


BREAKING ADVANCES

- 3809 | **Highlights from Recent Cancer Literature**

REVIEWS

- 3811 | **The Dormancy Dilemma: Quiescence versus Balanced Proliferation**
Alan Wells, Linda Griffith, Jakob Z. Wells, and Donald P. Taylor
- 3817 | **Optimal Targeting of HER2–PI3K Signaling in Breast Cancer: Mechanistic Insights and Clinical Implications**
Brent N. Rexer and Carlos L. Arteaga

CLINICAL STUDIES

- 3821 | **Combination of Protein Coding and Noncoding Gene Expression as a Robust Prognostic Classifier in Stage I Lung Adenocarcinoma**
 Ichiro Akagi, Hirokazu Okayama, Aaron J. Schetter, Ana I. Robles, Takashi Kohno, Elise D. Bowman, Dickran Kazandjian, Judith A. Welsh, Naohide Oue, Motonobu Saito, Masao Miyashita, Eiji Uchida, Toshihiro Takizawa, Seiichi Takenoshita, Vidar Skaug, Steen Mollerup, Aage Haugen, Jun Yokota, and Curtis C. Harris
- Précis:* This study identifies a molecular signature to stratify early-stage lung cancer in diverse patient populations, allowing a reliable identification of individuals at high risk of disease progression and/or suited to specific targeted therapies.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 3833 | **Coevolution of Solid Stress and Interstitial Fluid Pressure in Tumors During Progression: Implications for Vascular Collapse**
Triantafyllos Stylianopoulos, John D. Martin, Matija Snuderl, Fotios Mpekris, Saloni R. Jain, and Rakesh K. Jain
- Précis:* Improved understanding of the stresses that accumulate in solid tumors during their development may lead to better strategies to destroy them.

MICROENVIRONMENT AND IMMUNOLOGY

- 3842 | **Avirulent *Toxoplasma gondii* Generates Therapeutic Antitumor Immunity by Reversing Immunosuppression in the Ovarian Cancer Microenvironment**
Jason R. Baird, Barbara A. Fox, Kiah L. Sanders, Patrick H. Lizotte, Juan R. Cubillos-Ruiz, Uciane K. Scarlett, Melanie R. Rutkowski, Jose R. Conejo-Garcia, Steven Fiering, and David J. Bzik

Précis: Beginning with Coley's investigations a century ago, the immunotherapeutic properties of bacterial infections in cancer have been widely studied, but there has been virtually no study yet of the same potential in protist (parasite) infections, a first glimpse of which are illustrated in this seminal report.

- 3852 | **Critical Role of STAT3 in IL-6–Mediated Drug Resistance in Human Neuroblastoma**

Tasnim Ara, Rie Nakata, Michael A. Sheard, Hiroyuki Shimada, Ralf Buettner, Susan G. Groshen, Lingyun Ji, Hua Yu, Richard Jove, Robert C. Seeger, and Yves A. DeClerck

Précis: Drug resistance pathways in cancer are not necessarily confined to the cancer cell itself but may often also involve critical contributions of the pro-inflammatory tumor microenvironment, as shown in this study.

- 3865 | **Synergistic Induction of Adaptive Antitumor Immunity by Codelivery of Antigen with α -Galactosylceramide on Exosomes**

Ulf Gehrman, Stefanie Hiltbrunner, Anna-Maria Georgoudaki, Mikael C. Karlsson, Tanja I. Näslund, and Susanne Gabrielsson

Précis: Loading exosomes with tumor antigens and immune stimulatory glycolipids can create a highly efficacious vaccine preparation for cancer therapy.

- 3877 | **Melanoma-Educated CD14⁺ Cells Acquire a Myeloid-Derived Suppressor Cell Phenotype through COX-2–Dependent Mechanisms**

Yumeng Mao, Isabel Poschke, Erik Wennerberg, Yago Pico de Coaña, Suzanne Egyhazi Brage, Inkeri Schultz, Johan Hansson, Giuseppe Masucci, Andreas Lundqvist, and Rolf Kiessling

Précis: These results reveal how immune suppression by myeloid-derived suppressor cells can be initiated in the tumor microenvironment of human melanoma.

