

## BREAKING ADVANCES

- 2409 | **Highlights from Recent Cancer Literature**

## REVIEWS

- 2411 | **Tumor-Associated Neutrophils: New Targets for Cancer Therapy**  
Alyssa D. Gregory and A. McGarry Houghton
- 2417 | **BRAF<sup>V600E</sup> and Microenvironment in Thyroid Cancer: A Functional Link to Drive Cancer Progression**  
Carmelo Nucera, Jack Lawler, and Sareh Parangi

## PRIORITY REPORTS

- 2423 | **Functional EGFR Germline Polymorphisms May Confer Risk for EGFR Somatic Mutations in Non-Small Cell Lung Cancer, with a Predominant Effect on Exon 19 Microdeletions**  
Wanqing Liu, Lijun He, Jacqueline Ramirez, Soundararajan Krishnaswamy, Rajani Kanteti, Yi-Ching Wang, Ravi Salgia, and Mark J. Ratain  
*Précis:* This study illustrates how naturally occurring polymorphisms in a proto-oncogene may affect the susceptibility of an individual to somatic mutations that can activate the oncogene, thereby increasing cancer risks.
- 2428 | **Novel Human Single Chain Antibody Fragments that Are Rapidly Internalizing Effectively Target Epithelioid and Sarcomatoid Mesotheliomas**  
Arun K. Iyer, Xiaoli Lan, Xiaodong Zhu, Yang Su., Jinjin Feng, Xiaoju Zhang, Dongwei Gao, Youngho Seo, Henry F. VanBrocklin, V. Courtney Broaddus, Bin Liu, and Jiang He  
*Précis:* A novel radiolabeled scFv can rapidly and specifically target epithelioid and sarcomatoid tumor cells, establishing preclinical proof of concept as a versatile targeting ligand to image and treat all subtypes of mesothelioma.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2433 | **Integration of Genotypic and Phenotypic Screening Reveals Molecular Mediators of Melanoma-Stromal Interaction**  
Megan J. Stine, C. Joanne Wang, Whei F. Moriarty, Byungwoo Ryu, Raymond Cheong, William H. Westra, Andre Levchenko, and Rhoda M. Alani  
*Précis:* A novel heterotypic coculture system was developed to model tumor metastasis and define molecular mediators of the metastatic process.

## MICROENVIRONMENT AND IMMUNOLOGY

- 2445 | **Abrogating TNF- $\alpha$  Expression Prevents Bystander Destruction of Normal Tissues during iNOS-Mediated Elimination of Intraocular Tumors**  
Terry G. Coursey, Peter W. Chen, and Jerry Y. Niederkorn  
*Précis:* Intraocular tumor rejection can cause eye destruction and blindness, but this study shows that preventing TNF expression in the eye can permit tumor rejection while preserving its anatomical integrity.
- 2455 | **Cancer-Associated Adipocytes Exhibit an Activated Phenotype and Contribute to Breast Cancer Invasion**  
Béatrice Dirat, Ludivine Bochet, Marta Dabek, Danièle Daviaud, Stéphanie Dauvillier, Bilal Majed, Yuan Yuan Wang, Aline Meulle, Bernard Salles, Sophie Le Gonidec, Ignacio Garrido, Ghislaine Escourrou, Philippe Valet, and Catherine Muller  
*Précis:* Adipocyte enslavement in the tumor microenvironment of obese individuals may create a vicious cycle of inflammation and invasion that enhances progression risk.
- 2466 | **Activation of Toll-like Receptor 5 on Breast Cancer Cells by Flagellin Suppresses Cell Proliferation and Tumor Growth**  
Zhenyu Cai, Amir Sanchez, Zhongcheng Shi, Tingting Zhang, Mingyao Liu, and Dekai Zhang  
*Précis:* TLR5 is highly expressed in breast cancer cells and its activation there can elicit potent anti-tumor activity, suggesting a new therapeutic target for breast cancer therapy.

