### 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.

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.

### INTEGRATED SYSTEMS AND TECHNOLOGIES

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, Yordany 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 ERα 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, Xuezhen Luo, Chao Gu, Qizhi He, Hongyan Jin, Xiaojun Chen, Zhenshao 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.
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 Longhrian, Kerri Mowen, Yanning 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.

Neutralization of Tumor Acidity Improves Antitumor Responses to Immunotherapy


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.

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.

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.

ACK1 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-Ling Sun, Jongchan Kim, Hiroshi 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 ACK1 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.
HER2 Signaling Drives DNA Anabolism and Proliferation through SRC-3 Phosphorylation and EZF1-Regulated Genes

Bryan C. Nikolai, Rainer B. Lanz, Brian York, Subhamoy Dasgupta, Nicholas Mitsiades, Chad J. Creighton, Anna Tsimelzon, Susan C. 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.

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

Lise Boussenart, Isabelle Girault, Hélène Malka-Mahieu, Christine Mateus, Emilie Routier, Margot Rubington, Nyam Kamusu-Kom, Marina Thomas, Gorana Tomasic, Sandrine Aguouss, Marie Breckler, Mélanie Laporte, Ludovic Lacroix, Alexander M. Eggermont, Andrea Cavalcanti, Florent Grange, Julien Adam, Stéphan Vagner, and Caroline Robert

Précis: 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.

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, Alan Ashworth, Gillian Ross, Richard S. Houlston, and Olivia Fletcher

Précis: 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.
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<td>Inhibition of MUC1-C Suppresses MYC Expression and Attenuates Malignant Growth in KRAS Mutant Lung Adenocarcinomas&lt;br&gt;Audrey Bouillez, Hasan Rajabi, Sean Pitroda, Caining Jin, Maroof Alam, Akriti Khambanda, Ashujit Tagde, Kwok-Kin Wong, and Donald Kufe&lt;br&gt;Precis: 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.</td>
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<td>Delivery of Therapeutics Targeting the mRNA-Binding Protein HuR Using 3DNA Nanocarriers Suppresses Ovarian Tumor Growth&lt;br&gt;Yu-Hung Huang, Weidan Peng, Nanumi Furutuchi, Jacquelyn Gerhart, Kelly Rhodes, Neelanjan Mukherjee, Masaya Jimbo, Gregory E. Gonye, Jonathan R. Brody, Robert C. Getts, and Janet A. Sawicki&lt;br&gt;Precis: 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.</td>
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<td>Anticancer Effects of Mesothelin-Targeted Immunotoxin Therapy Are Regulated by Tyrosine Kinase DDR1&lt;br&gt;Fatima Ali-Rahmani, David J. FitzGerald, Scott Martin, Paresma Patel, Marco Prunotto, Pinar Ormanoglu, Craig Thomas, and Ira Pastan&lt;br&gt;Precis: 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.</td>
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<td>A Chimeric Switch-Receptor Targeting PD1 Augments the Efficacy of Second-Generation CAR T Cells in Advanced Solid Tumors&lt;br&gt;Xiaojun Liu, Raghveer Ranganathan, Shuguang Jiang, Chongyun Fang, Jing Sun, Soyeon Kim, Kheng Newick, Albert Lo, Carl H. June, Yangbing Zhao, and Edmund K. Moon&lt;br&gt;Precis: 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.</td>
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<td>1591</td>
<td>EGF816 Exerts Anticancer Effects in Non–Small Cell Lung Cancer by Irreversibly and Selectively Targeting Primary and Acquired Activating Mutations in the EGF Receptor&lt;br&gt;Yong Jia, Jose Juarez, Jie Li, Mari Manuia, Matthew J. Niederst, Celin Tompkins, Noelito Timple, Mei-Ting Vaillancourt, AnneMarie Culazzo Pendekmapper, Elizabeth L. Lockerman, Chun Li, Jennifer Anderson, Carlotta Costa, Debbie Liao, Eric Murphy, Michael DiDonato, Badry Bursulaya, Gerald Lelais, Jordi Barretina, Matthew McNell, Robert Epple, Thomas H. Mansile, Nuhat Pathan, Jeffrey A. Engelman, Pierre-Yves Michelliys, Peter McNamara, Jennifer Harris, Steven Bender, and Shailaja Rasbhata&lt;br&gt;Precis: 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.</td>
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## TUMOR AND STEM CELL BIOLOGY

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<td>Neural Cell Adhesion Protein CNTN1 Promotes the Metastatic Progression of Prostate Cancer&lt;br&gt;Judy Yan, Diane Ojo, Anil Kapoor, Xiaozeng Lin, Jehonathan H. Pinthus, Tariq Aziz, Tarek A. Bismar, Fenguang Wei, Nicholas Wong, Jason De Melo, Jean-Claude Cutz, Pierre Major, Geoffrey Wood, Hao Peng, and Danu Tang&lt;br&gt;Precis: This study reveals new clues into how prostate tumors hijack tissue-specific molecular programs to advance progression.</td>
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<td>miR-155 Drives Metabolic Reprogramming of ER+ Breast Cancer Cells Following Long-Term Estrogen Deprivation and Predicts Clinical Response to Aromatase Inhibitors&lt;br&gt;Marina Bacci, Elisa Giannoni, Antony Farns, Ricardo Ribas, Qiong Gao, Maria Letizia Taddei, Gianfranco Pintus, Mitch Dowsett, Clare M. Isacke, Lesley-Ann Martin, Paola Chiarugi, and Andrea Morandi&lt;br&gt;Precis: 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.</td>
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<td>1627</td>
<td>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&lt;br&gt;Fatémeh Dubois, Maureen Keller, Olivier Calvayrac, Fabrice Soncin, Lily Hoa, Alexander Hergovich, Maria-Carla Parrini, Julien Mazieres, Müller Vaisse-Leseven, Jacques Camonis, Guenaelle Levallet, and Gérard Zalcman&lt;br&gt;Precis: 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.</td>
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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.

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

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, pHILIP (courtesy of O. Andreev and Y. Reshennyuk, 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.