- 3888 **Identification of Two Distinct Carcinoma-Associated Fibroblast Subtypes with Differential Tumor-Promoting Abilities in Oral Squamous Cell Carcinoma**
 Daniela Elena Costea, Allison Hills, Amani H. Osman, Johanna Thurlow, Gabriela Kalna, Xiaohong Huang, Claudia Pena Murillo, Himalaya Parajuli, Salwa Suliman, Keerthi K. Kulasekara, Anne Chr. Johannessen, and Max Partridge
Précis: Cancer-associated fibroblasts sustain the tumor microenvironment, and unraveling their heterogeneity may point to targetable weaknesses.
- 3902 **Myeloid Cell Receptor LRP1/CD91 Regulates Monocyte Recruitment and Angiogenesis in Tumors**
 Nicole D. Staudt, Minji Jo, Jingjing Hu, Jeanne M. Bristow, Donald P. Pizzo, Alban Gaultier, Scott R. VandenBerg, and Steven L. Gonias
Précis: A signaling system that controls recruitment of tumor-associated macrophages may have a very important role in determining the amount of VEGF that is secreted into the tumor microenvironment.
- 3913 **miR-124 Inhibits STAT3 Signaling to Enhance T Cell–Mediated Immune Clearance of Glioma**
 Jun Wei, Fei Wang, Ling-Yuan Kong, Shuo Xu, Tiffany Doucette, Sherise D. Ferguson, Yuhui Yang, Kayla McEnery, Krishan Jethwa, Olsi Gjyshi, Wei Qiao, Nicholas B. Levine, Frederick F. Lang, Ganesh Rao, Gregory N. Fuller, George A. Calin, and Amy B. Heimberger
Précis: This study highlights approaches to plumb the untapped potential of microRNA in generalized immunotherapeutic strategies to treat cancer.
- 3927 **Dynamic Mast Cell–Stromal Cell Interactions Promote Growth of Pancreatic Cancer**
 Ying Ma, Rosa F. Hwang, Craig D. Logsdon, and Stephen E. Ullrich
Précis: Mast cells are being ascribed unexpected but important roles in the cancer microenvironment, increasing interest in targeting them for therapeutic purposes.
- 3938 **Membrane versus Soluble Isoforms of TNF- α Exert Opposing Effects on Tumor Growth and Survival of Tumor-Associated Myeloid Cells**
 Shidrokh Ardestani, Bin Li, Desirae L. Deskins, Huiyun Wu, Pierre P. Massion, and Pampee P. Young
Précis: Controversies about the role of TNF- α in cancer progression may be explained by the findings from this study, which offer a basis to understand its contradictory effects on tumor progression.
- 3951 **SENPI deSUMOylates and Regulates Pin1 Protein Activity and Cellular Function**
 Chun-Hau Chen, Che-Chang Chang, Tae Ho Lee, ManLi Luo, Pengyu Huang, Pei-Hsin Liao, Shuo Wei, Fu-An Li, Ruey-Hwa Chen, Xiao Zhen Zhou, Hsiu-Ming Shih, and Kun Ping Lu
Précis: Unraveling Pin1 regulation may improve strategies to attack cancer, given that Pin1 controls the function of numerous oncogenes and tumor suppressor genes.
- 3963 **Endothelial Cell Protein C Receptor Opposes Mesothelioma Growth Driven by Tissue Factor**
 Shiva Keshava, Sanghamitra Sahoo, Torry A. Tucker, Steven Idell, L. Vijaya Mohan Rao, and Usha R. Pendurthi
Précis: This study enhances our understanding of how the procoagulant protein tissue factor drives the growth of many human cancers.
- 3974 **Mitogenic Insulin Receptor-A Is Overexpressed in Human Hepatocellular Carcinoma due to EGFR-Mediated Dysregulation of RNA Splicing Factors**
 Hamza Chettouh, Laetitia Fartoux, Lynda Aoudjehane, Dominique Wendum, Audrey Clapéron, Yves Chrétien, Colette Rey, Olivier Scatton, Olivier Soubrane, Filomena Conti, Françoise Praz, Chantal Housset, Olivier Rosmorduc, and Christèle Desbois-Mouthon
Précis: Increased expression of a specific insulin receptor isoform may mediate adverse effects of hyperinsulinemia on liver cancer development.
- 3987 **Dysregulated Expression of FOXM1 Isoforms Drives Progression of Pancreatic Cancer**
 Xiangyu Kong, Lei Li, Zhaoshen Li, Xiangdong Le, Chen Huang, Zhiliang Jia, Jiujiu Cui, Suyun Huang, Liwei Wang, and Keping Xie
Précis: This study identifies a class of FOXO family transcription factors as key effectors in a program of pancreatic cancer development driven by the transcription factors Sp1 and KLH4, with potential implications for understanding the pathophysiology of other cancers in which these FOXO isoforms have been implicated.