2476

**Diagnosis of Prostate Cancer Using Differentially Expressed Genes in Stroma**

Zhenyu Jia, Yipeng Wang, Anne Sawyers, Huazhen Yao, Farahnaz Rahmatpanah, Xiao-Qin Xia, Qiang Xu, Rebecca Pio, Tolga Turan, James A. Koziol, Steve Goodison, Philip Carpenter, Jessica Wang-Rodriguez, Anne Simoneau, Frank Meyskens, Manuel Sutton, Waldemar Lernhardt, Thomas Beach, Joseph Monforte, Michael McClelland, and Dan Mercola

*Précis:* This study describes perhaps the first use of the tumor microenvironment as a practical test in oncology, namely to detect the presence of tumors in the absence of tumor cells.

2488

**The Efficacy of Radiotherapy Relies upon Induction of Type I Interferon-Dependent Innate and Adaptive Immunity**

Byron C. Burnette, Hua Liang, Youjin Lee, Lukasz Chlewicki, Nikolai N. Khodarev, Ralph R. Weichselbaum, Yang-Xin Fu, and Sogyong L. Auh

*Précis:* Whereas it is widely believed that radiotherapy acts by inducing DNA damage and cell death in tumor cells, this study shows that in immune competent animals the efficacy of local high-dose radiotherapy actually relies on induction of an interferon signaling cascade that stimulates immune attacks on the tumor.

2497

**IL-15 and Type I Interferon Are Required for Activation of Tumoricidal NK Cells by Virus-Infected Dendritic Cells**

Jeanette E. Boudreau, Kyle B. Stephenson, Fuan Wang, Ali A. Ashkar, Karen L. Mossman, Laurel L. Lenz, Kenneth L. Rosenthal, Jonathan L. Bramson, Brian D. Lichty, and Yonghong Wan

*Précis:* Findings suggest a critical importance to IL-15 and type I interferons in priming dendritic cell vaccines to activate tumoricidal NK cells, which emerging findings suggest may be critical for effective cancer immunotherapy.

2507

**Absence of Class II-Associated Invariant Chain Peptide on Leukemic Blasts of Patients Promotes Activation of Autologous Leukemia-Reactive CD4<sup>+</sup> T Cells**

Marvin M. van Luijn, Willemijn van den Ancker, Martine E.D. Chamuleau, Adri Zevenbergen, Theresia M. Westers, Gert J. Ossenkoppele, S. Marieke van Ham, and Arjan A. van de Loosdrecht

*Précis:* This study offers a clinical rationale to downmodulate an HLA class II-associated invariant chain peptide on primary leukemic blasts as a strategy to degrade immune escape and improve leukemia-specific T-cell immunity in AML patients.

2518

**Estrogen-Related Receptor Gamma Promotes Mesenchymal-to-Epithelial Transition and Suppresses Breast Tumor Growth**

Claire Tiraby, Bethany C. Hazen, Marin L. Gantner, and Anastasia Kralli

*Précis:* This study reveals insights into the basis for functional differences between two estrogen-related receptors of great timely interest in breast cancer studies, with implications for a new way to treat advanced disease with specific agonists of one of these receptors.

2529

**Helicobacter hepaticus-Induced Liver Tumor Promotion Is Associated with Increased Serum Bile Acid and a Persistent Microbial-Induced Immune Response**

Alexis García, Yu Zeng, Sureshkumar Muthupalani, Zhongming Ge, Amanda Potter, Melissa W. Mobley, Chakib Boussahmain, Yan Feng, John S. Wishnok, and James G. Fox

*Précis:* Findings suggest that the efficiency of metabolic detoxification of endobiotics associated with a chronic infection may be a critical factor in determining the impact of that infection on cancer progression.

