

BREAKING ADVANCES

- 1299** Highlights from Recent Cancer Literature


CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

- 1301** Commentary on Thomas and Epstein: "Bone Marrow Transplantation in Acute Leukemia"
Emil Freireich
- 1303** Intensive Combination Chemotherapy and X-Irradiation in Hodgkin's Disease
Vincent T. DeVita Jr, Elizabeth DeVita-Raeburn, and John H. Moxley III

REVIEW

- 1305** Single-Cell Sequencing for Precise Cancer Research: Progress and Prospects
Xiaoyan Zhang, Sadie L. Marjani, Zhaoyang Hu, Sherman M. Weissman, Xinghua Pan, and Shixiu Wu

PRIORITY REPORT

- 1313** Preclinical Anticancer Efficacy of BET Bromodomain Inhibitors Is Determined by the Apoptotic Response
 Andrew R. Conery, Richard C. Centore, Kerry L. Spillane, Nicole E. Follmer, Archana Bommi-Reddy, Charlie Hatton, Barbara M. Bryant, Patricia Greninger, Arnaud Amzallag, Cyril H. Benes, Jennifer A. Mertz, and Robert J. Sims III
Précis: These findings suggest predictive drug response biomarkers for a modality currently being tested in clinical trials, addressing the need for useful patient selection strategies.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 1320** Spatial Modeling of Drug Delivery Routes for Treatment of Disseminated Ovarian Cancer
Kimberly R. Kanigel Winner, Mara P. Steinkamp, Rebecca J. Lee, Maciej Swat, Carolyn Y. Muller, Melanie E. Moses, Yi Jiang, and Bridget S. Wilson
Précis: A mathematical model developed to explore the optimal delivery method for therapeutic agents in metastatic ovarian cancer reveals that the selection of intraperitoneal versus intravenous injection depends on tumor volume and vascularity.

MICROENVIRONMENT AND IMMUNOLOGY



- 1335** Activation of Hematopoietic Stem/Progenitor Cells Promotes Immunosuppression Within the Pre-metastatic Niche
Amber Jin Giles, Caitlin Marie Reid, Justin DeWayne Evans, Meera Murgai, Yorlenny Vicioso, Steven Lorenz Highfill, Miki Kasai, Linda Vahdat, Crystal Lee Mackall, David Lyden, Leonard Wexler, and Rosandra Natasha Kaplan
Précis: These findings show how hematopoietic progenitor cells help create an immunosuppressive microenvironment in the pre-metastatic niche, highlighting one of the earliest responders to metastatic progression.
- 1348** Dynamic Patterns of Clonal Evolution in Tumor Vasculature Underlie Alterations in Lymphocyte-Endothelial Recognition to Foster Tumor Immune Escape
 Daniel M. Corey, Yuval Rinkevich, and Irving L. Weissman
Précis: A new approach for visualizing the dynamics of the tumor microenvironment reveals clonal variation within the composition of blood vessels in response to pathological stimuli over time, enabling a radically new perspective on the tumor vasculature as a moving therapeutic target.
- 1354** Infiltrating Macrophages Induce ER α Expression through an IL17A-mediated Epigenetic Mechanism to Sensitize Endometrial Cancer Cells to Estrogen
 Chengcheng Ning, Bingying Xie, Lin Zhang, Chunsheng Li, Weiwei Shan, Bingyi Yang, Xuezheng Luo, Chao Gu, Qizhi He, Hongyan Jin, Xiaojun Chen, Zhenbo Zhang, and Youji Feng
Précis: This potentially seminal study suggests that inflammatory processes drive estrogen receptor expression and development of endometrial cancer, suggesting a new way to understand the roots of this disease and to define biomarkers of disease progression.