3997

The Steroid Receptor Coactivator-3 Is Required for the Development of Castration-Resistant Prostate Cancer

Jean C-Y. Tien, Zhaoliang Liu, Lan Liao, Fen Wang, Yixiang Xu, Ye-Lin Wu, Niya Zhou, Michael Ittmann, and Jianming Xu

Précis: *These findings offer a preclinical proof of concept to therapeutically target a transcriptional coactivator in castration-resistant prostate cancer, the development of which is responsible for nearly all prostate cancer deaths.*

4009

Tid1-L Inhibits EGFR Signaling in Lung Adenocarcinoma by Enhancing EGFR Ubiquitinylation and Degradation

Chi-Yuan Chen, Chia-Ing Jan, Jeng-Fan Lo, Shuenn-Chen Yang, Yih-Leong Chang, Szu-Hua Pan, Wen-Lung Wang, Tse-Ming Hong, and Pan-Chyr Yang

Précis: *The clinical validation of EGFR targeting approaches in lung non-small cell lung carcinoma, also known as lung adenocarcinoma, has increased the significance of studies to understand EGFR downregulation in this setting.*

PREVENTION AND EPIDEMIOLOGY

4020

Impact of Body Mass Index on the Risk of Colorectal Adenoma in a Metabolically Healthy Population

Kyung Eun Yun, Yoosoo Chang, Hyun-Suk Jung, Chan-Won Kim, Min-Jung Kwon, Sung Keun Park, Eunju Sung, Hocheol Shin, Hye Soon Park, and Seungho Ryu

Précis: *Excess weight confers an increased risk of developing colorectal adenomas, independent of whether an individual is metabolically healthy or not, suggesting a potential causal link between excess adipose tissue and colorectal cancer risk.*

4028

Genome-Wide Association Study of Genetic Predictors of Overall Survival for Non-Small Cell Lung Cancer in Never Smokers

Xifeng Wu, Liang Wang, Yuanqing Ye, Jeremiah A. Aakre, Xia Pu, Gee-Chen Chang, Pan-Chyr Yang, Jack A. Roth, Randolph S. Marks, Scott M. Lippman, Joe Y. Chang, Charles Lu, Claude Deschamps, Wu-Chou Su, Wen-Chang Wang, Ming-Shyan Huang, David W. Chang, Yan Li, V. Shane Pankratz, John D. Minna, Waun Ki Hong, Michelle A.T. Hildebrandt, Chao Agnes Hsiung, and Ping Yang

Précis: *Although most patients with lung cancer were smokers, the much smaller numbers of never-smokers with lung cancer are less understood with regard to the biologic underpinnings of their clinical outcomes.*

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4039

MEK1/2 Inhibition Decreases Lactate in BRAF-Driven Human Cancer Cells

Maria Falck Miniotis, Vaitha Arunan, Thomas R. Eykyn, Richard Marais, Paul Workman, Martin O. Leach, and Mounia Belouche-Babari