2541

**Oncogene-Mediated Human Lung Epithelial Cell Transformation Produces Adenocarcinoma Phenotypes In Vivo**

Ken Sasai, Taiko Sukezane, Emmy Yanagita, Harumi Nakagawa, Azusa Hotta, Tomoo Itoh, and Tsuyoshi Akagi

*Précis:* This is the first study to report fully malignant transformation of normal human lung epithelial cells in the absence of viral oncoproteins, with important implications for mechanism-based lung cancer drug discovery.

2550

**Lactate Influx through the Endothelial Cell Monocarboxylate Transporter MCT1 Supports an NF-κB/IL-8 Pathway that Drives Tumor Angiogenesis**

Frédéric Végran, Romain Boidot, Carine Michiels, Pierre Sonveaux, and Olivier Feron

*Précis:* This study identifies an unsuspected lactate signaling pathway in endothelial cells within the tumor microenvironment that bridges cancer cell metabolism and angiogenesis.

2561

**Integrative Genomics Identifies Molecular Alterations that Challenge the Linear Model of Melanoma Progression**

Amy E. Rose, Laura Polisenio, Jinhua Wang, Michael Clark, Alexander Pearlman, Guimin Wang, Eleazar C. Vega y Saenz de Miera, Ratna Medicherla, Paul J. Christos, Richard Shapiro, Anna Pavlick, Farbod Darvishian, Jiri Zavadil, David Polsky, Eva Hernando, Harry Ostrer, and Iman Osman

*Précis:* Findings reveal recurrent genomic deletions in more curable forms of superficial melanoma that are not present in aggressive nodular disease, challenging a long-held paradigm for linear models of melanoma progression.

2572

**Modulation of Cystatin A Expression in Human Airway Epithelium Related to Genotype, Smoking, COPD, and Lung Cancer**

Marcus W. Butler, Tomoya Fukui, Jacqueline Salit, Renat Shaykhiev, Jason G. Mezey, Neil R. Hackett, and Ronald G. Crystal

*Précis:* The level of expression of a cysteine anti-protease in human lung airway epithelia may contribute to chronic inflammatory states in the lung that can promote the development of certain types of lung cancer, at both early and late stages of disease development.

2582

**MicroRNA-95 Promotes Cell Proliferation and Targets Sorting Nexin 1 in Human Colorectal Carcinoma**

Zhaohui Huang, Shenglin Huang, Qifeng Wang, Linhui Liang, Shujuan Ni, Lisha Wang, Weiqi Sheng, Xianghuo He, and Xiang Du

*Précis:* Increasing evidence points to a central role for vesicle trafficking processes in oncogenesis and tumor suppression, here illustrated by the discovery of an oncogenic microRNA that targets a central regulator vesicle sorting to drive proliferation of colorectal cancer cells.

2590

**S6 Kinase 2 Promotes Breast Cancer Cell Survival via Akt**

Savitha Sridharan and Alakananda Basu

*Précis:* Important mechanistic findings suggest that targeting a specific homolog of S6 kinase that drives Akt activity and cancer cell survival might potentiate chemotherapeutic responses in many types of human cancer.

2600

**$\beta$ 2-Microglobulin Induces Epithelial to Mesenchymal Transition and Confers Cancer Lethality and Bone Metastasis in Human Cancer Cells**

Sajni Josson, Takeo Nomura, Jen-Tai Lin, Wen-Chin Huang, Daqing Wu, Haiyen E. Zhou, Majd Zayzafoon, M. Neale Weizmann, Murali Gururajan, and Leland W. K. Chung

*Précis:* The T-cell receptor complex protein  $\beta$ 2-microglobulin is elevated in many cancers, where it supports epithelial-mesenchyme transition and metastasis.

2611

**MicroRNA-205 Inhibits Src-Mediated Oncogenic Pathways in Renal Cancer**

Shahana Majid, Sharanjot Saini, Altaf A. Dar, Hiroshi Hirata, Varahram Shahryari, Yuichiro Tanaka, Soichiro Yamamura, Koji Ueno, Mohd Saif Zaman, Kamaldeep Singh, Inik Chang, Guoren Deng, and Rajvir Dahiya

*Précis:* The pleiotropic functions of the Src family of proto-oncogenic kinases (SFK) in cancer make them promising targets for intervention; this study demonstrates that miRNA-205 inhibits SFKs, indicating a therapeutic potential of miR-205 in the treatment of renal cancer.

