

BREAKING ADVANCES

- 1159** Highlights from Recent Cancer Literature


REVIEWS

- 1161** Adipose-Derived Stems Cells and Their Role in Human Cancer Development, Growth, Progression, and Metastasis: A Systematic Review
Kyle E. Freese, Lauren Kokai, Robert P. Edwards, Brian J. Phillips, M. Aamir Sheikh, Joseph Kelley, John Comerci, Kacey G. Marra, J. Peter Rubin, and Faina Linkov
- 1169** Cell Membrane Fluid–Mosaic Structure and Cancer Metastasis
Garth L. Nicolson

MEETING REPORT


- 1177** 26th Pezcoller Symposium: Cancers Driven by Hormones
Myles Brown, Arul Chinnaiyan, Antonella Farsetti, David M. Livingston, Massimo Loda, Roland Schuele, and Enrico Mihich

PRIORITY REPORTS

- 1181** Usp28 Counteracts Fbw7 in Intestinal Homeostasis and Cancer
Markus E. Diefenbacher, Atanu Chakraborty, Sophia M. Blake, Richard Mitter, Nikita Popov, Martin Eilers, and Axel Behrens
Précis: This study reveals an unusually direct antagonism between an E3 ligase and a deubiquitinase in modulating intestinal homeostasis and cancer, with potential implications for targeting the deubiquitinase therapeutically in colorectal tumors.
- 1187** VEGF-A Expression Correlates with TP53 Mutations in Non–Small Cell Lung Cancer: Implications for Antiangiogenesis Therapy
 Maria Schwaederlé, Vladimir Lazar, Pierre Validire, Johan Hansson, Ludovic Lacroix, Jean-Charles Soria, Yudi Pawitan, and Razelle Kurzrock
Précis: This important study suggests that the p53 mutation status of a tumor may predict its efficacious response to anti-VEGF drugs, with immediate clinical impact on p53 use as a ready biomarker to predict which patients could benefit the most from this leading class of approved antiangiogenic agents.

- 1191** Upregulation of Cytosolic Phosphoenolpyruvate Carboxykinase Is a Critical Metabolic Event in Melanoma Cells That Repopulate Tumors
Yong Li, Shunqun Luo, Ruihua Ma, Jing Liu, Pingwei Xu, Huafeng Zhang, Ke Tang, Jingwei Ma, Yi Zhang, Xiaoyu Liang, Yanling Sun, Tiantian Ji, Ning Wang, and Bo Huang

Précis: These findings unveil a unique feature of glucose metabolism in melanoma-repopulating cells, with implications for targeting a disease-selective aspect of melanoma that may also have broader relevance in cancer.

- 1197**  Dietary Microbes Modulate Transgenerational Cancer Risk
Theofilos Poutahidis, Bernard J. Varian, Tatiana Levkovich, Jessica R. Lakritz, Sheyla Mirabal, Caitlin Kwok, Yassin M. Ibrahim, Sean M. Kearney, Antonis Chatzigiagkos, Eric J. Alm, and Susan E. Erdman
Précis: These findings suggest the possibility of microbially inherited causes for the skyrocketing rates of obesity and cancer in industrialized countries, also implicating transgenerational effects of microbiomes that are influenced by diet.

CLINICAL STUDIES

- 1205** Evolutionary Action Score of TP53 Coding Variants Is Predictive of Platinum Response in Head and Neck Cancer Patients
Abdullah A. Osman, David M. Neskey, Panagiotis Katsonis, Ameeta A. Patel, Alexandra M. Ward, Teng-Kuei Hsu, Stephanie C. Hicks, Thomas O. McDonald, Thomas J. Ow, Marcus Ortega Alves, Curtis R. Pickering, Heath D. Skinner, Mei Zhao, Eric M. Sturgis, Merrill S. Kies, Adel El-Naggar, Federica Perrone, Lisa Licitra, Paolo Bossi, Marek Kimmel, Mitchell J. Frederick, Olivier Lichtarge, and Jeffrey N. Myers
Précis: These findings may enable a personalized approach to treat head and neck cancer based on a new way to score genetic p53 mutations in tumors.

