


BREAKING ADVANCES

- 2961** Highlights from Recent Cancer Literature

REVIEWS

- 2963**  Maintaining Tumor Heterogeneity in Patient-Derived Tumor Xenografts
John W. Cassidy, Carlos Caldas, and Alejandra Bruna
- 2969** Plasminogen Activator Inhibitor-1 in Cancer: Rationale and Insight for Future Therapeutic Testing
Veronica R. Placencio and Yves A. DeClerck

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2975** Neuroendocrine Transdifferentiation in Human Prostate Cancer Cells: An Integrated Approach
Marianna Cerasuolo, Debora Paris, Fabio A. Iannotti, Dominique Melck, Roberta Verde, Enrico Mazzarella, Andrea Motta, and Alessia Ligresti
Précis: These provocative findings show how depriving androgen-dependent prostate cancer cells of androgen not only compromises cell survival, but also helps create a nonmalignant neuroendocrine phenotype in surviving cells that can ultimately support the outgrowth of androgen-independent tumors.
- 2987** Identification of Prognostic Groups in High-Grade Serous Ovarian Cancer Treated with Platinum–Taxane Chemotherapy
Ping Chen, Kaisa Huhtinen, Katja Kaipio, Piia Mikkonen, Viljami Aittomäki, Rony Lindell, Johanna Hynninen, Annika Auranen, Seija Grénman, Rainer Lehtonen, Olli Carpén, and Samps Hautaniemi
Précis: This study introduces a novel computational method that may accurately predict whether a patient with high-grade ovarian cancer will benefit from first-line chemotherapy.
- 2999** IDH1 Mutation Induces Reprogramming of Pyruvate Metabolism
Jose L. Izquierdo-Garcia, Pavithra Viswanath, Pia Eriksson, Larry Cai, Marina Radoul, Myriam M. Chaumeil, Michael Blough, H. Artee Luchman, Samuel Weiss, J. Gregory Cairncross, Joanna J. Phillips, Russell O. Pieper, and Sabrina M. Ronen
Précis: Beyond their other effects, IDH1 mutations in brain tumors confer an imageable reduction in pyruvate dehydrogenase activity that is essential for proliferation of malignant cells, a finding with therapeutic implications.

3010


- A Systematic Approach to Defining the microRNA Landscape in Metastasis
Giridhar Mudduluru, Mohammed Abba, Jasmin Batliner, Nitin Patil, Maiké Scharp, Taral R. Lunavat, Jörg Hendrik Leupold, Olga Oleksiuk, Dilafuz Juraeva, Wilko Thiele, Melanie Rothley, Axel Benner, Yinon Ben-Neriah, Jonathan Sleeman, and Heike Allgayer
Précis: This article offers a systematic definition of the entire metastasis-associated miRNA landscape using an unbiased profiling approach of metastasis tissues from patients.

MICROENVIRONMENT AND IMMUNOLOGY


- 3020** Novel Cell-Penetrating Peptide-Based Vaccine Induces Robust CD4⁺ and CD8⁺ T Cell-Mediated Antitumor Immunity
Madiha Derouazi, Wilma Di Berardino-Besson, Elodie Belnoue, Sabine Hoepner, Romy Walther, Mahdia Benkhoucha, Patrick Teta, Yannick Dufour, Céline Yacoub Maroun, Andres M. Salazar, Denis Martinvalet, Pierre-Yves Dietrich, and Paul R. Walker
Précis: These results offer preclinical proof of concept for the use of a cell-penetrating peptide vaccine with robust antitumor activity in multiple aggressive tumor models.
- 3032** Oncogenic Transformation Can Orchestrate Immune Evasion and Inflammation in Human Mesenchymal Stem Cells Independently of Extrinsic Immune-Selective Pressure
Alex Miranda, Juan M. Funes, Nilda Sánchez, Celia M. Limia, Mónica Mesa, Sergio A. Quezada, Rolando Pérez, and Joel de León
Précis: This conceptually powerful study illuminates how the effects of oncogene activation extend beyond well-studied cell autonomous roles in proliferation, apoptosis, and invasion to suppressive effects on the local immune microenvironment, which are essential to license immune escape as the critical step in tumorigenesis.
- 3043**  Neuroblastoma Arginase Activity Creates an Immunosuppressive Microenvironment That Impairs Autologous and Engineered Immunity
Francis Mussai, Sharon Egan, Stuart Hunter, Hannah Webber, Jonathan Fisher, Rachel Wheat, Carmel McConville, Yordan Sbirkov, Kate Wheeler, Gavin Bendle, Kevin Petrie, John Anderson, Louis Chesler, and Carmela De Santo
Précis: These findings show how pediatric neuroblastomas inactivate antitumor immune responses, including in the setting of immunotherapy, correlating with a worse patient survival.