Précis: *The use of magnetic resonance spectroscopy to measure lactate depletion could provide a simple, noninvasive metabolic biomarker for evaluating pharmacodynamic responses to the many BRAF/MEK inhibitors currently in clinical trials.*

4050

Enhanced Inhibition of ERK Signaling by a Novel Allosteric MEK Inhibitor, CH5126766, That Suppresses Feedback Reactivation of RAF Activity

Nobuya Ishii, Naoki Harada, Eric W. Joseph, Kazuhiro Ohara, Takaaki Miura, Hiroshi Sakamoto, Yutaka Matsuda, Yasushi Tomii, Yukako Tachibana-Kondo, Hitoshi Iikura, Toshihiro Aoki, Nobuo Shimma, Mikio Arisawa, Yoshihiro Sowa, Poulivos I. Poulidakos, Neal Rosen, Yuko Aoki, and Toshiyuki Sakai

Précis: *A novel class of MEK inhibitor described in this preclinical study causes MEK to function as a dominant negative inhibitor of RAF, enhancing its therapeutic action in tumors driven by mutant RAS or RAF.*

4061

Targeting Transmembrane TNF- α Suppresses Breast Cancer Growth

Mingxia Yu, Xiaoxi Zhou, Lin Niu, Guohong Lin, Jin Huang, Wenjing Zhou, Hui Gan, Jing Wang, Xiaodan Jiang, Bingjiao Yin, and Zhuoya Li

Précis: *TNF antibody that specifically binds transmembrane TNF but not soluble TNF is highly effective in cancer treatment, with the capability to address patients who do not respond to existing TNF antagonists as a result of the ligand being shed by tumors.*


4075

Conditional Loss of ErbB3 Delays Mammary Gland Hyperplasia Induced by Mutant PIK3CA without Affecting Mammary Tumor Latency, Gene Expression, or Signaling

Christian D. Young, Adam D. Pfeifferle, Philip Owens, María G. Kuba, Brent N. Rexer, Justin M. Balko, Violeta Sánchez, Hailing Cheng, Charles M. Perou, Jean J. Zhao, Rebecca S. Cook, and Carlos L. Arteaga

Précis: *These findings suggest a rationale to combine inhibitors against PI3K and ErbB receptors in treating breast cancers that harbor PIK3CA activating mutations.*

TUMOR AND STEM CELL BIOLOGY

- 4086 **Th-MYCN Mice with Caspase-8 Deficiency Develop Advanced Neuroblastoma with Bone Marrow Metastasis**
 Tal Teitz, Madoka Inoue, Marcus B. Valentine, Kejin Zhu, Jerold E. Rehg, Wei Zhao, David Finkelstein, Yong-Dong Wang, Melissa D. Johnson, Christopher Calabrese, Marcelo Rubinstein, Razqallah Hakem, William A. Weiss, and Jill M. Lahti
Précis: An in vivo model of neuroblastoma that undergoes bone marrow metastasis will be useful to enable better studies of dissemination processes and therapeutic candidates.
- 4098 **miR-214 Coordinates Melanoma Progression by Upregulating ALCAM through TFAP2 and miR-148b Downmodulation**
 Elisa Penna, Francesca Orso, Daniela Cimino, Irene Vercellino, Elena Grassi, Elena Quaglino, Emilia Turco, and Daniela Taverna
Précis: By establishing a critical pathway to coordinate metastatic dissemination in melanoma, this study offers an initial preclinical proof of concept for targeting its elements as a rational approach to block or reverse this deadly process.
- 4112 **Cancer Stem-like Cell Marker CD44 Promotes Bone Metastases by Enhancing Tumorigenicity, Cell Motility, and Hyaluronan Production**
 Toru Hiraga, Susumu Ito, and Hiroaki Nakamura
Précis: This important study provides an initial glimpse of the functional meaning of a cell surface protein widely associated with stem-like cell properties in human cancer.
- 4123 **Stress-Response Protein RBM3 Attenuates the Stem-like Properties of Prostate Cancer Cells by Interfering with CD44 Variant Splicing**
 Yu Zeng, Dana Wodzinski, Dong Gao, Takumi Shiraishi, Naoki Terada, Youqiang Li, Donald J. Vander Griend, Jun Luo, Chuize Kong, Robert H. Getzenberg, and Prakash Kulkarni
Précis: This study focuses on a member of a little-studied family of stress regulators in cancer, the cold shock proteins, offering new perspectives on how stress alters RNA splicing for a modulator of stem cell-like character in malignant disease.