2622

**Light at Night Activates IGF-1R/PDK1 Signaling and Accelerates Tumor Growth in Human Breast Cancer Xenografts**

Jinghai Wu, Robert T. Dauchy, Paul C. Tirrell, Steven S. Wu, Darin T. Lynch, Potjana Jitawatanarat, Christine M. Berrington, Erin M. Dauchy, David E. Blask, and Michael W. Greene

*Précis:* This study offers a convincing demonstration of how disruption of diurnal rhythms can promote tumor growth in animals, by disrupting normal patterns of IGF-1 signaling that are strongly influenced by light-dark cycles.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

2632

**MRE11 Deficiency Increases Sensitivity to Poly(ADP-ribose) Polymerase Inhibition in Microsatellite Unstable Colorectal Cancers**

Eduardo Vilar, Catherine M. Bartnik, Stephanie L. Stenzel, Leon Raskin, Jaeil Ahn, Victor Moreno, Bhramar Mukherjee, Maria D. Iniesta, Meredith A. Morgan, Gad Rennert, and Stephen B. Gruber

*Précis:* This is the first report to suggest broader applications of experimental PARP-1 inhibitors to treat solid tumors beyond only those deficient in DNA repair pathways due to mutation of BRCA1 or BRCA2.

2643 **Protein Kinase C Inhibitor Sotrastaurin Selectively Inhibits the Growth of CD79 Mutant Diffuse Large B-Cell Lymphomas**

Tara L. Naylor, Huaping Tang, Boris A. Ratsch, Andreas Enns, Alice Loo, Liqing Chen, Peter Lenz, Nigel J. Waters, Walter Schuler, Bernd Dörken, Yung-mae Yao, Markus Warmuth, Georg Lenz, and Frank Stegmeier

*Précis:* Diffuse large B-cell lymphomas that harbor mutations in a certain regulator of the NF- $\kappa$ B pathway may render them therapeutically susceptible to PKC inhibitors.

2654 **eEF-2 Kinase Dictates Cross-Talk between Autophagy and Apoptosis Induced by Akt Inhibition, Thereby Modulating Cytotoxicity of Novel Akt Inhibitor MK-2206**

Yan Cheng, Xingcong Ren, Yi Zhang, Rajesh Patel, Arati Sharma, Hao Wu, Gavin P. Robertson, Li Yan, Eric Rubin, and Jin-Ming Yang

*Précis:* Findings suggest a mechanism-based therapeutic tactic to reinforce tumor cell killing by Akt inhibitors currently being evaluated in clinical trials.

2664 **COX-2 Blockade Suppresses Gliomagenesis by Inhibiting Myeloid-Derived Suppressor Cells**

Mitsugu Fujita, Gary Kohanbash, Wendy Fellows-Mayle, Ronald L. Hamilton, Yoshihiro Komohara, Stacy A. Decker, John R. Ohlfest, and Hideho Okada

*Précis:* Findings offer mechanistic support for the development of NSAID-based prophylactic strategies to target an important mechanism of immune escape that supports glioma progression.

2675 **Antiangiogenesis Enhances Intratumoral Drug Retention**

Jie Ma, Chong-Sheng Chen, Todd Blute, and David J. Waxman

*Précis:* Antiangiogenesis increases tumor drug retention and improves therapeutic activity of combination therapy.