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INTEGRATED SYSTEMS AND TECHNOLOGIES

1216 Exploring the Biomechanical Properties of Brain Malignancies and Their Pathologic Determinants *In Vivo* with Magnetic Resonance Elastography

Yann Jamin, Jessica K.R. Boulton, Jin Li, Sergey Popov, Philippe Garteiser, Jose L. Ulloa, Craig Cummings, Gary Box, Suzanne A. Eccles, Chris Jones, John C. Waterton, Jeffrey C. Bamber, Ralph Sinkus, and Simon P. Robinson

Précis: Unlike most malignancies, which tend to be stiffer than their surrounding tissue, brain malignancies tend to be softer than normal brain parenchyma, with implications for the uses of noninvasive magnetic resonance imaging for the clinical management of patients with brain tumors.

1225 Imaging Active Urokinase Plasminogen Activator in Prostate Cancer

Aaron M. LeBeau, Natalia Sevillano, Kate Markham, Michael B. Winter, Stephanie T. Murphy, Daniel R. Hostetter, James West, Henry Lowman, Charles S. Craik, and Henry F. VanBrocklin

Précis: A new human antibody imaging probe selectively targets the active form of uPA on prostate cancer cells, triggering its internalization and thereby resulting in high tumor uptake of the probe.

1236 *In Vivo* Tomographic Imaging of Deep-Seated Cancer Using Fluorescence Lifetime Contrast

William L. Rice, Daria M. Shcherbakova, Vladislav V. Verkhusa, and Anand T.N. Kumar

Précis: A novel optical approach for noninvasive imaging of early stage metastasis in mice offers a tool to assist the preclinical discovery and development of novel therapeutics to control advanced cancers.

MICROENVIRONMENT AND IMMUNOLOGY

1244 Tumor Endothelial Cells with Distinct Patterns of TGF β -Driven Endothelial-to-Mesenchymal Transition

Lin Xiao, Dae Joong Kim, Clayton L. Davis, James V. McCann, James M. Dunleavy, Alissa K. Vanderlinden, Nuo Xu, Samantha G. Pattenden, Stephen V. Frye, Xia Xu, Mark Onaitis, Elizabeth Monaghan-Benson, Keith Burridge, and Andrew C. Dudley

Précis: These findings deepen understanding of how a process of endothelial-to-mesenchymal transition that occurs in the tumor vasculature, often in parallel to EMT in tumor cells, generates dysfunctional and heterogeneous vessels that contribute to the growth and metastatic dissemination of tumor cells.

1255 Adaptive Upregulation of EGFR Limits Attenuation of Tumor Growth by Neutralizing IL6 Antibodies, with Implications for Combined Therapy in Ovarian Cancer



Carla S. Milagre, Ganga Gopinathan, Gemma Everitt, Richard G. Thompson, Hagen Kulbe, Haihong Zhong, Robert E. Hollingsworth, Richard Grose, David D.L. Bowtell, Daniel Hochhauser, and Frances R. Balkwill

Précis: These results offer a preclinical rationale to combine anti-IL6 and gefitinib to treat advanced stage ovarian cancer, with immediate implications for clinical evaluation.