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3054 Tristetraprolin Limits Inflammatory Cytokine Production in Tumor-Associated Macrophages in an mRNA Decay-Independent Manner

Franz Kratochvill, Nina Gratz, Joseph E. Qualls, Lee-Ann Van De Velde, Hongbo Chi, Pavel Kovarik, and Peter J. Murray

Précis: Manipulation of a p38 kinase-related signaling axis in macrophages appears to strongly affect the growth of solid tumors, suggesting a new strategy to reprogram inflammation in tumor microenvironments.

3098 Interleukin-6 Stimulates Defective Angiogenesis



Ganga Gopinathan, Carla Milagre, Oliver M.T. Pearce, Louise E. Reynolds, Kairbaan Hodivala-Dilke, David A. Leinster, Haihong Zhong, Robert E. Hollingsworth, Richard Thompson, James R. Whiteford, and Frances Balkwill

Précis: These findings have important implications for understanding abnormal angiogenic processes in cancer, as well as their connection to immune escape and the use of VEGF or IL6 targeting therapies in cancer patients.

MOLECULAR AND CELLULAR PATHOBIOLOGY

3065 Cytomegalovirus Immediate-Early Proteins Promote Stemness Properties in Glioblastoma

Liliana Soroceanu, Lisa Matlaf, Sabeena Khan, Armin Akhavan, Eric Singer, Vladimir Bezrookove, Stacy Decker, Saleena Ghanny, Piotr Hadaczek, Henrik Bengtsson, John Ohlfest, Maria-Gloria Luciani-Torres, Lualhati Harkins, Arie Perry, Hong Guo, Patricia Soteropoulos, and Charles S. Cobbs

Précis: This study unveils a novel paradigm in viral oncogenesis, exposing the role of human cytomegalovirus in driving the growth of cancer stem cells in glioblastoma.

3077 EGF Receptor Promotes Prostate Cancer Bone Metastasis by Downregulating miR-1 and Activating TWIST1

Yung-Sheng Chang, Wei-Yu Chen, Juan Juan Yin, Heather Sheppard-Tillman, Jiaoti Huang, and Yen-Nien Liu

Précis: The findings of this study raise the interesting idea that miRNA expression might be directly targeted by nuclear growth factor receptor isoforms, with relevance for the coordinated progression of malignancy.

3087 KIAA1324 Suppresses Gastric Cancer Progression by Inhibiting the Oncoprotein GRP78

Jin Muk Kang, Sujin Park, Staci Jakyong Kim, Hyojung Kim, Bona Lee, Junil Kim, Jinah Park, Shin Tae Kim, Han-Kwang Yang, Woo Ho Kim, and Seong-Jin Kim

Précis: These findings provide evidence of a novel mechanism of gastric carcinogenesis and also suggest a novel potential biomarker and therapeutic target for gastric cancer.

PREVENTION AND EPIDEMIOLOGY

3108 Implication of a Chromosome 15q15.2 Locus in Regulating UBR1 and Predisposing Smokers to MGMT Methylation in Lung

Shuguang Leng, Guodong Wu, Leonard B. Collins, Cynthia L. Thomas, Carmen S. Tellez, Andrew R. Jauregui, Maria A. Picchi, Xiequn Zhang, Daniel E. Juri, Dhimant Desai, Shantu G. Amin, Richard E. Crowell, Christine A. Stidley, Yushi Liu, James A. Swenberg, Yong Lin, Marc G. Wathélet, Frank D. Gilliland, and Steven A. Belinsky

Précis: Genetic polymorphisms that affect DNA methylation of the DNA repair gene MGMT have strong clinical relevance in smokers, not only for cancer risk assessment but also for stratification of lung cancer patients for alkylating agent chemotherapy.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3118 Erlotinib Pretreatment Improves Photodynamic Therapy of Non-Small Cell Lung Carcinoma Xenografts via Multiple Mechanisms

Shannon M. Gallagher-Colombo, Joann Miller, Keith A. Cengel, Mary E. Putt, Sergei A. Vinogradov, and Theresa M. Busch

Précis: These findings offer a strong impetus to incorporate the EGFR inhibitor erlotinib into clinical trials of photodynamic therapy, based on understanding drug mechanisms that rationalize its combination with other cytotoxic therapies.



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3127 Minor Changes in Expression of the Mismatch Repair Protein MSH2 Exert a Major Impact on Glioblastoma Response to Temozolomide

José L. McFaline-Figueroa, Christian J. Braun, Monica Stanciu, Zachary D. Nagel, Patrizia Mazzucato, Dewakar Sangaraju, Edvinas Cerniauskas, Kelly Barford, Amanda Vargas, Yimin Chen, Natalia Tretyakova, Jacqueline A. Lees, Michael T. Hemann, Forest M. White, and Leona D. Samson

Précis: Modest decreases in DNA mismatch repair factor MSH2 can dramatically alter chemosensitivity to a drug used commonly to treat aggressive cancers, with little effect on the mismatch repair itself, suggesting that subtle mismatch repair changes mediating drug resistance may be more prevalent than appreciated.