2686 **Differentiation of NUT Midline Carcinoma by Epigenomic Reprogramming**

Brian E. Schwartz, Matthias D. Hofer, Madeleine E. Lemieux, Daniel E. Bauer, Michael J. Cameron, Nathan H. West, Elin S. Agoston, Nicolas Reynoird, Saadi Khochbin, Tan A. Ince, Amanda Christie, Katherine A. Janeway, Sara O. Vargas, Antonio R. Perez-Atayde, Jon C. Aster, Stephen E. Sallan, Andrew L. Kung, James E. Bradner, and Christopher A. French

*Précis:* Findings prompt clinical evaluation of HDAC inhibitors to treat a deadly pediatric tumor by epigenetic induction of a differentiation program that effectively arrests tumor cell proliferation.

2697 **Expression Profiling of Liposarcoma Yields a Multigene Predictor of Patient Outcome and Identifies Genes That Contribute to Liposarcomagenesis**

Ryan M. Gobble, Li-Xuan Qin, Elliott R. Brill, Christina V. Angeles, Stacy Ugras, Rachael B. O'Connor, Nicole H. Moraco, Penelope L. DeCarolis, Cristina Antonescu, and Samuel Singer

*Précis:* This study reports a multigene predictor of metastatic potential in liposarcoma which includes genes that could serve as candidate therapeutic targets.

## TUMOR AND STEM CELL BIOLOGY

2706 **Cooperation between *Pik3ca* and p53 Mutations in Mouse Mammary Tumor Formation**

Jessica R. Adams, Keli Xu, Jeff C. Liu, Natalia M. Ruiz Agamez, Amanda J. Loch, Ruth G. Wong, Wei Wang, Katherine L. Wright, Timothy F. Lane, Eldad Zacksenhaus, and Sean E. Egan

*Précis:* This study offers the first report of a mouse model for PIK3CA-induced breast cancer, which displays an intriguingly wide spectrum of mammary tumors emerging from cooperation of mutations in p53 and the PI3K p110 subunit.

2718 **Coactivation of AKT and  $\beta$ -Catenin in Mice Rapidly Induces Formation of Lipogenic Liver Tumors**

Jimmy K. Stauffer, Anthony J. Scarzello, Jesper B. Andersen, Rachel L. De Kluyver, Timothy C. Back, Jonathan M. Weiss, Snorri S. Thorgeirsson, and Robert H. Wiltrout

*Précis:* This study presents a robust transgenic mouse model that could help determine the microenvironmental factors that drive malignant progression of obesity-related lipogenic tumors.

2728 **Taxol Resistance in Breast Cancer Cells Is Mediated by the Hippo Pathway Component TAZ and Its Downstream Transcriptional Targets *Cyr61* and *CTGF***

Dulcie Lai, King Ching Ho, Yawei Hao, and Xiaolong Yang

*Précis:* Findings define an important new pathway of Taxol resistance in breast cancer cells, suggesting novel therapeutic targets to treat Taxol-resistant cancers that arise commonly at advanced stages of disease.

2739 **The Androgen Receptor Induces Integrin  $\alpha 6\beta 1$  to Promote Prostate Tumor Cell Survival via NF- $\kappa$ B and Bcl-xL Independently of PI3K Signaling**

Laura E. Lamb, Jelani C. Zarif, and Cindy K. Miranti

*Précis:* Mechanistic findings suggest a strategy to enhance prostate cancer cell death by PI3K inhibitors, presently being evaluated in clinical trials.

2750 **PTEN Loss Confers BRAF Inhibitor Resistance to Melanoma Cells through the Suppression of BIM Expression**

Kim H.T. Paraiso, Yun Xiang, Vito W. Rebecca, Ethan V. Abel, Y. Ann Chen, A. Cecilia Munko, Elizabeth Wood, Inna V. Fedorenko, Vernon K. Sondak, Alexander R.A. Anderson, Antoni Ribas, Maurizia Dalla Palma, Katherine L. Nathanson, John M. Koomen, Jane L. Messina, and Keiran S.M. Smalley

*Précis:* Continued progress in melanoma treatment will require knowledge of how to blunt resistance arising to BRAF inhibitors, which are exhibiting robust but transient therapeutic effects in clinical trials.