Table of Contents

1367 Neutrophil Extracellular Traps Promote the Development and Progression of Liver Metastases after Surgical Stress

Samer Tohme, Hamza O. Yazdani, Ahmed B. Al-Khafaji, Alexis P. Chidi, Patricia Loughran, Kerri Mowen, Yanming Wang, Richard L. Simmons, Hai Huang, and Allan Tsung

Précis: This seminal study offers compelling evidence that tumor recurrence after surgical resection is attributable to a neutrophil-mediated immune response, the disruption of which can reduce risks of metastatic relapse.

1381 Neutralization of Tumor Acidity Improves Antitumor Responses to Immunotherapy



Shari Pilon-Thomas, Krithika N. Kodumudi, Asmaa E. El-Kenawi, Shonagh Russell, Amy M. Weber, Kimberly Luddy, Mehdi Damaghi, Jonathan W. Wojtkowiak, James J. Mulé, Arig Ibrahim-Hashim, and Robert J. Gillies

Précis: Simply raising intratumoral pH with a simple buffer therapy is shown to greatly improve responses to anti-CTLA-4, anti-PD1, or adoptive T-cell immunotherapy, with the potential for immediate clinical translation.

1391 Galectin-3 Cleavage Alters Bone Remodeling: Different Outcomes in Breast and Prostate Cancer Skeletal Metastasis

Kosei Nakajima, Dhong Hyo Kho, Takashi Yanagawa, Yosuke Harazono, Victor Hogan, Wei Chen, Rouba Ali-Fehmi, Rohit Mehra, and Avraham Raz

Précis: The finding that galectin-3 cleavage modulates its activity suggests a new strategy for therapeutic targeting of an important player in the bone tumor microenvironment, with implications for alleviating pain associated with osteolytic remodeling in bone metastases.

1403 Forced Activation of Notch in Macrophages Represses Tumor Growth by Upregulating miR-125a and Disabling Tumor-Associated Macrophages



Jun-Long Zhao, Fei Huang, Fei He, Chun-Chen Gao, Shi-Qian Liang, Peng-Fei Ma, Guang-Ying Dong, Hua Han, and Hong-Yan Qin

Précis: These results show that Notch signaling not only supports the differentiation of tumor-associated macrophages, but also antagonizes their protumorigenic function through an miRNA that might be targeted to program a macrophage antitumor attack.

1416 STAT3 Establishes an Immunosuppressive Microenvironment during the Early Stages of Breast Carcinogenesis to Promote Tumor Growth and Metastasis

Laura M. Jones, Miranda L. Broz, Jill J. Ranger, John Ozcelik, Ryuhjin Ahn, Dongmei Zuo, Josie Ursini-Siegel, Michael T. Hallett, Matthew Krummel, and William J. Muller

Précis: In using a novel model system to investigate the stepwise process of immunoeediting, this study suggests that immune escape processes may evolve relatively early.

MOLECULAR AND CELLULAR PATHOBIOLOGY

1429 MCPIP1 Selectively Destabilizes Transcripts Associated with an Antiapoptotic Gene Expression Program in Breast Cancer Cells That Can Elicit Complete Tumor Regression

Wenbao Lu, Huan Ning, Ling Gu, Hui Peng, Qinghong Wang, Rong Hou, Mingui Fu, Daniel F. Hoft, and Jianguo Liu

Précis: These findings define an RNA binding protein as a novel tumor suppressor in breast cancer and provide new insights into how apoptotic pathways become dysregulated in cancer.

1441 Detection of Pancreatic Cancer-Induced Cachexia Using a Fluorescent Myoblast Reporter System and Analysis of Metabolite Abundance

Paul T. Winnard Jr, Santosh K. Bharti, Marie-France Penet, Radharani Marik, Yelena Mironchik, Flonne Wildes, Anirban Maitra, and Zaver M. Bhujwala

Précis: These findings may help seed improvements in early detection and management of cancer-associated cachexia, a devastating muscle-wasting disease associated with malignant progression in over half of all cancer patients.