3139 Identification of Oncogenic and Drug-Sensitizing Mutations in the Extracellular Domain of FGFR2

Junko Tanizaki, Dalia Ercan, Marzia Capelletti, Michael Dodge, Chunxiao Xu, Magda Bahcall, Erin M. Tricker, Mohit Butaney, Antonio Calles, Lynette M. Sholl, Peter S. Hammerman, Geoffrey R. Oxnard, Kwok-Kin Wong, and Pasi A. Jänne

Précis: Based on other advances in targeting FGF receptors in cancer, the novel mutations identified in this study in the extracellular domain of the FGF receptor FGFR2 could offer therapeutic targets in a variety of solid tumors.

3147 Improving Drug Penetrability with iRGD Leverages the Therapeutic Response to Sorafenib and Doxorubicin in Hepatocellular Carcinoma

Christian Schmithals, Verena Köberle, Hüdayi Korkusuz, Thomas Pleli, Bianca Kakoschky, Eduardo Alonso Augusto, Ahmed Atef Ibrahim, Jose M. Arencibia, Vida Vafaizadeh, Bernd Groner, Horst-Werner Korf, Bernd Kronenberger, Stefan Zeuzem, Thomas J. Vogl, Oliver Waidmann, and Albrecht Piiper

Précis: These findings establish a clinically tractable method to safely widen the therapeutic window for chemotherapy in patients with liver cancer, along with a noninvasive method to identify candidate subjects, offering immediate translational impact for evaluation in human trials.

TUMOR AND STEM CELL BIOLOGY

3155 CASC15-S Is a Tumor Suppressor lncRNA at the 6p22 Neuroblastoma Susceptibility Locus

Mike R. Russell, Annalise Penikis, Derek A. Oldridge, Juan R. Alvarez-Dominguez, Lee McDaniel, Maura Diamond, Olivia Padovan, Pichai Raman, Yimei Li, Jun S. Wei, Shile Zhang, Janahan Gnanchandran, Robert Seeger, Shahab Asgharzadeh, Javed Khan, Sharon J. Diskin, John M. Maris, and Kristina A. Cole

Précis: This unbiased genetic association study identifies the involvement of a long noncoding RNA in initiating pediatric neuroblastoma, helping explain the low somatic mutation rates in protein coding genes observed in this lethal malignancy and suggesting new directions for therapeutic intervention.

3167 TP53 Silencing Bypasses Growth Arrest of BRAF^{V600E}-Induced Lung Tumor Cells in a Two-Switch Model of Lung Tumorigenesis

Anny Shai, David Dankort, Joseph Juan, Shon Green, and Martin McMahon

Précis: This study describes new mouse models for temporal dissociation of genetic events in lung carcinogenesis and establishes a core role for the p53 pathway in restricting lung cancer development.

3181 Amplification of Long Noncoding RNA ZFAS1 Promotes Metastasis in Hepatocellular Carcinoma

Tao Li, Junjie Xie, Chuan Shen, Dongfeng Cheng, Yuan Shi, Zhichong Wu, Xiaping Deng, Hao Chen, Baiyong Shen, Chenghong Peng, Hongwei Li, Qian Zhan, and Zhecheng Zhu

Précis: These findings illuminate the oncogenic function of a noncoding RNA that acts by opposing tumor-suppressive effects of miR-150, suggesting utility as a prognostic biomarker or target for clinical management of HCC.

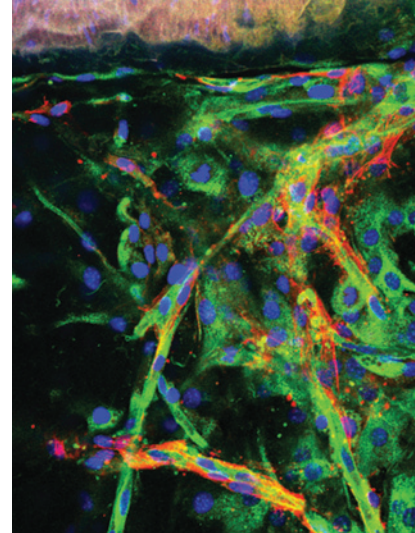
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ABOUT THE COVER

The immunofluorescence image is of an aortic ring treated with IL6 stained for vessels (green), pericytes (red), and cell nuclei (blue). Here, it is shown that IL6 stimulates angiogenesis with defective pericyte coverage. Treatment of peritoneal xenografts of ovarian cancer with an anti-IL6 antibody restored pericyte coverage of the tumor blood vessels. The authors' findings have implications for the use of cancer therapies that target IL6 and for understanding abnormal angiogenesis in cancers, chronic inflammatory disease, and stroke. For details, see article by Gopinathan and colleagues on page 3098.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

75 (15)

Cancer Res 2015;75:2961-3191.

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