2761 **Repression of Vascular Endothelial Growth Factor Expression by the Runt-Related Transcription Factor 1 in Acute Myeloid Leukemia**

Arja ter Elst, Bin Ma, Frank J.G. Scherpen, Hendrik J.M. de Jonge, Jenny Douwes, Albertus T.J. Wierenga, Jan Jacob Schuringa, Willem A. Kamps, and Eveline S.J.M. de Bont

*Précis:* This study offers new insights into how transcriptional control of VEGF-A varies in normal cells and cancer cells, with fundamental implications for understanding a central mechanism of tumor angiogenesis.

2772 **Role of Heparanase in Radiation-Enhanced Invasiveness of Pancreatic Carcinoma**

Amichay Meirovitz, Esther Hermano, Immanuel Lerner, Eyal Zcharia, Claudio Pisano, Tamar Peretz, and Michael Elkin

*Précis:* Findings suggest a strategy to radiosensitize pancreatic cancer by blocking the activity of an important proteoglycan endoglycosidase.

2781 **p53 Binds to and Is Required for the Repression of *Arf* Tumor Suppressor by HDAC and Polycomb**

Yaxue Zeng, Yojiro Kotake, Xin-Hai Pei, Matthew D. Smith, and Yue Xiong

*Précis:* Important findings reveal a second negative feedback loop of p53 control in which p53 transcriptionally represses its activator *Arf*, separate from the first one in which p53 transcriptionally activates its inhibitor *Mdm2*.

## LETTER TO THE EDITOR

2793 **Combined Treatment of Pancreatic Cancer with Mithramycin A and Tolfenamic Acid Promotes Sp1 Degradation and Synergistic Antitumor Activity—Letter**

Ting-Chao Chou

2794 **Combined Treatment of Pancreatic Cancer with Mithramycin A and Tolfenamic Acid Promotes Sp1 Degradation and Synergistic Antitumor Activity—Response**

J. Jack Lee and Maiying Kong

2796 **Rebuttal to the Response of Lee and Kong**

Ting-Chao Chou

2798 **Rebuttal to the Response of Chou**

J. Jack Lee and Maiying Kong

## OBITUARY

2801 **Gary D. Kruh: In Memoriam (1951–2011)**

Kenneth D. Tew

## CORRECTIONS

2803 **Correction: Poly(ADP-Ribose) Polymerase Is Hyperactivated in Homologous Recombination-Defective Cells**

2804

**Correction: MET Kinase Inhibitor SGX523 Synergizes with Epidermal Growth Factor Receptor Inhibitor Erlotinib in a Hepatocyte Growth Factor-Dependent Fashion to Suppress Carcinoma Growth**

2805

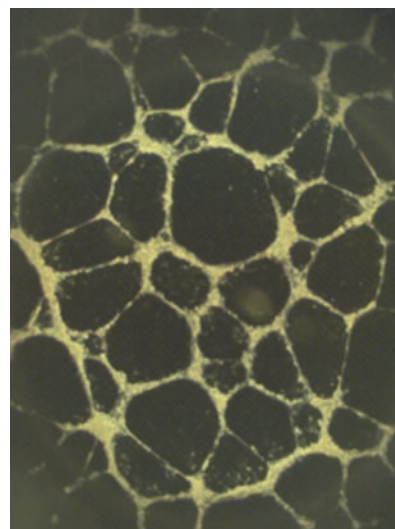
**Correction: PML-RAR $\alpha$  and Dnmt3a1 Cooperate *in vivo* to Promote Acute Promyelocytic Leukemia**

2806

**Correction: Reduced SMAD7 Leads to Overactivation of TGF- $\beta$  Signaling in MDS that Can Be Reversed by a Specific Inhibitor of TGF- $\beta$  Receptor I Kinase**

## ABOUT THE COVER

Lactate stimulates IL-8–dependent angiogenesis. Representative photograph of tube formation in lactate-containing medium from Matrigel-plated endothelial cells. For details, see the article by Végran and colleagues on page 2550 of this issue.



# Cancer Research

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