BREAKING ADVANCES

1 Highlights from Recent Cancer Literature

FROM THE EDITOR’S CHAIR

3 A Perspective on Cancer as an Abortive Autoimmune Response to Altered-Self
George C. Prendergast

REVIEWS

5 Cancer Immunotherapy and Breaking Immune Tolerance: New Approaches to an Old Challenge
Amani Makkouk and George J. Weiner

11 Regulation of Epithelial–Mesenchymal Transition through SUMOylation of Transcription Factors
Maria V. Bogachek, James P. De Andrade, and Ronald J. Weigel

PRIORITY REPORT

16 The Cyclic AMP Pathway Is a Sex-Specific Modifier of Glioma Risk in Type I Neurofibromatosis Patients
Nicole M. Warrington, Tao Sun, Jingqin Luo, Robert C. McKinstrey, Patricia C. Parkin, Sara Ganzhorn, Debra Spoljaric, Anne C. Albers, Amanda Merkelson, Douglas R. Stewart, David A. Stevenson, David Viskochil, Todd E. Druley, Jason T. Forys, Karlyne M. Reilly, Michael J. Fisher, Uti Tabori, Jeffrey C. Allen, Joshua D. Schiffman, David H. Gutmann, and Joshua B. Rubin

CLINICAL STUDIES

22 Oncolytic Measles Virus Expressing the Sodium Iodide Symporter to Treat Drug-Resistant Ovarian Cancer
Précis: Although clinical application of oncolytic viruses as experimental therapies has frequently been challenged on the grounds of efficacy, more recently engineered vectors based on measles virus may offer effective options to treat certain advanced cancers such as metastatic ovarian cancer.

INTEGRATED SYSTEMS AND TECHNOLOGIES

31 A Noninvasive Procedure for Early-Stage Discrimination of Malignant and Precancerous Vocal Fold Lesions Based on Laryngeal Dynamics Analysis
Jakob Unger, Jörg Lohscheller, Maximilian Reiter, Katharina Eder, Christian S. Betz, and Maria Schuster
Précis: This study offers a proof of concept for a procedure to diagnose most types of laryngeal cancers, possibly helping avoid current invasive diagnostic procedures that are associated with greater time, morbidity, and cost.

MICROENVIRONMENT AND IMMUNOLOGY

40 Akt1 and Akt3 Exert Opposing Roles in the Regulation of Vascular Tumor Growth
Précis: These findings offer a preclinical proof of concept for the therapeutic utility of treating poorly understood vascular tumors such as angiosarcoma with S6K inhibitors.
51 Paradoxical Decrease in the Capture and Lymph Node Delivery of Cancer Vaccine Antigen Induced by a TLR4 Agonist as Visualized by Dual-Mode Imaging
Deepak K. Kadayakkara, Michael J. Korner, Jeff W.M. Bulse, and Hyam I. Levitsky
Précis: An adjuvant molecule that enhances the therapeutic effects of a cancer vaccine was found paradoxically to reduce the efficiency of antigen delivery to lymph nodes, challenging what has been thought to be necessary in an effective adjuvant—at least as formed by expectations from studies of infectious disease vaccines.

62 Tropomodulin 1 Expression Driven by NF-κB Enhances Breast Cancer Growth
Taku Ito-Kureha, Naohiko Roshikawa, Mizuki Yamamoto, Rentaro Sembha, Noritaka Yamaguchi, Tadashi Yamamoto, Motoharu Seiki, and Jun-ichiro Inoue
Précis: These findings highlight a novel mechanistic linkage to help explain the NF-κB-dependent malignant phenotype of triple-negative breast cancer, with implications for defining useful theranostic targets in this aggressive disease.

73 Twist1 Is a Key Regulator of Cancer-Associated Fibroblasts
Keun-Woo Lee, So-Young Yeo, Chang Ohk Sung, and Seok-Hyung Kim
Précis: Already known as a central contributor to EMT, which drives metastatic progression in cancer cells, the transcription factor Twist1 is also found to function in cancer-associated fibroblasts, where it appears to offer a compelling target to deprogram the tumor-supporting features of the cancer microenvironment.

86 Intracellular Osteopontin Inhibits Toll-like Receptor Signaling and Impedes Liver Carcinogenesis
Xiaoyu Fan, Chunyan He, Wei Jing, Xuyu Zhou, Rui Chen, Lei Cao, Minhui Zhu, Rongjie Iia, Hao Wang, Yajun Guo, and Jian Zhao
Précis: Osteopontin is known to act in the tumor microenvironment to promote inflammatory processes that facilitate progression, but this study reveals that it also acts within macrophages that infiltrate budding liver tumors to achieve this end by altering Toll-like receptor signaling.

98 PLK1 Phosphorylates PAX3-FOXO1, the Inhibition of Which Triggers Regression of Alveolar Rhabdomyosarcoma
Verena Thalhammer, Laura A. Lopez-Garcia, David Herrera-Martín, Regina Hecker, Dominik Laubscher, María E. Gierisch, Marco Wachtel, Peter Bode, Paolo Nanni, Bernd Blank, Ewa Koscielnia, and Beat W. Schäfer
Précis: These findings offer a preclinical proof of concept to target the mitotic kinase PLK1 as a rational strategy to treat an aggressive pediatric tumor.

111 LASP1 Is a HIF1α Target Gene Critical for Metastasis of Pancreatic Cancer
Tiansuo Zhao, He Ren, Jing Li, Jing Chen, Huan Zhang, Wen Xin, Yan Sun, Lei Sun, Yongwei Yang, Junwei Sun, Xiuchao Wang, Song Cao, Chonghiao Huang, HuaFeng Zhang, Shengyu Yang, and Jiuli Hao
Précis: This study identifies a key mediator of metastasis in pancreatic ductal carcinomas that are typically already disseminated at the time of diagnosis, a central challenge in the management of this disease.

