Table of Contents

October 1, 2016 • Volume 76 • Number 19

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, Hiroiyuki 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 C. Shaw, Peter Silberstein, and Binth T. Ngo

5605  The Greater Genomic Landscape: The Heterogeneous Evolution of Cancer
       Luay M. Almassalha, Greta M. Bauer, John E. Chandler, Scott Gladstein, Igal Szleifer, 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 Renganasy, Weijia Zhang, Luigi Del Vecchio, Francesco Salvatore, and Martin J. Walsh

5628  RNA Sequencing Identifies Transcriptionally Viable Gene Fusions in Esophageal Adenocarcinomas

5634  Estrogen Receptor α Promotes Breast Cancer by Reprogramming Choline Metabolism
       Min Jia, Trygeve Andreassen, Lasse Jensen, Tone Frost Børten, Indranil Sinha, Hui Gao, Chunyan Zhao, Lars-Arne Haldosen, Yihai Cao, Leonard Giriuta, Siver Andreas Moestue, and Karin Dahlman-Wright

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

INTEGRATED SYSTEMS AND TECHNOLOGIES

5660  A New Perspective on the Role of Autophagy in Cancer

5663  The Use of Ambient Mass Spectrometry in Cancer Research

5666  The Future of Cancer Diagnostics

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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 Warri, Leena Hilakivi-Clarke, David D. Roberts, and Robert Clarke


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/TGFβ–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 TGFβ 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 Maroma, Magdalena Kozakowska, Mateusz Jez, Marta Sezynska, Agnieszka Loboda, Karolina Bukowska-Strakova, Agata Szadze, 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 Denua, Antoine Hubert, Stefanie Schrauwen, Yana Hoorne, Frédéric Amant, Etienne Waerlens, Anna Sablina, and Veerle Janssens

Précis: These results show how recurrent mutations in the Aα 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 Os-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
Xiaozen He, Bin Yan, Shuang Liu, Jianiao Jia, Weiwei Lai, Xing Xin, Can-e Tang, Dixian Luo, Tan Fan, Yiqun Jiang, Ying Shi, Yating Liu, Desheng Xiao, Lijing 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-mesenchymal transition in cancer cells through a metabolic pathway.
**PREVENTION AND EPIDEMIOLOGY**

5758  **Novel Association of Genetic Markers Affecting CYP2A6 Activity and Lung Cancer Risk**
Yehsa M. Patel, Sunghim L. Park, Younghun Han, Lynne R. Wilkens, Heike Bickbölker, Albert Rosenberger, Neil Caporaso, Maria Teresa Landi, Irene Brüseke, Angela Risch, Yongzhe Wei, David C. Christiani, Paul Brennan, Richard Houlston, James McKay, John McLaughlin, Rayjean Hung, Sharon Murphy, Daniel O. Stram, Christopher Amos, and Loic 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 enzyme that metabolizes nicotine.

5768  **Metastatic Progression of Prostate Cancer Is Mediated by Autonomous Binding of Galectin-4-O-Glycan to Cancer Cells**
Chih-Hsiun Tsai, Sheue-Fen Tseng, Tai-Kuang Chao, Chia-Yun Tsai, Yu-Chih Yang, Ming-Ting Lee, liuan-Jhuang 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.

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.

5778  **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.

5788  **Evaluation of Alternative In Vivo Drug Screening Methodology: A Single Mouse Analysis**

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.

5798  **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 Mareau, Magali Champion, Olivier Gavaert, Branimir I. Sikic, 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 chemotheraputic efflux pump.

5808  **Cytotoxic Properties of a DEPTOR-mTOR Inhibitor in Multiple Myeloma Cells**
Yijiang Shi, Tracy R. Daniels-Wells, Patrick Frost, Jihye Lee, Richard S. Finn, Caroleynne Bardeleben, Manuel L. Penichet, Michael E. Jung, Joseph Gera, and Alan Lichtstein

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

5818  **Mesenchymal Stem Cell–Derived Exosomes Stimulate Cycling Quiescence and Early Breast Cancer Dormancy in Bone Marrow**
Sarah A. Bliss, Carima Sinha, Olara A. Sandiford, Lisa M. Williams, Daniel J. Engelberth, Khadijatou Guirou, Leidy L. Isenalumhe, Steven J. Greco, Seda Ayer, Margarete Bryan, Rakesh Kumar, Nicholas M. Ponzio, and Pranela Rameshwar

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

5828  **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 Boğüçürcü, 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.

5838  **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 Boğüçürcü, 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.
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, Hitonobu 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
Précis: These striking results illuminate how the regulation of androgen-inactivating enzymes affects ERα+ 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 Houliberg 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 HIF2a/VEGF Signaling Pathway
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.
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