1451 AKT1 Inhibits Epithelial-to-Mesenchymal Transition in Breast Cancer through Phosphorylation-Dependent Twist1 Degradation

Chia-Wei Li, Weiya Xia, Seung-Oe Lim, Jennifer L. Hsu, Longfei Huo, Yun Wu, Long-Yuan Li, Chien-Chen Lai, Shih-Shin Chang, Yi-Hsin Hsu, Hui-Lung Sun, Jongchan Kim, Hirohito Yamaguchi, Dung-Fang Lee, Hongmei Wang, Yan Wang, Chao-Kai Chou, Jung-Mao Hsu, Yun-Ju Lai, Adam M. LaBaff, Qingqing Ding, How-Wen Ko, Fuu-Jen Tsai, Chang-Hai Tsai, Gabriel N. Hortobagyi, and Mien-Chie Hung

Précis: This study offers key mechanistic insights into how AKT1 inhibits epithelial-to-mesenchymal transition and stemness properties in breast cancer cells and provides new therapeutic approaches for reversing the aggressive features associated with basal-like breast cancer.

Table of Contents

1463 HER2 Signaling Drives DNA Anabolism and Proliferation through SRC-3 Phosphorylation and E2F1-Regulated Genes

Bryan C. Nikolai, Rainer B. Lanz, Brian York, Subhamoy Dasgupta, Nicholas Mitsiades, Chad J. Creighton, Anna Tsimelzon, Susan G. Hilsenbeck, David M. Lonard, Carolyn L. Smith, and Bert W. O'Malley

Précis: These findings define the transcriptional programs hijacked by aberrant HER2 signaling to promote promiscuous DNA replication and cell growth in breast cancer, offering new clues into how resistance to HER2 therapies are acquired.

1476 Secondary Tumors Arising in Patients Undergoing BRAF Inhibitor Therapy Exhibit Increased BRAF–CRAF Heterodimerization

Lise Boussebart, Isabelle Girault, H el ene Malka-Mahieu, Christine Mateus, Emilie Routier, Margot Rubington, Nyam Kamsu-Kom, Marina Thomas, Gorana Tomasic, Sandrine Agoussi, Marie Breckler, M elanie Laporte, Ludovic Lacroix, Alexander M. Eggermont, Andrea Cavalcanti, Florent Grange, Julien Adam, St ephane Vagner, and Caroline Robert

Pr ecis: Secondary tumor formation induced by BRAF inhibitor therapy for metastatic melanoma appears to be characterized by increased BRAF-CRAF dimerization, providing new insight into the potential mechanisms underlying the paradoxical effects of BRAF inhibition.

PREVENTION AND EPIDEMIOLOGY

1485 Cytochrome P450 Allele CYP3A7*1C Associates with Adverse Outcomes in Chronic Lymphocytic Leukemia, Breast, and Lung Cancer

Nichola Johnson, Paolo De Ieso, Gabriele Migliorini, Nick Orr, Peter Broderick, Daniel Catovsky, Athena Matakidou, Timothy Eisen, Christy Goldsmith, Frank Dudbridge, Julian Peto, Isabel dos-Santos-Silva, Alan Ashworth, Gillian Ross, Richard S. Houlston, and Olivia Fletcher

Pr ecis: A subset of cancer patients harboring a genetic variant that affects their ability to metabolize a diverse range of substrates, including chemotherapeutic agents, associates with poor treatment outcomes, providing a genetic rationale to consider stratifying patients into therapeutic regimens that could be more effective.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

1494 Targeting Calcium Signaling Induces Epigenetic Reactivation of Tumor Suppressor Genes in Cancer

No el J.-M. Raynal, Justin T. Lee, Youjun Wang, Annie Beaudry, Priyanka Madireddi, Judith Garriga, Gabriel G. Malouf, Sarah Dumont, Elisha J. Dettman, Vazganush Gharibyan, Saira Ahmed, Woonbok Chung, Wayne E. Childers, Magid Abou-Gharbia, Ryan A. Henry, Andrew J. Andrews, Jaroslav Jelinek, Ying Cui, Stephen B. Baylin, Donald L. Gill, and Jean-Pierre J. Issa

Pr ecis: This potentially seminal study shows how modulating calcium signaling in cancer cells by a panel of approved drugs can reactivate silenced tumor suppressor genes, with immediate implications for a new route of clinical exploration in epigenetic cancer therapy.