120 VEGF-Targeted Therapy Stably Modulates the Glycolytic Phenotype of Tumor Cells
Matteo Curtarello, Elisabetta Zulato, Giorgia Nardo, Silvia Vallorita, Giulia Guzzo, Elisabetta Rossi, Giovanni Esposito, Aichi Msaki, Anna Pastro, Andrea Rasola, Luca Persano, Francesco Ciccarese, Roberta Bertorelle, Sergio Todde, Mario Plebani, Henrike Schroer, Stefan Walenta, Wolfgang Mueller-Klieser, Alberto Amadori, Rosa Maria Moresco, and Stefano Indraccolo
Précis: These findings suggest that the application of antiangiogenic therapy in cancer selects for metabolic traits of tumors that not only confer treatment resistance but also potentially have a more aggressive character, challenging a central tenet of antiangiogenic therapy as inherently less susceptible to the evolution of resistance.

134 Foretinib Is Effective Therapy for Metastatic Sonic Hedgehog Medulloblastoma
Précis: These findings provide a strong rationale to clinically evaluate foretinib immediately as a therapy for a defined subset of patients with the most common form of malignant pediatric brain tumor.
Four-in-One Antibodies Have Superior Cancer Inhibitory Activity against EGFR, HER2, HER3, and VEGF through Disruption of HER/MET Crosstalk
Shi Hu, Wenyuan Fu, Weihao Xu, Yang Yang, Hiroaki Takeda, and Wangdong Zhu

Précis: These results establish a new principle to achieve combined HER receptor inhibition and limit drug resistance using a single antibody.

Genetic Disruption of Lactate/H+ Symporters (MCTs) and Their Subunit CD147/BASIGIN Sensitizes Glycolytic Tumor Cells to Phenformin
Ibtissam Marchiq, Renaud Le Floch, Danièle Roux, Marie-Pierre Simon, and Jacques Pouyssegur

Précis: This study offers preclinical proof of concept for targeting lactic acid export as a therapeutic approach, the effect of which can be magnified by coupling it with phenformin, an antidiabetic biguanide drug.

Mdm2 and Aurora Kinase A Inhibitors Synergize to Block Melanoma Growth by Driving Apoptosis and Immune Clearance of Tumor Cells
Anna E. Vilgelm, Jeff S. Pawlkowski, Yan Liu, Oriana E. Hawkins, Tyler A. Davis, Jessica Smith, Kevin P. Weller, Linda W. Horton, Colt M. McClain, Gregory D. Ayers, David C. Turner, David C. Essaka, Clinton F. Stewart, Jeffrey A. Sosman, Mark C. Kelley, Jeffrey A. Ecsedy, Jeffrey N. Johnston, and Ann Richmond

Précis: These findings offer preclinical proof of concept for a combination drug treatment that leverages both senescence and immune surveillance to improve therapeutic outcomes.

 Contributions to Drug Resistance in Glioblastoma Derived from Malignant Cells in the Sub-Ependymal Zone

Précis: A particular region of the adult brain analogous to the embryonic forebrain germinal zone, which harbors various neural stem cell populations, is discovered in glioblastoma patients to harbor tumor-initiating cells, identifying this region as a target for immediate therapeutic attention by neuro-oncologists.

α-Tubulin Acetylation Elevated in Metastatic and Basal-like Breast Cancer Cells Promotes Microtentacle Formation, Adhesion, and Invasive Migration
Amanda E. Boggs, Michele I Vitolo, Rebecca A. Whipple, Monica S. Charpentier, Olga G. Goloubeva, Olga B. Ioffe, Kimberly C. Tuttle, Jana Slovic, Yiling Lu, Gordon B. Mills, and Stuart S. Martin

Précis: These results identify a tight correlation between acetylated α-tubulin levels and aggressive metastatic behavior in breast cancer, with potential implications for the definition of a simple prognostic biomarker in patients with basal-like breast cancers.

B-Raf Inhibitors Induce Epithelial Differentiation in BRAF-Mutant Colorectal Cancer Cells
Ricarda Herr, Martin Köhler, Hana Andrilová, Florian Weinberg, Yvonne Möller, Sebastian Halbach, Lisa Lutz, Justin Mastroianni, Martin Klose, Nicola Bittermann, Silke Kowar, Robert Zeiner, Monilola A. Olayioye, Silke Lasmann, Hauke Busch, Melanie Boerries, and Tilman Brummer

Précis: This article reveals a novel facet of BRAF and MEK inhibitors currently in early clinical trials for evaluation in patients with metastatic prostate cancer.

SYK Is a Candidate Kinase Target for the Treatment of Advanced Prostate Cancer

Précis: These striking preclinical findings offer a mechanistic rationale to immediately reposition SYK kinase inhibitors currently in early clinical trials for evaluation in patients with metastatic prostate cancer.
ABOUT THE COVER

Timing of GLA in relation to vaccination impacts the pattern of OT1 cell accumulation. Representative bioluminescent images show site-specific accumulation of OT1 cells in different groups of mice 4 days post hind footpad vaccination. Vaccine-primed T cells accumulated in the draining lymph nodes in mice that received GVAX only or when GLA 24 was given 24 hrs post GVAX. However, when GLA is coadministered with GVAX, a systemic pattern of T-cell accumulation was observed. For details, see article by Kadayakkaza and colleagues on page 51.