- 4134 **G-CSF Receptor Positive Neuroblastoma Subpopulations Are Enriched in Chemotherapy-Resistant or Relapsed Tumors and Are Highly Tumorigenic**
 Danielle M. Hsu, Saurabh Agarwal, Ashley Benham, Cristian Coarfa, Denae N. Trahan, Zaowen Chen, Paris N. Stowers, Amy N. Courtney, Anna Lakoma, Eveline Barbieri, Leonid S. Metelitsa, Preethi Gunaratne, Eugene S. Kim, and Jason M. Shoheit
Précis: Stem-like cells in an aggressive pediatric tumor uniformly express the receptor for G-CSF, which, as a means to elevate white blood cell counts, is commonly given to patients where it might unsuspectingly contribute to progression.
- 4147 **Connective Tissue Growth Factor Activates Pluripotency Genes and Mesenchymal-Epithelial Transition in Head and Neck Cancer Cells**
 Cheng-Chi Chang, Wen-Hao Hsu, Chen-Chien Wang, Chun-Hung Chou, Mark Yen-Ping Kuo, Been-Ren Lin, Szu-Ta Chen, Shyh-Kuan Tai, Min-Liang Kuo, and Muh-Hwa Yang
Précis: These findings provide insights into epithelial plasticity during progression of head and neck cancers that are rapidly rising in incidence, perhaps also providing a basis for improvement in their classification.
- 4158 **Nrf2 Prevents Initiation but Accelerates Progression through the Kras Signaling Pathway during Lung Carcinogenesis**
 Hironori Satoh, Takashi Moriguchi, Jun Takai, Masahito Ebina, and Masayuki Yamamoto
Précis: The Nrf2 cellular antioxidant system has different roles during cancer initiation and progression, much like TNF, such that Nrf2 inhibitors offer more rational tools than Nrf2 activators to attack established malignancy.

CORRECTIONS

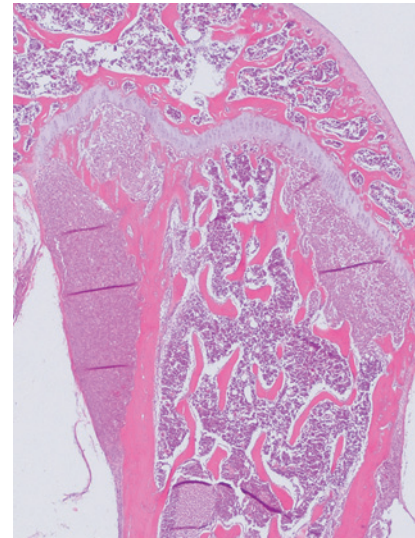
- 4169 **Correction: Cell Surface Expression of Epidermal Growth Factor Receptor and Her-2 with Nuclear Expression of Her-4 in Primary Osteosarcoma**
- 4170 **Correction: *Helicobacter pylori* Cytotoxin-Associated Gene A Activates the Signal Transducer and Activator of Transcription 3 Pathway *In Vitro* and *In Vivo***

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ABOUT THE COVER

CD44, a cancer stem-like cell marker, has been implicated in cancer cell migration, invasion, and metastasis. This study shows that CD44 expression in cancer cells promotes bone metastases by enhancing tumorigenicity, cell migration and invasion, and production of hyaluronan, the primary ligand for CD44. Using a mouse model of bone metastasis, it was found that 4-methylumbelliferone, an inhibitor of hyaluronan synthesis, inhibited bone metastases of MDA-MB-231 human breast cancer cells with reduced number of osteoclasts. For details, see article by Hiraga and colleagues on page 4112.



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