1265 Antitumor Responses Stimulated by Dendritic Cells Are Improved by Triiodothyronine Binding to the Thyroid Hormone Receptor β

Vanina A. Alamino, Iván D. Mascanfroni, María M. Montesinos, Nicolás Gigena, Ana C. Donadio, Ada G. Blidner, Sonia I. Milotich, Sheue-yann Cheng, Ana M. Masini-Repiso, Gabriel A. Rabinovich, and Claudia G. Pellizas

Précis: These results establish an adjuvant effect of thyroid hormone signaling in dendritic cells, with immediate implications for how to empower the antitumor efficacy of dendritic cells engineered for cancer immunotherapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

1275 SND1 Acts Downstream of TGF β 1 and Upstream of Smurf1 to Promote Breast Cancer Metastasis

Lin Yu, Xin Liu, Kang Cui, Yanbo Di, Lingbiao Xin, Xiaoming Sun, Wei Zhang, Xi Yang, Minxin Wei, Zhi Yao, and Jie Yang

Précis: Timely results in a very active area of research establish the biological significance of an AEG-1/MTDH/LYRIC-binding protein to TGF β signaling in breast tumorigenesis and metastasis, portending likely connections to EMT and stem-like functions.

1287 PARD3 Inactivation in Lung Squamous Cell Carcinomas Impairs STAT3 and Promotes Malignant Invasion

Ester Bonastre, Sara Verdura, Ilse Zondervan, Federica Facchinetti, Sylvie Lantuejoul, Maria Dolores Chiara, Juan Pablo Rodrigo, Julian Carretero, Enric Condom, Agustin Vidal, David Sidransky, Alberto Villanueva, Luca Roz, Elisabeth Brambilla, Suvi Savola, and Montse Sanchez-Céspedes

Précis: Inactivation of a cell polarity regulator that impacts tumor aggressiveness and metastasis is one of the more common events in lung squamous cell carcinomas.

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1298 **MicroRNA-22 Suppresses DNA Repair and Promotes Genomic Instability through Targeting of MDC1**



Jung-Hee Lee, Seon-Joo Park, Seo-Yeon Jeong, Min-Ji Kim, Semo Jun, Hyun-Seo Lee, In-Youb Chang, Sung-Chul Lim, Sang Pil Yoon, Jeongsik Yong, and Ho Jin You

Précis: These results suggest a molecular mechanism for how aberrant Akt1 activation and senescence lead to increased genomic instability, fostering an environment that promotes tumorigenesis.

1311 **Interaction of BARD1 and HP1 Is Required for BRCA1 Retention at Sites of DNA Damage**

Wenwen Wu, Hiroyuki Nishikawa, Takayo Fukuda, Vinayak Vittal, Masahide Asano, Yasuo Miyoshi, Rachel E. Klevit, and Tomohiko Ohta

Précis: These findings show how BARD1 mediates retention of the BRCA1 complex at sites of double-strand DNA breakage, acting to promote homologous recombination by inhibiting nonhomologous end joining, with implications for improving breast cancer therapy.

1322 **Long Noncoding RNA MALAT1 Promotes Aggressive Renal Cell Carcinoma through Ezh2 and Interacts with miR-205**

Hiroshi Hirata, Yuji Hinoda, Varahram Shahryari, Guoren Deng, Koichi Nakajima, Z. Laura Tabatabai, Nobuhisa Ishii, and Rajvir Dahiya

Précis: This study shows how overexpression of the long noncoding RNA MALAT1 confers a potent oncogenic signal in renal cancers, where it may offer a novel functional biomarker or therapeutic target.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

1332 **Chemotherapy-Induced miRNA-29c/Catenin- δ Signaling Suppresses Metastasis in Gastric Cancer**



Yuxuan Wang, Changzheng Liu, Min Luo, Zhengyi Zhang, Jianan Gong, Jingjing Li, Lei You, Lei Dong, Rui Su, Haishuang Lin, Yanni Ma, Fang Wang, Yi Wang, Jie Chen, Junwu Zhang, Hongyan Jia, Yan Kong, and Jia Yu

Précis: These findings define a global mechanism for understanding the efficacious effects of cytotoxic chemotherapy in stomach cancers, providing a mechanistic rationale for the development of a prognostic biomarker in patients receiving therapy.