1506 Non-Small Cell Lung Cancer Cells Acquire Resistance to the ALK Inhibitor Alectinib by Activating Alternative Receptor Tyrosine Kinases

Hideko Isozaki, Eiki Ichihara, Nagio Takigawa, Kadoaki Ohashi, Nobuaki Ochi, Masayuki Yasugi, Takashi Ninomiya, Hiromichi Yamane, Katsuyuki Hotta, Katsuya Sakai, Kunio Matsumoto, Shinobu Hosokawa, Akihiro Bessho, Toshiaki Sendo, Mitsune Tanimoto, and Katsuyuki Kiura

Pr ecis: These findings uncover new mechanisms through which non-small cell lung cancer cells become resistant to alectinib, suggesting how to engineer next-gen therapeutic strategies to improve upon this agent.

1517 Dual HER2 Targeting with Trastuzumab and Liposomal-Encapsulated Doxorubicin (MM-302) Demonstrates Synergistic Antitumor Activity in Breast and Gastric Cancer

Christopher W. Espelin, Shannon C. Leonard, Elena Geretti, Thomas J. Wickham, and Bart S. Hendriks

Pr ecis: Liposomal delivery of chemotherapeutic agents in combination with anti-HER2 treatment appears to provide a "one-two punch" that combats HER2⁺ breast cancer cells while mitigating off-target side effects.

1528 The Dual MEK/FLT3 Inhibitor E6201 Exerts Cytotoxic Activity against Acute Myeloid Leukemia Cells Harboring Resistance-Confering FLT3 Mutations

Weiguo Zhang, Gautam Borthakur, Chen Gao, Ye Chen, Hong Mu, Vivian R. Ruvolo, Kenichi Nomoto, Nanding Zhao, Marina Konopleva, and Michael Andreeff

Pr ecis: One-third of acute myeloid leukemia patients harboring FLT3 mutations may benefit from a dual MAPK/FLT3 inhibitor with potent anticancer effects, including in cells resistant to FLT3 monotherapy.

Table of Contents

- 1538** **Inhibition of MUC1-C Suppresses MYC Expression and Attenuates Malignant Growth in KRAS Mutant Lung Adenocarcinomas**
Audrey Bouillez, Hasan Rajabi, Sean Pitroda, Caining Jin, Maroof Alam, Akriti Kharbanda, Ashujit Tagde, Kwok-Kin Wong, and Donald Kufe
Précis: MYC overexpression, a feature of most aggressive solid tumors that has remained a siren for targeted therapy for over three decades, might be selectively attenuated in certain lung cancer settings by blocking a cell surface adhesion molecule.
- 1549** **Delivery of Therapeutics Targeting the mRNA-Binding Protein HuR Using 3DNA Nanocarriers Suppresses Ovarian Tumor Growth**
Yu-Hung Huang, Weidan Peng, Narumi Furuuchi, Jacquelyn Gerhart, Kelly Rhodes, Neelanjan Mukherjee, Masaya Jimbo, Gregory E. Gonye, Jonathan R. Brody, Robert C. Getts, and Janet A. Sawicki
Précis: This study offers preclinical proof of concept for an effective method of systemic delivery of RNAi-based therapeutics, addressing a long-standing challenge to develop such agents for cancer treatment.
- 1560** **Anticancer Effects of Mesothelin-Targeted Immunotoxin Therapy Are Regulated by Tyrosine Kinase DDR1**
Fatima Ali-Rahmani, David J. FitzGerald, Scott Martin, Paresma Patel, Marco Prunotto, Pinar Ormanoglu, Craig Thomas, and Ira Pastan
Précis: These findings show how an immunotoxin therapy can be enhanced by concomitant inhibition of a collagen-activated tyrosine kinase, with implications for optimizing combination immunotherapy strategies.
- 1569** **Mass Spectrometry–Based Metabolomics Identifies Longitudinal Urinary Metabolite Profiles Predictive of Radiation-Induced Cancer**
John A. Cook, Gadisetti V.R. Chandramouli, Miriam R. Anver, Anastasia L. Sowers, Angela Thetford, Kristopher W. Krausz, Frank J. Gonzalez, James B. Mitchell, and Andrew D. Patterson
Précis: Urine metabolite profiles from mice receiving total body radiation appear to predict for cancer before tumors become clinically detectable, with implications for early detection strategies in individuals at risk for exposure to ionizing radiation.
- 1578** **A Chimeric Switch-Receptor Targeting PD1 Augments the Efficacy of Second-Generation CAR T Cells in Advanced Solid Tumors**
Xiaojun Liu, Raghuvier Ranganathan, Shuguang Jiang, Chongyun Fang, Jing Sun, Soyeon Kim, Kheng Newick, Albert Lo, Carl H. June, Yangbing Zhao, and Edmund K. Moon
Précis: Combining a chimeric PD1 antibody with an adoptive CAR T-cell therapy appears to overcome the primary weakness of such adoptive therapies—the lack of efficacy in solid tumors—with immediate exciting implications for clinical trial design.

