**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 Milkonen, Viljami Aittomäki, Rony Lindell, Johanna Hynninen, Annika Auranen, Seija Grénman, Rainer Lehtonen, Olli Carpién, and Sampsa 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


*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.

**MICROENVIRONMENT AND IMMUNOLOGY**

3009 A Systematic Approach to Defining the microRNA Landscape in Metastasis


*Précis:* This article offers a systematic definition of the entire metastasis-associated miRNA landscape using an unbiased profiling approach of metastasis tissues from patients.

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 F. 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


*Précis:* These findings show how pediatric neuroblastomas inactivate antitumor immune responses, including in the setting of immunotherapy, correlating with a worse patient survival.
3054 Tristetraprolin Limits Inflammatory Cytokine Production in Tumor-Associated Macrophages in an mRNA Decay-Independent Manner
Franz Kratochvill, Nina Grat, Joseph E. Qualti, Lee-Am 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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

3065 Cytomegalovirus Immediate-Early Proteins Promote Stemness Properties in Glioblastoma
Liliana Sorocoeanu, Lisa Matlaf, Sabeena Khan, Armin Akhavan, Eric Singer, Vladimir Bezrookove, Stacy Decker, Saleema Ghanny, Piotr Hadaczek, Henrik Bengtsson, John Ohlfest, Maria-Gloria Luciani-Torres, Lualhati Harkins, Ari 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 EGFR 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, Sujein 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

3098 Interleukin-6 Stimulates Defective Angiogenesis
Ganga Gopinathan, Carla Milagre, Oliver M.T. Pearce, Louise E. Reynolds, Kairbaan Hodivala-Dille, 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.

3108 Implication of a Chromosome 15q15.2 Locus in Regulating UBR1 and Predisposing Smokers to MGMT Methylation in Lung
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.
Minor Changes in Expression of theMismatchRepair Protein MSH2 Exert a Major Impact onGlioblastoma Response to Temozolomide
Précis: Modest decreases in DNA mismatch repair factorMSH2 can dramatically alter chemosensitivity to a drugused commonly to treat aggressive cancers, with littleeffect on the mismatch repair itself, suggesting that subtlemismatch repair changes mediating drug resistance maybe more prevalent than appreciated.

Identification of Oncogenic and Drug-Sensitizing Mutations in the ExtracellularDomain of FGFR2
Précis: Based on other advances in targeting FGFR receptorsin cancer, the novel mutations identified in this study inthe extracellular domain of the FGFR2 receptor couldoffer therapeutic targets in a variety of solid tumors.

Improving Drug Penetrability with iRGD Leverages the Therapeutic Response toSorafenib and Doxorubicin in Hepatocellular Carcinoma
Précis: These findings establish a clinically tractablemethod to safely widen the therapeutic window forchemotherapy in patients with liver cancer, along with ainnovative method to identify candidate subjects,offering immediate translational impact for evaluation inhuman trials.

CASC15-S Is a Tumor Suppressor lncRNA at the6p22 Neuroblastoma Susceptibility Locus
Précis: This unbiased genetic association study identifies theinvolvement of a long noncoding RNA in initiatingpediatric neuroblastoma, helping explain the low somaticmutation rates in protein coding genes observed in thislethal malignancy and suggesting new directions fortherapeutic intervention.

TP53 Silencing Bypasses Growth Arrest ofBRAFV600E-Induced Lung Tumor Cells in aTwo-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.

Amplification of Long Noncoding RNA ZFAS1Promotes Metastasis in Hepatocellular Carcinoma
Tao Li, Junjie Xie, Chuan Shen, Dongfeng Cheng,Yuan Shi, Zhichung Wu, Xiaoxing 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.
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.
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