1345 **BMX Negatively Regulates BAK Function, Thereby Increasing Apoptotic Resistance to Chemotherapeutic Drugs**



Joanna L. Fox and Alan Storey

Précis: These findings suggest opportunities to improve the efficacy of existing chemotherapy by potentiating BAK-driven cell death in cancer cells.

1356 **Treatment of Invasive Brain Tumors Using a Chain-like Nanoparticle**

Pubudu M. Peiris, Aaron Abramowski, James Mcginnity, Elizabeth Doolittle, Randall Toy, Ramamurthy Gopalakrishnan, Shruti Shah, Lisa Bauer, Ketan B. Ghaghada, Christopher Hoimes, Susann M. Brady-Kalnay, James P. Basilion, Mark A. Griswold, and Efstathios Karathanasis

Précis: This study demonstrates the ability of a chain-like nanoparticle to effectively deliver chemotherapy across the brain-tumor barrier, resulting in widespread distribution of drug throughout the primary brain tumor and its invasive sites.

1366 **BH3 Inhibitor Sensitivity and Bcl-2 Dependence in Primary Acute Lymphoblastic Leukemia Cells**

Sarah E. Alford, Anisha Kothari, Floris C. Loeff, Joshua M. Eichhorn, Nandini Sakurikar, Henriette M. Goselink, Robert L. Saylor, Inge Jedema, J.H. Frederik Falkenburg, and Timothy C. Chambers

Précis: A primary cell model of a particular human leukemia proves far more appropriate as a model to test and develop antitumor drugs, compared with established cell lines that have been commonly used, and as such may stimulate a change in laboratory investigations in this disease setting.

1376 **Tumor Radiosensitization by Monomethyl Auristatin E: Mechanism of Action and Targeted Delivery**



Lisa Buckel, Elamprakash N. Savariar, Jessica L. Crisp, Karra A. Jones, Angel M. Hicks, Daniel J. Scanderbeg, Quyen T. Nguyen, Jason K. Sicklick, Andrew M. Lowy, Roger Y. Tsien, and Sunil J. Advani

Précis: Selective radiosensitizers have long been sought as tools to improve outcomes of the increasingly sophisticated and effective techniques of modern radiotherapy.

1388 **Omega-3 Polyunsaturated Fatty Acids Upregulate 15-PGDH Expression in Cholangiocarcinoma Cells by Inhibiting miR-26a/b Expression**

Lu Yao, Chang Han, Kyoungsub Song, Jinqiang Zhang, Kyu Lim, and Tong Wu

Précis: These results reveal a lipid modifier pathway in human cholangiocarcinoma and provide a preclinical rationale for the evaluation of ω -3 PUFA in treatment of this malignancy.

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1399 PDK1 and SGK3 Contribute to the Growth of BRAF-Mutant Melanomas and Are Potential Therapeutic Targets

Marzia Scortegagna, Eric Lau, Tongwu Zhang, Yongmei Feng, Chris Sereduk, Hongwei Yin, Surya K. De, Katrina Meeth, James T. Platt, Casey G. Langdon, Ruth Halaban, Maurizio Pellecchia, Michael A. Davies, Kevin Brown, David F. Stern, Marcus Bosenberg, and Ze'ev A. Ronai

Précis: These findings highlight the potential significance of the AKT kinase PDK1 as a therapeutic target to improve the treatment of melanomas that are BRAF-mutant and PTEN-wild type, representing 70% of all human melanomas.

1413 Intracrine Androgens and AKR1C3 Activation Confer Resistance to Enzalutamide in Prostate Cancer

Chengfei Liu, Wei Lou, Yezi Zhu, Joy C. Yang, Nagalakshmi Nadiminty, Nilesh W. Gaikwad, Christopher P. Evans, and Allen C. Gao

Précis: Targeting the identified resistance mechanisms will overcome enzalutamide resistance and improve survival of advanced prostate cancer patients.