- 1591** **EGF816 Exerts Anticancer Effects in Non–Small Cell Lung Cancer by Irreversibly and Selectively Targeting Primary and Acquired Activating Mutations in the EGF Receptor**
Yong Jia, Jose Juarez, Jie Li, Mari Manuia, Matthew J. Niederst, Celin Tompkins, Noelito Timple, Mei-Ting Vaillancourt, AnneMarie Culazzo Pferdekammer, Elizabeth L. Lockerman, Chun Li, Jennifer Anderson, Carlotta Costa, Debbie Liao, Eric Murphy, Michael DiDonato, Badry Bursulaya, Gerald Lelais, Jordi Barretina, Matthew McNeill, Robert Epple, Thomas H. Marsilje, Nuzhat Pathan, Jeffrey A. Engelman, Pierre-Yves Michellys, Peter McNamara, Jennifer Harris, Steven Bender, and Shailaja Kasibhatla
Précis: This preclinical proof of concept for a mutant-selective EGFR inhibitor justifies its clinical development as a candidate therapeutic option for lung cancer patients who develop innate or acquired resistance to current EGFR-targeted therapies.

TUMOR AND STEM CELL BIOLOGY

- 1603** **Neural Cell Adhesion Protein CNTN1 Promotes the Metastatic Progression of Prostate Cancer**
Judy Yan, Diane Ojo, Anil Kapoor, Xiaozeng Lin, Jehonathan H. Pinthus, Tariq Aziz, Tarek A. Bismar, Fengxiang Wei, Nicholas Wong, Jason De Melo, Jean-Claude Cutz, Pierre Major, Geoffrey Wood, Hao Peng, and Damu Tang
Précis: This study reveals new clues into how prostate tumors hijack tissue-specific molecular programs to advance progression.
- 1615** **miR-155 Drives Metabolic Reprogramming of ER⁺ Breast Cancer Cells Following Long-Term Estrogen Deprivation and Predicts Clinical Response to Aromatase Inhibitors**
Marina Bacci, Elisa Giannoni, Antony Fearn, Ricardo Ribas, Qiong Gao, Maria Letizia Taddei, Gianfranco Pintus, Mitch Dowsett, Clare M. Isacke, Lesley-Ann Martin, Paola Chiarugi, and Andrea Morandi
Précis: Adaptation and resistance of ER-positive breast cancer cells to first-line aromatase inhibition appears to involve metabolic reprogramming through miR-155, a potential predictive marker of therapeutic response.
- 1627** **RASSF1A Suppresses the Invasion and Metastatic Potential of Human Non–Small Cell Lung Cancer Cells by Inhibiting YAP Activation through the GEF-H1/RhoB Pathway**
Fatéméh Dubois, Maureen Keller, Olivier Calvayrac, Fabrice Soncin, Lily Hoa, Alexander Hergovich, Maria-Carla Parrini, Julien Mazières, Mélissa Vaisse-Lesteven, Jacques Camonis, Guénaëlle Levallet, and Gérard Zalcman
Précis: These findings elucidate a basis to understand the poor prognosis of patients harboring lung cancers where the tumor suppressor RASSF1A is inactivated by DNA hypermethylation, where RhoB control of the Hippo oncogenic pathway is implicated.

