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, Yorleny 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
Chengchong 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.
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 Longhnan, Kerri Mowen, Yanning Wang, Richard L. Simmons, Hai Huang, and Allan Tsung

Precis: 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

Precis: 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

Precis: 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

Precis: 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.

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 Oxelik, Ryhijin Ahn, Dongmei Zuo, Josie Unnisi-Siegel, Michael T. Hallett, Matthew Krummel, and William J. Muller

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

MCPIP1 Selectively Destabilizes Transcripts Associated with an Antiapoptotic Gene Expression Program in Breast Cancer Cells That Can Elicit Complete Tumor Regression
Wenbao Lu, Huan Nüng, Ling Gu, Hui Peng, Qinghong Wang, Rong Hou, Mengxi Fu, Daniel F. Hoñ, and Jianguo Liu

Precis: 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.

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. Bhujwalla

Precis: 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.

AKT1 Inhibits Epithelial-to-Mesenchymal Transition in Breast Cancer through Phosphorylation-Dependent Twist1 Degradation
Chia-Wei Li, Weiya Xia, Seung-Oh Lim, Jennifer L. Hsu, Longfei Huo, Yun Wu, Long-Yuan Li, Chien-Chen Lai, Shih-Shin Chang, Yi-Hsin Hsu, Hui-Lang Sun, Jongchan Kim, Hirohito Yamaguchi, Dung-Fang Lee, Hongmei Wang, Yan Wang, Chao-Kai Chiou, 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

Precis: 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.
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 Boussemart, Isabelle Girault, Hélène Malka-Mahieu, Christine Mateus, Emilie Routier, Margot Rubington, Nyam Kamu-Kom, Marina Thomas, Gorana Tomasic, Sandrine Agoussi, 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, Frank Dumont, William Figg, 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.

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

Précis: 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.

Non–Small Cell Lung Cancer Cells Acquire Resistance to the ALK Inhibitor Alectinib by Activating Alternative Receptor Tyrosine Kinases
Hideko Isozaki, Eiki Ichihi, Nagio Takigawa, Kadoaki Ohashi, Nobuaki Ochi, Masayuki Yasugi, Takashi Ninomiya, Hiromichi Yamane, Katsuji Hotta, Katsuya Sakai, Kunio Matsumoto, Shinobu Hosokawa, Akihiro Bessho, Toshiaki Sendo, Mitsume Tanimoto, and Katsuyuki Kiura

Précis: 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.

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

Précis: Liposomal delivery of chemotherapeutic agents in combination with anti-HER2 treatment appears to provide a “one-two punch” that combats HER2þ breast cancer cells while mitigating off-target side effects.

The Dual MEK/FLT3 Inhibitor E6201 Exerts Cytotoxic Activity against Acute Myeloid Leukemia Cells Harboring Resistance-Conferring FLT3 Mutations
Weiguo Zhang, Gautam Borthakur, Chen Gao, Ye Chen, Hong Mu, Vivian R. Ruvolo, Kenichi Nomoto, Nanding Zhao, Marina Konopleva, and Michael Andreeff

Précis: 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.
A Chimeric Switch-Receptor Targeting PD1

Mass Spectrometry

Anticancer Effects of Mesothelin-Targeted Delivery of Therapeutics Targeting the mRNA-Binding Protein HuR Using 3DNA Nanocarriers Suppresses Ovarian Tumor Growth

Yu-Hung Huang, Weidan Peng, Nanumi Furushchi, Jacquelyn Gerhart, Kelly Rhodes, Neelanjan Mukherjee, Masaya Jimbo, Gregory E. Gonye, Jonathan R. Brody, Robert C. Gets, and Janet A. Savicki

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.

Precis: These findings show how an immunotoxin therapy can be enhanced by concomitant inhibition of a collagen-activated tyrosine kinase, with implications for optimizing combinatorial immunotherapy strategies.

Precis: 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.

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.

EGF816 Exerts Anticancer Effects in Non–Small Cell Lung Cancer by Irreversibly and Selectively Targeting Primary and Acquired Activating Mutations in the EGF Receptor

Kwok-Kin Wong, and Donald Kufe

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.

TUMOR AND STEM CELL BIOLOGY

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, Fenguang Wei, Nicholas Wong, Jason De Melo, Jean-Claude Cutz, Pierre Major, Geoffrey Wood, Hao Peng, and Damu Tang

Precis: This study reveals new clues into how prostate tumors hijack tissue-specific molecular programs to advance progression.

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 Fears, Ricardo Ribas, Qiong Gao, Maria Letizia Taddei, Gianfranco Pintus, Mitch Dowsett, Clare M. Isacke, Lesley-Ann Martin, Paola Chiarugi, and Andrea Morandi

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.

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 Mazieres, Melissa Vaisse-Lesteven, Jacques Camonis, Guenaelle Levallet, and Gérard Zalcman

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.
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.

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, pHLIP (courtesy of O. Andreev and Y. Reshennyak, 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.