TUMOR AND STEM CELL BIOLOGY

1423 Small-Molecule ONC201/TIC10 Targets Chemotherapy-Resistant Colorectal Cancer Stem-like Cells in an Akt/Foxo3a/TRAIL-Dependent Manner

Varun V. Prabhu, Joshua E. Allen, David T. Dicker, and Wafik S. El-Deiry

Précis: These results highlight a novel biomarker in colon cancer stem-like cells that could be monitored in tumor biopsies or circulating tumor cells, possibly assisting in treatment responses and promoting patient survival.

1433 Targeting of Runx2 by miR-135 and miR-203 Impairs Progression of Breast Cancer and Metastatic Bone Disease

Hanna Taipaleenmäki, Gillian Browne, Jacqueline Akech, Jozef Zustin, Andre J. van Wijnen, Janet L. Stein, Eric Hesse, Gary S. Stein, and Jane B. Lian

Précis: These findings show how deregulated miRNAs in breast tumors can be therapeutically targeted to inhibit bone metastatic development from the primary site.

1445 Lysine Demethylase LSD1 Coordinates Glycolytic and Mitochondrial Metabolism in Hepatocellular Carcinoma Cells

Akihisa Sakamoto, Shinjiro Hino, Katsuya Nagaoka, Kotaro Anan, Ryuta Takase, Haruka Matsumori, Hidenori Ojima, Yae Kanai, Kazunori Arita, and Mitsuyoshi Nakao

Précis: A histone demethylase contributes to rewiring of the metabolic network in cancer cells through epigenetic and transcriptional mechanisms.

1457 Loss of TGF β Receptor Type 2 Expression Impairs Estrogen Response and Confers Tamoxifen Resistance

Susann Busch, Andrew H. Sims, Olle Stål, Mårten Fernö, and Göran Landberg

Précis: This important study not only advances understanding of tamoxifen resistance in breast cancer, but it also raises concerns about the use of TGF β -targeting therapies to attack ER+ tumors, given evidence of how disruption of TGF β signaling appears to generate endocrine resistance.

1470 CYP3A5 Functions as a Tumor Suppressor in Hepatocellular Carcinoma by Regulating mTORC2/Akt Signaling

Feng Jiang, Lei Chen, Ying-Cheng Yang, Xian-ming Wang, Ruo-Yu Wang, Liang Li, Wen Wen, Yan-Xin Chang, Cai-Yang Chen, Jing Tang, Gao-Mi-Yang Liu, Wen-Tao Huang, Lin Xu, and Hong-Yang Wang

Précis: An enzyme that acts in the liver to metabolize many cancer drugs and carcinogens is found that functions as a tumor suppressor in liver cancer, with possible utility as a prognostic biomarker.

1482 Aldehyde Dehydrogenase Is Regulated by β -Catenin/TCF and Promotes Radioresistance in Prostate Cancer Progenitor Cells

Monica Cojoc, Claudia Peitzsch, Ina Kurth, Franziska Trautmann, Leoni A. Kunz-Schughart, Gennady D. Telegeev, Eduard A. Stakhovskiy, John R. Walker, Karl Simin, Stephen Lyle, Susanne Fuessel, Kati Erdmann, Manfred P. Wirth, Mechthild Krause, Michael Baumann, and Anna Dubrovskaya

Précis: These results indicate that expression of a stem cell marker contributes to radioresistance in prostate cancer stem-like cells, suggesting a strategy to enhance the effectiveness of radiotherapy in prostate cancer.

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1495 Phosphotyrosine Signaling Analysis in Human Tumors Is Confounded by Systemic Ischemia-Driven Artifacts and Intra-Specimen Heterogeneity

Aaron S. Gajadhar, Hannah Johnson, Robbert J.C. Slebos, Kent Shaddox, Kerry Wiles, Mary Kay Washington, Alan J. Herline, Douglas A. Levine, Daniel C. Liebler, and Forest M. White on behalf of the Clinical Proteomic Tumor Analysis Consortium (CPTAC)

Précis: Ischemia induced by temporal delays between resection and freezing of human tumors leads to patient-specific effects on tyrosine phosphorylation signaling networks, obscuring the phosphorylation level of multiple potential therapeutic biomarkers.