Table of Contents

1641 Aberrant Notch Signaling in the Bone Marrow Microenvironment of Acute Lymphoid Leukemia Suppresses Osteoblast-Mediated Support of Hematopoietic Niche Function

Weihuan Wang, Grant Zimmerman, Xiaoran Huang, Shuiliang Yu, Jay Myers, Yiwei Wang, Stephen Moreton, Joseph Nthale, Amad Awadallah, Rose Beck, Wei Xin, David Wald, Alex Y. Huang, and Lan Zhou

Précis: These findings suggest that a niche-targeted therapy that can restore homeostasis in the bone marrow microenvironment can improve patient outcomes.

1653 Breast Tumor Kinase (Brk/PTK6) Is Induced by HIF, Glucocorticoid Receptor, and PELP1-Mediated Stress Signaling in Triple-Negative Breast Cancer

Tarah M. Regan Anderson, Shi Hong Ma, Ganesh V. Raj, John A. Cidlowski, Taylor M. Helle, Todd P. Knutson, Raisa I. Krutilina, Tiffany N. Seagroves, and Carol A. Lange

Précis: An integration of hormonal and stress signaling pathways defined in this study reveals why a key protumorigenic factor is expressed in triple-negative breast cancer, highlighting the intersection as a possible therapeutic target in this poorly managed disease.

CORRECTIONS

1664 Correction: Hydrogen Peroxide-Mediated Cytosolic Acidification Is a Signal for Mitochondrial Translocation of Bax during Drug-Induced Apoptosis of Tumor Cells

1668 Correction: p53: Protection against Tumor Growth beyond Effects on Cell Cycle and Apoptosis

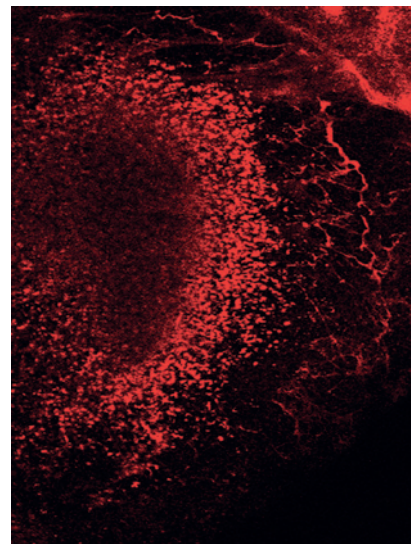
1669 Correction: The Tyrosine Phosphatase Shp2 Interacts with NPM-ALK and Regulates Anaplastic Lymphoma Cell Growth and Migration

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ABOUT THE COVER

The tumor microenvironment is acidic. Image shows ZR75.1 breast cancer tumor growing in a dorsal window chamber. Twenty-four hours prior to imaging, mice were injected with Alexa546 dye conjugated to a pH-low inserting peptide, pHLLIP (courtesy of O. Andreev and Y. Reshentnyak, University of Rhode Island, Kingston, RI), showing uptake in the tumor and surrounding stroma. Neutralization of this acidity with oral buffers can improve response to checkpoint inhibitors and adoptive T-cell transfer immune therapies, as described in this issue. (Image courtesy of V. Estrella). For details, see article by Pilon-Thomas and colleagues on page 1381.



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