Muñoz, Miguel-Angel Pujana, Lourdes Planelles, and Eva González-Suárez

Précis: These findings show how neoadjuvant therapy with inhibitors of RANK signaling can provide a differentiation therapy in breast cancer, through the depletion of cancer stem-like cells, extending the use of these inhibitors beyond simply the management of skeletal-related events.

5870 An Integrated Nanotechnology-Enabled Transbronchial Image-Guided Intervention Strategy for Peripheral Lung Cancer

Cheng S. Jin, Hironobu Wada, Takashi Anayama, Patrick Z. McVeigh, Hsin Pei Hu, Kentaro Hirohashi, Takahiro Nakajima, Tatsuya Kato, Shaf Keshavjee, David Hwang, Brian C. Wilson, Gang Zheng, and Kazuhiro Yasufuku

Précis: Use of a multifunctional porphyrin-nanoparticle along with a unique fluorescence bronchoscope permits a minimally invasive type of transbronchial imaging to guide localized treatments for peripheral lung cancer.

5881 Androgen and Estrogen Receptors in Breast Cancer Coregulate Human UDP-



Glucuronosyltransferases 2B15 and 2B17

Dong G. Hu, Luke A. Selth, Gerard A. Tarulli, Robyn Meech, Dhilushi Wijayakumara, Apichaya Chanawong, Roslin Russell, Carlos Caldas, Jessica L.L. Robinson, Jason S. Carroll, Wayne D. Tilley, Peter I. Mackenzie, and Theresa E. Hickey

Précis: These striking results illuminate how the regulation of androgen-inactivating enzymes affects ER α ⁺ breast cancers in a disease subtype-specific manner, with implications for disease progression and outcomes.

5894 Paired Exome Analysis Reveals Clonal Evolution and Potential Therapeutic Targets in Urothelial Carcinoma

Philippe Lamy, Iver Nordentoft, Karin Birkenkamp-Demtröder, Mathilde Borg Houlberg Thomsen, Palle Villesen, Søren Vang, Jakob Hedegaard, Michael Borre, Jørgen Bjerggaard Jensen, Søren Høyer, Jakob Skou Pedersen, Torben F. Ørntoft, and Lars Dyrskjøt

Précis: These findings suggest that targeted treatment decisions should be based ideally on an analysis of biopsies from paired tumor samples, so that therapeutic targets of clonal origin can be identified.

CORRECTIONS

5907 Correction: Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer

5908 Correction: ASC-J9 Suppresses Renal Cell Carcinoma Progression by Targeting an Androgen Receptor-Dependent HIF2 α /VEGF Signaling Pathway

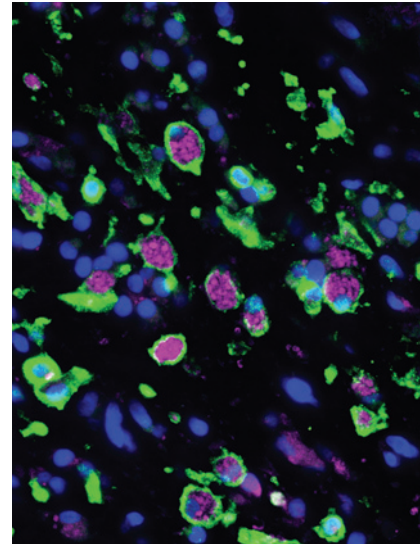
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ABOUT THE COVER

The tumor microenvironment in glioblastoma is often characterized by the infiltration of immunosuppressive macrophages, regulatory T cells (Treg), and myeloid-derived suppressor cells (MDSC). High gene expression levels of the chemokine CCL2 are associated with significantly reduced overall survival in glioblastoma patients. Using double-immunofluorescence labeling of glioblastoma patient samples, tumor-infiltrating macrophages were identified as a source of CCL2. Follow-up mechanistic studies in murine gliomas found that macrophage-derived CCL2 recruits Treg cells and monocytic MDSCs through CCR4- and CCR2-dependent interactions, respectively. For details, see article by Chang and colleagues on page 5671.



Cancer Research

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

76 (19)

Cancer Res 2016;76:5585-5908.

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