1504 Cytidine Deaminase Axis Modulated by miR-484 Differentially Regulates Cell Proliferation and Chemoresistance in Breast Cancer

Fu-Gui Ye, Chuan-Gui Song, Zhi-Gang Cao, Chen Xia, Dan-Na Chen, Li Chen, Shan Li, Feng Qiao, Hong Ling, Ling Yao, Xin Hu, and Zhi-Ming Shao

Précis: These findings illustrate the pathogenic tradeoffs that are associated with evolution of chemoresistance in cancer, where the same pathway that promotes drug resistance also limits cell proliferation.

1516 CLK2 Is an Oncogenic Kinase and Splicing Regulator in Breast Cancer

Taku Yoshida, Jee Hyun Kim, Kristopher Carver, Ying Su, Stanislaw Weremowicz, Laura Mulvey, Shoji Yamamoto, Cameron Brennan, Shenglin Mei, Henry Long, Jun Yao, and Kornelia Polyak

Précis: The oncogenic kinase CLK2 appears to regulate luminal and basal cellular phenotypes in breast cancer via effects on alternative gene splicing patterns.

1527 Evolutionary Action Score of TP53 Identifies High-Risk Mutations Associated with Decreased Survival and Increased Distant Metastases in Head and Neck Cancer



David M. Neskey, Abdullah A. Osman, Thomas J. Ow, Panagiotis Katsonis, Thomas McDonald, Stephanie C. Hicks, Teng-Kuei Hsu, Curtis R. Pickering, Alexandra Ward, Ameeta Patel, John S. Yordy, Heath D. Skinner, Uma Giri, Daisuke Sano, Michael D. Story, Beth M. Beadle, Adel K. El-Naggar, Merrill S. Kies, William N. William, Carlos Caulin, Mitchell Frederick, Marek Kimmel, Jeffrey N. Myers, and Olivier Lichtarge

Précis: This study reports initial validation of a novel computational tool that may be useful in clinical prognosis of tumors harboring p53 mutations.

CORRECTIONS

1537 Correction: Resveratrol Inhibits Drug-Induced Apoptosis in Human Leukemia Cells by Creating an Intracellular Milieu Nonpermissive for Death Execution

1538 Correction: Genetic Polymorphisms and Protein Expression of NRF2 and Sulfiredoxin Predict Survival Outcomes in Breast Cancer

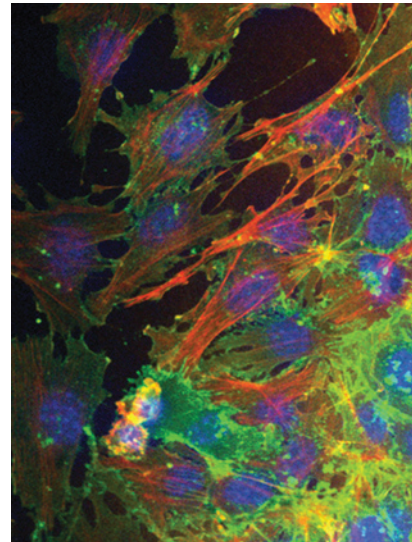
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ABOUT THE COVER

The immunofluorescence image shows myofibroblast-like tumor endothelial cells that have turned on smooth muscle actin (SMA) after TGF β stimulation. Colocalization of an endothelial marker CD31 (green) and SMA-positive stress fibers (red) can be seen in the same cells. Thus, endothelial heterogeneity creates a spectrum of fibroblast-like cells with different functions in the tumor microenvironment. For details, see article by Xiao and colleagues on page 1244.



Cancer Research

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